CompleteMCAsyndromes occur most often when an embolus occludes the stem of the artery. Cortical collateral blood flow and differing arterial configurations are probably responsible for the development of many partial syndromes. Partial syndromes also may be due to emboli that enter the proximal MCA without complete occlusion, occlude distal MCA branches, or fragment and move distally.

Partial syndromes due to embolic occlusion of a single branch include hand, or arm and hand, weakness alone (brachial syndrome) or facial weakness with nonfluent (expressive, Broca) aphasia (Chap 25), with or without arm weakness (frontal opercular syndrome). A combination of sensory disturbance, motor weakness, and nonfluent aphasia suggests that an embolus has occluded the proximal superior division and infarcted large portions of the frontal and parietal cortices (Fig. 361-3). If a fluent (Wernicke's) aphasia occurs without weakness, the inferior division of theMCAsupplying the posterior part (temporal cortex) of the dominant hemisphere is probably involved (Fig. 361-3). Jargon speech and an inability to comprehend written and spoken language are prominent features, often accompanied by a contralateral, homonymous superior quadrantanopia. Hemineglect or spatial agnosia without weakness indicates that the inferior division of the MCA in the nondominant hemisphere is involved.

ANTERIOR CEREBRAL ARTERY The anterior cerebral artery is divided into two segments: the precommunal (A1) circle of Willis, or stem, which connects the internal carotid artery to the anterior communicating artery, and the postcommunal (A2) segment distal to the anterior communicating artery (Figs. 361-1 and361-4). The A1 segment gives rise to several deep penetrating branches that supply the anterior limb of the internal capsule, the anterior perforate substance, amygdala, anterior hypothalamus, and the inferior part of the head of the caudate nucleus (Fig. 361-2).

Occlusion of the proximal anterior cerebral artery is usually well tolerated because of collateral flow. Occlusion of a single A2 segment results in the contralateral symptoms noted in the legend of Fig. 361-4. If both A2 segments arise from a single anterior cerebral stem (contralateral A1 segment atresia), the occlusion affects both hemispheres. Profound abulia (a delay in verbal and motor response) and bilateral pyramidal signs with paraparesis and urinary incontinence result.

ANTERIOR CHOROIDAL ARTERY This artery arises from the internal carotid artery and supplies the posterior limb of the internal capsule and the white matter posterolateral to it, through which pass some of the geniculocalcarine fibers (Figs. 361-2 and361-5). The complete syndrome of anterior choroidal artery occlusion consists of contralateral hemiplegia, hemianesthesia (hypesthesia), and homonymous hemianopia. However, because this territory is also supplied by penetrating vessels of the proximalMCA and the posterior communicating and posterior choroidal arteries, minimal deficits may occur, and patients frequently recover substantially.

INTERNAL CAROTID ARTERY The clinical picture of internal carotid occlusion varies depending on whether the cause of ischemia is propagated thrombus, embolism, or low flow. The cortex supplied by the middle cerebral territory is affected most often. With a competent circle of Willis, occlusion may go unnoticed. If the thrombus propagates up the internal carotid artery into theMCA, or embolizes it, symptoms are identical to proximal MCA occlusion (see above). Sometimes there is massive infarction of the

entire deep white matter and cortical surface. When the origins of both the anterior and middle cerebral arteries are occluded at the top of the carotid artery, abulia or stupor occurs with hemiplegia, hemianesthesia, and aphasia or anosognosia. When the posterior cerebral artery arises from the internal carotid artery (an unusual configuration called a *fetal posterior cerebral artery*), it also may become occluded and give rise to symptoms referable to its peripheral territory (Figs. 361-4 and 361-5).

In addition to supplying the ipsilateral brain, the internal carotid artery perfuses the optic nerve and retina via the ophthalmic artery. In about 25% of symptomatic internal carotid disease, recurrent transient monocular blindness (TMB or amaurosis fugax) warns of the lesion. Patients typically describe a horizontal shade that sweeps down or up across the field of vision. They may also complain that their vision was blurred in that eye or that the upper or lower half of vision disappeared. In most cases, these symptoms last only a few minutes. Rarely, ischemia or infarction of the ophthalmic artery or central retinal arteries occurs at the time of cerebral TIA or infarction.

A high-pitched prolonged carotid bruit fading into diastole is often associated with tightly stenotic lesions. As the stenosis grows tighter and flow distal to the stenosis becomes reduced, the bruit becomes fainter and may disappear when occlusion is imminent. A stenosis is said to be *asymptomatic* if the patient has never experienced TIA or stroke that can be explained by the carotid lesion. The risk of stroke with this finding is low. *Symptomatic carotid stenosis*, in distinction, carries a significantly higher risk for stroke (see "Treatment," below).

COMMON CAROTID ARTERY All symptoms and signs of internal carotid occlusion may also be present with occlusion of the common carotid artery. Bilateral common carotid artery occlusions at their origin may occur in Takayasu's arteritis (Chap. 317).

Large Vessel Stroke within the Posterior Circulation The posterior circulation is composed of the paired vertebral arteries, the basilar artery, and the paired posterior cerebral arteries. The vertebral arteries join to form the basilar artery at the pontomedullary junction. The basilar artery divides into two posterior cerebral arteries in the interpeduncular fossa (Fig. 361-1). These major arteries gives rise to long and short circumferential branches and to smaller deep penetrating branches that supply the cerebellum, medulla, pons, midbrain, subthalamus, thalamus, hippocampus, and medial temporal and occipital lobes. Occlusion of each vessel produces its own distinctive syndrome.

Pathophysiology

POSTERIOR CEREBRAL ARTERY In 75% of cases, both posterior cerebral arteries arise from the bifurcation of the basilar artery; in 20%, one has its origin from the ipsilateral internal carotid artery via the posterior communicating artery; in 5%, both originate from the respective ipsilateral internal carotid arteries (Fig. 361-1). The precommunal, or P1, segment of the true posterior cerebral artery is atretic in such cases.

Atheroma formation or emboli that lodge at the top of the basilar artery or along the P1 segment may cause symptoms by occluding one or more of the small

brainstem-penetrating branches ([Figs. 361-1](#) and[361-5](#)) that supply the middle cerebral peduncles, the substantia nigra, red nucleus, oculomotor nuclei, midbrain reticular formation, subthalamic nucleus, decussation of the superior cerebellar peduncles, the medial longitudinal fasciculus, and the medial lemniscus. The *artery of Percheron* arises from either the right or the left precommunal segment of the posterior cerebral artery; it divides in the subthalamus to supply the inferomedial and anterior portions of the thalamus and subthalamus bilaterally. The *thalamogeniculate branches*, which also originate from the precommunal portion of the posterior cerebral artery, supply the dorsal, dorsomedial, anterior and inferior thalamus, and the medial geniculate body. The *medial posterior choroidal artery* supplies the superior dorsomedial and dorsoanterior thalamus and the medial geniculate body in addition to the tela choroidea of the third ventricle. The *lateral posterior choroidal artery* supplies the choroid plexus of the lateral ventricle.

Occlusions in the posterior cerebral artery distal to the junction with the posterior communicating artery (P2 segment) ([Fig. 361-5](#)) may disrupt small circumferential branches that course around the midbrain to supply the lateral part of the cerebral peduncles, medial lemniscus, tegmentum of the midbrain, superior colliculi, lateral geniculate body, and posterolateral nucleus of the thalamus, choroid plexus, and hippocampus. On the rare occasions when atheroma occur more distally in the posterior cerebral artery ([Fig. 361-5](#)), occlusion may produce ischemia in the inferomedial temporal lobe, parahippocampal and hippocampal gyri, and occipital lobe -- including the primary visual cortex and the visual association areas.

In addition to atherothrombosis and embolism, posterior circulation disease may also be caused by dissection of either vertebral artery and fibromuscular dysplasia.

VERTEBRAL AND POSTERIOR INFERIOR CEREBELLAR ARTERIES The vertebral artery, which arises from the innominate artery on the right and the subclavian artery on the left, divides into four anatomic segments. The first (V1) extends from its origin to its entrance into the sixth or fifth transverse vertebral foramen. The second segment (V2) transverses the vertebral foramina from C6 to C2. The third (V3) passes through the transverse foramen and circles around the arch of the atlas to pierce the dura at the foramen magnum. The fourth (V4) segment courses upward to join the other vertebral artery to form the basilar artery; only the fourth segment gives rises to branches that supply the brainstem and cerebellum. The *posterior inferior cerebellar artery* (PICA) in its proximal segment supplies the lateral medulla and, in its distal branches, the inferior surface of the cerebellum. Anastomotic channels exist among the ascending cervical arteries, the thyrocervical arteries, the occipital artery (branch of the external carotid artery), and the second segment of the vertebral artery.

Atherothrombotic lesions have a predilection for V1 and V4 segments of the vertebral artery. The first segment may become diseased at the origin of the vessel and may produce posterior circulation emboli; collateral flow from the contralateral vertebral artery or the ascending cervical, thyrocervical, or occipital arteries is usually sufficient to prevent low-flow[TIAs](#) or stroke. When one vertebral artery is atretic and an atherothrombotic lesion threatens the origin of the other, the collateral circulation, which may also include retrograde flow down the basilar artery, is often insufficient ([Figs. 361-1](#) and[361-5](#)). In this setting, low-flow TIAs may occur, consisting of syncope,

vertigo, and alternating hemiplegia; this state also sets the stage for thrombosis. Disease of the distal fourth segment of the vertebral artery can promote thrombus formation manifest as embolism or with propagation as basilar artery thrombosis. Stenosis proximal to the origin of the posterior inferior cerebellar artery can threaten the lateral medulla and posterior inferior surface of the cerebellum.

If the subclavian artery is occluded proximal to the origin of the vertebral artery, there is a reversal in the direction of blood flow in the ipsilateral vertebral artery. Exercise of the ipsilateral arm may increase demand on vertebral flow, producing posterior circulationTIAs, or "subclavian steal."

Although atheromatous disease rarely narrows the second and third segments of the vertebral artery, this region is subject to dissection, fibromuscular dysplasia, and, rarely, encroachment by osteophytic spurs within the vertebral foramina.

*BASILAR ARTERY*Branches of the basilar artery supply the base of the pons and superior cerebellum and fall into three groups: (1) paramedian, 7 to 10 in number, which supply a wedge of pons on either side of the midline; (2) short circumferential, 5 to 7 in number, which supply the lateral two-thirds of the pons and middle and superior cerebellar peduncles; and (3) bilateral long circumferential (superior cerebellar and anterior inferior cerebellar arteries), which course around the pons to supply the cerebellar hemispheres.

Atheromatous lesions can occur anywhere along the basilar trunk but are most frequent in the proximal basilar and distal vertebral segments. Typically, lesions occlude either the proximal basilar and one or both vertebral arteries. The clinical picture varies depending on the availability of retrograde collateral flow from the posterior communicating arteries. Rarely, dissection of a vertebral artery may involve the basilar artery and, depending on the location of true and false lumen, may produce multiple penetrating artery strokes.

Although atherothrombosis occasionally occludes the distal portion of the basilar artery, emboli from the heart or proximal vertebral or basilar segments are more commonly responsible for "top of the basilar" syndromes.

Clinical Manifestations

*POSTERIOR CEREBRAL ARTERY*Embolic occlusion is the usual cause of stroke in this vascular territory. Two syndromes are commonly observed: (1) midbrain, subthalamic, and thalamic signs, which are due to disease of the P1 segment or of its penetrating branches; and (2) cortical temporal and occipital lobe signs, due to occlusion of the P2 segment.

1. *P1 syndromes*. If the P1 segment is occluded, infarction usually occurs in the ipsilateral subthalamus and medial thalamus and in the ipsilateral cerebral peduncle and midbrain (Fig. 361-5). A third nerve palsy with contralateral ataxia (Claude's syndrome) or with contralateral hemiplegia (Weber's syndrome) may result. The ataxia indicates involvement of the red nucleus or dentatorubrothalamic tract; the hemiplegia is localized to the cerebral peduncle. If the subthalamic nucleus is involved, contralateral

hemiballismus may occur. Occlusion of the artery of Percheron produces paresis of upward gaze and drowsiness, and often abulia. Extensive infarction in the midbrain and subthalamus occurring with bilateral proximal posterior cerebral artery occlusion presents as coma, unreactive pupils, bilateral pyramidal signs, and decerebrate rigidity.

Atheromatous occlusion of the penetrating branches of thalamic and thalamogeniculate arteries produces less extensive thalamic and thalamocapsular lacunar syndromes. The *thalamic Dejerine-Roussy syndrome* is the best known. Its main feature is contralateral hemisensory loss followed later by an agonizing, searing or burning pain in the affected areas. It is persistent and responds poorly to analgesics. Anticonvulsants (carbamazepine or gabapentin) or tricyclic antidepressants may be beneficial. Associated motor signs include hemiparesis, hemiballismus, choreoathetosis, intention tremor, incoordination, and posturing of the hand and arm, particularly while walking.

2. *P2 syndromes* (see also Fig. 361-5). Occlusion of the distal posterior cerebral artery causes infarction of the medial temporal and occipital lobes. Contralateral homonymous hemianopia with macula sparing is the usual manifestation. Occasionally, only the upper quadrant of visual field is involved. If the visual association areas are spared and only the calcarine cortex is involved, the patient may be aware of visual defects. Medial temporal lobe and hippocampal involvement may cause an acute disturbance in memory, particularly if it occurs in the dominant hemisphere. The defect usually clears because memory has bilateral representation. If the dominant hemisphere is affected and the infarct extends to involve the splenium of the corpus callosum, the patient may demonstrate alexia without agraphia. Visual agnosia for faces, objects, mathematical symbols, and colors and anomia with paraphasic errors (amnestic aphasia) may also occur in this setting, even without callosal involvement. Occlusion of the posterior cerebral artery can produce *peduncular hallucinosis* (visual hallucinations of brightly colored scenes and objects).

Bilateral infarction in the distal posterior cerebral arteries produces cortical blindness (blindness with preserved pupillary light reaction). The patient is often unaware of the blindness or may even deny it (*Anton's syndrome*). Tiny islands of vision may persist, and the patient may report that vision fluctuates as images are captured in the preserved portions. Rarely, only peripheral vision is lost and central vision is spared, resulting in "gun-barrel" vision. A constellation of symptoms termed *Balint's syndrome* can occur, usually with bilateral visual association area lesions. It includes optic ataxia (inability to visually guide limb movements), ocular ataxia (inability to direct eyes to a precise point in the visual field), inability to enumerate objects in a picture (simultagnosia) or extract meaning from a picture, and inability to avoid objects in one's path. Balint's syndrome occurs most often with infarctions secondary to low flow in the "watershed" between the distal posterior and middle cerebral artery territories, as occurs after cardiac arrest. Patients may even experience persistence of a visual image for several minutes despite gazing at another scene (*palinopia*). Embolic occlusion of the top of the basilar artery can produce any or all of the central or peripheral territory symptoms. The hallmark is the sudden onset of bilateral signs, including ptosis, pupillary asymmetry or lack of reaction to light, and somnolence.

VERTEBRAL AND POSTERIOR INFERIOR CEREBELLAR ARTERIES Embolic occlusion or thrombosis of a V4 segment causes ischemia of the lateral medulla. The

constellation of vertigo, numbness of the ipsilateral face and contralateral limbs, diplopia, hoarseness, dysarthria, dysphagia, and ipsilateral Horner's syndrome is called the lateral medullary (or Wallenberg's) syndrome (Fig. 361-6). Most cases result from ipsilateral vertebral artery occlusion; in the remainder,PICAocclusion is responsible. Occlusion of the medullary penetrating branches of the vertebral artery or PICA results in partial syndromes. *Hemiparesis is not a feature of vertebral artery occlusion*.

Rarely, a *medial medullary syndrome* occurs with infarction of the pyramid and contralateral hemiparesis of the arm and leg, sparing the face. If the medial lemniscus and emerging hypoglossal nerve fibers are involved, contralateral loss of joint position sense and ipsilateral tongue weakness occur.

Cerebellar infarction with edema can lead to *sudden respiratory arrest* due to raised intracranial pressure (ICP) in the posterior fossa. Drowsiness, Babinski signs, dysarthria, and bifacial weakness may be absent, or present only briefly, before respiratory arrest ensues. Gait unsteadiness, dizziness, nausea, and vomiting may be the only early symptoms and signs and should arouse suspicion of this impending complication, which may require neurosurgical decompression, often with an excellent outcome.

*BASILAR ARTERY*Because the brainstem contains many structures in close apposition, a diversity of clinical syndromes may emerge with ischemia, reflecting involvement of the corticospinal and corticobulbar tracts, ascending sensory tracts, and cranial nerve nuclei (Figs. 361-7,361-8, and361-9).

The symptoms of transient ischemia or infarction in the territory of the basilar artery often do not indicate whether the basilar artery itself or one of its branches is diseased, yet this distinction has important implications for therapy. *The picture of complete basilar occlusion, however, is easy to recognize as a constellation of bilateral long tract signs (sensory and motor) with signs of cranial nerve and cerebellar dysfunction*. A "locked-in" state of preserved consciousness with quadriplegia and cranial nerve signs suggest complete pontine and lower midbrain infarction. The therapeutic goal is to identify *impending* basilar occlusion before devastating infarction occurs. A series ofTIAs and a slowly progressive, fluctuating stroke are extremely significant as they often herald an atherothrombotic occlusion of the distal vertebral or proximal basilar artery.

TIAsin the proximal basilar distribution may produce dizziness (often described by patients as "swimming," "swaying," "moving," "unsteadiness" or "light-headedness"). Other symptoms that warn of basilar thrombosis include diplopia, dysarthria, facial or circumoral numbness, and hemisensory symptoms. In general, symptoms of basilar branch TIAs affect one side of the brainstem, whereas symptoms of basilar artery TIAs usually affect both sides, though a "herald" hemiparesis has been emphasized as an initial symptom of basilar occlusion. Most often TIAs, whether due to impending occlusion of the basilar artery or a basilar branch, are short-lived (5 to 30 min) and repetitive, occurring several times a day. The pattern suggests intermittent reduction of flow. Many neurologists treat with heparin to prevent clot propagation.

Atherothrombotic occlusion of the basilar artery with infarction usually causes *bilateral* brainstem signs. A gaze paresis or internuclear ophthalmoplegia associated with

ipsilateral hemiparesis may be the only manifestations of bilateral brainstem ischemia. More often, unequivocal signs of bilateral pontine disease are present. Complete basilar thrombosis carries a high mortality.

Occlusion of a branch of the basilar artery usually causes *unilateral* symptoms and signs involving motor, sensory, and cranial nerves. As long as symptoms remain unilateral, concern over pending basilar occlusion should be reduced.

SUPERIOR CEREBELLAR ARTERY Occlusion results in severe ipsilateral cerebellar ataxia, nausea and vomiting, dysarthria, and contralateral loss of pain and temperature sensation over the extremities, body, and face (spino- and trigeminothalamic tract). Partial deafness, ataxic tremor of the ipsilateral upper extremity, Horner's syndrome, and palatal myoclonus may occur rarely. Partial syndromes occur frequently (Fig. 361-7). With large strokes, swelling and mass effects may compress the midbrain or produce hydrocephalus; these symptoms may evolve rapidly. Neurosurgical intervention may be lifesaving in such cases.

ANTERIOR INFERIOR CEREBELLAR ARTERY Occlusion produces variable degrees of infarction because the size of this artery and the territory it supplies vary inversely with those of the PICA. The principal symptoms include: (1) ipsilateral deafness, facial weakness, vertigo, nausea and vomiting, nystagmus, tinnitus, cerebellar ataxia, Horner's syndrome, and paresis of conjugate lateral gaze; and (2) contralateral loss of pain and temperature sensation. An occlusion close to the origin of the artery may cause corticospinal tract signs (Fig. 361-9).

Occlusion of one of the short circumferential branches of the basilar artery affects the lateral two-thirds of the pons and middle or superior cerebellar peduncle, whereas occlusion of one of the paramedian branches affects a wedge-shaped area on either side of the medial pons (Figs. 361-7, 361-8, and 361-9).

Small Vessel "Lacunar" Stroke The term *lacunar infarction* refers to infarction following atherothrombotic or lipohyalinotic occlusion of one of the small, penetrating branches of the circle of Willis, middle cerebral artery stem, or vertebral and basilar arteries. The term *small vessel stroke* denotes occlusion of a small penetrating artery, regardless of mechanism.

Pathophysiology The middle cerebral artery stem, the arteries comprising the circle of Willis (A1 segment, anterior and posterior communicating arteries, and P1 segment), and the basilar and vertebral arteries all give rise to 100- to 300-um branches that penetrate the deep gray and white matter of the cerebrum or brainstem (Fig. 361-1). Each of these small branches can occlude either by atherothrombotic disease at its origin or by the development of lipohyalinotic thickening. Thrombosis of these vessels causes small infarcts that are referred to as *lacunes* (Latin for "lake" of fluid noted at autopsy). They range in size from 3 or 4 mm to 1 or 2 cm. Hypertension and age are the principal risk factors. Lacunar infarcts cause approximately 20% of all strokes.

Clinical Manifestations The most common *lacunar syndromes* are the following: (1) Pure motor hemiparesis from an infarct in the posterior limb of the internal capsule or basis pontis; the face, arm and leg are almost always involved. (2) Pure sensory stroke from

an infarct in the ventrolateral thalamus. (3) Ataxic hemiparesis from an infarct in the base of the pons. (4) Dysarthria and a clumsy hand or arm due to infarction in the base of the pons or in the genu of the internal capsule. (5) Pure motor hemiparesis with "motor (Broca's) aphasia" due to thrombotic occlusion of a lenticulostriate branch supplying the genu and anterior limb of the internal capsule and adjacent white matter of the corona radiata.

Syndromes 1 and 2 often overlap. Syndromes resulting from occlusion of the penetrating arteries of the proximal posterior cerebral artery were discussed above. Syndromes resulting from occlusion of the penetrating arteries of the basilar artery (Figs. 361-7, 261-8, and361-9) include ipsilateral ataxia and contralateral crural (leg) paresis, hemiparesis with horizontal gaze palsy, and hemiparesis with a crossed sixth nerve palsy. Lower basilar branch syndromes include internuclear ophthalmoplegia, horizontal gaze palsy, and appendicular cerebellar ataxia.

An anarthric pseudobulbar syndrome due to bilateral infarctions in the internal capsule can occur from disease in the lenticulostriate arteries. Before the advent of effective therapy for hypertension, multiple lacunes often caused pseudobulbar palsy (predominantly dysarthria and dysphagia) with emotional instability, a slowed abulic state, and bilateral pyramidal signs.

Transient symptoms (lacunarTIAs) may herald a lacunar infarct; they may occur several times a day and last only a few minutes. Recovery from a lacunar stroke often begins within hours or days, and over weeks or months may be nearly complete; in some cases, however, there is severe permanent disability. Often, institution of combined antithrombotic treatments does not prevent eventual stroke in "stuttering lacunes."

A large vessel source (either thrombosis or embolism) may manifest initially as a lacunar syndrome with small vessel infarction. Therefore, the search for embolic sources (carotid and heart) should not be abandoned in the evaluation of these patients.

FINDING THE CAUSE OF STROKE

The clinical presentation, temporal profile, and signs found on examination often establish the cause or narrow the possibilities to a few. Judicious use of laboratory testing and imaging studies complete the initial evaluation. For stroke without an identified cause (cryptogenic stroke), the exact diagnosis may be made months or years later as new symptoms develop. Unfortunately, nearly 30% of strokes remains unexplained despite extensive evaluation; nevertheless, they occur in patients with the same clinical profiles as those whose strokes are due to atherothrombosis.

Clinical examination should be focused on the peripheral vascular system (carotid auscultation for bruits, blood pressure, and pressure comparison between arms), the heart (dysrhythmia, murmurs), extremities (peripheral emboli), and retina [effects of hypertension and cholesterol emboli (Hollenhorst plaques)]; with a complete neurologic examination to localize the site of stroke. A chest x-ray, electrocardiogram (ECG), urinalysis, complete blood count, erythrocyte sedimentation rate, serum electrolytes, blood urea nitrogen, creatinine, blood sugar, serologic test for syphilis, serum lipid profile, prothrombin time, and partial thromboplastin time should be evaluated in all

patients. An ECG may demonstrate conduction abnormalities and arrhythmias or reveal evidence of recent myocardial infarction. A lumbar puncture (LP) will generally confirm or exclude subarachnoid hemorrhage (SAH) and can reveal meningitis as a cause for stroke. However, an LP should not be performed on patients with a possible intracranial mass lesion and therefore should generally be avoided in patients with a suspected stroke who are comatose or who have lateralizing neurologic signs with indications of increasedICP. Finally, an imaging study of the brain is nearly always performed and is required for patients being considered for thrombolysis.

BRAIN IMAGING (See alsoChap. 358)

Computed Tomographic Scans Computed tomography (CT) images identify or exclude hemorrhage as the cause of stroke, and they identify extraparenchymal hemorrhages, neoplasms, abscesses, and other conditions masquerading as stroke. Scans obtained in the first several hours after an infarction generally show no abnormality, and the infarct may not be seen reliably for 24 to 48 h. Even later, CT may fail to show small ischemic strokes in the posterior fossa because of bone artifact and may also miss small infarcts on the cortical surface. The CT scan documents most supratentorial lacunar infarcts. Lacunar infarction is diagnosed when the infarct size is <2 cm and its location is consistent with occlusion of a small penetrating branch of a major artery at the base of the brain. Larger deep white matter infarcts in the territory of theMCA may present as a lacunar syndrome but are caused by occlusions of large vessels and compensatory collateral perfusion.

Contrast-enhancedCT scans add specificity by showing contrast enhancement of subacute infarcts and allow visualization of venous structures. Coupled with newer generation scanners, administration of intravenous contrast allows visualization of large cerebral arteries. Such "CT angiograms" may be useful in acute stroke management to reveal the presence or absence of large vessel pathology.

Magnetic Resonance Imaging (MRI) MRI reliably documents the extent and location of infarction in all areas of the brain, including the posterior fossa and cortical surface, if appropriate imaging sequences are obtained. It also identifies intracranial hemorrhage and other abnormalities. The higher the field strength, the more reliable and precise the image. Diffusion-weighted imaging is more sensitive for early brain infarction than standard magnetic resonance (MR) sequences (Fig. 361-10) as is FLAIR (fluid-attenuated inversion recovery) imaging (Chap. 358). MR angiography is highly sensitive for extracranial internal carotid plaque as well as intracranial stenosis of large vessels. With higher degrees of stenosis, MR angiography tends to overestimate the degree of stenosis when compared to conventional x-ray angiography. MRI with fat saturation is an imaging sequence used to visualize extra- or intracranial arterial dissection. This sensitive technique images clotted blood within the dissected vessel wall and has revealed carotid or vertebral dissection as the cause of stroke in a sizable fraction of young patients (age<45). Stroke with neck, jaw, or retroauriclar pain, with or without Horner's syndrome, should prompt this imaging modality or conventional x-ray angiography.

MRIis less sensitive for acute blood products thanCT and is more expensive and less readily available. Claustrophobia also limits its application. Most acute stroke protocols

use CT because of these limitations. However, outside this setting, MRI provides superior information compared with CT in nearly every case of stroke.

Cerebral Angiography Conventional x-ray cerebral angiography is the "gold standard" for identifying and quantifying atherosclerotic stenoses of the cerebral arteries and other pathologies, including aneurysm, vasospasm, intraluminal thrombi, fibromuscular dysplasia, arteriovenous fistula, vasculitis, and collateral channels of blood flow. Endovascular techniques, which are evolving rapidly, can be used to deploy stents within delicate intracranial vessels and perform balloon angioplasty of stenotic lesions. Recent studies have documented that intraarterial delivery of thrombolytic agents to patients with acuteMCAstroke can effectively recanalize vessels and improve clinical outcomes. Although investigational in many centers, use of cerebral angiography coupled with endovascular techniques for cerebral revascularization may become routine in the near future.

Ultrasound Techniques Stenosis at the origin of the internal carotid artery can be identified and quantified reliably by ultrasonography that combines a B-mode ultrasound image with a Doppler ultrasound assessment of flow velocity ("Duplex" ultrasound). Transcranial Doppler (TCD) assessment of middle, anterior, and posterior cerebral artery flow and of vertebrobasilar flow is also useful. This latter technique can detect stenotic lesions in the middle cerebral stem, the distal vertebral arteries, and the basilar artery because such lesions increase systolic flow velocity. When there is an occlusion or hemodynamically significant stenosis at the origin of the internal carotid artery or in the carotid siphon, TCD assesses collateral flow across the anterior or posterior circle of Willis. In many cases,MRangiography combined with carotid and transcranial ultrasound studies eliminates the need for conventional x-ray angiography in evaluating carotid artery lesions for surgery. The combination of the two studies is less expensive than x-ray angiography and reduces the risk of stroke secondary to the procedure.

Ultrasound cannot distinguish reliably between complete and near-complete carotid occlusion; this distinction can be made reliably only by x-ray angiography.

Other Techniques Both xenon techniques (principally xenon-CT) and positron emission tomography (PET) can quantify cerebral blood flow. These tools are generally used for research (Chap. 358) but can be useful for determining the significance of arterial stenosis and planning for revascularization surgery. Single photon emission tomography (SPECT), CT-perfusion, andMR-perfusion techniques report relative cerebral blood flow and currently are research tools.

FINDING EMBOLIC SOURCES

If the clinical syndrome of stroke suggests large vessel ischemia or is sudden in onset or if imaging studies reveal infarction consistent with embolism, a search for the cause of embolism is warranted. Documentation of the exact embolic source can direct therapy that can lessen mortality and morbidity. Embolic stroke is classified by the artery involved (e.g., embolicMCAstroke, as discussed above) or by the source of embolism, either from another artery (artery-to-artery embolic stroke) or cardioembolic. Both causes of embolic stroke are discussed below.

Cardioembolic Stroke

Pathophysiology Cardioembolism causes approximately 20% of all ischemic strokes. Stroke caused by heart disease is primarily due to embolism of thrombotic material forming on the atrial or ventricular wall or the left heart valves. These thrombi then detach and embolize the arterial circulation. The thrombus may fragment or lyse quickly, producing only TIA. Alternatively, the arterial occlusion may last longer, producing stroke. Subsequent thrombosis distal to the obstruction may occur, producing stroke in progression.

Emboli from the heart most often lodge in the MCA or one of its branches; infrequently, the anterior cerebral artery territory is involved. Emboli large enough to occlude the stem of the MCA (3 to 4 mm) lead to large infarcts that involve both deep gray and white matter and some portions of the cortical surface and its underlying white matter. A smaller embolus may occlude a small cortical or penetrating arterial branch. The location and size of an infarct within a vascular territory often depend on the extent of the collateral circulation.

Vascular congestion of varying degree is common to all ischemic strokes, but extravasation of blood is often associated with embolic infarcts. Because emboli migrate and lyse, recirculation into the infarcted brain may cause petechial hemorrhages. Sometimes there is enough seepage of blood into the infarct to cause visible hemorrhagic infarction on a CT scan. This *hemorrhagic transformation* of a pale infarct typically occurs from 12 to 36 h after embolization and is often asymptomatic. Frank hemorrhage into the infarct sometimes occurs and almost always causes clinical worsening. This is more likely to occur when the stem of the MCA is occluded and a large infarct develops in the territory of the lenticulostriate arteries before recirculation occurs. Edema invariably accompanies the tissue necrosis. In large infarcts, massive edema may compress adjacent tissue, adding to the ischemic process; it also increases ICP and may cause herniation of the brain from one intracranial compartment to another.

The most frequent causes of cardioembolic stroke in most of the world are nonrheumatic (often called nonvalvular) atrial fibrillation, myocardial infarction, prosthetic valves, rheumatic heart disease, and ischemic cardiomyopathy (Table 361-2). Cardiac disorders causing brain embolism are discussed in the respective chapters on heart diseases. A few pertinent aspects are highlighted here.

Nonrheumatic atrial fibrillation is the most common cause of cerebral embolism. Patients with atrial fibrillation have an average annual risk of stroke of ~5%. The risk varies according to the presence of certain risk factors, including older age, hypertension, poor left ventricular function, prior cardioembolism, diabetes, and thyrotoxicosis. Patients younger than 60 with none of these risk factors have an annual risk for stroke of about 0.5%, while those with most of the factors have a rate of about 15%. Guidelines for the use of warfarin are based on risk factors (Table 361-5). The presumed stroke mechanism is thrombus formation in the fibrillating atrium or atrial appendage with subsequent embolization. Left atrial enlargement and congestive heart failure are additional risk factors for formation of atrial thrombi. Rheumatic heart disease usually causes ischemic stroke when there is prominent mitral stenosis or atrial

fibrillation.

The cardioembolic causes of stroke are enumerated in Table 361-2. A recent myocardial infarction may be a source of emboli, especially when transmural and involving the anteroapical ventricular wall. Mitral valve prolapse is not usually a source of emboli unless the prolapse is severe.

Paradoxical embolization occurs when venous thrombi migrate to the arterial circulation, usually via a patent foramen ovale or atrial septal defect, which may be occult. Bubble-contrast echocardiography (intravenous injection of agitated saline coupled with either transthoracic or transesophageal echocardiography) can demonstrate a right-to-left shunt, revealing the conduit for paradoxical embolization. Alternatively, a right-to-left shunt is implied if immediately following intravenous injection of agitated saline, high-intensity transients (HITs) can be observed during TCD insonation of the MCA. Both techniques are highly sensitive for detection of right-to-left shunts. Fat and tumor emboli, bacterial endocarditis, and air and amniotic fluid emboli associated with delivery may occasionally be responsible.

Bacterial endocarditis causes valvular vegetations that can give rise to multiple septic emboli (Chap. 126). The appearance of multifocal or diffuse symptoms and signs in a patient with stroke makes bacterial endocarditis a more likely consideration. Infarcts of microscopic size occur, and large septic infarcts may evolve into brain abscesses. Large septic emboli may cause hemorrhage into the infarct, which usually precludes use of anticoagulation or thrombolytics. Mycotic aneurysms caused by septic emboli give rise to SAH or intracerebral hemorrhage.

Clinical Manifestations The stroke is nearly always sudden and maximal at onset. Certain neurologic syndromes suggest embolism, often cardioembolism, as their cause. In the MCA territory these include (1) the frontal opercular syndrome, with facial weakness and severe aphasia or dysarthria; (2) the brachial or hand plegia syndrome, in which the arm or hand is paralyzed with or without cortical sensory abnormalities; (3) Broca's or Wernicke's aphasia alone; or (4) left visual neglect, when the nondominant parietal lobe is involved. Sudden hemianopia suggests a posterior cerebral artery embolus, and sudden foot and shoulder weakness suggests an anterior cerebral embolus. Sudden sleepiness and inability to look up associated with bilateral ptosis suggest an embolus to the top of the basilar artery, specifically to the artery of Percheron (see above).

Seizures at the time of stroke occur in 3 to 5% of infarctions, are more often associated with embolic stroke rather than thrombosis, and are usually associated with supratentorial cortical surface infarctions. Another 3 to 5% of patients develop epilepsy 6 to 18 months after stroke. Many cases of idiopathic epilepsy in the elderly are probably the result of silent cortical infarction.

Artery-to-Artery Stroke Thrombus formation on atherosclerotic plaques may embolize to distant arteries. The most common source is the carotid bifurcation, but any diseased vessel may be a source, including the aortic arch and common carotid, internal carotid, and vertebral-basilar arteries.

Dissection of the internal carotid or vertebral arteries or even vessels beyond the circle of Willis is a common source of embolic stroke in young patients. The dissection is usually painful and precedes stroke by several hours or days. Extracranial dissections rarely cause hemorrhage because of the tough adventitia of these vessels. Intracranial dissections, on the other hand, may produce SAH because the adventitia of intracranial vessels is thin, and pseudoaneurysms may form, requiring treatment to prevent rerupture. The cause of dissection is usually unknown and recurrence is rare. Ehlers-Danlos type IV, Marfan's disease, cystic medial necrosis, and fibromuscular dysplasia are associated with dissections. Trauma (usually a motor vehicle accident or a sports injury) can cause carotid and vertebral artery dissections. Chiropractic neck manipulation is also associated with dissection and stroke.

Laboratory and Imaging Evaluation for Embolic Stroke A thorough cardiac evaluation should be undertaken in patients in whom the suspicion of cardioembolism is high. This includes the young, those with a history of heart disease, those with multifocal or hemorrhagic infarcts, and those with seizures at onset. Continuous ECG monitoring may reveal intermittent atrial fibrillation. An echocardiogram may disclose mitral valve disease, an intracardiac thrombus or tumor, or a dyskinetic area of myocardium. Spontaneous echo contrast within the atrial appendage is associated with stroke and may represent a tendency for spontaneous clotting of blood within the atrium. Transesophageal echocardiography is superior to the transthoracic technique for visualization of valves, left atrium, and aortic arch. Intravenous bubble contrast should be administered to all patients undergoing echocardiography in search of an embolic source. The presence of atrial fibrillation alone is sufficient to establish cause, even in the absence of a left atrial clot.

Embolic infarction may appear as a single low-density area compatible with pale infarction on CT imaging. Petechial hemorrhages within the area may be seen as well and are more likely a day or two after the infarction. MRI scanning better documents infarction both supra- and infratentorially; when coupled with MR angiography, it can help identify arterial sources of emboli from either the extra- or intracranial vessels. MRI with fat saturation should be performed on patients with neck pain preceding stroke, as this technique is highly sensitive for detecting arterial dissection. Carotid ultrasonography and TCD techniques may reveal carotid atherosclerosis or intracranial stenosis, respectively. Conventional x-ray angiography is rarely indicated.

Arterial imaging (CT or MR angiography or TCD) performed in the early hours of stroke often shows occlusion of one or more vessels. Complete lysis of emboli often occurs, and angiography performed after several days may be normal.

LESS COMMON CAUSES OF STROKE (Table 361-2)

Hypercoagulable disorders (Chap. 62) primarily cause increased venous thrombotic risk and therefore may cause venous sinus thrombosis. Protein S deficiency and homocysteinemia may cause arterial thromboses as well. Systemic lupus erythematosus with Libman-Sacks endocarditis can be a cause of embolic stroke. These conditions overlap with the antiphospholipid syndrome, which probably requires long-term anticoagulation to prevent further stroke.

Venous sinus thrombosis of the lateral or sagittal sinus or of small cortical veins (cortical vein thrombosis) occurs as a complication of pregnancy and the postpartum period, sepsis, and intracranial infections (meningitis). It is seen with increased incidence in patients with laboratory-confirmed thrombophilia (Table 361-2) including polycythemia, sickle cell anemia, proteins C and S deficiency, factor V Leiden mutation (resistance to activated protein C), antithrombin III deficiency, homocysteinemia, and the prothrombin G20210 mutation. Women who take oral contraceptives and have the prothrombin G20210 mutation may be at high risk for sinus thrombosis. Patients present with headache, focal neurologic signs (especially paraparesis), and seizures. Often,CTimaging is normal unless an intracranial venous hemorrhage has occurred, but the venous sinus occlusion is readily visualized usingMRvenography or conventional x-ray angiography. With greater degrees of sinus thrombosis, the patient may develop signs of increasedICP and coma. Intravenous heparin, regardless of the presence of intracranial hemorrhage, has been shown to reduce morbidity and mortality, and the long-term outcome is generally good. Heparin prevents further thrombosis and reduces venous hypertension and ischemia. If an underlying hypercoagulable state is not found, many physicians treat with warfarin for 3 to 6 months then convert to aspirin, depending on the degree of resolution of the venous sinus clot, and continue indefinite anticoagulation if thrombophilia is diagnosed.

Fibromuscular dysplasia affects the cervical arteries and occurs mainly in women. The carotid or vertebral arteries show multiple rings of segmental narrowing alternating with dilatation. Occlusion is usually incomplete. The process is often asymptomatic but occasionally is associated with an audible bruit,TIAs, or stroke. The cause and natural history of fibromuscular dysplasia is unknown (Chap. 248). TIA or stroke generally occurs only when the artery is severely narrowed or dissects. Anticoagulation or antiplatelet therapy may be helpful.

Temporal (giant cell) arteritis (Chap. 317) (Figs. 28-CD1 and28-CD2) is a relatively common affliction of elderly persons in which the external carotid system, particularly the temporal arteries, becomes the site of a subacute granulomatous inflammation with giant cells. Occlusion of posterior ciliary arteries derived from the ophthalmic artery results in blindness in one or both eyes and can be prevented with glucocorticoids. It rarely causes stroke as the internal carotid artery is usually not inflamed. Idiopathic giant cell arteritis involving the great vessels arising from the aortic arch (Takayasu's arteritis) may cause carotid or vertebral thrombosis; it is rare in the western hemisphere.

Necrotizing (or granulomatous) arteritis, occurring alone or in association with generalized polyarteritis nodosa or Wegener's granulomatosis, involves the distal small branches (<2 mm diameter) of the main intracranial arteries and produces small ischemic infarcts in the brain, optic nerve, and spinal cord. The cerebrospinal fluid often shows pleocytosis, and the protein level is elevated. *Primary central nervous system vasculitis* is rare; small or medium-sized vessels are usually affected. Brain biopsy or high-resolution conventional x-ray angiography is usually required to make the diagnosis. Patients with any form of vasculitis may present with insidious progression of combined white and gray matter infarctions, prominent headache, and cognitive decline. Aggressive immunosuppression with glucocorticoids, and often cyclophosphamide, is usually necessary to reverse the ischemia. Depending upon the duration of the disease, many patients can make an excellent recovery.

Drugs, in particular amphetamines and perhaps cocaine, may cause stroke on the basis of acute hypertension and drug-induced vasculitis. Abstinence appears to be the best treatment, as no data exist on use of any treatment.

Arteritis can also occur as a consequence of bacterial, tuberculous, and syphilitic meningitis.

Moyamoya disease is a poorly understood occlusive disease involving large intracranial arteries, especially the distal internal carotid artery and the stem of the middle and anterior cerebral arteries. Vascular inflammation is absent. The lenticulostriate arteries develop a rich collateral circulation around the occlusive lesion, which gives the impression of a "puff of smoke" ("moyamoya" in Japanese) on conventional x-ray angiography. Other collaterals include transdural anastomoses between the cortical surface branches of the meningeal and the scalp arteries. The disease occurs mainly in Asian children or young adults but can occur in adults who have atherosclerosis. The etiology of the childhood form is unknown. Because of the occurrence of SAH from rupture of the transdural anastomotic channels, anticoagulation is risky. Breakdown of dilated lenticulostriate arteries may produce parenchymal hemorrhage, and progressive occlusion of large surface arteries can occur, producing large artery distribution strokes. Bypass of extracranial carotid arteries to the dura or MCAs may prevent stroke and hemorrhage.

Reversible widespread cerebral segmental vasoconstriction is hypothesized to occur in certain patients with headache and fluctuating neurologic symptoms and signs. Sometimes cerebral infarction ensues. The cause is unknown. Head injury, migraine, sympathomimetic drug use, eclampsia, and the postpartum period have all been associated with this entity. Conventional x-ray angiography is the only means of establishing the diagnosis, but because angiography itself can cause spasm of vessels, even the existence of this vascular entity is debated.

Binswanger's disease (chronic progressive subcortical encephalopathy) is a rare condition in which infarction of the subcortical white matter occurs subacutely. CT or MRI scans detect periventricular white matter infarcts and gliosis. There is lipohyalinosis in the small arteries of the deep white matter, as in hypertension. There are usually associated lacunar infarcts. Binswanger's disease may represent a type of border zone ischemic infarction in the deep white matter between the penetrating arteries of the circle of Willis and of the cortex. The pathophysiologic basis of the disease is unclear, but it typically occurs in older patients with severe long-standing hypertension.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is an inherited disorder that presents as small vessel strokes, progressive dementia, and extensive symmetric white matter changes visualized by MRI. Approximately 40% of patients have migraine with aura, often manifest as transient motor or sensory deficits. Onset is usually in the fourth or fifth decade of life. This autosomal dominant condition is caused by a missense mutation in Notch-3, a member of a highly conserved gene family characterized by epidermal growth factor repeats in its extracellular domain. Definitive diagnosis is made by brain biopsy revealing typical

osmophilic inclusions within smooth-muscle cells of blood vessels; these inclusions may also be present in skin biopsy sections. CADASIL is the only monogenic ischemic stroke syndrome so far described. Genetic testing is not currently available except on a research basis.

TREATMENT

Acute Stroke Management After the clinical diagnosis of stroke is made, an orderly process of evaluation and treatment should follow (Table 361-4). The first goal is to prevent or reverse brain injury. After initial stabilization, an emergency noncontrast headCT scan should be performed to differentiate ischemic from hemorrhagic stroke; there are no reliable clinical findings that conclusively separate ischemia from hemorrhage, although a more depressed level of consciousness and higher initial blood pressure favor hemorrhage, and a deficit that remits suggests ischemia. The second goal is to obtain an accurate understanding of the stroke mechanism so one can halt progression of brain injury or begin to prevent a second stroke. Often this is done during an acute hospitalization, but depending on stroke severity, it may be performed in the outpatient setting. There exists no consensus on the rate with which this evaluation should proceed, primarily because there are few data on the daily risks of recurrence following an initial stroke.

General Principles During focal brain ischemia, a gradation in brain perfusion exists such that a core of tissue is infarcted within minutes but a shell of surrounding tissue is only marginally ischemic. This *ischemic penumbra* may progress to infarction within minutes to hours depending on a number of factors (Chap. 376). Salvage of this "at risk" tissue is the goal of emergency stroke therapy. The penumbral tissue will infarct with only minor drops in systemic blood pressure because cerebral autoregulation within this zone is impaired. *Therefore, a patient's blood pressure at presentation should not be lowered* unless it is >185/110 and thrombolytic therapy will be given (see below). Revascularization of the parent vessel occlusion can restore blood flow to the penumbra and prevent infarction. This concept fuels research into intravenous and intraarterial thrombolysis as well as mechanical means of arterial thrombectomy.

Treatments designed to reverse or lessen the amount of tissue infarction fall within five categories: (1) medical support, (2) thrombolysis, (3) anticoagulation, (4) antiplatelet agents, and (5) neuroprotection.

Medical Support When cerebral infarction occurs, the immediate goal is to optimize cerebral perfusion in the surrounding ischemic area. Attention is also directed toward preventing the common complications of bedridden patients -- infections (pneumonia, urinary tract, and skin) and deep venous thrombosis with pulmonary embolism.

Elevated blood pressure should not be lowered unless there is malignant hypertension (Chap. 246) or concomitant myocardial ischemia. When faced with the competing demands of myocardium and brain, heart rate lowering with the b_1-adrenergic blocker esmolol can be a first step to decrease cardiac work and maintain blood pressure. If the blood pressure is low, raising it is advisable, using intravenous fluids or vasopressor drugs to enhance perfusion within the ischemic penumbra. Fever is detrimental and should be treated with antipyretics.

Between 5 and 10% of patients develop enough cerebral edema to cause obtundation or brain herniation. Edema peaks on the second or third day but causes mass effect for 10 days. The larger the infarct, the greater the likelihood that clinically significant edema will develop. Even small amounts of cerebellar edema can acutely increaseICP in the posterior fossa. The resulting brainstem compression may result in coma and respiratory arrest and require emergency surgical decompression. Water restriction and intravenous mannitol may be used to raise the serum osmolarity, but hypovolemia should be avoided as this may contribute to hypotension and worsening infarction. Trials are under way to test the clinical benefits of craniotomy and elevation of the skull (hemicraniectomy) for large hemispheric infarcts with marked cerebral edema.

Thrombolysis The use of thrombolytic agents in acute cerebral infarction has been studied extensively. Angiography performed within a few hours of infarction frequently demonstrates arterial occlusions corresponding to patients' presenting signs and symptoms. It is this association of arterial occlusion with acute neurologic symptoms that prompted the study of thrombolytic agents in stroke patients.

Three early intravenous streptokinase trials were stopped because of a higher death rate in the streptokinase-treated patients, mainly due to symptomatic intracranial bleedings. These trials enrolled patients several hours into the stroke process, which may account for the high hemorrhage rates.

The European Cooperative Acute Stroke Study (ECASS) tested intravenous recombinant tissue plasminogen activator (rtPA; 1.1 mg/kg to a 100 mg max.; 10% as a bolus, then the remainder over 60 min) vs. placebo in patients with ischemic stroke within 6 h of onset of symptoms. The median time to treatment was 4 h. Overall, thrombolysis was not beneficial because of an excess of cerebral hemorrhage. However, in those patients who had no signs of major infarction on the initialCT scan, the functional outcome was improved.

The National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study showed a clear benefit forrtPA in selected patients with acute stroke. The NINDS study used intravenous rtPA (0.9 mg/kg to a 90 mg max.; 10% as a bolus, then the remainder over 60 min) vs. placebo in patients with ischemic stroke within 3 h of onset. Half of the patients were treated within 90 min. Symptomatic intracerebral hemorrhage occurred in 6.4% of patients on rtPA and 0.6% on placebo. There was a nonsignificant 4% reduction in mortality on rtPA, (21% on placebo and 17% on rtPA) and a significant 12% absolute increase in the number of patients with only minimal disability (32%on placebo and 44% on rtPA.) Thus, despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous rtPA within 3 h of the onset of ischemic stroke improved clinical outcome. A lower dose of rtPA was used than in theECASS, and half of the patients were treated within 90 min of stroke onset. These two features may account for much of the increase in benefit and decrease in bleeding hazard compared to the results seen in ECASS.

Finally,ECASS-II tested theNINDSdose ofrtPA(0.9 mg/kg, maximum dose 90 mg) but allowed patients to receive drug up to the sixth hour, as in ECASS-I. No significant benefit was found, but improvement was found in post hoc analyses.

Because of the marked differences in trial design, including drug and dose used, time to thrombolysis, and severity of stroke, the precise efficacy of intravenous thrombolytics for acute ischemic stroke remains unclear. The risk of intracranial hemorrhage appears to rise with larger strokes, longer times from onset of symptoms, and higher doses of rtPA administered. The established dose of 0.9 mg/kg administered intravenously within 3 h of stroke onset appears safe. Many hospitals have developed expert stroke teams to facilitate this treatment. The drug is now approved in the United States and Canada for acute stroke when given within 3 h from the time the stroke symptoms began, and efforts should be made to give it as early in this 3-h window as possible. The time of stroke onset is defined as the time the patient's symptoms began or the time the patient was last seen as normal. A patient who awakens with stroke has the onset defined as when they went to bed.Table 361-6 summarizes eligibility criteria and instructions for administration ofrtPA.

A recent trial of the fibrinolytic agent ancrod provides further evidence that this approach is effective in acute ischemic stroke.

There is growing interest in using thrombolytics via an intraarterial route to increase the concentration of drug at the clot and minimize systemic bleeding complications. Two recent trials [PROACT and PROACT II (prolyse in acute cerebral thromboembolism)] using intraarterial thrombolysis for acuteMCAocclusions up to the sixth hour following onset of stroke showed benefit. Nevertheless, intraarterial use in ischemic stroke is not approved by the FDA. Intraarterial treatment of basilar artery occlusions may also be beneficial for selected patients, but all intraarterial therapy remains experimental.

Anticoagulation The role of anticoagulation in atherothrombotic cerebral ischemia is uncertain. Several recent trials have investigated antiplatelet versus anticoagulant medications given within 12 to 24 h of the initial event. The U.S. Trial of Organon 10172 in Acute Stroke Treatment (TOAST), an investigational low-molecular-weight heparin, failed to show any benefit over aspirin. Use of subcutaneous unfractionated heparin versus aspirin was tested in two trials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST). Taken together, the trials, which studied an aggregate of 40,541 patients, showed a reduction in stroke and death by 1% within 2 to 4 weeks in patients treated with aspirin rather than placebo. Heparin given subcutaneously [without monitoring the partial thromboplastin time (PTT)] afforded no additional benefit over aspirin and increased bleeding rates. Therefore, trials do not support the use of heparin for patients with atherothrombotic stroke of ³12 h duration.

The use of antiplatelet or anticoagulant medication in acute stroke (i.e., <6 h) is less well studied. Heparin is widely used for crescendoTIAs, despite the absence of data from controlled studies regarding this indication. In approximately 20% of patients with acute stroke, deficits will progress over several hours to 1-2 days. Many physicians heparinize all patients with recent mild ischemic stroke in order to prevent some of this worsening. Theoretically, heparin may prevent propagation of clot within a thrombosed vessel or may prevent more emboli from occurring. Some neurologists use heparin until carotid and intracranial vessel patency can be assessed then convert to aspirin if the large vessels are patent. The bleeding complication rate for 7 days of heparin is about 10% with a serious bleed rate of ~2%. Clearly the value of this approach must be clarified.

Heparinization is generally accomplished by beginning an infusion without bolus and is monitored to maintain the activated PTT at approximately twice normal. This regimen is maintained for 2 to 5 days. During this time the patient is monitored for hemorrhagic complications, the evaluation is completed, and a decision is made regarding the need for carotid endarterectomy, long-term anticoagulation, or an antiplatelet therapy. If long-term anticoagulation is chosen, warfarin is administered and heparin discontinued when the international normalized ratio (INR) is in the range of 2 to 3.

Antiplatelet Agents Aspirin is the only antiplatelet agent that has been prospectively studied for the treatment of acute ischemic stroke. The recent large trials, IST and CAST, found that the use of aspirin within 48 h of stroke onset reduced both stroke recurrence risk and mortality minimally. Among 19,435 patients in IST, those allocated to aspirin had slightly fewer deaths within 14 days (9.0 vs. 9.4%), significantly fewer recurrent ischemic strokes (2.8 vs. 3.9%), no excess of hemorrhagic strokes (0.9 vs. 0.8%), and a trend towards a reduction in death or dependence at 6 months (61.2 vs. 63.5%). In CAST, 21,106 patients with ischemic stroke received 160 mg/d of aspirin or a placebo for up to 4 weeks. There were very small reductions in the aspirin group in early mortality (3.3 vs. 3.9%), recurrent ischemic strokes (1.6 vs. 2.1%), and dependency at discharge or death (30.5 vs. 31.6%). These trials demonstrate that the use of aspirin in the treatment of acute ischemic stroke is safe and produces a small but definite net benefit. For every 1000 acute strokes treated with aspirin, about 9 deaths or nonfatal stroke recurrences will be prevented in the first few weeks and approximately 13 fewer patients will be dead or dependent at 6 months.

Agents that act at the glycoprotein IIb/IIIa receptor are undergoing clinical trials in acute stroke treatment.

Neuroprotection Neuroprotection is the concept of providing a treatment that prolongs the brain's tolerance to ischemia long enough to allow other measures to be employed to mitigate ischemia. Hypothermia is probably the most powerful neuroprotectant but is only now the subject of clinical trials. Drugs that block the excitatory amino acid pathways have been shown to protect neurons and glia in animals, but despite multiple clinical trials they have not yet been proven to be beneficial in humans.

Primary and Secondary Prevention

General Principles A number of medical and surgical interventions, as well as life-style modifications, are available for preventing stroke. Some of these can be widely applied because of their low cost and minimal risk; others are expensive and carry substantial risk, but may be valuable for selected high-risk patients.

Evaluation of a patient's *clinical risk profile* can help determine which preventive treatments to offer. In addition to known risk factors for ischemic stroke (above), certain clinical characteristics also contribute to an increased risk of stroke (Table 361-3). The North American Symptomatic Carotid Endarterectomy Trial (NASCET; see below) found that even in patients with the same degree of carotid artery stenosis, specifically 70 to 99%, nine prospectively selected risk factors predicted the risk of vascular outcomes in the medically treated patients. The overall risk of stroke was much greater in a high-risk

group (those with more than six risk factors) than in a low-risk group (those with fewer than six risk factors). Fully 39% of patients in the high-risk group treated medically experienced an ipsilateral stroke within 2 years. The rate for the low-risk group was less than half that but was still 17%.

Atherosclerosis Risk Factors The relationship of various factors to the risk of atherosclerosis is described in Chap. 241. Older age, family history of thrombotic stroke, diabetes mellitus, hypertension, tobacco smoking, elevated blood cholesterol, and other factors are either proven or probable risk factors for ischemic stroke, largely by their link to atherosclerosis. Hypertension is the most significant of the risk factors; in general, all hypertension should be treated. The presence of known cerebrovascular disease is not a contraindication to treatment aimed at achieving normotension. Also, the value of treating systolic hypertension in older patients has been clearly established. Care must be taken to avoid overtreatment of hypertension, however; the treatment goal is to achieve normotension gradually.

Treatment of hypercholesterolemia has been well established for coronary artery disease but has been studied little in the prevention of stroke. In several recent studies, statin drugs were found to lower stroke risk. Since coronary artery disease is the most common cause of death in patients with cerebrovascular disease, treatment of hypercholesterolemia seems prudent for both the heart and brain. Tobacco smoking should be discouraged in all patients (Chap. 390). Whether or not tight control of blood sugar in patients with diabetes lowers stroke risk is uncertain.

Antiplatelet Agents

ATHEROTHROMBOTIC STROKE Platelet antiaggregation agents can prevent atherothrombotic events, including TIA and stroke, by inhibiting the formation of intraarterial platelet aggregates. These can form on diseased arteries, induce thrombus formation, and occlude the artery or embolize into the distal circulation. Aspirin, clopidogrel, and the combination of aspirin plus extended-release dipyridamole are the antiplatelet agents used most for this purpose. Ticlopidine has been largely abandoned because of its adverse effects.

Aspirin is the most widely studied antiplatelet agent. Its antiplatelet effect is accomplished by acetylating the cyclooxygenase enzyme in platelets. This irreversibly inhibits the formation in platelets of thromboxane A_2, a platelet aggregating and vasoconstricting prostaglandin. This effect is permanent and lasts for the usual 8-day life of the platelet. Paradoxically, aspirin also inhibits the formation in endothelial cells of prostacyclin, an antiaggregating and vasodilating prostaglandin. This effect is transient. As soon as the aspirin is cleared from the blood, the nucleated endothelial cells again produce prostacyclin. Aspirin in low doses given once daily inhibits the production of thromboxane A_2 in platelets without substantially inhibiting prostacyclin formation. The FDA recommends 50 to 325 mg of aspirin daily for stroke prevention.

Ticlopidine blocks the ADP receptor on platelets and thus prevents the cascade resulting in activation of the glycoprotein IIb/IIIa receptor that leads to fibrinogen binding to the platelet and consequent platelet aggregation. Ticlopidine is more effective than aspirin; however, it has the disadvantage of causing diarrhea, skin rash, a low incidence

of neutropenia, and thrombotic thrombocytopenic purpura. Clopidogrel works by the same mechanism as ticlopidine and is not associated with these important side effects. Although many physicians have accepted clopidogrel as equivalent to ticlopidine in stroke prevention, the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, which led to FDA approval, showed less robust efficacy. Studies of clopidogrel in combination with aspirin are in progress in both cerebrovascular and cardiovascular patients.

Dipyridamole is an antiplatelet agent that inhibits the uptake of adenosine by a variety of cells, including those of the vascular endothelium. The accumulated adenosine is an inhibitor of aggregation. At least in part through its effects on platelet and vessel wall phosphodiesterases, dipyridamole also potentiates the antiaggregatory effects of prostacyclin and nitric oxide produced by the endothelium and acts by inhibiting platelet phosphodiesterase, which is responsible for the breakdown of cyclic AMP. The resulting elevation in cyclic AMP inhibits aggregation of platelets. Dipyridamole has a controversial history in stroke prevention. The European Stroke Prevention Study-2 showed efficacy of both 50 mg daily of aspirin and extended-release dipyridamole in preventing stroke, and a significantly better risk reduction when the two agents were combined. A combination capsule of extended-release dipyridamole and aspirin is approved for prevention of stroke.

Many large clinical trials have demonstrated clearly that most antiplatelet agents reduce the risk of all important vascular atherothrombotic events (i.e., ischemic stroke, myocardial infarction, and death due to all vascular causes) in patients at risk for these events. The overall *relative* reduction in risk of nonfatal stroke is about 25 to 30% and of all vascular events is about 25%. The *absolute* reduction varies considerably depending on the particular patient's risk. Individuals at very low risk for stroke seem to experience the same relative reduction, but their risk may be so low that the "benefit" is meaningless. On the other hand, individuals with a 10 to 15% risk of vascular events per year experience a reduction to about 7.5 to 11%.

Aspirin is inexpensive, can be given in low doses, and could be recommended for all adults to prevent both stroke and myocardial infarction. However, it causes epigastric discomfort, gastric ulceration, and gastrointestinal hemorrhage, which may be asymptomatic or life-threatening. Consequently, not every 40- or 50-year old should be advised to take aspirin regularly because the risk of atherothrombotic stroke is extremely low and is outweighed by the risk of adverse side effects. Conversely, every patient who has experienced an atherothrombotic stroke and has no contraindication should be taking an antiplatelet agent regularly because the average annual risk of another stroke is 8 to 10%; another few percent will experience a myocardial infarction or vascular death. Clearly, the likelihood of benefit far outweighs the risks of treatment.

The choice of antiplatelet agent, and dose, similarly must balance the risk of stroke against the risks and cost of the treatments against the expected benefits. But these data are less definitive, and opinions therefore vary. Many authorities believe low-dose (30 to 75 mg daily) and high-dose (650 to 1300 mg daily) aspirin are about equally effective. Some advocate very low doses to avoid adverse effects, and still others advocate very high doses to be sure the benefit is maximal. Most physicians in North America recommend 325 mg daily, while most Europeans recommend 50 to 100 mg.

Similarly, the choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are more effective than aspirin but the cost is higher.

EMBOLIC STROKE Although warfarin is more effective than aspirin in preventing ischemic stroke associated with atrial fibrillation, some patients with atrial fibrillation have a low rate of ischemic stroke, and others have a high risk of hemorrhage and lose all of the expected benefit of anticoagulation by this complication. Still others are at such high risk for ischemic stroke that the benefits of warfarin override even the high hemorrhage rate. Preventive treatment depends on knowing the relative risks and benefits for the particular patient.

The Stroke Prevention in Atrial Fibrillation II trial showed that in "low-risk" patients (those without hypertension, recent heart failure, or prior thromboembolism) younger than 75 years given aspirin, the thromboembolism rate was only 0.5% per year. Consequently, one could reasonably recommend that patients <75 years with no risk factors be treated with aspirin only (Table 361-5).

Anticoagulation Therapy

ATHEROTHROMBOTIC STROKE There are few data to support the use of long-term warfarin for preventing atherothrombotic stroke, either intracranially or extracranially. Several large trials are in progress.

EMBOLIC STROKE Several recent trials demonstrated that anticoagulation (INR range 2 to 3) in patients with chronic nonvalvular (nonrheumatic) atrial fibrillation prevents cerebral embolism and is safe. For primary prevention and for patients who have experienced stroke or TIA, anticoagulation with warfarin reduces the risk by about 65% and clearly outweighs the 1% per year rate of major bleeding complication.

The decision to use anticoagulation for primary prevention is based primarily on risk factors (Table 361-5). The presence of any risk factor tips the balance in favor of anticoagulation.

Because of the high annual stroke risk in untreated rheumatic heart disease, primary prophylaxis against stroke has not been studied in a double-blind fashion. These patients generally receive long-term anticoagulation.

Anticoagulation also reduces the risk of embolism in acute myocardial infarction. Most clinicians recommend a 3-month course of anticoagulation when there is anterior Q-wave infarction, substantial left ventricular dysfunction, congestive heart failure, mural thrombosis, or atrial fibrillation. Warfarin is recommended long-term if atrial fibrillation persists.

Thromboembolism is one of the most serious complications of prosthetic heart valve implantation. Anticoagulation has been proven effective for preventing strokes in this situation, while antiplatelet therapy alone has not. However, coupled with warfarin anticoagulation, aspirin adds substantial benefit. A greater degree of anticoagulation (INR of 3 to 4, depending on valve type) is recommended for prosthetic heart valve patients.

If the embolic source cannot be eliminated, anticoagulation should in most cases be continued indefinitely. Many neurologists recommend combining antiplatelet agents with anticoagulants for patients who "fail" one form of therapy (i.e., have another stroke of TIA). This empirical approach subjects the patient to an increased bleeding risk.

Secondary prophylaxis for ischemic stroke of unknown origin is controversial. Some physicians prescribe anticoagulation for 3 to 6 months followed by antiplatelet treatment. The results of ongoing stroke trials may help to clarify the best treatment.

SURGICAL THERAPY Surgery for atherosclerotic occlusive disease is largely limited to *carotid endarterectomy* for plaques located at the origin of the internal carotid artery in the neck (see below).

Balloon angioplasty coupled with stenting is being used with increasing frequency to open stenotic carotid arteries and maintain their patency. This method has not been compared prospectively with endarterectomy. Concern exists about distal embolization of plaque during vessel dilation. Some neurointerventional centers are treating *intracranial* atherosclerotic disease with angioplasty and stenting. Surgery in the proximal common carotid, the subclavian, and the vertebral arteries is uncommon and is being replaced by endovascular stenting and angioplasty. Extracranial to intracranial bypass surgery has been proven ineffective for atherosclerotic stenoses that are inaccessible to conventional carotid endarterectomy. Although experimental, bypass surgery may have a role in patients with moyamoya disease or the unusual patient with intracranial stenosis and flow-related TIA.

Carotid Disease Carotid endarterectomy is a proven effective prophylaxis against stroke and TIA. Approximately 100,000 of these procedures are performed annually in the United States to remove obstructing atherosclerotic plaques. The most important clinical distinction is between symptomatic and asymptomatic carotid stenosis. Symptomatic stenosis is defined as carotid stenosis ipsilateral to the vascular distribution of a stroke or TIA; e.g., a left carotid stenosis in a patient with transient expressive aphasia. Asymptomatic carotid stenosis is defined by the absence of clinical signs or symptoms of stroke or TIA relevant to the carotid lesion. The distinction is important because the natural history of these conditions is markedly different.

Symptomatic carotid stenosis was studied in the NASCET and the European Carotid Surgery Trial (ECST). Both showed a substantial benefit for surgery in patients with a stenosis of >70%. In NASCET, the average cumulative ipsilateral stroke rate at 2 years was 26% for patients treated medically and 9% for those receiving the same medical treatment plus a carotid endarterectomy. This 17% *absolute* reduction in the surgical group is a 65% *relative* risk reduction favoring surgery. NASCET also showed a significant benefit for patients with 50 to 70% stenosis, although less robust. ECST found harm for patients with stenosis in the 0 to 30% range treated surgically.

A patient's risk of stroke and possible benefit from surgery is related to the presence of retinal versus hemispheric symptoms, degree of arterial stenosis, extent of associated medical conditions, institutional surgical morbidity and mortality, and other factors. A patient with multiple atherosclerosis risk factors, symptomatic hemispheric ischemia,

very high grade stenosis in the appropriate internal carotid artery, and an institutional perioperative morbidity and mortality rate of£6% generally should undergo carotid endarterectomy. If the perioperative stroke rate is>6% for any particular surgeon, however, the benefits of carotid endarterectomy are lost.

The indications for surgical treatment of *asymptomatic carotid disease* have been clarified by the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS), which randomized patients with ³60% stenosis to medical treatment with aspirin or the same medical treatment plus carotid endarterectomy. The surgical group had a risk over 5 years for ipsilateral stroke (and any perioperative stroke or death) of 5.1%, compared to a risk in the medical group of 11%. While this demonstrates a 53% *relative* risk reduction, the *absolute* risk reduction is only 5.9% over 5 years, or 1.2% annually. The perioperative complication rate was higher in women, so they received only a 17% relative risk reduction over 5 years. Nearly half of the strokes in the surgery group were caused by preoperative angiograms.

The natural history of asymptomatic stenosis is an approximate 2% per year stroke rate, while symptomatic patients experience a 13% per year risk of stroke. Whether to recommend carotid revascularization for an asymptomatic patient remains controversial and depends on many factors including patient preference, age, and comorbidities. Medical therapy for reduction of atherosclerosis risk factors and aspirin, 325 mg/d, are generally recommended for patients with asymptomatic carotid stenosis. As with atrial fibrillation, it is imperative to counsel the patient aboutTIAs so their therapy can be revised if they become symptomatic.

Stroke Centers and Rehabilitation Comprehensive stroke units that care for the acute patient followed by rehabilitation services have been shown to improve neurologic outcomes and reduce mortality. Use of clinical pathways and dedicating staff to the stroke patient can improve the efficacy of care. Stroke teams that provide emergency 24-h evaluation of acute stroke patients for consideration of thrombolysis and acute medical management are essential components of the care process.

Proper rehabilitation of the stroke patient includes early physical, occupational, and speech therapy. It is directed toward educating the patient and family about the patient's neurologic deficit, preventing the complications of immobility (e.g., pneumonia, deep vein thrombosis and pulmonary embolism, pressure sores of the skin, muscle contractures), and providing encouragement and instruction in overcoming the deficit. The goal of rehabilitation is to return the patient to home and to maximize recovery by providing a safe, progressive regimen suited to the individual patient.

INTRACRANIAL HEMORRHAGE

Blood can extravasate anywhere within the cranial vault or spinal column. Hemorrhages are classified by their location and the underlying vascular pathology. Bleeding into subdural and epidural spaces is principally produced by trauma (Chap. 369). Intraparenchymal, intraventricular, and subarachnoid hemorrhage will be considered here.

DIAGNOSIS

Intracranial hemorrhage is often discovered on noncontrastCTimaging of the brain during the acute evaluation of stroke. CT is more sensitive than routineMRI for acute blood. The location of hemorrhage narrows the differential diagnosis to a few entities. Table 361-7 lists the causes and anatomic spaces involved in hemorrhages.

EMERGENCY MANAGEMENT

Close attention should be paid to airway management since a reduction in the level of consciousness is common. The initial blood pressure should be maintained until the results of theCT scan are reviewed. Patients with acuteSAHshould have blood pressure lowered to a normal range with nonvasodilating agents such as labetalol or esmolol. Patients with cerebellar hemorrhages or with depressed mental status and radiographic evidence of hydrocephalus should undergo urgent neurosurgical evaluation. Based on the clinical examination and CT findings, further imaging studies may be necessary, includingMRI or conventional x-ray angiography. Stuporous or comatose patients generally are treated presumptively for elevatedICP, with tracheal intubation and hyperventilation, mannitol administration, and elevation of the head of the bed while surgical consultation is obtained (Chap. 376).

INTRAPARENCHYMAL HEMORRHAGE

Intraparenchymal hemorrhage is the most common type of intracranial hemorrhage. It is an important cause of stroke, especially in Asians and blacks. Hypertension, trauma, and cerebral amyloid angiopathy cause the majority of these hemorrhages. Advanced age and heavy alcohol consumption increase the risk, and cocaine use is one of the most important causes in the young.

Hypertensive Intraparenchymal Hemorrhage

Pathophysiology Hypertensive parenchymal hemorrhage (hypertensive hemorrhage or hypertensive intracerebral hemorrhage) usually results from spontaneous rupture of a small penetrating artery deep in the brain. The most common sites are the basal ganglia (putamen, thalamus, and adjacent deep white matter), deep cerebellum, and pons. When hemorrhages occur in other brain areas or in nonhypertensive patients, greater consideration should be given to hemorrhagic disorders, neoplasms, vascular malformations, and other causes. The small arteries in these areas seem most prone to hypertension-induced vascular injury. The hemorrhage may be small or a large clot may form and compress adjacent tissue, causing herniation and death. Blood may dissect into the ventricular space, which substantially increases morbidity and may cause hydrocephalus. If the patient survives, the clot liquefies, is absorbed, and leaves only a small residual cleft.

Most hypertensive intraparenchymal hemorrhages develop over 30 to 90 min, whereas those associated with anticoagulant therapy may evolve for as long as 24 to 48 h. Within 48 h macrophages begin to phagocytize the hemorrhage at its outer surface. After 1 to 6 months, the hemorrhage is generally resolved to a slitlike orange cavity lined with glial scar and hemosiderin-laden macrophages.

Clinical Manifestations Although not particularly associated with exertion, intracerebral hemorrhages almost always occur while the patient is awake and sometimes when stressed. The hemorrhage generally presents as the abrupt onset of focal neurologic deficit. Seizures are uncommon. The focal deficit typically worsens steadily over 30 to 90 min and is associated with a diminishing level of consciousness and signs of increasedICP, such as headache and vomiting.

The putamen is the most common site for hypertensive hemorrhage, and the adjacent internal capsule is invariably damaged (Fig. 361-11). Contralateral hemiparesis is therefore the sentinel sign. When mild, the face sags on one side over 5 to 30 min, speech becomes slurred, the arm and leg gradually weaken, and the eyes deviate away from the side of the hemiparesis. The paralysis may worsen until the affected limbs become flaccid or extend rigidly with a Babinski sign on the same side. When hemorrhages are large, drowsiness gives way to stupor as signs of upper brainstem compression appear. Coma ensues, accompanied by deep, irregular, or intermittent respiration; a dilated and fixed ipsilateral pupil; bilateral Babinski signs; and decerebrate rigidity. In milder cases, edema in adjacent brain tissue may cause progressive deterioration over 12 to 72 h.

Thalamic hemorrhages also produce a contralateral hemiplegia or hemiparesis from pressure on, or dissection into, the adjacent internal capsule. A prominent sensory deficit involving all modalities is usually present. Aphasia, often with preserved verbal repetition, may occur after hemorrhage into the dominant thalamus, and apractognosia or mutism occurs in some cases of nondominant hemorrhage. There may also be a homonymous visual field defect. Thalamic hemorrhages cause several typical ocular disturbances by virtue of extension medially into the upper midbrain. These include deviation of the eyes downward and inward so that they appear to be looking at the nose, unequal pupils with absence of light reaction, skew deviation with the eye opposite the hemorrhage displaced downward and medially, ipsilateral Horner's syndrome, absence of convergence, paralysis of vertical gaze, and retraction nystagmus. Patients may later develop a chronic, contralateral pain syndrome (see Dejerine-Roussy syndrome, above).

In pontine hemorrhages, deep coma with quadriplegia usually occurs over a few minutes. There is often prominent decerebrate rigidity and "pin-point" (1 mm) pupils that react to light. There is impairment of reflex horizontal eye movements evoked by head turning (doll's-head or oculocephalic maneuver) or by irrigation of the ears with ice water (Chap. 24). Hyperpnea, severe hypertension, and hyperhidrosis are common. Death usually occurs within a few hours, but there are occasional survivors.

Cerebellar hemorrhages usually develop over several hours and are characterized by occipital headache, repeated vomiting, and ataxia of gait. In mild cases there may be no other neurologic signs other than gait ataxia. Dizziness or vertigo may be prominent. There is often paresis of conjugate lateral gaze toward the side of the hemorrhage, forced deviation of the eyes to the opposite side, or an ipsilateral sixth nerve palsy. Less frequent ocular signs include blepharospasm, involuntary closure of one eye, ocular bobbing, and skew deviation. Dysarthria and dysphagia may occur. There are no Babinski signs until late in the evolution of the hemorrhage as it compresses or dissects into the ventral brainstem. As the hours pass, the patient often becomes stuporous and

then comatose from brainstem compression or obstructive hydrocephalus; immediate surgical evacuation may be lifesaving.

Laboratory and Imaging Evaluation The CT scan reliably detects acute focal hemorrhages in the supratentorial space. Small pontine hemorrhages may not be identified because of motion and bone-induced artifact that obscure structures in the posterior fossa. After the first 2 weeks, x-ray attenuation values of clotted blood diminish until they become isodense with surrounding brain. Mass effect and edema may remain. In some cases, a surrounding rim of contrast enhancement appears after 2 to 4 weeks and may persist for months. MRI, though more sensitive for delineating posterior fossa lesions, is generally not necessary in most instances. Images of flowing blood on MRI scan may identify arteriovenous malformations (AVMs) as the cause of the hemorrhage. MRI and conventional x-ray angiography are used when the cause of intracranial hemorrhage is uncertain, particularly if the patient is young or not hypertensive and the hematoma is not in one of the four usual sites for hypertensive hemorrhage. For example, hemorrhage into the temporal lobe suggests rupture of a MCA saccular aneurysm.

Since these patients typically have focal neurologic signs and obtundation, and often show signs of increased ICP, an LP should be avoided as it may induce cerebral herniation.

TREATMENT

Acute Management Nearly 50% of patients with a hypertensive intracerebral hemorrhage die. The volume and location of the hematoma determine the prognosis. In general, supratentorial hematomas with volumes <30 mL have a good prognosis, 30 to 60 mL an intermediate prognosis, and >60 mL a poor prognosis during initial hospitalization. Infratentorial pontine hematomas >3 cm are usually fatal. Extension into the ventricular system, especially the fourth ventricle, worsens the prognosis. Except in patients who are on therapeutic anticoagulation or who have a bleeding disorder, little can be done about the hemorrhage itself. Hematomas may expand for several hours following the initial hemorrhage, so treating severe hypertension seems reasonable to prevent hematoma progression. As with ischemic stroke, lowering blood pressure too much or too quickly might cause cerebral ischemia around the hemorrhage cavity.

Evacuation of the hematoma is usually not helpful, except in cerebellar hemorrhages. For cerebellar hemorrhages, a neurosurgeon should be consulted immediately to assist with the evaluation; most cerebellar hematomas >3 cm in diameter will require surgical evacuation. If the patient is alert without focal brainstem signs and if the hematoma is <1 cm in diameter, surgical removal is usually unnecessary. Patients with hematomas between 1 and 3 cm require careful observation for signs of impaired consciousness, which usually means surgery is required.

Tissue surrounding hematomas is displaced and compressed but not necessarily infarcted. Hence, in survivors, major improvement commonly results as the hematoma is reabsorbed and the adjacent tissue regains its function. Careful management of the patient during the acute phase of the hemorrhage can lead to considerable recovery.

Surprisingly, despite large intraparenchymal hemorrhages, ICP is often not elevated. However, if the hematoma causes marked midline shift of structures with consequent obtundation or coma or hydrocephalus, osmotic agents coupled with induced hyperventilation can be instituted to lower ICP (Chap. 376). These maneuvers will provide enough time to place a ventriculostomy or ICP monitor. Once ICP is recorded, further hyperventilation and osmotic therapy can be tailored to the individual patient. For example, if ICP is found to be high, cerebrospinal fluid (CSF) can be drained from the ventricular space and osmotic therapy continued; persistent or progressive elevation in ICP may prompt surgical evacuation of the clot or withdrawal of support. Alternately, if ICP is normal or only mildly elevated, induced hyperventilation can be reversed and osmotic therapy tapered. Since hyperventilation may actually produce ischemia by cerebral vasoconstriction, as a general management principal induced hyperventilation should be limited to acute resuscitation of the patient with presumptive high ICP and eliminated once other treatments (osmotic therapy or surgical treatments) have been instituted. Glucocorticoids are not helpful for the edema from intracerebral hematoma.

Prevention Hypertension is the leading cause of primary intracerebral hemorrhage. Prevention is aimed at reducing hypertension, excessive alcohol use, and use of illicit drugs such as cocaine and amphetamines.

OTHER CAUSES OF INTRACEREBRAL HEMORRHAGE

Cerebral amyloid angiopathy is a disease of the elderly in which arteriolar degeneration occurs and amyloid is deposited in the walls of the cerebral arteries but not elsewhere. Amyloid angiopathy causes both single and recurrent lobar hemorrhages and is probably the most common cause of lobar hemorrhage in the elderly. It accounts for some intracranial hemorrhages associated with intravenous thrombolysis given for myocardial infarction. This disorder can be suspected in patients who present with multiple hemorrhages (and infarcts) over several months or years, but it is definitively diagnosed by demonstration of Congo red staining of amyloid in cerebral vessels.

Cocaine-induced stroke is an important cause of stroke, particularly in patients<40. Intracerebral hemorrhage, ischemic stroke, and SAH are all associated with cocaine use. Angiographic findings vary from completely normal arteries to large vessel occlusion or stenosis, vasospasm, or changes consistent with vasculitis. The mechanism of cocaine-related stroke is not known, but cocaine enhances sympathetic activity causing acute, sometimes severe, hypertension, and this may lead to hemorrhage. Slightly more than half of cocaine-related intracranial hemorrhages are intracerebral, and the rest are subarachnoid. In cases of SAH, a saccular aneurysm is usually identified. Presumably, acute hypertension causes aneurysmal rupture.

Head injury often causes intracranial bleeding. The common sites are intracerebral (especially temporal and inferior frontal lobes) and into the subarachnoid, subdural, and epidural spaces. Trauma must be considered in any patient with an unexplained acute neurologic deficit (hemiparesis, stupor, or confusion), particularly if the deficit occurred in the context of a fall (Chap. 369).

Intracranial hemorrhages associated with *anticoagulant therapy* can occur at any location; they are often lobar or subdural. Anticoagulant-related intracerebral

hemorrhages may evolve slowly, over 24 to 48 h. Coagulopathy should be reversed with fresh-frozen plasma and vitamin K to limit the volume of hemorrhage. When intracerebral hemorrhage is associated with thrombocytopenia (platelet count<50,000/ul), transfusion of fresh platelets is indicated. Intracerebral hemorrhage associated with *hematologic disorders* (leukemia, aplastic anemia, thrombocytopenic purpura) can occur at any site and may present as multiple intracerebral hemorrhages. Skin and mucous membrane bleeding is usually evident and offers a diagnostic clue.

Hemorrhage into a *brain tumor* may be the first manifestation of neoplasm. Choriocarcinoma, malignant melanoma, renal cell carcinoma, and bronchogenic carcinoma are among the most common metastatic tumors associated with intracerebral hemorrhage. Glioblastoma multiforme in adults and medulloblastoma in children may also have areas of intracerebral hemorrhage.

Hypertensive encephalopathy is a complication of malignant hypertension. In this acute syndrome, severe hypertension is associated with headache, nausea, vomiting, convulsions, confusion, stupor, and coma. Focal or lateralizing neurologic signs, either transitory or permanent, may occur but are infrequent and therefore suggest some other vascular disease (hemorrhage, embolism, or atherosclerotic thrombosis). There are retinal hemorrhages, exudates, papilledema (hypertensive retinopathy grade IV), and evidence of renal and cardiac disease. In most casesICP andCSFprotein levels are elevated. The hypertension may be essential or due to chronic renal disease, acute glomerulonephritis, acute toxemia of pregnancy, pheochromocytoma, or other causes. Lowering the blood pressure reverses the process, but stroke can occur. Neuropathologic examination reveals multifocal to diffuse cerebral edema and hemorrhages of various sizes from petechial to massive. Microscopically, there are necrosis of arterioles, minute cerebral infarcts, and hemorrhages. The term *hypertensive encephalopathy* should be reserved for this syndrome and not for chronic recurrent headaches, dizziness, recurrentTIAs, or small strokes that often occur in association with high blood pressure.

Primary intraventricular hemorrhage is rare. It usually begins within the substance of the brain and dissects into the ventricular system without leaving signs of intraparenchymal hemorrhage. Vasculitis, usually polyarteritis nodosa or lupus erythematosus, can produce hemorrhage into any region of the central nervous system; most hemorrhages are associated with hypertension, but the arteritis itself may cause bleeding by disrupting the vessel wall. *Sepsis* can cause small petechial hemorrhages throughout the cerebral white matter. *Moyamoya disease*, mainly an occlusive arterial disease that causes ischemic symptoms, may on occasion produce multiple small aneurysms that rupture. Hemorrhages into the spinal cord are usually the result of anAVM or metastatic tumor. *Epidural spinal hemorrhage* produces a rapidly evolving syndrome of spinal cord or nerve root compression (Chap. 368).

Clinical Manifestations Symptoms and signs appear over several minutes. Most lobar hemorrhages are small and cause a restricted clinical syndrome that simulates an embolus to an artery supplying one lobe. For example, the major neurologic deficit with an occipital hemorrhage is hemianopia; with a left temporal hemorrhage, aphasia and delirium; with a parietal hemorrhage, hemisensory loss; and with frontal hemorrhage, arm weakness. Large hemorrhages may be associated with stupor or coma if they

compress the thalamus or midbrain. Most patients with lobar hemorrhages have focal headaches, and more than half vomit or are drowsy. Stiff neck and seizures are uncommon. Spinal hemorrhages usually present with sudden back pain and some manifestation of myelopathy.

Laboratory and Imaging Evaluation CT scanning reliably detects even very small supratentorial hemorrhages. MRI is more sensitive for delineating associated abnormalities, such as aneurysm, vascular malformation, and neoplasm, and is superior for imaging the posterior fossa and spinal column. MRI with gadolinium contrast enhancement is useful for revealing tumors and AVMs. Using special sequences sensitive for hemosiderin, MRI may show evidence of multiple prior hemorrhages, suggesting amyloid angiopathy and vascular anomalies. Repeating an MRI scan at 4 to 8 weeks may be necessary to reveal the underlying cause of hemorrhage, as the acute hematoma may obscure an underlying vascular anomaly or tumor. Conventional x-ray angiography is used when the cause of hemorrhage is uncertain, especially in the young and the middle-aged, or when better delineation of vascular anomalies is necessary.

Treatment The recommendations for management of hypertensive intracerebral hemorrhage generally apply. If a causative lesion is found, it is treated appropriately.

SUBARACHNOID HEMORRHAGE

Excluding head trauma, the most common cause of SAH is rupture of a saccular aneurysm. Other causes include bleeding from a vascular anomaly and extension into the subarachnoid space from a primary intracerebral hemorrhage. Many idiopathic SAHs are localized to the perimesencephalic cisterns and are benign; they probably have a venous or capillary source, and angiography is unrevealing.

Saccular Aneurysm Autopsy studies have found that 3 to 4% of the population harbor aneurysms, for a prevalence of 8 to 10 million people in the United States. The incidence of bleeding is only 25,000 to 30,000 cases per year. The mortality rate for patients who arrive alive at hospital is about 50% during the first month. Of those who survive, more than half are left with major neurologic deficits as a result of the initial hemorrhage, cerebral vasospasm with infarction, or hydrocephalus. If the patient survives but the aneurysm is not obliterated, the annual rebleed rate is about 3%. Given these alarming figures, the major therapeutic emphasis is on preventing the predictable early complications of the rupture.

Unruptured, asymptomatic aneurysms are much less dangerous than a recently ruptured aneurysm. The annual risk of rupture for aneurysms <10 mm in size is approximately 0.1%, and for aneurysms ³10 mm in size is approximately 0.5%; the surgical morbidity far exceeds these percentages. As more data become available, a true risk-benefit analysis for treating these aneurysms will result.

Giant aneurysms, those >2.5 cm in diameter, occur at the same sites (see below) as small aneurysms and account for 5% of cases. The three most common locations are the terminal internal carotid artery, MCA bifurcation, and top of the basilar artery. Their risk of rupture is about 6% in the first year after identification and may remain high

indefinitely. They often cause symptoms by compressing the adjacent brain or cranial nerves.

Mycotic aneurysms are usually located distal to the first bifurcation of major arteries of the circle of Willis. Most result from infected emboli due to bacterial endocarditis causing septic degeneration of arteries and subsequent dilatation and rupture. Whether these lesions should be sought and repaired prior to rupture, or left to heal spontaneously, is controversial.

Pathophysiology Saccular aneurysms occur at the bifurcations of the large arteries at the base of the brain; rupture is into the subarachnoid space in the basal cisterns and often into the parenchyma of the adjacent brain. Approximately 85% of aneurysms occur in the anterior circulation, mostly on the circle of Willis. Common sites include the junction of the anterior communicating artery with the anterior cerebral artery, the junction of the posterior communicating artery with the internal carotid artery, the bifurcation of the MCA, the top of the basilar artery, the junction of the basilar artery and the superior cerebellar artery or the anterior inferior cerebellar artery, and the junction of the vertebral artery and the posterior inferior cerebellar artery. About 20% of patients have multiple aneurysms, many at mirror sites bilaterally. As an aneurysm develops, it typically forms a neck with a dome. The length of the neck and the size of the dome vary greatly and are factors that are important in planning both neurosurgical obliteration or endovascular embolization. The arterial internal elastic lamina disappears at the base of the neck. The media thins, and connective tissue replaces smooth-muscle cells. At the site of rupture (most often the dome) the wall thins, and the tear that allows bleeding is often no more than 0.5 mm long. It is not currently possible to predict which aneurysms are likely to rupture, but limited data suggest that most ruptured aneurysms are>7 mm in diameter.

Clinical Manifestations Most aneurysms present as a sudden SAH. At the moment of aneurysmal rupture with major SAH, the ICP suddenly rises. Abrupt, severe, and generalized vasospasm may occur transiently. These events may account for the sudden transient loss of consciousness that occurs in nearly half of patients. Sudden loss of consciousness may be preceded by a brief moment of excruciating headache, but most patients first complain of headache upon regaining consciousness. In 10% of cases, aneurysmal bleeding is severe enough to cause loss on consciousness for several days. In about 45% of cases, severe headache associated with exertion is the presenting complaint. The patient often calls the headache "the worst headache of my life." However, the clinician should be sensitive to the less dramatic features of sudden onset of headache or to a new or different headache than what the patient has ever experienced. The headache is usually generalized, and vomiting is common.

Although sudden headache in the absence of focal neurologic symptoms is the hallmark of aneurysmal rupture, focal neurologic deficits may occur. Anterior communicating artery or middle cerebral bifurcation aneurysms may rupture into the adjacent brain or subdural space and form a hematoma large enough to produce mass effect. The common deficits that result include hemiparesis, aphasia, and abulia.

Occasionally, prodromal symptoms suggest the location of a progressively enlarging unruptured aneurysm. A third cranial nerve palsy (Video 28-1), particularly when

associated with pupillary dilatation, loss of light reflex, and focal pain above or behind the eye, may occur with an expanding aneurysm at the junction of the posterior communicating artery and the internal carotid artery. A sixth nerve palsy (Video 28-2) may indicate an aneurysm in the cavernous sinus, and visual field defects can occur with an expanding supraclinoid carotid or anterior cerebral artery aneurysm. Occipital and posterior cervical pain may signal a posterior inferior cerebellar artery or anterior inferior cerebellar artery aneurysm. Pain in or behind the eye and in the low temple can occur with an expandingMCAaneurysm. Growing aneurysms rarely cause head pain in the absence of neurologic symptoms and signs.

Aneurysms can undergo small ruptures and leaks of blood into the subarachnoid space, so-called sentinel bleeds. Sudden unexplained headache at any location should raise suspicion ofSAH and be investigated because a major hemorrhage may be imminent.

DELAYED NEUROLOGIC DEFICITS There are four major causes of delayed neurologic deficits; rerupture, hydrocephalus, vasospasm, and hyponatremia.

1. *Rerupture* The incidence of rerupture of an untreated aneurysm in the first month followingSAH is about 30% with the peak at 7 days. It is associated with a 60% mortality and poor outcome. Early treatment eliminates this risk.

2. *Hydrocephalus* Acute hydrocephalus can cause stupor and coma. More often, subacute hydrocephalus develops over a few days or weeks and causes progressive drowsiness or slowed mentation (abulia) with incontinence. Differentiating hydrocephalus from cerebral vasospasm is accomplished with aCT scan,TCDultrasound, or conventional x-ray angiography. Hydrocephalus may clear spontaneously or require temporary ventricular drainage. Chronic hydrocephalus may develop weeks to months afterSAH and manifest as gait difficulty, incontinence, or impaired mentation. Subtle signs may be a lack of initiative in conversation or a failure to recover independence.

3. *Vasospasm* Narrowing of the arteries at the base of the brain followingSAHoccurs regularly. This vasospasm causes symptomatic ischemia and infarction in approximately 30% of patients and is the major cause of delayed morbidity or death. Signs of ischemia appear 4 to 14 days after the hemorrhage, most frequently at about 7 days. The severity and distribution of vasospasm determine whether infarction will occur.

The mechanism of delayed vasospasm is likely to be related to direct effects of clotted blood and its breakdown products on the artery. In general, the more blood that surrounds the arteries, the greater the chance of symptomatic vasospasm. Spasm of theMCAtypically causes contralateral hemiparesis and dysphasia (dominant hemisphere). Proximal anterior cerebral artery vasospasm causes abulia and incontinence, while severe vasospasm of the posterior cerebral artery causes hemianopia. Severe spasm of the basilar or vertebral arteries occasionally produces focal brainstem ischemia. All of these focal symptoms may present abruptly, fluctuate, or develop over a few days.

Vasospasm can be detected reliably with conventional x-ray angiography, but this invasive procedure is expensive and carries risk of stroke and other

complications.TCDultrasound is based on the principle that the velocity of blood flow within an artery will rise as the lumen diameter is narrowed. By directing the probe along the MCAand proximal anterior cerebral, carotid terminus, vertebral, and basilar arteries on a daily or every-other-day basis, vasospasm can be reliably detected noninvasively and treatments initiated to prevent cerebral ischemia (see below).

Severe cerebral edema in patients with infarction from vasospasm may increase theICPenough to reduce cerebral perfusion pressure. Treatment is with mannitol and hyperventilation (Chap. 376).

4. *Hyponatremia* Hyponatremia may be profound and develop quickly in the first 2 weeks followingSAH. It usually results from inappropriate secretion of vasopressin (Chap. 329) and secretion of atrial and brain natriuretic factors, which produce a natriuresis. This "cerebral salt-wasting syndrome" clears over the course of 1 to 2 weeks and, in the setting of SAH, arguably should not be treated with free-water restriction (see below).

Laboratory Evaluation and Imaging (Fig. 361-12) The hallmark of aneurysmal rupture is blood in theCSF. More than 95% of cases have enough blood to be visualized on a high-quality noncontrastCT scan obtained within 72 h. If the scan fails to establish the diagnosis ofSAH and no mass lesion or obstructive hydrocephalus is found, anLPshould be performed to establish the presence of subarachnoid blood. Lysis of the red blood cells and subsequent conversion of hemoglobin to bilirubin stains the spinal fluid yellow within 6 to 12 h of SAH. This xanthochromic spinal fluid peaks in intensity at 48 h and lasts for 1 to 4 weeks, depending on the amount of subarachnoid blood.

The extent and location of subarachnoid blood on noncontrastCT scan help locate the underlying aneurysm, identify the cause of any neurologic deficit, and predict delayed vasospasm. A high incidence of symptomatic vasospasm in the middle and anterior cerebral arteries has been found when early CT scans show subarachnoid clots >5´ 3 mm in the basal cisterns or layers of blood>1 mm thick in the cerebral fissures. CT scans less reliably predict vasospasm in the vertebral, basilar, or posterior cerebral arteries.

LPprior to scanning is indicated only if aCT scan is not available at the time of the suspectedSAH. Once the diagnosis of hemorrhage from a ruptured saccular aneurysm is suspected, four-vessel conventional x-ray angiography (both carotids and both vertebrals) is generally performed to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist. At certain centers, the ruptured aneurysm can be treated using endovascular techniques at the time of the initial angiogram (see following treatment).

TheECGfrequently shows ST-segment and T-wave changes similar to those associated with cardiac ischemia. Prolonged QRS complex, increased QT interval, and prominent "peaked" or deeply inverted symmetric T waves are usually secondary to the intracranial hemorrhage. The cause of these changes is debated, but there is evidence that structural myocardial lesions produced by circulating catecholamines may occur afterSAH.

Serum electrolytes are obtained because hyponatremia may develop. Close monitoring (daily or twice daily) of serum sodium is important since hyponatremia can occur precipitously during the first 2 weeks followingSAH (see above).

TCDultrasound assessment of proximal middle, anterior, and posterior cerebral and basilar artery flow is helpful in detecting the onset of vasospasm and in following its course and response to therapy.

TREATMENT

Aneurysm rerupture is common in the early days afterSAH and is associated with a 60% incidence of death or poor outcome. Early aneurysm repair prevents future hemorrhage and allows the safe application of techniques to improve blood flow (e.g., induced hypertension and hypervolemia) should symptomatic vasospasm develop. An aneurysm can be "clipped" by a neurosurgeon or "coiled" by a neurointerventional radiologist. Surgical repair involves placing a metal clip across the aneurysm neck, with the advantage that rebleeding risk is eliminated immediately. This approach requires craniotomy and brain retraction, which is associated with neurologic deficits. The newer endovascular technique involves placing platinum coils within the aneurysm via a catheter from the femoral artery. The aneurysm is packed tightly to enhance thrombosis and over time is walled-off from the circulation. The safety and efficacy of these two techniques are being compared in an ongoing European trial.

The medical management ofSAHcenters on airway protection, blood pressure management before and after aneurysm treatment, preventing rebleeding prior to treatment, managing vasospasm, treating hydrocephalus, and treating hyponatremia.

Intracranial hypertension following aneurysmal rupture occurs secondary to subarachnoid blood, parenchymal hematoma, acute hydrocephalus, or loss of vascular autoregulation. Patients who are stuporous should undergo emergent ventriculostomy to prevent cerebral ischemia from highICP. Medical therapies designed to combat raised ICP (e.g., mild hyperventilation, mannitol, and sedation) can also be used as needed (Chap. 376). High ICP refractory to treatment carries a poor prognostic sign.

Prior to definitive treatment of the ruptured aneurysm, care is required to maintain adequate cerebral perfusion pressure while avoiding excessive elevation of arterial pressure. Occasionally an intracranial hematoma causing neurologic deterioration requires removal.

Because rebleeding is common, all patients who are not candidates for early surgical treatment are put on bed rest in a quiet, preferably darkened, room and are given stool softeners to prevent constipation. If headache or neck pain is severe, mild sedation and analgesia are prescribed. Extreme sedation is avoided because it can obscure changes in neurologic status. Adequate hydration is necessary to avoid a decrease in blood volume predisposing to brain ischemia.

Seizures are uncommon at the onset of aneurysmal rupture. The quivering, jerking, and extensor posturing that often accompany loss of consciousness are probably related to the sharp rise inICP or, perhaps, acute generalized vasospasm. However, phenytoin is

often given as prophylactic therapy since a seizure may promote rebleeding.

Glucocorticoids may help reduce the head and neck ache caused by the irritative effect of the subarachnoid blood. There is no good evidence they reduce cerebral edema, are neuroprotective, or reduce vascular injury, and their routine use therefore is controversial.

Antifibrinolytic agents are not routinely prescribed but may be considered in patients in whom aneurysm treatment cannot proceed immediately. They are associated with a reduced incidence of aneurysmal rerupture but are also associated with an increased incidence of delayed cerebral infarction and deep venous thrombosis.

Vasospasm remains the leading cause of morbidity and mortality following aneurysmalSAH and treatment of the aneurysm. Treatment with the calcium channel antagonist nimodipine (60 mg orally q6h) has been reported to be beneficial, but the effects seem to be modest. Nimodipine can cause significant hypotension in some patients, which may worsen cerebral ischemia in patients with vasospasm. The most widely accepted therapy for symptomatic cerebral vasospasm is to increase the cerebral perfusion pressure by raising mean arterial pressure through plasma volume expansion and the judicious use of vasopressor agents, usually phenylephrine or dopamine. Raised perfusion pressure has been associated with clinical improvement in many patients, but high arterial pressure may promote rebleeding in unprotected aneurysms. Treatment with induced hypertension and hypervolemia generally requires monitoring of arterial and central venous pressures and in severe cases, the pulmonary artery wedge pressure. Volume expansion helps prevent hypotension, augments cardiac output, and reduces blood viscosity by reducing hematocrit. This method is called "triple-H" (hypertension, hemodilution, and hypervolemic) therapy.

If symptomatic vasospasm persists despite optimal medical therapy, intraarterial papaverine and percutaneous transluminal angioplasty are considered. Vasodilatation following angioplasty appears to be permanent, allowing triple-H therapy to be tapered sooner. The vasodilating effects of papaverine do not last more than 12 to 24 h.

Acute hydrocephalus can cause stupor or coma. It may clear spontaneously or require temporary ventricular drainage. When chronic hydrocephalus develops, ventricular shunting is the treatment of choice.

Free-water restriction is contraindicated in patients withSAH at risk for vasospasm because hypovolemia and hypotension may occur and precipitate cerebral ischemia. Many patients continue to experience a decline in serum sodium despite normal saline parenteral fluids. Frequently, supplemental oral salt coupled with normal saline will mitigate hyponatremia, but often patients will need hypertonic saline in addition. Care must be taken to not correct serum sodium too quickly in patients with marked hyponatremia of several days' duration, as central pontine myelinolysis (Chap. 376) may occur. All patients should have pneumatic compression stockings applied to prevent pulmonary embolism. Systemic heparin is contraindicated in patients with ruptured and untreated aneurysms; it is a relative contraindication following craniotomy, and it may delay thrombosis of a coiled aneurysm.

Vascular Anomalies Vascular anomalies can be divided into congenital vascular malformations and acquired vascular lesions.

Congenital Vascular Malformations True AVMs, venous anomalies, and capillary telangiectasias are congenital lesions that usually remain clinically silent through life.

True *arteriovenous malformations* are congenital shunts between the arterial and venous systems that may present as headache, focal seizures, and intracranial hemorrhage. AVMs consist of a tangle of abnormal vessels across the cortical surface or deep within the brain substance. AVMs vary in size from a small blemish a few millimeters in diameter to a huge mass of tortuous channels composing an arteriovenous shunt of sufficient magnitude to raise cardiac output. The blood vessels forming the tangle interposed between arteries and veins are usually abnormally thin and do not have a normal structure. AVMs occur in all parts of the cerebral hemispheres, brainstem, and spinal cord, but the largest ones are most frequently in the posterior half of the hemispheres, commonly forming a wedge-shaped lesion extending from the cortex to the ventricle.

Although the lesion is present from birth, bleeding or other symptoms are most common between the ages of 10 and 30, occasionally as late as the fifties. AVMs are more frequent in men, and rare familial cases have been described.

Headache (without bleeding) may be hemicranial and throbbing, like migraine, or diffuse. Focal seizures, with or without generalization, occur in about 30% of cases. Half of AVMs become evident as intracerebral hemorrhages. In most, the hemorrhage is mainly intraparenchymal with a small amount of spillage into the subarachnoid space. Blood is usually not deposited in the basal cisterns, and symptomatic cerebral vasospasm is rare. The threat of rerupture in the early weeks is low. Hemorrhages may be massive, leading to death, or may be as small as 1 cm in diameter, leading to minor focal symptoms or no deficit. The AVM may be large enough to steal blood away from adjacent normal brain tissue or to increase venous pressure significantly to produce venous ischemia locally and in remote areas of the brain. This is seen most often with large AVMs in the territory of the MCA.

Large AVMs of the anterior circulation may be associated with a systolic and diastolic bruit (sometimes self-audible) over the eye, forehead, or neck and a bounding carotid pulse. Headache at the onset of AVM rupture is not generally as explosive as with aneurysmal rupture. MRI is better than CT for diagnosis, although contrast CT scanning sometimes detects calcification of the AVM.

Surgical treatment of symptomatic AVMs, often with preoperative embolization to reduce operative bleeding, is generally indicated for accessible lesions. Sterotaxic radiation, an alternative to surgery, can produce a slow sclerosis of arterial channels over 1 to 2 years.

Most data suggest that patients with asymptomatic AVMs have a low risk for hemorrhage; the risk increases after a first hemorrhage to about 2 to 3% annually. Several angiographic features of the AVM can be used to help predict future bleeding risk. Paradoxically, smaller lesions seem to have a higher hemorrhage rate. The

mortality rate with each bleed is about 15%.

Venous anomalies are the result of development of anomalous cerebral, cerebellar, or brainstem drainage. These structures, unlike AVMs, are functional venous channels. They are of little clinical significance and should be ignored if found incidentally on brain imaging studies. Surgical resection of these anomalies may result in venous infarction and hemorrhage. Venous anomalies may be associated with cavernous malformations (see below), which do carry some bleeding risk. If resection of a cavernous malformation is attempted, the venous anomaly should not be disturbed.

Capillary telangiectasias are true capillary malformations that often form extensive vascular networks through an otherwise normal brain structure. The pons and deep cerebral white matter are typical locations, and these capillary malformations can be seen in patients with hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber) syndrome. If bleeding does occur, it rarely produces mass effect or significant symptoms. No treatment options exist.

Acquired Vascular Lesions Cavernous angiomas are tufts of capillary sinusoids that form within the deep hemispheric white matter and brainstem with no normal intervening neural structures. The pathogenesis is unclear. Familial cavernous angiomas have been mapped to several different chromosomal loci; the gene responsible for 7q-linked form encodes a protein that interacts with a member of the RAS family of GTPases. Cavernous angiomas are typically <1 cm in diameter and are often associated with a venous anomaly. Bleeding is usually of small volume, causing slight mass effect only. The bleeding risk for single cavernous malformations is 0.7 to 1.5% per year and may be higher for patients with prior clinical hemorrhage or multiple malformations. Seizures may occur if the malformation is located near the cerebral cortex. Surgical resection eliminates bleeding risk and may reduce seizure risk, but it is reserved for those malformations that form near the brain surface. Radiation treatment has not been shown to be of benefit.

Dural arteriovenous fistulas are acquired connections usually from a dural artery to a dural sinus. Patients may complain of a pulse-synchronous cephalic bruit ("pulsatile tinnitus") and headache. Depending on the magnitude of the shunt, venous pressures may rise high enough to cause cortical ischemia or venous hypertension and hemorrhage. Surgical and endovascular techniques are usually curative. These fistulas may form because of trauma, but most are idiopathic. There is an association between fistulas and dural sinus thrombosis. Fistulas have been observed to appear months to years following venous sinus thrombosis, suggesting that angiogenesis factors elaborated from the thrombotic process may cause these anomalous connections to form. Alternatively, dural arteriovenous fistulas can produce venous sinus occlusion over time, perhaps from the high pressure and high flow through a venous structure.

(Bibliography omitted in Palm version)

362. ALZHEIMER'S DISEASE AND OTHER PRIMARY DEMENTIAS- *Thomas D. Bird*

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common cause of dementia in western countries. Approximately 10% of all persons over the age of 70 have significant memory loss; in more than half the cause is AD. This translates into approximately 3 to 4 million persons with AD in the United States, with a total health care cost of more than $80 billion per year. It is estimated that the annual total cost of caring for a single AD patient in an advanced stage of the disease is $47,000. The disease also exacts a heavy emotional toll on family members and caregivers. AD was first described in 1907 in a 55-year-old woman by Professor Alois Alzheimer in Germany. The condition was initially thought to represent a relatively uncommon form of presenile dementia. However, it has become clear that AD can occur in any decade of adulthood and is the most common cause of dementia in the elderly. The disease is defined as a clinical-pathologic entity. Clinically, AD most often presents with subtle onset of memory loss followed by a slowly progressive dementia that has a course of several years. Pathologically there is gross, diffuse atrophy of the cerebral cortex with secondary enlargement of the ventricular system. Microscopically there are extracellular neuritic plaques containing Abamyloid, silver-staining neurofibrillary tangles in neuronal cytoplasm, and accumulation of Ab amyloid in arterial walls of cerebral blood vessels (see "Pathogenesis," below). The recent identification of four different susceptibility genes for AD has provided a foundation for rapid progress in understanding the biologic basis of the disease.

Clinical Manifestations In the early stages of the disease, the memory loss may go unrecognized or may be ascribed to benign forgetfulness. Slowly the cognitive problems begin to interfere with daily activities, such as keeping track of finances, following instructions on the job, driving, shopping, and housekeeping. Some patients are unaware of these difficulties (agnosognosia), and others have considerable insight, resulting in frustration and anxiety. These major differences in insight have no clear explanation. Change of environment may be bewildering, and the patient may become lost on walks or while driving an automobile. In the middle stages of the disease, the patient is unable to work, is easily lost and confused, and requires daily supervision. Social graces, routine behavior, and superficial conversation may be surprisingly retained. Language may be impaired, especially comprehension and naming of objects. In some patients, aphasia is an early and prominent feature. Word-finding difficulties and circumlocution may be a problem even when formal testing demonstrates intact naming and fluency. Although confrontation naming is frequently deficient, there are often other language deficits as well, including impairments in fluency, comprehension, and repetition. Various apraxias are also common, i.e., deficits in performing sequential motor tasks such as dressing, eating, solving simple puzzles, and copying geometric figures. Patients may be unable to do simple calculations or tell time. Rarely,ADpatients may have a form of cortical blindness in which they deny their inability to see. This correlates at autopsy with severe neuropathologic changes in the visual cortex. In the late stages of the disease, some persons remain ambulatory but wander aimlessly and may have complete loss of judgment, reason, and cognitive abilities. Hallucinations and delusions are common; they are usually concrete and not too complex or bizarre. For example, patients may falsely accuse a spouse of infidelity, not recognize an old friend, think a visitor is a burglar, or become frightened of their own image in a mirror. Loss of

inhibitions and belligerence may occur and may even alternate with passivity and social withdrawal. Sleep-wake patterns may be disturbed, and nighttime wandering may be very disruptive to the household. Some patients develop a shuffling gait with generalized muscle rigidity associated with slowness and awkwardness of movement. The patients often look parkinsonian but rarely have a rapid, rhythmic, resting tremor. In end-stage AD, patients frequently, but not always, become rigid, mute, incontinent, and bedridden. Help may be needed with the simplest tasks, such as eating, dressing, and toilet function. They may show hyperactive tendon reflexes and primitive sucking and snouting reflexes. Myoclonic jerks (sudden brief contractions of various muscles or the whole body) may occur spontaneously or in response to physical or auditory stimulation. This phenomenon raises the possibility of Creutzfeldt-Jakob disease (CJD) (Chap. 375), but the course of AD is much more prolonged. Generalized seizures may also occur. Death usually results from malnutrition, secondary infections, or heart disease. The typical duration of AD is 8 to 10 years, but the course can range from 1 to 25 years. For unknown reasons, some AD patients show a steady downhill decline in function, while others have prolonged plateaus without major deterioration.

Differential Diagnosis Early in the disease course, other etiologies of dementia should be excluded. These include treatable entities such as thyroid disease, vitamin deficiencies, brain tumor, drug and medication intoxication, chronic infection, and severe depression (pseudodementia) (see Chap. 26). Neuroimaging studies [computed tomography (CT) and magnetic resonance imaging (MRI)] are not specific for AD and may be normal early in the course of the disease. However, neuroimaging helps to exclude other disorders, such as primary and secondary neoplasms, multi-infarct dementia, diffuse white matter disease, and normal-pressure hydrocephalus. As AD progresses, diffuse cortical atrophy becomes apparent, and detailed MRI scans show atrophy of the hippocampus (Fig. 362-1A). The electroencephalogram (EEG) in AD may be normal or show nonspecific slowing. Routine spinal fluid examination gives normal results. Research studies have indicated a general decrease in cerebrospinal fluid (CSF) Ab amyloid levels with an increase in tau protein. There is considerable overlap of these levels with those of the normal aged population, and the usefulness of these measurements in diagnosis remains unclear. Combining the results of both measurements may prove to be most helpful. The use of blood apolipoprotein (Apo) E genotyping is discussed under "Pathogenesis," below. Slowly progressive decline in memory and orientation, normal results on laboratory tests, and an MRI or CT scan showing only diffuse cortical atrophy including the hippocampus is highly suggestive of AD. A clinical diagnosis of AD reached after careful evaluation is confirmed at autopsy 80 to 90% of the time. The misdiagnosed cases usually represent one of the other dementing disorders described later in this chapter. Relatively simple clinical clues are useful in the differential diagnosis. Early prominent gait disturbance with only mild memory loss suggests normal-pressure hydrocephalus (see below). Resting tremor with stooped posture, bradykinesia, and masked face suggests Parkinson's disease (Chap. 363). Chronic alcoholism suggests vitamin deficiency. Loss of sensibility to position and vibration stimuli accompanied by Babinski responses suggests vitamin B_{12} deficiency (Chap. 368). Early onset of a seizure suggests a metastatic or primary brain neoplasm (Chap. 370). A past history of long-term depression suggests pseudodementia (see below). A history of treatment for insomnia, anxiety, psychiatric disturbance, or epilepsy suggests chronic drug intoxication. Rapid progression over a few weeks or months associated with ataxia, rigidity, and myoclonus suggests CJD (Chap. 375). Prominent

behavioral changes with intact memory and lobar atrophy on brain imaging suggests frontotemporal dementia (FTD). A positive family history of dementia suggests either one of the familial forms of AD or one of the other genetic disorders associated with dementia, such as Huntington's disease (see below), familial FTD (see below), familial forms of prion diseases, or rare forms of hereditary ataxias (Chap. 364).

Pathogenesis The most important risk factors for AD are old age and a positive family history. The frequency of AD increases with each decade of adult life to reach 20 to 40% of the population over the age of 85. A positive family history of dementia suggests a genetic cause of AD, as discussed below. Female gender may also be a risk factor independent of the greater longevity of women. Unconfirmed studies have suggested that postmenopausal estrogen use is associated with a decreased frequency of AD. Some AD patients have a past history of head trauma with concussion, but this appears to be a relatively minor risk factor. There is some suggestion that AD is more common in groups with lower educational attainment, but education influences test-taking ability, and it is clear that AD can affect persons of all intellectual levels. One unconfirmed study found that the capacity to express complex written language in early adulthood correlated with a decreased risk for AD. Numerous environmental factors, including aluminum, mercury, viruses, and prions, have been proposed as causes of AD, but none has been proved to play a role. Preliminary studies have suggested that inflammation may play some role in the pathogenesis of AD, as the use of nonsteroidal anti-inflammatory agents is associated with decreased risk. Vascular disease does not seem to be a direct cause of AD, even though there is an associated amyloid angiopathy.

Positron emission tomography (PET) has indicated that the earliest metabolic changes in AD occur in parietal cortex (Fig. 362-1 *C, D*). At autopsy, the most severe pathology is usually seen in the hippocampus, temporal cortex, and nucleus basalis. The most important microscopic findings are neuritic "senile" plaques and cytoplasmic neurofibrillary tangles (NFTs). These two lesions accumulate in small numbers during normal aging of the brain but occur in quantitative excess in the dementia of AD. The neuritic plaques contain a central core that includes Ab amyloid, proteoglycans, Apo E, a_1 antichymotrypsin, and other proteins. Ab amyloid is a 4.2-kDa protein of 39 to 42 amino acids that is derived proteolytically from a larger transmembrane protein (amyloid precursor protein, APP) through cleavage by two enzymes termed b and g secretase. The normal function of Ab amyloid is unknown. APP has been shown to have neurotrophic and neuroprotective activities. The plaque core is surrounded by the debris of degenerating neurons, microglia, and macrophages. The accumulation of Ab amyloid in cerebral arterioles is termed *amyloid angiopathy*. The NFTs were first noted by Alzheimer. They are silver-staining, twisted neurofilaments in neuronal cytoplasm that represent abnormally phosphorylated tau (t) protein and appear as paired helical filaments by electron microscopy. Tau is a microtubule-associated protein that may function to assemble and stabilize the microtubules that convey cell organelles, glycoproteins, and other important materials through the neuron. The ability of tau protein to bind to microtubule segments is determined partly by the number of phosphate groups attached to it. Increased phosphorylation of tau protein may disturb this normal process. Biochemically, AD is associated with a decrease in the cerebral cortical levels of several proteins and neurotransmitters, especially acetylcholine, its synthetic enzyme choline acetyltransferase (CAT), and nicotinic cholinergic receptors.

Reduction of acetylcholine may be related in part to degeneration of cholinergic neurons in the nucleus basalis of Meynert that project to many areas of cortex. There is also reduction in norepinephrine levels in brainstem nuclei such as the locus coeruleus.

Several genetic factors are known to play important roles in the pathogenesis of at least some cases of AD. One is the *APP* gene on chromosome 21. Adults with trisomy 21 (Down's syndrome) consistently develop the typical neuropathologic hallmarks of AD if they survive beyond age 40. Many also develop a progressive dementia superimposed on their baseline mental retardation. APP is a membrane-spanning protein that is subsequently processed into smaller units, including the Ab amyloid that is deposited in the neuritic plaques of AD. Presumably the extra dose of the *APP* gene on chromosome 21 is the initiating cause of AD in adult Down's syndrome and eventually results in an excess of cerebral Ab amyloid. Furthermore, a few families with early-onset familial AD (FAD) have been discovered to have point mutations in the *APP* gene. Although very rare, these families were the first indication of a single-gene autosomal dominant transmission of AD. The most frequent of these *APP* mutations is substitution of valine for isoleucine at position 717. Elevated plasma Ab peptide may be a risk factor for developing AD in the general population.

Investigation of large families with multigenerational FAD led subsequently to the discovery of two additional AD genes, termed the *presenilins*. Presenilin-1 (*PS-1*) is on chromosome 14 and encodes a protein called S182. Mutations in this gene cause an early-onset AD (onset before age 60 and often before age 50) that is transmitted in an autosomal dominant, highly penetrant fashion. More than 40 different mutations have been found in the *PS-1* gene in families from a wide range of ethnic backgrounds. Presenilin-2 (*PS-2*) is on chromosome 1 and encodes a protein called STM2. A mutation in the *PS-2* gene was first found in a group of American families with Volga German ethnic background. The two genes (*PS-1* and *PS-2*) are highly homologous and encode similar proteins that at first appeared to have seven transmembrane domains (hence the designation *STM*), but subsequent studies have suggested eight such domains with a ninth submembrane region. The normal function of these proteins and the means by which mutations affecting them result in AD is unknown. Both S182 and STM2 are cytoplasmic neuronal proteins that are widely expressed throughout the nervous system. They are homologous to a cell-trafficking protein, sel 12, that is found in the nematode *Coenorhabditis elegans.* Knockout of the *PS-1* gene in mice causes embryonic death, but PS-2 knockout mice have only mild pulmonary pathology, suggesting very different primary functions of the two proteins. The AD pathology in transgenic mice carrying both APP and PS-1 mutations is worse than that in mice with only a single mutation. Also, the mutant human *PS-1* gene protects PS-1 knockout mice from embryonic lethality, and this observation fits with the idea that *PS-1* mutations cause disease by a toxic gain of function. Patients with mutations in these genes have elevated plasma levels of Ab amyloid, suggesting a possible link between the presenilins and APP. There is evidence that presenilin-1 may normally cleave APP at the g secretase site, and mutations in either gene (*PS-1* or *APP*) may disturb this function. Mutations in *PS-1* have thus far proved to be the most common cause of early-onset FAD, representing 40 to 70% of this relatively rare syndrome. Mutations in *PS-1* tend to produce AD with an earlier age of onset (mean, 45 years) and a shorter, more rapidly progressive course (mean duration, 6 to 7 years) than the disease caused by mutations in *PS-2* (onset, 53 years; duration, 11 years). Some carriers of uncommon

PS-2 mutations have had onset of dementia after the age of 70. Mutations in the presenilins are rarely involved in the more common sporadic cases of late-onset AD occurring in the general population. Molecular DNA blood testing for these uncommon mutations is now possible on a research basis, and mutation analysis of *PS-1* is commercially available. Such testing is likely to be positive only in early-onset cases of FAD. Any testing of asymptomatic persons at risk must be done in the context of formal, thoughtful genetic counseling (Chap. 359).

A discovery of great importance has implicated the *Apo E* gene on chromosome 19 in the pathogenesis of late-onset familial and sporadic forms of AD. Apo E is involved in cholesterol transport (Chap. 344) and has three alleles:e2, e3, ande4. The e4 allele of *Apo E* shows a strong association with AD in the general population, including sporadic and late-onset familial cases. Approximately 24 to 30% of the normal white population has at least onee4 allele (12 to 15% allele frequency), and about 2% aree4/4 homozygotes. In a group of AD patients, approximately 40 to 65% have at least onee4 allele, a highly significant difference compared with controls. On the other hand, many AD patients have noe4 allele, and individuals withe4 may never develop AD. Therefore,e4 is neither necessary nor sufficient as a cause of AD. Nevertheless, it is clear that the Apo E e4 allele, especially in the homozygous 4/4 state, is an important risk factor for AD. It appears to act as a dose-dependent modifier of age of onset, with the earliest onset associated with the e4/4 homozygous state. One study found a 45% risk for developing AD by age 73 in females who were 4/4 homozygotes. It is unknown how Apo E functions as a risk factor modifying age of onset. Apo E is present in the neuritic amyloid plaques of AD, and may also be involved inNFTformation, because it binds to tau protein. Apo E4 decreases neurite outgrowth in cultures of dorsal root ganglion neurons. There is suggestive evidence that the e2 allele may be "protective." Interesting but unconfirmed reports suggest that AD patients with ane4 allele may be less responsive cholinesterase inhibitor drugs. The use of Apo E testing in the diagnosis of AD is controversial. It is not indicated as a predictive test in normal persons, because its precise predictive value is unclear, and many individuals with thee4 allele never develop dementia. However, some cognitively normal e4/4 homozygotes have been found byPET to have decreased cerebral cortical metabolic rates, suggesting possible presymptomatic abnormalities compatible with the earliest stage of AD. Studies show that in demented persons who meet clinical criteria for AD, the finding of an e4 allele increases the reliability of diagnosis. However, the absence of an e4 allele does not eliminate the diagnosis of AD. Furthermore, all patients with dementia, including those with an e4 allele, require a search for reversible causes of their cognitive impairment. Nevertheless, Apo E remains the single most important biologic marker associated with risk for AD, and studies of its functional role and diagnostic usefulness are progressing rapidly. Its association (or lack thereof) with other dementing illnesses needs to be fully evaluated. The e4 allele is not associated with the dementia of Parkinson's disease,FTD, orCJD.

Additional genes are also likely to be involved inAD, including a potential candidate on chromosome 12 (a2-macroglobulin).

TREATMENT

The management of Alzheimer's disease is difficult and frustrating, because there is no

specific treatment and the primary focus is on long-term amelioration of associated behavioral and neurologic problems. Building rapport with the patient, family members, and other caregivers is essential to successful management.

Tacrine (tetrahydroaminoacridine) and donepezil (Aricept) are the only drugs presently approved by the U.S. Food and Drug Administration (FDA) for treatment of AD. Their pharmacologic action is presumed to be inhibition of cholinesterase, with a resulting increase in cerebral levels of acetylcholine. Double-blind, placebo-controlled, crossover studies with cholinesterase inhibitors have shown them to be associated with improved caregiver ratings of patients' functioning and with an apparent decreased rate of decline in cognitive test scores over periods of up to 2 years. Such studies are difficult to perform because of the subjective nature of many of the observations and the lack of a uniform rate of decline among patients. Nevertheless, a small but important minority of AD patients (approximately 10 to 20%) appear to show a modest response to these agents and tolerate their side effects (which include dose-related nausea, vomiting, diarrhea, bradycardia, and dizziness). Even without actual improvement these agents may provide stabilization of the patient's condition for a period of months. There is no evidence that these drugs are beneficial in the late stages of AD. Tacrine may be hepatotoxic, necessitating frequent testing of liver function and adjustment of the dose. Donepezil is not hepatotoxic and can be administered once daily (5 to 10 mg). Contraindications for cholinesterase inhibitor treatment include liver disease, alcoholism, peptic ulcer disease, chronic obstructive pulmonary disease; and bradycardia. Clinical trials of other anticholinesterase drugs are in progress.

In a recent prospective observational study, the use of estrogen replacement therapy appeared to protect -- by about 50% -- against development of AD in women. This study appeared to confirm the results of two earlier case-controlled studies. On the other hand, a prospective treatment study of women with AD found no difference between estrogen and placebo. The mechanism of possible estrogen effects on Alzheimer's disease is unknown but may result from direct effects on cholinergic neurons, antioxidant properties, or a lowering of levels of Apo E. A prospective randomized clinical trial of estrogen replacement therapy in women is underway.

In patients with moderately advanced AD, a prospective trial of the antioxidants selegiline, atocopherol (vitamin E), or both demonstrated no significant benefit on primary outcomes of progression. However, a modest beneficial effect of each treatment compared to placebo was present in secondary analyses that controlled for intergroup difference in baseline dementia scores. These possible beneficial effects are small in magnitude and require confirmation.

A randomized, double-blind, placebo-controlled trial of an extract of *Ginkgo biloba* found modest improvement in cognitive function in subjects with AD and vascular dementia. This study requires confirmation before *G. biloba* is considered an effective treatment for dementia, because there was a high subject dropout rate and no improvement on a clinician's judgment scale.

As noted above, several retrospective studies have also suggested a protective effect on dementia of nonsteroidal anti-inflammatory agents. Controlled prospective studies are in progress.

In an APP mutation mouse model of AD, weekly immunization with Ab peptide both prevented the occurrence and reversed the accumulation of amyloid plaques in the brain. The possible benefit of this treatment strategy in humans is unknown and is under evaluation. In addition, the identification of a protease that acts as the APPb secretase has raised the possibility that inhibiting this enzyme might decrease amyloid accumulation in brain, another potential therapeutic strategy for AD.

Mild to moderate depression is common in the early stages of AD and may respond to antidepressant medication. Selective serotonin reuptake inhibitors (SSRIs) are commonly used, as are tricyclic antidepressants with low anticholinergic side effects (desipramine and nortriptyline). Generalized seizures should be treated with an appropriate anticonvulsant, such as phenytoin or carbamazepine. Agitation, insomnia, hallucinations, and belligerence are especially troublesome characteristics of some AD patients and often are responsible for nursing home placement. Mild sedation with benadryl may help insomnia, and agitation has been variously treated with phenothiazines (such as thioridazine), haloperidol, risperidone, and benzodiazepines (such as lorazepam). These medications frequently have untoward side effects, including sedation, confusion, increased muscle tone, and adventitious movements. Low-dose haloperidol (0.5 to 2 mg), trazodone, buspirone, propranolol, and olanzapine may be the most helpful and have the fewest side effects. The few controlled studies comparing drugs with behavioral intervention in the treatment of agitation suggest that both approaches are equally effective. However, careful, daily, nondrug behavior management is often not available, rendering medication necessary. In the early stages of AD, memory aids such as notebooks and posted daily reminders are helpful. Common sense and clinical studies have shown that family members should emphasize activities that are pleasant and deemphasize those that are unpleasant. Kitchens, bathrooms, and bedrooms need to be made safe, and patients eventually must stop driving. Loss of independence and change of environment may worsen confusion, agitation, and anger. Communication and repeated calm reassurance are necessary. Caregiver "burnout" is common, often resulting in nursing home placement of the patient and respite breaks for the caregiver help to maintain successful long-term management of the patient. Use of adult daycare centers can be most helpful. Local and national support groups, such as the Alzheimer's Disease and Related Disorders Association, are valuable resources.

VASCULAR DEMENTIA

Dementia associated with cerebral vascular disease can be divided into two general categories: multi-infarct dementia and diffuse white matter dementia (also called subcortical arteriosclerotic encephalopathy or Binswanger's disease). Cerebral vascular disease appears to be a more common cause of dementia in Asia than in Europe and North America. Individuals who have had several strokes may develop chronic cognitive deficits, commonly called *multi-infarct dementia*. The strokes may be large or small (sometimes lacunar) and usually involve several different brain regions. In fact, one study has shown that lacumar stroke is the most common stroke subtype associated with dementia. The occurrence of dementia seems to depend partly on the total volume of damaged cortex, but it is also more common in individuals with left-hemisphere lesions, independent of any language disturbance, and when the stroke involves the

hippocampus. Subcortical infarction has been associated with both frontal and global cerebral hypometabolism, which may in turn lead to dementia. The patients give a history of episodes of sudden neurologic deterioration. Multi-infarct dementia patients usually also have a history of hypertension, diabetes, coronary artery disease, or other manifestations of diffuse atherosclerosis. Physical examination usually reveals focal neurologic deficits such as hemiparesis, unilateral Babinski reflex, a visual field defect, or pseudobulbar palsy. The recurrent strokes result in a stepwise progression of disease. Neuroimaging studies clearly show the multiple areas of infarction. Thus, the history and neuroimaging findings differentiate this condition from AD. However, AD and multiple infarctions are both common and sometimes occur together. With normal aging, there is also an accumulation of amyloid in cerebral blood vessels, leading to a condition called *cerebral amyloid angiopathy of aging* (not associated with dementia), which predisposes older persons to hemorrhagic lobar stroke. AD patients with amyloid angiopathy and hypertension also appear to be at increased risk of cerebral infarction. Apo Ee4 has been reported to be a risk factor for amyloid angiopathy independent of AD.

Some persons with dementia are discovered on MRI studies to have bilateral abnormalities of subcortical white matter, termed *diffuse white matter disease* (or leukoaraiosis) (Fig. 362-2). The dementia may be of subtle onset and slow progression, features that distinguish it from multi-infarct dementia. (A few such patients have been described with apparently sudden onset of cognitive impairment.) Early symptoms are mild confusion, apathy, change in personality, and memory deficit. Marked difficulties in judgment and orientation and dependence on others for daily activities develop later. Euphoria, elation, or aggressive behavior are common. A mixed picture of pyramidal and cerebellar signs may be present in the same patient. Lateralizing motor signs are uncommon. A gait disorder appears in at least half the patients. In advanced cases, urinary incontinence and dysarthria with or without pseudobulbar features are frequent. Seizures and myoclonic jerks appear in a minority of patients. This disorder appears to be the result of chronic ischemia due to occlusive disease of small penetrating cerebral arteries and arterioles (microangiopathy). The patients usually, but not always, have a history of hypertension, but any disease causing stenosis of small cerebral vessels may be the critical underlying factor. An association with abnormalities of the coagulation-fibrinolysis pathway has been reported. Binswanger described several patients with this condition, but the term *Binswanger's disease* should be used with caution, because it does not really identify a single entity. Other rare causes of white matter disease may also present with dementia, such as adult metachromatic leukodystrophy and progressive multifocal leukoencephalopathy (papovavirus infection). The term *CADASIL* refers to an inherited form of diffuse white matter disease described as *c*erebral *a*utosomal *d*ominant *a*rteriopathy with *s*ubcortical *i*nfarcts and *l*eukoencephalopathy. Clinically there is a progressive dementia developing in the fifth to seventh decades in multiple family members who may also have a history of migraine and recurrent stroke without hypertension. Skin biopsy may show characteristic dense bodies in the media of arterioles. The disease is caused by mutations in the notch 3 gene, but there is no commercially available genetic test. The frequency of this disorder is unknown.

Treatment of vascular dementia must be focused on the underlying causes, such as hypertension, atherosclerosis, and diabetes. Recovery of lost cognitive function is not

likely to occur.

FRONTOTEMPORAL DEMENTIA AND PICK'S DISEASE

FTDmay be the cause of as many as 10% of all cases of dementia and an even greater proportion of presenile onset (<65 years) cases. The patients are often irritable; have loss of inhibitions; and do better on construction, copying, and calculation tasks than patients withAD. Memory is often intact early in the disease. Patients may be socially inappropriate or remote and withdrawn. Hoarding, overeating, and weight gain are common. Rigidity and mutism often occur late in the disease. Imaging studies reveal atrophy confined to the frontal or frontal and temporal lobes. The condition is heterogeneous, and the broad designation FTD usually includes Pick's disease (discussed below) as a subcategory. An autosomal dominant genetic form of FTD has been linked to DNA markers on chromosome 17. Some of these families have disinhibition dementia associated with motor neuron disease, whereas others display parkinsonian features. Cytoplasmic aggregations of tau protein are found in many neurons of cortex, striatum, and substantia nigra. These aggregates sometimes resemble those found in progressive supranuclear palsy (Chap. 363) or AD. This condition is referred to as *frontotemporal dementia with parkinsonism linked to chromosome 17* (FTDP-17). Many FTDP-17 families have been found to inherit missense mutations in the tau gene that disturb the microtubule-binding function of tau or alter the carefully regulated alternative splicing of the gene. Recent studies show that only a small portion of sporadic FTD patients have tau mutations, which are more commonly found in familial FTD cases with known tau neuropathology at autopsy.

Pick's disease is a commonly discussed disorder that is difficult to differentiate clinically fromAD and is less well defined as a distinct entity. The major distinguishing hallmark is marked symmetric lobar atrophy of temporal and/or frontal lobes, which can be visualized by neuroimaging studies (CT,MRI, or single photon emission CT) and is readily apparent at autopsy. The atrophy is sometimes asymmetric and may involve the basal ganglia. Microscopic findings include gliosis, neuronal loss, and swollen or ballooned neurons, which frequently contain silver-staining cytoplasmic inclusions referred to as *Pick bodies*. Pick bodies consist of straight and constricted fibrils that share antigenic determinants with theNFTs of AD, including the microtubule-associated protein tau, suggesting that Pick bodies derive from altered components of the neuronal cytoskeleton. Onset is usually in the fifth through seventh decades. Clinically, there is a slowly progressive dementia often associated with hyper-oral behavior, bulimia, language disturbance, emotional disinhibition, irritability, and persistent aimless wandering. In the early stages the behavioral changes are more prominent than memory loss. The language disturbance may be aphasia or forced repetitive speech patterns, sometimes progressing to echolalia, language impoverishment, and mutism. These clinical characteristics may sometimes occur in AD, so that the clinical diagnosis of Pick's disease often requires confirmation at autopsy. Some brains containing Pick bodies may also have varying quantities of amyloid plaques and NFTs, blurring the distinction from AD. Examples of familial Pick's disease that display an autosomal dominant-like pattern of inheritance have been reported. There is no specific treatment.

DIFFUSE LEWY BODY DISEASE

Lewy bodies are intraneuronal cytoplasmic inclusions that stain with periodic acid-Schiff and ubiquitin. They are composed of straight neurofilaments 7 to 20 nm long with surrounding amorphous material. They contain epitopes recognized by antibodies against phosphorylated and nonphosphorylated neurofilament proteins, ubiquitin, and a presynaptic protein called a-synuclein. Lewy bodies are traditionally found in the substantia nigra of patients with idiopathic Parkinson's disease (Chap. 363). Large numbers of such inclusions have also been discovered in cortical neurons in patients with dementia. In patients without other pathologic features, the condition is referred to as *diffuse Lewy body disease*. In patients whose brains also contain amyloid plaques andNFTs, the condition is called the *diffuse Lewy body variant of Alzheimer's disease*. The quantity of Lewy bodies required to establish the diagnosis is uncertain. The diagnosis is primarily a neuropathologic entity; however, there is some evidence that there is a characteristic clinical syndrome. In addition to chronic progressive dementia, these patients often also have parkinsonian features, in particular rigidity, which may be combined with an intention tremor. Frequent fluctuations of behavior, cognitive ability, and level of alertness may occur. These fluctuations can be marked, with the occurrence of episodic confusion and lucid intervals suggesting delirium. However, despite the fluctuating pattern, the clinical features persist over a long period, unlike a typical transient delirium. Delusions and visual hallucinations are common, and auditory hallucinations may also occur. Repeated unexplained falls are often noted. Frequently there is an unusual sensitivity to neuroleptic medications and benzodiazepines, with exaggerated adverse responses to standard doses. In most patients, this condition is difficult to distinguish fromAD or Parkinson's disease with dementia. The population prevalence of diffuse Lewy body disease is not known, but it is now more commonly diagnosed than in the past because of the use of ubiquitin staining during neuropathologic studies. At autopsy, 10 to 30% of demented patients may show cortical Lewy bodies. It is not yet clear what role Apo E may play in Lewy body disease without AD changes. There is no specific treatment.

NORMAL-PRESSURE HYDROCEPHALUS (VIDEO 361-4)

Normal-pressure hydrocephalus (NPH) is a syndrome with distinct clinical, physiologic, and neuroimaging characteristics. The clinical triad includes an abnormal gait (ataxic or apractic), dementia (usually mild to moderate), and urinary incontinence. Neuroimaging studies of the brain reveal enlarged lateral ventricles (hydrocephalus) with little or no cortical atrophy. This is a communicating hydrocephalus with a patent aqueduct of Sylvius and upward stretching of the corpus callosum (Fig. 362-3). Lumbar puncture opening pressure is in the high normal range, and theCSFprotein and sugar concentrations and cell count are normal. NPH is presumed to be caused by obstruction to normal flow of CSF over the cerebral convexity and delayed absorption into the venous system. The indolent nature of the process results in enlarged lateral ventricles but relatively little increase in CSF pressure. There is presumably stretching and distortion of white matter tracts in the corona radiata, but the exact physiologic cause of the clinical syndrome is unclear. Some patients with NPH have a history of conditions producing scarring of the basilar meninges (blocking upward flow of CSF) such as previous meningitis, subarachnoid hemorrhage, or head trauma. Most patients seem to have no pertinent past history. In contrast to patients withAD, the patient with NPH has an early and prominent gait disturbance and no evidence of cortical atrophy onCT orMRI. A number of attempts have been made to use various special studies to improve

the diagnosis of NPH and predict the success of ventricular shunting. These include radionuclide cisternography (showing a delay in CSF absorption over the convexity) and various attempts to monitor and alter CSF flow dynamics, including a constant-pressure infusion test. None of these studies has proven to be specific or consistently useful. There is sometimes a transient improvement in gait or cognition following lumbar puncture (or serial punctures) with removal of 30 to 50 mL of CSF, but this finding also has not proved to be consistently predictive of post-shunt improvement. One study determined that no more than 1 to 2% of a large group of demented patients had NPH. AD often masquerades as NPH, because the gait may be abnormal in AD and cortical atrophy is sometimes difficult to determine by CT or MRI early in the disease. Hippocampal atrophy on MRI may be a clue suggesting AD (Fig. 362-1). Approximately 30 to 50% of patients identified by careful diagnosis as having NPH will show improvement with a ventricular shunting procedure. Gait may improve more than memory. Transient, short-lasting improvement is common. Patients should be carefully selected for this operation, because subdural hematoma and infection are known complications. A recent study limited to four patients showed benefit from aggressive siphoning of CSF to reduce ventricular size, but there were frequent perioperative complications.

HUNTINGTON'S DISEASE

Huntington's disease (HD) is a genetic, autosomal dominant, degenerative brain disorder. It has a population frequency of about 10/100,000. The two clinical hallmarks of the disease are chorea and behavioral disturbance. The illness may begin with either or both of these symptoms predominating. Onset is usually in the fourth or fifth decade, but there is a wide range in age of onset, from childhood to>75 years. The chorea begins as subtle fidgeting that may be unrecognized by the patient and family. However, the movement disorder is usually slowly progressive and eventually may become disabling. There are frequent, irregular, sudden jerks and movements of any of the limbs or trunk. Grimacing, grunting, and poor articulation of speech may be prominent. The gait is disjointed and poorly coordinated and has a so-called dancing (choreic) quality. Memory is frequently not impaired until late in the disease, but attention, judgment, awareness, and executive functions may be seriously deficient at an early stage. Depression, apathy, social withdrawal, irritability, and intermittent disinhibition are common. Delusions and obsessive-compulsive behavior may occur. Schizophrenia is occasionally the initial diagnosis. The disease duration is typically about 15 years but also shows a wide range. Early onset before the age of 20 (juvenile HD) is associated with rigidity, ataxia, cognitive decline, and more rapid progression, with a typical duration of about 8 years. Seizures are rare with adult-onset HD but more common with juvenile-onset disease. There is no specific treatment, but the adventitious movements and behavioral changes may partially respond to phenothiazines, haloperidol, benzodiazepines, or olanzepine.SSRIsmay help with the frequently associated depression.

Neuropathologically, the disease predominantly strikes the striatum. Atrophy of the caudate nuclei, which form the lateral margins of the lateral ventricles, can be visualized on neuroimaging studies in the middle and late stages of the disease (Fig. 362-4). More diffuse cortical atrophy can be seen late in the disease. Microscopically there are no dramatic pathologic characteristics, such as the plaques and tangles seen withAD.

However, there is gliosis and neuronal loss, especially of medium-sized spiny neurons in the caudate and putamen. Some neurons contain intranuclear inclusions that stain with antibodies to polyglutamine. There is relative sparing of large cholinergic aspiny neurons. (Treatment with 3-nitroproprionic acid, a succinate dehydrogenase inhibitor, has produced HD-like pathologic changes in experimental animals). Neurochemically there is a marked decrease of g-aminobutyric acid (GABA) and its synthetic enzyme glutamic acid decarboxylase throughout the basal ganglia. The levels of other neurotransmitters, including substance P and enkephalins, are also reduced. Magnetic resonance spectroscopy (MRS) in living subjects with HD has shown elevated levels of lactate in the basal ganglia.

The HD gene, called *IT15*, is located on chromosome 4p, contains a CAG trinucleotide repeat expansion, and codes for a protein called *huntingtin*. The protein is found in neurons throughout the brain; its normal function is unknown. Inactivation of the homologous gene in mice causes embryonic death in homozygotes, but heterozygotes are phenotypically normal. Transgenic mice with an expanded CAG repeat in the HD gene develop a progressive movement disorder. The CAG repeat codes for a long polyglutamine domain in the expressed protein. The disease process may result from a toxic gain of function (Chap. 359). One hypothesis is that these polyglutamine tracts cause abnormal protein-binding reactions, which then interfere with other cell processes such as mitochondrial activity. The HD mutation may lead to abnormal cleavage of the huntingtin protein, passage of protein fragments from cytoplasm to nucleus, and interference of nuclear mechanisms leading to apoptosis and neuronal death.

The DNA repeat expansion forms the basis of a diagnostic blood test for the disease gene. Persons having 38 or more CAG repeats in the HD gene have inherited the disease mutation and will eventually develop symptoms if they live to an advanced age. Each of their children has a 50% risk of also inheriting the abnormal gene. There is a rough correlation between a larger number of repeats and an earlier age of onset, but most patients fall into a range of intermediate repeat numbers (40 to 49 repeats) in which this correlation is not clinically useful. For unclear reasons, juvenile onset with a large repeat expansion most often occurs when the father is the affected parent (a form of genetic anticipation). There is a CAG repeat range (about 26 to 37) in the HD gene that is rarely associated with clinical symptoms, but it is unstable and may expand to a symptomatic range when passed to a child. Asymptomatic adult children at risk for HD should receive careful genetic counseling prior to DNA testing, because a positive result may have serious emotional and social consequences. Detailed testing and counseling protocols have been published. In addition to use in genetic counseling of persons at risk for HD, the DNA test can also be used in differential diagnosis. For example, some persons with late-onset, apparently sporadic "senile" chorea have been found to carry the HD mutation. Also, disorders that may mimic HD, such as schizophrenia, benign familial chorea, inherited ataxias, neural acanthocytosis, and FAD, will not show the CAG expansion in the HD gene.

OTHER DEGENERATIVE DEMENTIAS

Several other primary neurologic disorders have been associated with dementia and are the result of various poorly understood degenerative neuronal processes. These conditions include progressive supranuclear palsy, cortical basal degeneration, primary

progressive aphasia, and the amyotrophic lateral sclerosis (ALS)/parkinsonian/dementia complex of Guam. These are progressive dementing illnesses of unknown cause whose names are descriptive of the typical clinical signs or the anatomic brain areas that are involved with nonspecific atrophy and neuronal degeneration.

Progressive supranuclear palsy (Chap. 363) is a degenerative disease that involves both the brainstem and neocortex with diffuseNFTs. Clinically, this disorder begins with vertical supranuclear gaze paresis and progresses slowly to include symmetric rigidity and dementia. Stiff, unstable posture with hyperextension of the neck and slow gait with frequent falls are common. Early in the disease, the patients have difficulty with downgaze and lose vertical opticokinetic nystagmus on downward movement of the target. Although the patients have very limited voluntary eye movements, their eyes still retain oculocephalic reflexes (doll's head maneuver). The dementia is considered to be of the subcortical type, with slowed thought processes, impaired verbal fluency, and difficulty with sequential actions and with shifting from one task to another. Seizures and sleep apnea may occur. There is only a limited response to L-dopa, and there is no other effective treatment. Death occurs within 5 to 10 years. At autopsy, the NFTs are found in multiple subcortical structures (including the subthalamus, globus pallidus, substantia nigra, locus coeruleus, periaqueductal gray matter, superior colliculi, and oculomotor nuclei) as well as in the neocortex. The NFTs have similar staining characteristics to those ofAD, but on electron microscopy they generally are seen to consist of straight tubules rather than the paired helical filaments found in AD.

Progressive supranuclear palsy is often confused with idiopathic *Parkinson's disease* (Chap. 363). Although elderly Parkinson's patients may have some difficulty with upgaze, they do not develop significant downgaze paresis or progressive supranuclear palsy, and neurologic findings in Parkinson's disease are more likely to be asymmetric. However, dementia does occur in approximately 20% of Parkinson's disease patients. The occurrence of dementia in Parkinson's disease is more likely with increasing age, increasing severity of extrapyramidal signs, and the presence of depression. These patients may also show cortical atrophy on brain imaging. Neuropathologically, there may be Alzheimer changes in the cortex (amyloid plaques andNFTs), neuronal Lewy body inclusions in both the substantia nigra and the cortex, or no specific microscopic changes other than gliosis and neuronal loss.

Cortical basal ganglionic degeneration is a slowly progressive dementing illness associated with severe gliosis and neuronal loss in both the neocortex and basal ganglia (substantia nigra and striatum). There is often a unilateral onset with rigidity, dystonia, and apraxia of one arm and hand ("alien hand" syndrome). Eventually the condition becomes bilateral and includes dysarthria, slow gait, action tremor, and dementia. The microscopic features include enlarged, achromatic neurons in the cortex, and there may also beNFTs and amyloid plaques. The condition is rarely familial; the cause is unknown; and there is no specific treatment.

Another entity is *primary progressive aphasia* (Chap. 25). Patients with this disorder have aphasia associated with asymmetric atrophy of the left hemisphere and occasionally go on to develop dementia. Neuroimaging studies show the left hemisphere atrophy. Some patients are nonfluent, with hesitant, telegraphic speech associated with impaired comprehension and naming. Neuropathologic studies have

shown a heterogeneous group of abnormalities, including Pick's disease,AD,CJD, and nonspecific gliosis.

The ALS/parkinsonian/dementia complex of Guam is a rare degenerative disease that occurs in the Chamorro natives on the island of Guam. Individual patients may have any combination of parkinsonian features, dementia, and motor neuron disease. The most characteristic pathologic features are the presence of NFTs in degenerating neurons of the cortex and substantia nigra and loss of motor neurons in the spinal cord. Epidemiologic evidence supports a probable environmental cause, such as exposure to a neurotoxin with a long latency period. One interesting but unproven candidate neurotoxin occurs in the seed of the false palm tree (cycad), which Guamanians traditionally used to make flour. The possibility of a contributing genetic factor has not been excluded. The ALS syndrome is decreasing in frequency on Guam, but a dementing illness with rigidity continues to be seen.

Finally, rare forms of degenerative dementia continue to be reported, such as dementia lacking specific histologic features and an early-onset hereditary dementia caused by mutations in neuroserpin, a type of serine protease inhibitor.

(Bibliography omitted in Palm version)

PARKINSON'S DISEASE

Parkinsonism is a syndrome consisting of a variable combination of tremor, rigidity, bradykinesia, and a characteristic disturbance of gait and posture. Parkinson's disease is a chronic, progressive disorder in which idiopathic parkinsonism occurs without evidence of more widespread neurologic involvement.

Parkinson's disease generally commences in middle or late life and leads to progressive disability with time. The disease occurs in all ethnic groups, has an equal sex distribution, and is common, with a prevalence of 1 to 2 per 1000 of the general population and 2 per 100 among people older than 65 years. Signs of parkinsonism are extremely common in the elderly; one survey indicated that 15% of individuals between 65 and 74 years of age, and more than half of all individuals after age 85, have abnormalities on examination consistent with the presence of an extrapyramidal disorder.

Neuroanatomy Symptoms of Parkinson's disease are caused by loss of nerve cells in the pigmented substantia nigra pars compacta and the locus coeruleus in the midbrain. Cell loss also occurs in the globus pallidus and putamen. Eosinophilic intraneural inclusion granules (Lewy bodies) are present in the basal ganglia, brainstem, spinal cord, and sympathetic ganglia.

Pars compacta neurons of the substantia nigra provide dopaminergic input to the striatum, which is part of the basal ganglia (Fig. 22-4*A*). In Parkinson's disease, loss of pars compacta neurons leads to striatal dopamine depletion and ultimately to reduced thalamic excitation of the motor cortex (Fig. 22-4*B*). Other neurotransmitters, such as norepinephrine, are also depleted, with clinical consequences that are uncertain but perhaps contribute to depression, dysautonomia, and "freezing" episodes of marked akinesia.*The neural pathways that modulate motor activity are considered in detail in Chap. 22*.

Pathogenesis Parkinsonism can be induced in primates by exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is converted by monoamine oxidase B to *N*-methyl-4-phenylpyridinium (MPP+), an active toxin. MPP+ is taken up by dopaminergic nigral neurons through an active transport system that is normally involved in dopamine reuptake, and then inhibits oxidative phosphorylation, possibly at the level of complex I in the respiratory chain. This results in the death of nigrostriatal neurons, dopamine depletion in the basal ganglia, and parkinsonism. In addition to energy failure, MPP+ may also generate free radicals and oxidative stress.

The cause of Parkinson's disease is unknown. One suggested cause is exposure to an unrecognized environmental toxin, perhaps structurally similar toMPTP. Such exposure may have occurred years before the onset of any clinical disturbance, because symptoms will not develop until the cumulative cell loss from toxin exposure and natural aging approximates 80% of the original cell population. Alternatively or additionally, endogenous toxins may be responsible. In particular, the normal neurotransmitter

dopamine readily oxidizes to produce free radicals, which can cause cell death. Although the precise role of dopamine itself remains unclear, the evidence relating Parkinson's disease to damage by free radicals is compelling.

Oxidative stress is likely when dopamine turnover is increased, glutathione is reduced (leaving neurons more vulnerable to oxidant stress), and reactive iron is increased (promoting the generation of potentially toxic hydroxyl radicals). A mitochondrial complex 1 defect occurs in Parkinson's disease and may contribute to neuronal vulnerability and loss through free radical generation.

Accumulating evidence suggests a genetic susceptibility to the disease. An increased incidence of parkinsonism has been noted in the monozygotic twins of patients developing Parkinson's disease prior to the age of 50. First-degree relatives of patients are twice as likely to develop the disease as controls. Approximately 5% of parkinsonian patients have a familial form of the disorder. Three genes for the parkinsonian phenotype have recently been identified. Two different mutations of thea synuclein gene (in the q21-23 region of chromosome 4) have been identified in dominantly inherited parkinsonism; thea synuclein protein is of uncertain function but is abundant in neurons, especially at synaptic terminals, and in Lewy bodies. Homozygous deletions of the parkin gene (6q25.2-q27) have been associated with autosomal recessive parkinsonism; parkin is a protein expressed in the substantia nigra. Finally, a heterozygous missense mutation of the gene for ubiquitin carboxy-terminal hydrolase L1 has been identified in a parkinsonian family. The mechanism by which these mutations leads to parkinsonism remains to be determined, but the phenotype clearly has genetic heterogeneity.

Clinical Manifestations ([Video 361-1](#)) The 4- to 6-Hz *tremor* is typically most conspicuous at rest and worsens with emotional stress. It often begins with rhythmic flexion-extension of the fingers, hand, or foot, or with rhythmic pronation-supination of the forearm, and may be confined initially to one limb or to the two limbs on one side before becoming more generalized. It may also involve the mouth and chin. In 10 to 15% of patients, however, the tremor is faster (7 to 8 Hz) and postural, resembling essential tremor (see below) both clinically and in its response to pharmacotherapy.

Rigidity, defined as an increase in resistance to passive movement ([Chap. 22](#)), is a common clinical feature that accounts for the flexed posture of many patients. The most disabling feature, however, is *bradykinesia* (or, in its most severe form, akinesia), a slowness of voluntary movement and an associated reduction in automatic movements, such as swinging of the arms when walking. There is a fixity of facial expression, with widened palpebral fissures and infrequent blinking. There may be blepharoclonus (fluttering of the closed eyelids), blepharospasm (involuntary closure of the eyelids), and drooling of saliva from the mouth. The voice is hypophonic and poorly modulated. Power is preserved, but fine or rapidly alternating movements are impaired. The combination of tremor, rigidity, and bradykinesia results in small, tremulous, and often illegible handwriting. Patients have difficulty in rising from bed or an easy chair and tend to assume a flexed posture when erect. Walking is often difficult to initiate, and patients may have to lean forward increasingly until they can advance. They walk with small, shuffling steps, have no arm swing, are unsteady (especially on turning), and may have difficulty in stopping. Some patients walk with a *festinating gait*, i.e., at an increasing

speed to prevent themselves from falling because of their abnormal center of gravity.

The tendon reflexes are unaltered, and the plantar responses are flexor. Repetitive tapping (at about 2 Hz) over the glabella produces a sustained blink response (Myerson's sign), in contrast to the response of normal subjects. A depressed mood is common, and an impairment of cognitive function -- sometimes amounting to a frank dementia -- is frequently evident in advanced cases.

Differential Diagnosis Parkinsonism is simulated by certain disorders. *Depression* is associated with changes in the voice and facial appearance and a poverty of spontaneous activity, such as occur in Parkinson's disease. A trial of treatment with antidepressant drugs helps to clarify the diagnosis if uncertainty persists and other signs of parkinsonism are absent. *Essential (benign, familial) tremor* may be mistaken for parkinsonian tremor, but a family history of tremor is common; alcohol in small quantities may ameliorate the tremor, and other neurologic signs are lacking. Moreover, essential tremor commonly involves the head (with a nodding or no-no tremor), whereas parkinsonism spares the head but affects the face and lips. *Normal-pressure hydrocephalus* (Chap. 362) causes an apraxic gait disturbance (sometimes resembling the gait of parkinsonism), urinary incontinence, and dementia. Imaging studies reveal dilation of the ventricular system without cortical atrophy, and surgical shunting procedures to bypass any obstruction to the flow of cerebrospinal fluid (CSF) may be helpful.

Parkinsonism may occur as part of various neurologic diseases that are important to distinguish from Parkinson's disease for prognostic and therapeutic purposes. In *Wilson's disease* (Chap. 348), other abnormal movements are also usually present. The family history, early age of onset, associated Kayser-Fleischer rings, and low serum copper and ceruloplasmin levels distinguish it from Parkinson's disease. *Huntington's disease* (Chap. 362) sometimes presents with rigidity and akinesia, but the family history and any accompanying dementia point to the correct diagnosis, which can be confirmed by genetic studies. The *Shy-Drager syndrome* (Chap. 366) is a degenerative disorder characterized by parkinsonism, impaired autonomic function (resulting in postural hypotension, abnormal thermoregulatory sweating, disturbances of bladder and bowel control, impotence, and gastroparesis) and by signs of more widespread neurologic involvement (pyramidal, cerebellar, or lower motor neuron signs). There is generally no treatment except for the postural hypotension, which may respond to the measures discussed in Chap. 366. The response to antiparkinsonian agents is usually disappointing. *Striatonigral degeneration* (see below) leads to bradykinesia and rigidity, but tremor is usually inconspicuous. Cerebellar deficits sometimes occur (multisystem atrophy), and there may be autonomic insufficiency (Shy-Drager syndrome). Antiparkinsonian drugs are generally ineffective. *Progressive supranuclear palsy* (discussed separately, below) causes bradykinesia and rigidity, but conspicuous abnormalities of voluntary eye movements (especially vertical gaze), dementia, pseudobulbar palsy, and axial dystonia distinguish it from Parkinson's disease. There is little or no response to antiparkinsonian drugs. *Cortical-basal ganglionic degeneration* may be mistaken for Parkinson's disease, but intellectual decline, aphasia, apraxia, sensory neglect, and other evidence of cortical dysfunction should suggest the correct diagnosis. In *diffuse Lewy body disease*, parkinsonism is joined with a conspicuous dementia and with evidence of more widespread neurologic involvement. In

Creutzfeldt-Jakob disease, any parkinsonian features are overshadowed by the rapidly progressive dementia; myoclonus is common, ataxia or pyramidal signs may occur, visual disturbances are sometimes conspicuous, and the electroencephalographic findings are often characteristic. Similarly, in *Alzheimer's disease* there may be minor extrapyramidal deficits, but these are generally inconsequential compared with the marked cognitive impairment that characterizes the disorder. *Alzheimer's disease and diffuse Lewy body disease are considered in Chap. 362, and Creutzfeldt-Jakob disease is discussed in Chap. 375.*

Parkinsonism sometimes occurs as a consequence of a systemic disorder. Drug-induced *secondary parkinsonism* is especially common (discussed below).MPTP-induced parkinsonism has occurred in several humans who inadvertently took this meperidine analogue for recreational purposes. The mechanisms involved are discussed above, and the history of exposure, unusually early age of onset, and rapid progression should suggest the correct diagnosis. Exposure to various toxins, such as manganese dust or carbon disulfide, also causes parkinsonism, and the diagnosis is suggested by an accurate occupational history. Parkinsonism sometimes occurs as a result of severe carbon monoxide poisoning or develops after an encephalitic illness. Postencephalitic parkinsonism was especially common after the outbreak of encephalitis lethargica that occurred in an early part of the twentieth century.

TREATMENT

Approaches to treatment are summarized in Fig. 363-1.

Symptomatic Pharmacologic Treatment Nonselective muscarinic antagonists (*anticholinergic drugs*) are sometimes helpful, especially in relieving tremor. Various preparations are available, including trihexyphenidyl, benztropine, procyclidine, and orphenadrine. The usual maintenance doses are shown in Table 363-1. Common side effects include dryness of the mouth, constipation, urinary retention, and blurred vision. Narrow-angle glaucoma may be aggravated. Confusion and hallucinations are especially troublesome in the elderly. Treatment is started with the preparation of choice in a small initial dose that is gradually increased, depending on response and tolerance. If the drug is unhelpful, another anticholinergic preparation is substituted.

Amantadine, either alone or combined with an anticholinergic agent, is sometimes helpful for mild parkinsonism; it acts by potentiating the release of endogenous dopamine. It may improve all major clinical features of the disorder, has relatively uncommon side effects (restlessness, confusion, skin rashes, edema, disturbances of cardiac rhythm), and is given in a standard dose (100 mg twice daily). However, many patients derive only transient, if any, benefit from it.

Levodopa, the metabolic precursor of dopamine (Fig. 363-2), provides symptomatic benefit in most patients with parkinsonism and is often particularly helpful in relieving bradykinesia. The presence in the intestinal mucosa of dopa decarboxylase, which converts levodopa to dopamine, means that most of an ingested dose of levodopa is lost before it even enters the general circulation. Administration of levodopa in combination with an extracerebral dopa-decarboxylase inhibitor reduces the extracerebral metabolism of levodopa and also reduces the incidence of peripheral side

effects. Levodopa is therefore administered routinely in combination with a peripheral dopa-decarboxylase inhibitor (carbidopa in the United States; benserazide in Europe). In the United States, the combination of carbidopa and levodopa (in 1:10 and 1:4 ratios) is available commercially as Sinemet. Standard formulations are Sinemet 25/100, 10/100, and 25/250 mg. A common starting dose is 25/100 mg three times daily, which is increased gradually to 25/250 mg three or four times daily, taken 1 h before or 2 h after meals to maximize absorption and transport across the blood-brain barrier.

There was initially concern that the early introduction of levodopa might accelerate the death of nigrostriatal neurons because of a hypothetical increase in dopamine-mediated neurotoxity. It is now clear that levodopa should be introduced as soon as is warranted by the patient's clinical state, rather than postponed out of concern for this theoretical possibility. However, initial treatment with a dopamine agonist may provide similar benefit to levodopa and thus allow introduction of the latter to be postponed; in consequence, emergence of late side effects may be delayed. The most common initial side effects of levodopa are nausea, vomiting, postural hypotension, and, occasionally, cardiac arrhythmias. Abnormal movements (dyskinesias), restlessness (akathisia), and confusion tend to occur somewhat later and are dose-related. Dyskinesias may be present during most of the day, occur only when plasma levodopa levels peak, or develop when the plasma levodopa concentration reaches a certain submaximal level. Management depends on distinguishing these possibilities by the temporal profile of the dyskinesia. When dyskinesias occur only at a certain submaximal blood level of levodopa, adjustment of the daily dose to produce higher or lower blood levels may alleviate them; dyskinesias related to peak blood levels of levodopa are helped by a reduction in dose.

Important late complications of levodopa therapy are the wearing-off effect (transient deterioration shortly before the next dose is due) and the "on-off" phenomenon -- abrupt but transient fluctuations in clinical state that occur frequently during the day, without warning or an obvious relationship to dosing schedule, resulting in alternating periods of marked akinesia or greater mobility accompanied by iatrogenic dyskinesias. Response fluctuations can be controlled in part by reducing dosing intervals, administering levodopa 1 h before meals and restricting dietary protein intake (to reduce any competition by various amino acids with levodopa for the active carrier system that transports it into the blood and from the blood into the brain), or treatment with dopamine agonists. The addition of selegiline (5 mg at breakfast and lunch), a monoamine oxidase B inhibitor, reduces the metabolic breakdown of dopamine and may also be helpful (see "Neuroprotective Treatment," below).

Response fluctuations to oral levodopa may also be reduced or eliminated by catechol-*O*-methyltransferase (COMT) inhibitor agents or by frequent or continuous administration of levodopa intravenously, intraduodenally, or by intragastric infusion. A commercially available controlled-release formulation of Sinemet (Sinemet CR 25/100 or 50/200 mg) sometimes helps in reducing the dosing frequency and maintaining steady blood levels of levodopa, but it is of only limited benefit in reducing response fluctuations. Surgical treatment is also effective (see later). The pathogenesis of the on-off phenomenon is obscure, but proposed mechanisms relate to the pharmacokinetics of levodopa, degeneration of presynaptic dopaminergic nerve terminals, altered sensitivity of dopamine receptors, and abnormalities of

nondopaminergic neurotransmitter systems.

Dopamine agonist drugs may produce symptomatic benefit by direct stimulation of dopamine receptors (Fig. 363-2). There are five major dopamine-receptor subtypes classified into two groups. The D_1 group is made of the D_1 and D_5 subtypes, and the D_2 group consists of D_2, D_3, and D_4 subtypes. Drug efficacy and toxicity may relate to receptor specificity of dopamine agonists. The absorption and cerebral distribution of dopamine agonist drugs are less erratic than with levodopa, and they do not require enzymatic conversion to an active metabolite. Their early introduction either prior to Sinemet or in conjunction with low-dose Sinemet therapy (25/100 mg three times daily) yields sustained benefit and a lower incidence of late complications (such as response fluctuations and dyskinesias) than when levodopa is used alone and in a higher dose.

The agonists initially available were bromocriptine and pergolide, which are ergot derivatives. Bromocriptine, which stimulates dopamine D_2 receptors (Fig. 22-4), is introduced in a dose of 1.25 mg/d for 1 week and 2.5 mg/d for the next week, after which the daily dose is increased by 2.5-mg increments every 2 weeks, depending on response and tolerance. Maintenance doses range between 2.5 and 10 mg three times daily when the drug is taken with Sinemet. Pergolide activates both D_1 and D_2 dopamine receptors. It is introduced in a dose of 0.05 mg daily for 2 days; the dose is then increased by 0.1 to 0.15 mg/d every 3 days for 12 days and by 0.25 mg/d every 3 days thereafter. The usual maintenance dose is 1 mg three times daily. Side effects are similar to those of levodopa, but psychiatric effects such as delusions or hallucinations are more common, and dyskinesias are less common, than with levodopa. Other adverse effects include headache, nasal congestion, erythromelalgia, pleural and retroperitoneal fibrosis, pulmonary infiltrates, and vasospam. These agonists are contraindicated in patients with psychotic disorders and are best avoided in those with recent myocardial infarction, severe peripheral vascular disease, or active peptic ulceration.

Pramipexole and ropinirole are new dopamine agonists. Their selective nature suggested that they might be more effective and have fewer side effects that the first-generation agonists, but this remains uncertain from the few studies comparing them to bromocriptine or pergolide. Because of their non-ergoline structure, adverse effects such as erythromelalgia, vasospasm, and pleural or retroperitoneal fibrosis are unlikely. Both agents, however, may cause postural hypotension, lassitude, sleep disturbances, peripheral edema, constipation, nausea, dyskinesias, and confusion. Excessive or uncontrollable somnolence may require withdrawal of the medication.

Pramipexole, an aminobenzthiazol-derived selective D_3 agonist, provides worthwhile benefit when used alone for mild parkinsonism or when taken together with Sinemet for advanced disease. It permits a reduction in Sinemet dosage and smooths response fluctuations. It may also benefit associated affective symptoms. Pramipexole is absorbed rapidly from the gastrointestinal tract, reaches peak plasma concentrations in about 2 h, and is excreted by the kidneys; renal failure may therefore necessitate reduction in daily dose. The starting dose is 0.125 mg three times daily, with doubling of the dose after 1 week, and again after another week. The daily dose is then increased by 0.75 mg at weekly intervals depending on need and tolerance. The usual maintenance dose is 0.5 to 1.5 mg three times daily. Ropinirole, a selective D_2 agonist, is

also effective for mild or advanced disease. It is started at 0.25 mg three times daily; total daily dose is increased by 0.75 mg at weekly intervals until the fourth week and then by 1.5 mg as needed. The usual maintenance dose is between 2 and 8 mg three times daily. It is metabolized by CYP1A2, and its clearance may be reduced by drugs undergoing hepatic metabolism.

Various new dopamine agonists are being evaluated, and new means of administering them (e.g., by subcutaneous infusion pump or transdermally) may lead to a steadier clinical response.

Selective COMT inhibitors such as tolcapone and entacapone enhance the benefits of levodopa therapy by reducing the conversion of levodopa to 3-*O*-methyldopa (which competes with levodopa for an active carrier mechanism) and by increasing the availability in the brain of levodopa. They are helpful in patients with response fluctuations to Sinemet, leading to a smoother response, greater "on" time, and reduction in daily levodopa requirement. Both agents are absorbed rapidly, bound to plasma proteins, and metabolized before being excreted. Both have peripheral effects, but tolcapone is also active centrally. Tolcapone is slightly more potent, has a longer duration of action, and is usually taken in a dose of 100 mg (rarely, 200 mg) three times daily, whereas entacapone (200 mg) is taken with each dose of Sinemet and may thus be taken four to six times daily. When COMT inhibitors are introduced, the daily dose of Sinemet may have to be reduced by up to 30% in the first 48 h to prevent or minimize such complications as dyskinesias, nausea, and confusion. Other adverse effects include diarrhea, abdominal pain, postural hypotension, sleep disturbances, and discolored urine. Acute hepatic failure has occurred in rare patients receiving tolcapone, and a transient increase in liver enzymes is not uncommon. Accordingly, when tolcapone is prescribed, a consent form should be signed by the patient and liver function monitored every 2 weeks for the first year and less frequently thereafter, as recommended by the manufacturer.

Experimental studies suggest that glutamate antagonists may benefit patients with Parkinson's disease, and clinical studies of such agents are planned. G_{M1}ganglioside and various neurotrophic factors influence dopaminergic nigrostriatal cells, and work is continuing to develop delivery systems that will permit their use in the treatment of Parkinson's disease.

Surgical Treatment Destructive neurosurgical procedures were used for some years to treat parkinsonism, but their use declined with the advent of levodopa. Unilateral posteroventral pallidotomy or thalamotomy was resurrected in the 1990s as a therapeutic approach for relieving rigidity, bradykinesia, and tremor in patients with advanced disease in whom antiparkinsonian medication was ineffective or poorly tolerated. A positive (but incomplete) response to surgery is reported in>90% of patients; the beneficial effect predominates on the side contralateral to the procedure. Complications include cerebral infarction or hemorrhage, dysarthria or hypophonia, cognitive disturbances, and -- after pallidotomy -- visual field defects. Bilateral procedures have a higher morbidity and are generally discouraged. Such surgery is being replaced in some centers by high-frequency stimulation of selected locations in the brain, using an implanted electrode and stimulator, to induce a functional but reversible lesion. Thalamic stimulation is very effective in relieving tremor, and

preliminary studies suggest that stimulation of the globus pallidus internus or subthalamic nucleus increases "on" time and improves clinical status in those with advanced parkinsonism and response fluctuations. Brain stimulation surgery has a lower morbidity than ablative surgery, but neither approach is warranted in patients with secondary or atypical parkinsonism or dementia.

There is ongoing interest in transplantation of fetal midbrain dopaminergic (nigral) cells into the putamen of patients with Parkinson's disease. Survival of engrafted cells has been documented by enhancement of fluorodopa uptake as visualized by positron emission tomography (PET), and in one autopsy study there was extensive striatal reinnervation by the transplanted cells. Fetal nigral transplantation remains an experimental procedure, and the nature of any long-term benefit is uncertain. Transplantation of autologous adrenal medullary tissue has also been attempted for Parkinson's disease, with mixed results; benefit seems most likely to occur in individuals younger than 50 years of age.

Neuroprotective Treatment Selective inhibitors of monoamine oxidase B such as selegiline (Eldepryl; Deprenyl) may reduce oxidative damage and thus slow disease progression, but the evidence for this effect is incomplete. In a large multicenter study, treatment with selegiline delayed the need for symptomatic therapy in patients with untreated parkinsonism, suggesting that progression of the disease had been retarded, but it was subsequently found that selegiline itself has a mild effect on symptoms. Thus, the basis of the observed effect is uncertain. The use of selegiline for protective purposes should probably be discussed with all patients unless they have end-stage disease or are very elderly, but the uncertainty of any benefit should be indicated. Selegiline in a standard dose (5 mg with breakfast and 5 mg with lunch) is not associated with the hypertensive ("cheese") effect of nonselective monoamine oxidase inhibitors. Acute toxic interactions may, however, occur with meperidine, tricyclic drugs, or serotonin reuptake inhibitors, and selegiline should not be prescribed to patients receiving those medications. Selegiline is metabolized to amphetamine and methamphetamine, so some patients may experience anxiety or insomnia. Moreover, an increased mortality rate has recently been found among patients receiving selegiline, raising concerns about its long-term safety. Patients must understand that selegiline is not intended to relieve symptoms and that there is no means of determining whether it is affecting disease progression in individual cases. Other inhibitors of monamine oxidase B are currently being evaluated for their effect on the natural history of Parkinson's disease and may clarify the issue.

Tocopherol (vitamin E) is an important scavenger of free radicals, but in a large study it failed to provide any protective benefit when taken in a dose of 2000 units daily. The extent to which it penetrates the brain, however, is not clear.

General Measures Physical therapy and speech therapy may help patients with moderately severe parkinsonism. In advanced cases, the quality of life can be improved by certain aids to daily living, such as extra rails or banisters placed in the home, table cutlery with large handles, nonslip table mats, voice amplifiers, and chairs that can gently eject the occupant.

FAMILIAL OR BENIGN ESSENTIAL TREMOR ([VIDEO 361-2](#))

A postural tremor (Chap. 22) may develop in otherwise normal individuals, sometimes on a familial basis with autosomal dominant inheritance. The pathophysiologic basis of the disorder is unknown.

Symptoms can develop at any age but often do not appear until middle or later life. Typically one or both hands, the head, and the voice are affected in any combination; the legs are generally spared. Apart from the tremor, no other abnormalities are present on neurologic examination. The tremor may worsen with time and ultimately become an embarrassment, but it generally causes no disability except when it disturbs handwriting or performance of fine tasks with the hands. A small quantity of alcohol sometimes relieves the tremor for a short period.

TREATMENT

Treatment is often unnecessary and is best delayed for as long as possible because, once initiated, it generally needs to be continued indefinitely. Propranolol, 40 to 120 mg orally twice daily, may reduce the amplitude of the tremor. A single oral dose (40 to 120 mg) may be taken in anticipation of known precipitating circumstances. Primidone is also effective but has to be introduced gradually. Other agents that may be helpful include alprazolam and mirtazapine. Thalamic stimulation (discussed earlier) may be helpful for severe tremor unresponsive to medical treatment.

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (also referred to as *Steele-Richardson-Olszewski syndrome*) is a sporadic degenerative disorder characterized pathologically by neuronal loss, gliosis, and neurofibrillary tangles in the midbrain, pons, basal ganglia, and dentate nuclei of the cerebellum. The neurofibrillary tangles of this disorder are distinct from those of Alzheimer's disease in that they are composed of straight filaments rather than paired helical filaments. The microtubule-associated protein tau is a constituent of the tangles, and a genetic association between an intrinsic polymorphism of tau and progressive supranuclear palsy has recently been reported. Thus, progressive supranuclear palsy may represent a tau pathologic process. There are also decreased concentrations of dopamine and homovanillic acid in the caudate nucleus and putamen.

Clinical Manifestations This uncommon disorder generally begins between the ages of 45 and 75 years; it affects men twice as frequently as women. Supranuclear ophthalmoplegia is characteristic. There is conspicuous failure of voluntary saccadic gaze (and of the fast phase of optokinetic nystagmus) in a vertical plane, especially downward, with later involvement of horizontal gaze. Eventually, smooth pursuit movements are also affected. Oculocephalic (e.g., doll's-head) and oculovestibular (caloric) reflexes are intact. Axial dystonia in extension, especially of the neck, is common and is frequently accompanied by limb rigidity and bradykinesia that may mimic Parkinson's disease. Tremor, however, is unusual. The combination of supranuclear ophthalmoplegia and axial rigidity accounts for the common presenting complaint of frequent falls. There may be facial weakness, dysarthria, dysphagia, and exaggerated jaw jerk and gag reflexes (pseudobulbar palsy) as well as exaggerated and inappropriate emotional responses (pseudobulbar affect). Brisk tendon reflexes,

extensor plantar responses, and cerebellar signs are sometimes encountered. A global impairment of intellectual function is frequent, but focal cortical dysfunction is rare.

Progressive supranuclear palsy should be considered whenever a middle-aged or elderly person with repeated falls has an extrapyramidal syndrome accompanied by nuchal dystonia and paralysis of voluntary downgaze. The marked impairment of voluntary downward and horizontal gaze distinguishes this disorder from Parkinson's disease, as does the extended rather than flexed dystonic posturing of the axial musculature, the absence of tremor, and the poor response to antiparkinsonian medications.

TREATMENT

The course is generally progressive, with aspiration or inanition leading to a fatal outcome within 10 years. Dopaminergic preparations sometimes reduce rigidity and bradykinesia, and anticholinergic (trihexyphenidyl, 6 to 15 mg/d) or tricyclic drugs (amitriptyline, 50 to 75 mg at bedtime) may benefit speech, gait, and pseudobulbar affect, but any benefit is limited and not sustained.

CORTICAL-BASAL GANGLIONIC DEGENERATION

This rare sporadic disorder typically begins in middle or later life with functional impairment of one or more limbs. Examination reveals signs of parkinsonism, but the extrapyramidal abnormalities are generally insufficient to account for the clinical deficit, which results from apraxia. As the disorder progresses, other evidence of cortical dysfunction also appears, such as aphasia, agnosia, sensory inattention, and mild dementia. Pathologically there is cell loss and gliosis in the cerebral cortex as well as the substantia nigra. The response to antiparkinsonian medication is disappointing, and the course is generally progressive, with increasing disability and dependence leading ultimately to death.

STRIATONIGRAL DEGENERATION

In a few patients with seemingly classic Parkinson's disease, there is little or no response to dopaminergic medication, and pathologic study at autopsy reveals neuronal loss and gliosis in the putamen, globus pallidus, caudate and subthalamic nuclei, and substantia nigra. This disorder has therefore been called *striatonigral degeneration*. It has an age and gender distribution similar to those of Parkinson's disease. Clinical examination reveals the findings of parkinsonism, but tremor is usually relatively inconspicuous. Cognitive function is preserved.

There may be an accompanying impairment of autonomic function (Shy-Drager syndrome;Chap. 366), and examination in such cases often reveals that a combination of pyramidal and cerebellar signs is also present. Indeed, in some cases the cerebellar findings are so conspicuous that the disorder is more properly called *spinocerebellar ataxia type 1* (olivopontocerebellar atrophy; Chap. 364).

The management of patients with striatonigral degeneration is difficult. Antiparkinsonian medications generally are prescribed but are usually ineffective.

MACHADO-JOSEPH DISEASE (SPINOCEREBELLAR ATAXIA TYPE 3)

Machado-Joseph disease is an autosomal dominant form of striatonigral degeneration that generally begins in the third or fourth decade. Most affected individuals are of Portuguese ancestry. There may be only mild parkinsonian signs, whereas spasticity, hyperreflexia, extensor plantar responses, cerebellar findings, external ophthalmoplegia and, sometimes, peripheral neuropathy are conspicuous. Cognitive function is preserved. Pathologically the findings are similar to those of striatonigral degeneration, but the dentate nucleus of the cerebellum is also involved. There is no specific treatment.*The different clinical subtypes of the disease, their genetic basis, and related autosomal dominant ataxias with some extrapyramidal features are discussed in Chap. 364.*

IDIOPATHIC TORSION DYSTONIA

The occurrence of dystonic movements and postures without other neurologic signs in patients with a normal birth and developmental history is designated *idiopathic torsion dystonia*. The pathophysiologic and biochemical basis of this entity is unknown. Pathologic examination reveals no specific abnormalities, but the disorder is attributed to basal ganglia dysfunction partly because of observations made in cases of secondary dystonia. Other possible causes of dystonia (Chap. 22) should be excluded before this diagnosis is made. The disorder may occur on a sporadic or hereditary basis. In cases with onset in childhood or adolescence, inheritance is commonly autosomal dominant, with the gene, designated DYT1, localized to 9q32-34 and involving a GAG deletion. The gene codes for the protein Torsin A, the function of which is unclear. Onset is typically in a limb (commonly the leg), with subsequent spread to the other limbs and trunk, but sparing of the cranial muscles. Other autosomal dominant forms present in children or adults and begin in limb, axial, or cranial muscles; cranial involvement (facial, laryngeal, cervical) is common. This gene (DYT6) has been mapped to chromosome 8 in certain families. In a few families with autosomal dominant, adult-onset cranial, cervical, or upper limb dystonia, the responsible gene (DYT7) has been mapped to chromosome 18p. In other families, other unmapped genetic loci appear to be involved. Autosomal recessive and X-linked recessive (Xq21.3) forms are also described. Onset in childhood is associated with a positive family history, symptoms that begin in the legs, and greater disability than with later onset. About one-third of patients eventually become chair- or bedbound.*A summary of the genetic loci responsible for the various dystonic disorders is provided in Table 359-1.*

Examination reveals the abnormal movements and sustained postures that characterize the disorder. There may be involvement of the neck, trunk, limbs, and face (blepharospasm or oromandibular dystonia). A description of these various motor abnormalities is provided in Chap. 22. Initially they may be brought out by voluntary activity, but eventually they are present constantly, leading to deformity and disability.

Occasional patients have *dopa-responsive dystonia*, which is inherited in an autosomal dominant manner with incomplete penetrance. The responsible gene (DYT5) maps to chromosome 14q. Onset is usually in childhood, and examination typically reveals associated bradykinesia and rigidity. The response to low-dose levodopa therapy is

dramatic.

TREATMENT

Treatment is symptomatic and is often unsatisfactory. Anticholinergic drugs in high doses (e.g., trihexyphenidyl, 30 to 50 mg/d) are probably the most effective means of providing some relief of the abnormal movements and postures. They are introduced in a low dose and built up gradually, depending on response and tolerance. Phenothiazines or haloperidol are sometimes helpful but usually cause mild parkinsonism. Diazepam, baclofen, and carbamazepine are helpful occasionally. Stereotactic thalamotomy may be beneficial when dystonia is predominantly unilateral and involves the limbs.

FOCAL TORSION DYSTONIA

Dystonia may occur as an isolated phenomenon affecting a discrete part of the body, rather than having the more generalized distribution described above. Such focal or segmental dystonias probably represent variants of idiopathic torsion dystonia; its genetic basis was discussed earlier. Both *blepharospasm* (spontaneous, involuntary forced closure of the eyelids) and *oromandibular dystonia* can occur as isolated focal dystonias. Oromandibular dystonia consists of involuntary contractions of the masticatory, lingual, and perioral muscles, leading to opening or closure of the mouth; pouting, pursing, or retraction of the lips; and roving or protruding movements of the tongue. The combination of blepharospasm and oromandibular dystonia is called *Meige syndrome*.

Spasmodic torticollis is characterized by a tendency for the head to turn to one side. The designation *anterocollis* indicates that the head is flexed forward, and *retrocollis* that it is pulled backward. These cervical dystonias are often intermittent initially, but eventually the head is held continuously in the abnormal position. Spontaneous remission occurs occasionally, especially in the first few months after onset, but thereafter the disorder is likely to be permanent and may worsen with time.

TREATMENT

Pharmacotherapy is usually unrewarding, but the drugs used in treating idiopathic torsion dystonia are helpful in some patients. Local injection of botulinum toxin into the overactive muscles often produces a benefit lasting several weeks or months by producing a temporary presynaptic block of neuromuscular transmission, and injections can be repeated as needed. This is the most effective treatment available for most focal dystonias. Selective section of the spinal accessory nerve (cranial nerve XI) and the upper cervical nerve roots is sometimes helpful for patients with cervical dystonia unresponsive to other measures.

TASK-SPECIFIC FOCAL DYSTONIA

Writer's cramp is a task-specific dystonia in which abnormal posturing of the hand and forearm occurs when the hand is used for writing. As the disorder worsens, abnormal posturing may also occur with other tasks, such as applying cosmetics, shaving, or

using table cutlery. Drug treatment is usually unrewarding, and it is often necessary for patients to learn to use the other hand for these tasks. Injections of botulinum toxin into the involved muscles are sometimes helpful, but function usually remains impaired. Other task-specific dystonias include violinist's cramp, barber's cramp, and telegrapher's cramp, in each of which dystonic posturing occurs when the hand is used for a skilled, occupationally related function. The pathophysiologic basis of these disorders is uncertain, but recent work relates it to abnormal processing of sensory input from the affected extremity during the activity.

DRUG-INDUCED MOVEMENT DISORDERS

Parkinsonism Parkinsonism is a frequent complication of treatment with dopamine-depleting agents such as reserpine or antipsychotic dopamine antagonists such as the phenothiazines or butyrophenones. The antipsychotic drugs most likely to cause parkinsonism are those that are potent D_2receptor antagonists having little anticholinergic effect, such as piperazine phenothiazines, haloperidol, and thiothixene. Women and the elderly have an increased risk of this complication. In comparison with Parkinson's disease, tremor is less common and bradykinesia is typically symmetric, but the two disorders are sometimes impossible to distinguish except by the history of drug ingestion. Signs usually develop within 3 months of starting the causal agent and may persist for several months (or longer) after its withdrawal. Drug-induced parkinsonism is best managed by discontinuing the antipsychotic drug when possible, substituting an antipsychotic with greater anticholinergic potency, or adding an anticholinergic drug such as trihexyphenidyl. Levodopa should not be prescribed -- it is of no help if the offending neuroleptic agent is continued, and it may worsen the underlying psychotic disorder.

Acute Dystonia or Dyskinesia Acute dystonia (such as blepharospasm or torticollis) or dyskinesia (such as chorea or facial grimacing) may complicate treatment with a dopamine receptor antagonist. It typically commences within 1 week of the introduction of such medication, usually in the first 48 h, and is more common in young patients. Its pathophysiologic basis is uncertain. Treatment with an anticholinergic drug (e.g., benztropine, 2 mg, or diphenhydramine, 50 mg intravenously) is usually helpful.

Tardive Akathisia *Akathisia* denotes a motor restlessness. Patients are unable to sit still and feel obliged to move about. It is commonly induced by chronic antipsychotic drug treatment, especially in women, and is treated like drug-induced parkinsonism.

Tardive Dyskinesia or Dystonia Tardive dyskinesia or dystonia is a common complication of long-term antipsychotic drug treatment (with dopamine receptor antagonists). The risk of its development increases with advancing age, but its pathogenesis is unclear. One suggestion is that it is related to drug-induced supersensitivity of striatal dopamine receptors. However, although supersensitivity is an inevitable accompaniment of chronic antipsychotic drug treatment, tardive dyskinesia does not always occur. Moreover, the time courses of the two phenomena are different. Supersensitivity occurs relatively early during treatment and reverses when medication is withdrawn, whereas tardive dyskinesia usually requires exposure for at least 6 months before it develops and may persist indefinitely. Another suggestion is that it involves an abnormality of g-aminobutyric acid (GABA)-ergic neurons. This is supported

by observations that GABA and glutamic acid decarboxylase (its synthesizing enzyme) are depleted in the basal ganglia by long-term administration of antipsychotic drugs to animals and that CSF levels of GABA are reduced in patients with tardive dyskinesia.

The clinical features of tardive dyskinesia include abnormal choreoathetoid movements, especially involving the face and mouth in adults and the limbs in children. Tardive dystonia may be focal, producing, for example, blepharospasm, torticollis, or oromandibular dystonia, or it may affect contiguous body parts (e.g., the face and neck or arm and trunk). Generalized dystonia is uncommon, especially in older patients. It may be impossible to distinguish these disturbances from those of Huntington's disease (Chap. 362), Sydenham's chorea (Chap. 235), or idiopathic torsion dystonia except by the history of drug exposure. The iatrogenic disorder often resolves spontaneously in children or young adults but frequently persists in middle-aged or older individuals.

TREATMENT

Treatment of the established disorder is often unsatisfactory. It is therefore important that antipsychotic drugs be prescribed only when necessary and that their long-term use be accompanied by periodic drug holidays to determine whether treatment is still required. Drug holidays may actually unmask incipient dyskinesias, which often worsen on withdrawal of the causal agent. In such circumstances, permanent withdrawal of the antipsychotic medication, if this is possible, may lead to remission of the dyskinesia. Treatment with antidopaminergic agents such as haloperidol or phenothiazines (which cause the disorder) often suppresses the dyskinesias at least for a period, but these agents are best avoided, because they may exacerbate the underlying problem. Treatment with dopamine-depleting agents, such as reserpine, 0.25 mg gradually increased to 2 to 4 mg/d, or tetrabenazine (in countries where it is available), 12.5 mg gradually increased to as much as 200 mg/d, is sometimes worthwhile in reducing the severity of the dyskinesia. Other pharmacologic approaches are unrewarding in most instances. Tardive dystonia may respond to tetrabenazine (if available) or to anticholinergic drugs used as for idiopathic torsion dystonia.

Tardive tic resembles Gilles de la Tourette's syndrome (see below) and is best treated with clonidine or clonazepam.

Neuroleptic Malignant Syndrome Rigidity, hyperthermia, altered mental status resembling catatonia, labile blood pressure, and autonomic dysfunction characterize this serious complication of treatment with antipsychotic (neuroleptic) agents, especially haloperidol. Associated clinical features include tachycardia, tachypnea, metabolic acidosis, and myoglobinuria that may be fatal. The cause is unknown, but antagonism of dopamine is a likely contributor. The prevalence of this syndrome among patients receiving neuroleptics is <2%, with the disorder occurring most commonly in young adults. Symptoms evolve over 1 to 2 days. The syndrome can develop at any time during exposure to the medication, but it usually occurs within the first 30 days of use.

The differential diagnosis includes infection, malignant hyperthermia, and alcohol- or drug-withdrawal states. Drug-induced parkinsonism may be similar but is not associated with fever or the autonomic features described above.

TREATMENT

Treatment includes immediate withdrawal of antipsychotic drugs and also of lithium and anticholinergic agents, which may increase the risk of developing the disorder. Symptomatic treatment is also necessary and includes antipyretics and artificial cooling, rehydration, and measures to maintain the blood pressure. Serum potassium should be monitored. Dantrolene, bromocriptine or another dopamine agonist, levodopa, amantadine, or benzodiazepines are sometimes helpful, but the mortality rate is on the order of 5 to 20%. Subcutaneous heparin administration reduces the risk of venous thrombosis. Most survivors recover completely, but potential complications include renal failure, pulmonary embolism, and a chronic cerebellar syndrome (related to the hyperthermia). Recovery generally occurs over 2 to 3 weeks.

Other Drug-Induced Movement Disorders Dyskinesia or dystonia may complicate therapy with levodopa or dopamine agonists as a dose-related phenomenon that is reversed by withdrawal of the medication or reduction of the dose. Reversible chorea may also complicate treatment with anticholinergic drugs, phenytoin, carbamazepine, amphetamines, lithium, and oral contraceptives; dystonia may follow treatment with lithium, carbamazepine, and metoclopramide; and postural tremor from theophylline, caffeine, lithium, thyroid hormone, tricyclic antidepressants, valproic acid, and isoproterenol.

GILLES DE LA TOURETTE'S SYNDROME

Gilles de la Tourette's syndrome, which has a prevalence in the United States of approximately 0.05%, consists of chronic multiple motor and phonic tics that have no known cause. The disorder is not related to social or ethnic background or to perinatal abnormalities. Symptoms typically begin between 5 and 15 years of age and follow a relapsing and remitting course. A family history is sometimes obtained, and partial expression of the trait may occur in siblings or offspring of patients. In most families with chronic tic disorders, there is an autosomal dominant mode of inheritance with variable penetrance that is gender related. Boys are affected much more commonly than girls.

The pathophysiology is obscure, and no structural pathology has been recognized. A dopaminergic excess has been suggested by the clinical observation that the tics may respond to treatment with dopamine-blocking drugs.

Clinical Manifestations The first signs consist of single or multiple motor tics in 80% of cases and of phonic tics in 20%. Motor tics commonly affect the face and may consist of repetitive sniffing, winking, blinking, elevation of the eyelids, eye closure, pursing of the lips, or facial twitching. Patients eventually develop several different motor and phonic tics, the latter frequently taking the form of grunts, barks, hisses, sighs, throat-clearing, coughing, and verbal utterances that may involve coprolalia (involuntary and inappropriate swearing or obscene speech), echolalia (involuntary repetition of the phrases of others), and palilalia (repetition of words or phrases). The tics may change in location, severity, complexity, and character with time; are worsened by emotional stress; and can be suppressed voluntarily for short periods. In some cases, tics are complex (such as jumping up in the air) or involve repetitive self-mutilating activities (such as nail-biting, hair-pulling, or lip-biting). Tics that involve repetitive sensory

phenomena, such as pressure, tickle, or thermal sensations, also occur. Many patients have associated behavioral abnormalities, especially obsessive-compulsive disorder and attention deficit hyperactivity disorder.

Apart from the presence of tics, physical examination typically reveals no other abnormalities, but the incidence of left-handedness or ambidexterity is greater than among normal persons, and many patients have nonspecific electroencephalographic abnormalities of no diagnostic significance.

The diagnosis is often delayed for years, the symptoms sometimes being attributed to psychiatric illness. Patients may be subjected to unnecessary and expensive treatment before the correct diagnosis is made. Depression, sometimes leading to suicide, may result from social embarrassment caused by the tics.

Differential Diagnosis Many children develop transient or chronic simple tics, and these have a benign prognosis and require no treatment. In some instances, simple or multiple tics persist for several years but resolve in late adolescence. Wilson's disease, a treatable cause of dyskinesias and tics, is generally associated with hepatic and renal involvement, Kayser-Fleischer corneal rings, low serum copper and ceruloplasmin levels, and increased 24-h urinary copper excretion (Chap. 348). The associated dementia, the character of the abnormal movements, and genetic studies distinguish Huntington's disease (Chap. 362). Sydenham's chorea (Chap. 235) may be confused with Gilles de la Tourette's syndrome when a history of rheumatic fever or polyarthritis is lacking and there is no cardiac involvement, but it usually resolves over 3 to 6 months. Tics may also occur in postencephalitic syndromes and as a side effect of stimulant or neuroleptic medication.

TREATMENT

Treatment is symptomatic and may need to be continued indefinitely.

Clonidine alleviates motor and phonic tics in some children, possibly by reducing activity in noradrenergic neurons of the locus coeruleus. The initial dose is 2 to 3 ug/kg per day, increased after 2 weeks to 4 ug/kg per day and then, if required, to 5 ug/kg per day. There may be a transient fall in blood pressure when this agent is introduced. Other side effects are sedation, reduced or excessive salivation, and diarrhea.

Haloperidol has been used widely for many years. It is introduced in a low daily dose (0.25 mg), which is gradually increased by 0.25 mg every 5 days, depending on response and tolerance. The optimal dose is usually 2 to 8 mg/d. Side effects include extrapyramidal movement disorders, sedation, xerostomia, blurred vision, and gastrointestinal disturbances. Pimozide, another dopaminergic-receptor antagonist, may be of benefit when haloperidol is unhelpful or poorly tolerated. It may produce widening of the QT interval and sudden death at high doses, so the electrocardiogram should be monitored routinely. Its long-term safety is unknown. It is introduced in a dose of 1 mg/d, and the dose is then increased by 2 mg every 10 days; most patients require 7 to 16 mg/d. The total dose should not exceed 0.3 mg/kg per day. Phenothiazines such as fluphenazine sometimes help, but patients unresponsive to haloperidol do not usually benefit from these drugs. Clonazepam or carbamazepine can also be tried. Family

counseling and psychotherapy are sometimes helpful.

RESTLESS LEGS SYNDROME

The restless legs syndrome is a common, chronic disorder that often has a familial basis, with evidence of autosomal dominant inheritance. It is characterized by a need to move because of unpleasant creeping sensations that arise deep within the legs and occasionally also in the arms, especially when patients are relaxed. For this reason, there is often difficulty in settling down to sleep at night. Periodic leg movements may also occur during sleep and can be documented by polysomnography. The cause is unknown, although the disorder is common during pregnancy and is sometimes associated with uremic or diabetic neuropathy, primary amyloidosis, or malignancy. Clinical examination may reveal evidence of underlying systemic disease or mild peripheral neuropathy but is more often normal. Symptoms may respond to correction of coexisting iron-deficiency anemia or to treatment with dopaminergic medication (such as levodopa, bromocriptine, or pergolide), benzodiazepines (diazepam or clonazepam), or opiates (codeine, propoxyphene, or oxycodone).

(Bibliography omitted in Palm version)

364. ATAXIC DISORDERS - *Roger N. Rosenberg*

Approach to the Patient

Ataxia is a common and important neurologic finding. Symptoms and signs of ataxia consist of gait impairment, unclear ("scanning") speech, visual blurring due to nystagmus, hand incoordination, and tremor with movement (Chap. 22). These result from the involvement of the cerebellum and its afferent and efferent pathways including the spinocerebellar pathways, and the frontopontocerebellar pathway originating in the rostral frontal lobe (Brodmann's area 10). True cerebellar ataxia must be distinguished from ataxia associated with vestibular nerve or labyrinthine disease, as the latter results in a disorder of gait associated with a significant degree of dizziness, light-headedness, or the perception of movement (Chap. 21). True cerebellar ataxia is devoid of these vertiginous complaints and is clearly an unsteady gait due to imbalance. Weakness of proximal leg muscles and a variant of acute idiopathic polyneuritis (Miller-Fisher syndrome) can on occasion simulate the imbalance of cerebellar disease. In the patient who presents with ataxia, the rate and pattern of the development of cerebellar symptoms are important in determining the diagnostic possibilities (Table 364-1). A gradual and progressive increase in symptoms with bilateral and symmetric involvement suggests a biochemical, metabolic, immune, or toxic etiology. Conversely, focal, unilateral symptoms with headache and impaired level of consciousness accompanied by ipsilateral cranial nerve palsies and contralateral weakness imply a space-occupying cerebellar lesion.

Symmetric Ataxia Progressive and symmetric ataxia can be classified with respect to onset as acute (over hours or days), subacute (weeks or months), or chronic (months to years). Acute and reversible ataxias include those caused by intoxication with alcohol, phenytoin, lithium, barbiturates, and other drugs. Intoxication caused by toluene exposure, gasoline sniffing, glue sniffing, spray painting, or exposure to methyl mercury or bismuth are additional causes of acute or subacute ataxia, as is treatment with cytotoxic chemotherapeutic drugs such as flourouracil and paclitaxel. Children with a postinfectious syndrome (especially after varicella) may develop gait ataxia and mild dysathria, which are both reversible (Chap. 371). Rare infectious causes of acquired ataxia include poliovirus, coxsackievirus, echovirus, Epstein-Barr virus, toxoplasmosis, *Legionella*, and the prion protein responsible for Creutzfeldt-Jakob disease. The subacute development of ataxia of gait over weeks to months (acute cerebellar degeneration of the vermis) may be due to the combined effects of alcoholism and malnutrition, particularly with deficiencies of vitamins B_1 and B_{12}. Hyponatremia has also been associated with ataxia. A paraneoplastic syndrome, which may be associated with myoclonus and opsoclonus, may present as incapacitating gait ataxia. Specific autoantibodies (Yo, Ri, and PCD) have been identified that are responsible for cerebellar degeneration involving principally the midline or vermis (Chap. 101). Female patients may present with cerebellar ataxia before the identification of a breast or ovarian carcinoma. Removal of the tumor may prevent further progression of symptoms and in some patients result in gait improvement. Chronic symmetric gait ataxia of months' to years' duration suggests an inherited ataxia (discussed below), a metabolic disorder, or a chronic infection. Hypothyroidism must always be considered as a readily treatable and reversible form of gait ataxia. Infectious diseases that can present with ataxia are meningovascular syphilis and tabes dorsalis due to degeneration of the

posterior columns and spinocerebellar pathways in the spinal cord. Lyme disease may cause ataxic symptoms.

Focal Ataxia Acute focal ataxia commonly results from cerebrovascular disease, usually ischemic infarction, hemorrhagic infarction, or cerebellar hemorrhage. These lesions typically produce cerebellar symptoms ipsilateral to the injured cerebellum and may be associated with an impaired level of consciousness due to brainstem compression and increased intracranial pressure; ipsilateral pontine signs, including sixth and seventh nerve palsies, may be present. Focal and worsening signs of acute ataxia should also prompt consideration of a posterior fossa subdural hematoma, bacterial abscess, primary or metastatic cerebellar tumor, or acute demyelinating lesion of multiple sclerosis. Computed tomography (CT) or magnetic resonance imaging (MRI) studies will reveal clinically significant processes of this type, which may require surgical decompression. Many of these lesions represent true neurologic emergencies, as sudden herniation, either rostrally through the tentorium or caudal herniation of cerebellar tonsils through the foramen magnum can occur and is usually devastating (Chap. 376). Lymphoma or progressive multifocal leukoencephalopathy (PML) in a patient with AIDS may present with an acute or subacute focal cerebellar syndrome. Chronic etiologies of ataxia include multiple sclerosis and congenital lesions such as the Chiari type I malformation, and congenital cysts of the posterior fossa (Dandy-Walker syndrome).

THE INHERITED ATAXIAS

Of the syndromes that constitute the inherited ataxias, some show autosomal dominant or autosomal recessive modes of inheritance, and some are caused by mitochondrial mutations and thus show a maternal mode of inheritance. Substantial progress has been made in recent years in identifying the molecular basis of these syndromes (Table 364-2), so that a genomic classification is superseding previous ones based on clinical expression alone.

Although the clinical manifestations and neuropathologic findings of cerebellar disease dominate the clinical picture, there may also be characteristic changes in the basal ganglia, brainstem, spinal cord, optic nerves, retina, and peripheral nerves. In large families with dominantly inherited disease, there are many gradations from purely cerebellar manifestations to mixed cerebellar and brainstem disorders, cerebellar and basal ganglia syndromes, and spinal cord or peripheral nerve disease. Rarely, dementia is present as well. The clinical picture may be consistent within a family with dominantly inherited ataxia, but sometimes most affected family members show one characteristic syndrome, while one or several members have an entirely different phenotype.

The autosomal spinocerebellar ataxias (SCAs) are caused by CAG triplet repeat expansions in different genes including SCA1, SCA2, MJD, SCA6, SCA7, and SCA13. SCA8 is due to a CTG repeat expansion (Table 364-2). The clinical phenotypes of these SCAs overlap. A single phenotype can result from several different genotypes, and conversely a single genotype can be associated with more than one different phenotype. The genotype has become the gold standard for diagnosis and classification. CAG encodes glutamine, and these expanded CAG triplet repeat expansions result in expanded polyglutamine proteins, termed *ataxins*, that produce a

toxic gain of function with autosomal dominant inheritance. Although the phenotype is variable for any given disease gene, a pattern of neuronal loss with gliosis is produced that is relatively unique for each ataxia. Immunohistochemical and biochemical studies have shown cytoplasmic (SCA2), neuronal (SCA1, MJD, SCA7), and nucleolar (SCA7) accumulation of the specific mutant polyglutamine containing ataxin proteins. Expanded polyglutamine ataxins with more than approximately 40 glutamines are potentially toxic to neurons for a variety of reasons including the following: high levels of gene expression for the mutant polyglutamine ataxin in affected neurons; conformational change of the aggregated protein to ab-pleated structure; abnormal transport of the ataxin into the nucleus (SCA1, MJD, SCA7); binding to other polyglutamine proteins, including the TATA-binding transcription protein and the CREB-binding protein, impairing their functions; altering the efficiency of the ubiquitin-proteosome system of protein turnover; and inducing neuronal apoptosis. An earlier age of onset (anticipation) and more aggressive disease in subsequent generations are due to further expansion of the CAG triplet repeat and increased polyglutamine number in the mutant ataxin. A new classification based on the genotype and its specific mutant ataxin is presented inTable 364-2, and the salient features of the most common disorders are discussed below.

AUTOSOMAL DOMINANT ATAXIAS

The new genomic classification of the dominantly inherited ataxias includes SCA type 1 through SCA13, dentatorubropallidoluysian atrophy (DRPLA), and episodic ataxia (EA) types 1 and 2 (Table 364-2).

SCA1 SCA1 was previously referred to as *olivopontocerebellar atrophy*, but genomic data have shown that that entity represents several different genotypes with overlapping clinical features.

Symptoms and signs SCA1 is characterized by the development in early or middle adult life of progressive cerebellar ataxia of the trunk and limbs, impairment of equilibrium and gait, slowness of voluntary movements, scanning speech, nystagmoid eye movements, and oscillatory tremor of the head and trunk. Dysarthria, dysphagia, and oculomotor and facial palsies may also occur. Extrapyramidal symptoms include rigidity, an immobile face, and parkinsonian tremor. The reflexes are usually normal, but knee and ankle jerks may be lost, and extensor plantar responses may occur. Dementia may be noted but is usually mild. Impairment of sphincter function is common, with urinary and sometimes fecal incontinence. Cerebellar and brainstem atrophy are evident onMRI(Fig. 364-1).

Marked shrinkage of the ventral half of the pons, disappearance of the olivary eminence on the ventral surface of the medulla, and atrophy of the cerebellum are evident on gross postmortem inspection of the brain. Variable loss of Purkinje cells, reduced numbers of cells in the molecular and granular layer, demyelination of the middle cerebellar peduncle and the cerebellar hemispheres, and severe loss of cells in the pontine nuclei and olives are found on histologic examination. Degenerative changes in the striatum, especially the putamen, and loss of the pigmented cells of the substantia nigra may be found in cases with extrapyramidal features. More widespread degeneration in the central nervous system (CNS), including involvement of the posterior columns and the spinocerebellar fibers, is often present, especially in the

cases with autosomal dominant inheritance.

GENETIC CONSIDERATIONS

SCA1 was mapped positionally to chromosome 6 (6p22-p23), and the causal gene was found to contain CAG expanded DNA repeats (Chap. 359). The mutant allele has>40 CAG repeats, whereas alleles from unaffected individuals have £36 repeats. A few patients with 38 to 40 CAG repeats have been described. There is a direct correlation between a larger number of repeats and a younger age of onset for SCA1. Juvenile patients have higher numbers of repeats, and anticipation is present in subsequent generations. The SCA1 gene is 450 kilobases (kb) long and has nine exons, with the first seven exons located in a 5¢untranslated region and the last two exons containing the coding region. The SCA1 transcript contains 10,660 bases and is transcribed from both the wild-type allele and SCA1 alleles. The CAG repeat, which codes for a polyglutamine tract, lies within the coding region. The SCA1 gene product, called ataxin-1, is a novel protein of unknown function. Recently, polyglutamine aggregates bound to ubiquitin have been described in neuronal nuclei that are undergoing degeneration. Similar neuronal nuclear inclusions have been seen in cerebellar Purkinje cells of transgenic mice overexpressing an expanded variant of the ataxin-1 gene that causes human SCA1. Other transgenic mice carrying the SCA1 gene but with the self-association region deleted, so that polyglutamine aggregation did not occur, still developed ataxia and Purkinje cell pathology. Thus, although nuclear localization of ataxin-1 is necessary, nuclear aggregation of ataxin-1 is not required to initiate pathogenesis in transgenic mice.

SCA2

Symptoms and signs Another clinical phenotype, SCA2, has been described in Cubans. These patients probably are descendants of a common ancestor, and the population may be the largest homogeneous group of patients with ataxia yet described. The age of onset ranges from 2 to 65 years, and there is considerable clinical variability within families. Although neuropathologic and clinical findings are compatible with a diagnosis of SCA1, including parkinsonian rigidity, optic disk pallor, mild spasticity, and retinal degeneration, it appears that SCA2 is a unique form of cerebellar degenerative disease.

GENETIC CONSIDERATIONS

The gene inSCA2 families has been mapped to 12q23-q24.1. Thus, the similar clinical phenotypes of SCA1 and SCA2, mapped respectively to 6p and 12q, represent different genotypes. The gene has recently been identified, and it also contains CAG repeat expansions coding for a polyglutamine-containing protein, ataxin-2. Normal alleles contain 15 to 24 repeats; mutant alleles have 35 to 59 repeats.

Machado-Joseph Disease/SCA3 Machado-Joseph disease (MJD) is an autosomal dominant spinocerebellar degenerative disease first described among the Portuguese and their descendants in New England and California. Subsequently, MJD has been found in families from Portugal, Australia, Brazil, Canada, China, England, France, India, Israel, Italy, Japan, Spain, Taiwan, and the United States. In most populations, it is the most common inherited autosomal dominant ataxia.

Symptoms and signs MJD has been classified into three clinical types. In type I MJD (amyotrophic lateral sclerosis-parkinsonism-dystonia type), neurologic deficits appear in the first two decades and involve weakness and spasticity of extremities, especially the legs, often with dystonia of the face, neck, trunk, and extremities. Patellar and ankle clonus are common, as are extensor plantar responses. The gait is slow and stiff, with a slightly broadened base and lurching from side to side; this gait results from spasticity, not true ataxia. There is no truncal titubation. Pharyngeal weakness and spasticity cause difficulty with speech and swallowing. Of note is the prominence of horizontal and vertical nystagmus, loss of fast saccadic eye movements, hypermetric and hypometric saccades, and impairment of upward vertical gaze. Facial fasciculations, facial myokymia, lingual fasciculations without atrophy, ophthalmoparesis, and ocular prominence are common and early manifestations.

In type II MJD (ataxic type), true cerebellar deficits appear, including dysarthria and gait and extremity ataxia, beginning in the second to fourth decades, along with corticospinal and extrapyramidal deficits of spasticity, rigidity, and dystonia. Type II is the most common form of MJD. Ophthalmoparesis, upward vertical gaze deficits, and facial and lingual fasciculations are also present. Type II MJD must be distinguished from the clinically similar disorders SCA1 and SCA2.

Type III MJD (ataxic-amyotrophic type) presents in the fifth to the seventh decades with a pancerebellar disorder that includes dysarthria and gait and extremity ataxia. Distal sensory loss involving pain, touch, vibration, and position senses and distal atrophy are prominent, indicating the presence of peripheral neuropathy. The deep tendon reflexes are depressed to absent, and there are no corticospinal or extrapyramidal findings.

The mean age of onset of symptoms in MJD is 25 years. Neurologic deficits invariably progress and lead to death from debilitation within 15 years of onset, especially in patients with types I and II disease. Usually, patients retain full intellectual function.

The major pathologic findings are variable loss of neurons and glial replacement in the corpus striatum and severe loss of neurons in the pars compacta of the substantia nigra. A moderate loss of neurons occurs in the dentate nucleus of the cerebellum and in the red nucleus. Purkinje cell loss and granule cell loss occur in the cerebellar cortex. Cell loss also occurs in the dentate nucleus and in the cranial nerve motor nuclei. Sparing of the inferior olives distinguishes MJD from other dominantly inherited ataxias.

GENETIC CONSIDERATIONS

The gene locus for MJD has been mapped to 14q24.3-q32. The genes from families with MJD in Japan and North and South America all map to the same locus. Unstable CAG repeat expansions are present in the MJD gene coding for a polyglutamine-containing protein named ataxin-3 or MJD-ataxin. An earlier age of onset is associated with longer repeats. Alleles from normal individuals have between 12 and 37 CAG repeats, and MJD alleles have 60 to 84 CAG repeats. A patient with autonomic dysfunction and ataxia has been described with 56 CAG repeats. Polyglutamine-containing aggregates of ataxin-3 (MJD-ataxin) have been described in neuronal nuclei undergoing degeneration.

SCA6 Genomic screening for CAG repeats in other families with autosomal dominant ataxia and vibratory and proprioceptive sensory loss have yielded another locus. Of interest is that different mutations in the same gene for thea_{1A}voltage-dependent calcium channel subunit (CACNLIA4) (also referred to as the CACNA1A gene) at 19p13 result in different clinical disorders. CAG repeat expansions (21 to 27 in patients; 4 to 16 triplets in normal individuals) result in late onset progressive ataxia with cerebellar degeneration. Missense mutations in this gene result in familial hemiplegic migraine. Non-sense mutations resulting in termination of protein synthesis of the gene product yield hereditary paroxysmal cerebellar ataxia or episodic ataxia. Some patients with familial hemiplegic migraine develop progressive ataxia and also have cerebellar atrophy.

Dentatorubropallidoluysian Atrophy DRPLA is a disorder of variable clinical presentation that is characterized by progressive ataxia, choreoathetosis, dystonia, seizures, myoclonus, and dementia. DRPLA is due to unstable CAG triplet repeats in the open reading frame of a gene named atrophin located on chromosome 12p12-ter. Larger expansions are found in patients with earlier onset. The number of repeats is³49 in patients with DRPLA; it is£26 in normal individuals. Anticipation occurs; successive generations in individual families show progressively earlier onset of disease in association with an increasing CAG repeat number. Larger expansions occur in children who inherit the disease from their father.

Episodic Ataxia Types 1 and 2 are two rare dominantly inherited disorders that have been mapped to chromosomes 12p (a potassium channel gene) for type 1 and 19p for type 2. Patients with EA-1 have brief episodes of ataxia with myokymia and nystagmus that last only minutes. Startle, sudden change in posture, and exercise can induce episodes. Acetazolamide or anticonvulsants may be therapeutic. Patients with EA-2 have episodes of ataxia with nystagmus that can last for hours or days. Stress, exercise, or excessive fatigue may be precipitants. Acetazolamide may be therapeutic and can reverse the relative intracellular alkalosis detected by MR spectroscopy. Stop codon, non-sense mutations causing EA-2 have been found in the CACNA1A gene, encoding thea_{1A}voltage-dependent calcium channel subunit (see SCA6 above). SeeTable 364-2 for details.

AUTOSOMAL RECESSIVE ATAXIAS

Friedreich's Ataxia This is the most common form of inherited ataxia, comprising one-half of all hereditary ataxias. It can occur in a classic form or in association with a genetically determined vitamin E deficiency syndrome; the two forms are clinically indistinguishable.

Symptoms and signs Friedreich's ataxia presents before 25 years of age with progressive staggering gait, frequent falling, and titubation. The lower extremities are more severely involved than the upper ones. Dysarthria occasionally is the presenting symptom; and rarely progressive scoliosis, foot deformity, nystagmus, or cardiopathy are initial signs.

The neurologic examination reveals nystagmus, loss of fast saccadic eye movements,

truncal titubation, dysarthria, dysmetria, and ataxia of extremity and truncal movements. Extensor plantar responses (with normal tone in trunk and extremities), absence of deep tendon reflexes, and weakness (greater distally than proximally) are usually found. Loss of vibratory and proprioceptive sensation occurs. The median age of death is 35 years. Women have a significantly better prognosis than men; the 20-year survival rate is 100% in women and 63% in men.

Cardiac involvement occurs in 90% of patients. Cardiomegaly, symmetric hypertrophy, murmurs, and conduction defects are reported. Idebenone, a free-radical scavenger, has been shown in preliminary studies to protect heart muscle from iron-induced injury and to decrease myocardial hypertrophy. Iron chelators and antioxidant drugs are potentially harmful. Moderate mental retardation or psychiatric syndromes are present in a small percentage of patients. A high incidence of diabetes mellitus (20%) is found and is associated with insulin resistance and pancreaticb-cell dysfunction. However, no linkage is reported between the Friedreich's ataxia gene and loci predisposing to diabetes mellitus. Musculoskeletal deformities are common and include pes cavus, pes equinovarus, and scoliosis.MRI of the spinal cord shows significant cord atrophy in affected patients (Fig. 364-2).

The primary sites of pathology are the spinal cord, dorsal root ganglion cells, and the peripheral nerves. Slight atrophy of the cerebellum and cerebral gyri may occur. Sclerosis and degeneration occur predominantly in the spinocerebellar tracts, lateral corticospinal tracts, and posterior columns. Degeneration of the glossopharyngeal, vagus, hypoglossal, and deep cerebellar nuclei is described. The cerebral cortex is histologically normal except for loss of Betz cells in the precentral gyri. The peripheral nerves are extensively involved, with a loss of large myelinated fibers. The density of small myelinated fibers is normal, but axonal size and myelin thickness are diminished. Cardiac pathology consists of myocytic hypertrophy and fibrosis, focal vascular fibromuscular dysplasia with subintimal or medial deposition of periodic acid-Schiff (PAS)-positive material, myocytopathy with unusual pleomorphic nuclei, and focal degeneration of myelinated and unmyelinated nerves and cardiac ganglia.

GENETIC CONSIDERATIONS

The classic form of Friedreich's ataxia has been mapped to 9q13-q21.1, and the mutant gene, frataxin, contains expanded GAA triplet repeats in the first intron. There is homozygosity for expanded GAA repeats in most patients. Normal persons have 7 to 22 GAA repeats, and patients have 200 to 900 GAA repeats. Patients with Friedreich's ataxia have undetectable or extremely low levels of frataxin mRNA, as compared with carriers and unrelated individuals; thus, disease appears to be caused by a loss of expression of the frataxin protein. Frataxin is a mitochondrial protein involved in iron homeostasis. Mitochondrial iron accumulation due to loss of the iron transporter coded by the mutant frataxin gene results in oxidized intramitochondrial iron. Excess oxidized iron results in turn in the oxidation of cellular components and irreversible cell injury.

Two forms of hereditary ataxia associated with abnormalities in the interactions of vitamin E (a-tocopherol) with very-low-density lipoprotein (VLDL) have been delineated. Ataxia of the Friedreich's phenotype with vitamin E deficiency (AVED) and abetalipoproteinemia (Bassen-Kornzweig syndrome) have both been clarified at the

molecular genetic level. Abetalipoproteinemia is caused by mutations in the gene coding for the larger subunit of the microsomal triglyceride transfer protein (MTP). Defects in MTP result in impairment of formation and secretion of VLDL in liver. This defect results in a deficiency of delivery of vitamin E to tissues, including the central and peripheral nervous system, as VLDL is the transport molecule for vitamin E and other fat-soluble substitutes. AVED is due to mutations in the gene for a-tocopherol transfer protein (a-TTP) on chromosome 8 (8q13). These patients have an impaired ability to bind vitamin E into the VLDL produced and secreted by the liver, resulting in a deficiency of vitamin E in peripheral tissues. Hence, either absence of VLDL (abetalipoproteinemia) or impaired binding of vitamin E to VLDL (AVED) causes an ataxic syndrome. Once again, a genotype classification has proved to be essential in sorting out the various clinical forms of the Friedreich's disease syndrome.

Ataxia Telangiectasia

Symptoms and signs Patients present in the first decade of life with progressive telangiectatic lesions associated with deficits in cerebellar function and nystagmus. The neurologic manifestations correspond to those in Friedreich's disease, which should be included in the differential diagnosis. Truncal ataxia, extremity ataxia, dysarthria, extensor plantar responses, myoclonic jerks, areflexia, and distal sensory deficits may develop. There is a high incidence of recurrent pulmonary infections and neoplasms of the lymphatic and reticuloendothelial system in patients with ataxia telangiectasia (AT) as well as an increased incidence of cancer. Thymic hypoplasia with cellular and humoral (IgA and IgG2) immunodeficiencies, premature aging, and endocrine disorders such as insulin-dependent diabetes mellitus are described. There is an increased incidence of lymphomas, Hodgkin's disease, and acute leukemias of the T cell type. There is also an increased incidence of breast cancer in women who are heterozygous for AT. The immunologic defects and increased susceptibility to cancer have been causally linked to cellular disorders in AT. Exposure of cultured cells to ionizing radiation slows the rate of DNA replication and increases the frequency of chromosomal aberrations.

The most striking neuropathologic changes include loss of Purkinje, granule, and basket cells in the cerebellar cortex as well as of neurons in the deep cerebellar nuclei. The inferior olives of the medulla also may have neuronal loss. There is a loss of anterior horn neurons in the spinal cord and of dorsal root ganglion cells associated with posterior column spinal cord demyelination. A poorly developed or absent thymus gland is the most consistent defect of the lymphoid system.

GENETIC CONSIDERATIONS

The gene for AT (the *ATM* gene) has been positionally mapped to chromosome 11q22-q23. *ATM*, which has a 12-kb transcript, was mutated in AT patients from all complementation groups described previously. A partial *ATM* cDNA clone of 5.9 kb encodes a protein that is similar to several yeast and mammalian phosphatidylinositol-3¢-kinases involved in mitogenic signal transduction, meiotic recombination, and cell cycle control. Defective DNA repair in AT fibroblasts exposed to ultraviolet light has been demonstrated. The discovery of *ATM* will make possible the identification of heterozygotes who are at risk for cancer (e.g., breast cancer) and permit

early diagnosis.

Mitochondrial Ataxias Spinocerebellar syndromes have been identified with mutations in mitochondrial DNA (mtDNA). Thirty pathogenic mtDNA point mutations and>60 different types of mtDNA deletions are known, several of which cause or are associated with ataxia ([Chap. 383](#)).

Xeroderma Pigmentosum Xeroderma pigmentosum is a rare autosomal recessive neurocutaneous disorder caused by the inability to repair damage to DNA, such as that produced by ultraviolet radiation. In addition to skin lesions, patients may show progressive mental deterioration, microcephaly, ataxia, spasticity, choreoathetosis, and hypogonadism. Nerve deafness, peripheral neuropathy (predominantly axonal), electroencephalographic abnormalities, and seizures are reported. Neuronal death occurs in pyramidal cells, cerebellar Purkinje cells, the deep nuclei of the cerebellum, the brainstem, the spinal cord, and peripheral nerves.

Cockayne Syndrome This is a rare autosomal recessive disorder first described by Cockayne in 1936. Clinical features are mental retardation, optic atrophy, dwarfism, neural deafness, hypersensitivity of skin to sunlight, cataracts, and retinal pigmentary degeneration. Cerebellar, pyramidal, and extrapyramidal deficits and peripheral neuropathy may occur, with a "bird-headed" facial appearance and normal-pressure hydrocephalus. Skin fibroblasts exposed to ultraviolet light demonstrate defective DNA repair.

Marinesco-Sjogren Syndrome This rare syndrome, in which progressive cerebellar deficits begin early in childhood, is another example in which a Friedreich's syndrome is associated with additional specific features. In this case, cataracts, mental retardation, multiple skeletal abnormalities, hypogonadotropic hypogonadism, and severe cerebellar atrophy are associated. The syndrome is likely a lysosomal storage disorder caused by an enzymatic defect, but the pathophysiology is unknown.

TREATMENT

The physician's most important task in the management of patients with ataxia is to identify treatable disease entities. Malignancies may present with chronic progressive ataxia either directly with a mass effect in the posterior fossa or indirectly by paraneoplastic degeneration. Other mass lesions can be treated appropriately. Malabsorption syndromes leading to vitamin E deficiency may lead to ataxia. The vitamin E deficiency form of Friedreich's ataxia must be considered, and serum vitamin E levels measured. Vitamin E therapy is indicated for these rare patients. There is preliminary evidence that idebenone, a free-radical scavenger, is therapeutic for patients with classic Friedreich ataxia by reducing myocardial hypertrophy. There is no current evidence that it improves neurologic function. Iron chelators and antioxidant drugs are potentially harmful as they may increase heart muscle injury. Vitamin B_1 and B_{12}levels in serum must be measured, and the vitamins should be administered to patients having deficient levels. The deleterious effects of diphenylhydantoin and alcohol on the cerebellum are well known. Hypothyroidism is easily treated. Aminoacidopathies, leukodystrophies, urea-cycle abnormalities, and mitochondrial encephalomyopathies may produce ataxia, and some dietary or metabolic therapies are

available. The cerebrospinal fluid should be tested for a syphilitic infection in patients with progressive ataxia and other features of tabes dorsalis. Similarly, antibody titers for Lyme disease and *Legionella* should be measured, and appropriate antibiotic therapy should be instituted in antibody-positive patients. There is no proven therapy for the dominant ataxias (SCA1 to 13). The identification of gene defects will, it is hoped, lead to specific pharmacologic therapy. At present, identification of an at-risk person's genotype, together with appropriate family and genetic counseling, can reduce the incidence of these cerebellar syndromes (Chaps. 68,359).

(Bibliography omitted in Palm version)

365. AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES - *Robert H. Brown, Jr.*

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is the most common form of progressive motor neuron disease. It is a prime example of a neuronal system disease and is arguably the most devastating of the neurodegenerative disorders.

Pathology The pathology of motor neuron degenerative disorders involves lower motor neurons (consisting of anterior horn cells in spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (emanating from layer five of motor cortex to descend via the pyramidal tract to synapse with lower motor neurons, either directly or indirectly via interneurons; (Chap. 22). Although at its onsetALS may involve selective loss of function of only upper or lower motor neurons, it ultimately causes progressive loss of both categories of motor neurons. Indeed, in the absence of clear involvement of both motor neuron types, the diagnosis of ALS is questionable.

Other motor neuron diseases involve only particular subsets of motor neurons (Tables 365-1 and365-2). Thus, in bulbar palsy and spinal muscular atrophy (SMA, also called progressive muscular atrophy), the lower motor neurons of brainstem and spinal cord, respectively, are most severely involved. By contrast, pseudobulbar palsy, primary lateral sclerosis (PLS), and familial spastic paraplegia (FSP) affect only upper motor neurons innervating the brainstem and spinal cord.

In each of these diseases, the affected motor neurons undergo shrinkage, often with accumulation of the pigmented lipid (lipofuscin) that normally develops in these cells with advancing age. InALS, the motor neuron cytoskeleton is typically affected early in the illness. Focal enlargements are frequent in proximal motor axons; ultrastructurally, these "spheroids" are composed of accumulations of neurofilaments. Beyond some astroglial proliferation, which is the inevitable accompaniment of all degenerative processes in the central nervous system (CNS), the interstitial and supportive tissues and the macrophage system remain largely inactive, and there is no inflammation.

The death of the peripheral motor neurons in the brainstem and spinal cord leads to denervation and consequent atrophy of the corresponding muscle fibers. Histochemical and electrophysiologic evidence indicates that in the early phases of the illness denervated muscle can be reinnervated by sprouting of nearby distal motor nerve terminals, although reinnervation in this disease is considerably less extensive than in most other disorders affecting motor neurons (e.g., poliomyelitis, peripheral neuropathy). As denervation progresses, muscle atrophy is readily recognized in muscle biopsies and on clinical examination. This is the basis for the term *amyotrophy* in the name for the disease. The loss of cortical motor neurons results in thinning of the corticospinal tracts that travel via the internal capsule and brainstem to the lateral and anterior white matter columns of the spinal cord. The loss of fibers in the lateral columns and resulting fibrillary gliosis impart a particular firmness (*lateral sclerosis*) (Fig. 365-1). A remarkable feature of the disease is the selectivity of neuronal cell death. By light microscopy, the entire sensory apparatus, the regulatory mechanisms for the control

and coordination of movement, and the components of the brain that are needed for cognitive processes remain intact. However, immunostaining indicates that neurons bearing ubiquitin, a marker for degeneration, are also detected in nonmotor systems. Moreover, studies of glucose metabolism in the illness also indicate that there is neuronal dysfunction outside of the motor system. Within the motor system, there is some selectivity of involvement. Thus, motor neurons required for ocular motility remain unaffected, as do the parasympathetic neurons in the sacral spinal cord (the nucleus of Onufrowicz, or Onuf) that innervate the sphincters of the bowel and bladder.

Clinical Manifestations The manifestations of ALS are somewhat variable depending on whether corticospinal or lower motor neurons in the brainstem and spinal cord are more prominently involved. Typically, with lower motor neuron dysfunction and early denervation, the initial sign of the disease is insidiously developing asymmetric weakness, usually first evident distally in one of the limbs. A detailed history often discloses recent development of cramping with volitional movements, typically in the early hours of the morning (e.g., while stretching in bed). Weakness caused by denervation is associated with progressive wasting and atrophy of muscles and, particularly early in the illness, spontaneous twitching of motor units, or fasciculations. In the hands, a preponderance of extensor over flexor weakness is common. When the initial denervation involves bulbar rather than limb muscles, the problem at onset is difficulty with chewing, swallowing, and movements of the face and tongue. Early involvement of the muscles of respiration may lead to death before the disease is far advanced elsewhere.

With prominent corticospinal involvement, there is hyperactivity of the muscle-stretch reflexes (tendon jerks) and, often, spastic resistance to passive movements of the affected limbs. Patients with significant reflex hyperactivity complain of muscle stiffness often out of proportion to weakness. Degeneration of the corticobulbar projections innervating the brainstem results in dysarthria and exaggeration of the motor expressions of emotion. The latter leads to involuntary excess in weeping or laughing (so-called pseudobulbar affect).

Virtually any muscle group may be the first to show signs of the disease, but, as time passes, more and more muscles become involved until ultimately the disorder takes on a symmetric distribution in all regions. It is characteristic of ALS that, regardless of whether the initial disease involves upper or lower motor neurons, both will eventually be implicated. Even in the late stages of the illness, sensory, bowel and bladder, and cognitive functions are preserved. Even when there is severe brainstem disease, ocular motility is spared until the very late stages of the illness. Dementia is not a component of sporadic ALS. In some families, ALS is co-inherited with frontotemporal dementia, characterized by early behavioral abnormalities with prominent behavioral features indicative of frontal lobe dysfunction.

A committee of the World Federation of Neurology has established diagnostic guidelines for ALS. Essential for the diagnosis is the presence of simultaneous upper and lower motor neuron involvement with progressive weakness, and the exclusion of all alternative diagnoses. The disorder is classified as "definite" ALS when three or four of the following sites are involved: bulbar, cervical, thoracic, and lumbosacral motor neurons. When two sites are involved, the diagnosis is "probable"; when only one site is

implicated, the diagnosis is "possible." An exception is made for those who have progressive upper and lower motor neuron signs at only one site and a mutation in the gene encoding superoxide dismutase (below).

Epidemiology The illness is relentlessly progressive, leading to death from respiratory paralysis; the median survival is from 3 to 5 years. There are very rare reports of stabilization or even regression of ALS. In most societies there is an incidence of 1 to 3 per 100,000 and a prevalence of 3 to 5 per 100,000. Several endemic foci of higher prevalence exist in the western Pacific (e.g., in specific regions of Guam or Papua New Guinea). In the United States and Europe, males are somewhat more frequently affected than females. While ALS is overwhelmingly a sporadic disorder, some 5 to 10% of cases are inherited as an autosomal dominant trait.

Familial ALS Several forms of selective motor neuron disease are heritable (Table 365-2). Two involve both corticospinal and lower motor neurons. The most common is familial ALS (FALS). Apart from its inheritance as an autosomal dominant trait, it is clinically indistinguishable from sporadic ALS. Genetic studies have identified mutations in the gene encoding the cytosolic enzyme superoxide dismutase (SOD1) as the cause of one form of FALS. However, this accounts for only 20% of inherited cases of ALS; there clearly are other ALS genes to be identified. There is a juvenile-onset, dominantly inherited form of ALS that is genetically mapped to the long-arm of chromosome 9. Two recessively inherited forms of juvenile-onset ALS with long survival map to chromsomes 2 and 15. Another familial, adult-onset disorder that may mimic aspects of ALS is Kennedy's syndrome, described below.

Differential Diagnosis Because ALS is currently untreatable, it is imperative that potentially remediable causes of motor neuron dysfunction be excluded (Table 365-3). This is particularly true in cases that are atypical by virtue of (1) restriction to either upper or lower motor neurons, (2) involvement of neurons other than motor neurons, and (3) evidence of motor neuronal conduction block on electrophysiologic testing. Compression of the cervical spinal cord or cervicomedullary junction from tumors in the cervical regions or at the foramen magnum or from cervical spondylosis with osteophytes projecting into the vertebral canal can produce weakness, wasting, and fasciculations in the upper limbs and spasticity in the legs, closely resembling ALS. The absence of cranial nerve involvement may be helpful in differentiation, although some foramen magnum lesions may compress the twelfth cranial (hypoglossal) nerve, with resulting paralysis of the tongue. Absence of pain or of sensory changes, normal bowel and bladder function, normal roentgenographic studies of the spine, and normal cerebrospinal fluid (CSF) all favor ALS. Where doubt exists, magnetic resonance imaging (MRI) scans should be performed to visualize the cervical spinal cord.

Another important entity in the differential diagnosis of ALS is multifocal motor neuropathy (MMN) with conduction block, discussed below and in Chap. 378. A diffuse, lower motor axonal neuropathy mimicking ALS sometimes evolves in association with hematopoietic disorders such as lymphoma (Chap. 101). The underlying marrow pathology is often signaled by the presence of an M-component in serum which, in this clinical setting, should prompt consideration of a bone marrow biopsy. Lyme infection may also cause an axonal, lower motor neuropathy.

Other treatable disorders that occasionally mimic ALS are chronic lead poisoning and thyrotoxicosis. These disorders may be suggested by the patient's social or occupational history or by unusual clinical features. When the family history is positive, disorders involving the genes encoding SOD1, hexosaminidase A, or a-glucosidase deficiency must be excluded (Chap. 349). These are readily identified by appropriate laboratory tests. Benign fasciculations are occasionally a source of concern because on inspection they resemble the fascicular twitchings that accompany motor neuron degeneration. The absence of weakness, atrophy, or denervation phenomena on electrophysiologic examination usually excludes ALS or other serious neurologic disease. Patients who have recovered from poliomyelitis may experience a delayed deterioration of motor neurons that presents clinically with progressive weakness, atrophy, and fasciculations. Its cause is unknown but is thought to reflect sublethal prior injury to motor neurons by poliovirus (Chap. 193).

Rarely, ALS develops concurrently with features indicative of more widespread neurodegeneration. Thus, one infrequently encounters otherwise typical ALS patients with a Parkinsonian movement disorder or dementia. It remains unclear whether this reflects the unlikely simultaneous occurrence of two disorders or a primary defect triggering two forms of neurodegeneration. The latter is suggested by the observation that multisystem neurodegenerative diseases may be inherited. For example, prominent amyotrophy has been described as a dominantly inherited disorder in individuals with bizarre behavior and a movement disorder suggestive of parkinsonism; many such cases have now been ascribed to mutations that alter the expression of isoforms of tau protein in brain (Chap. 362). In other cases, ALS develops simultaneously with a striking frontotemporal dementia. These disorders may be dominantly co-inherited; in some families, this trait is linked to a locus on chromosome 9q, although the underlying genetic defect is not established.

Pathogenesis The cause of sporadic ALS is not well defined. Some data suggest that excitotoxic neurotransmitters such as glutamate may participate in the death of motor neurons in ALS. This may be a consequence of diminished uptake of synaptic glutamate by an astroglial glutamate transporter, EAAT2. In one study of sporadic ALS brains, this loss of transport function was attributed to abnormal splicing of the mRNA transcript for the EAAT2 transporter selectively in motor cortex. It is striking that one cellular defense against such excitotoxicity is the enzyme SOD1, which detoxifies the free radical superoxide anion. Because SOD1 is mutated in some familial cases of ALS, it may be that glutamate excitotoxicity and ALS result from free radical accumulations in motor neurons. Precisely why the SOD1 mutations are toxic to motor nerves is not established, although it is clear that the effect is not simply loss of normal scavenging of the superoxide anion.

TREATMENT

There is no treatment capable of arresting the underlying pathologic process in ALS. The drug riluzole was approved for use in ALS because it produces a modest lengthening of survival. In one trial, the survival rate at 18 months with riluzole (100 mg/d) was similar to placebo at 15 months. The mechanism of this effect is not known with certainty; it may reduce excitotoxicity by diminishing glutamate release. Side effects of riluzole may include nausea, dizziness, weight loss, and elevated liver enzymes. In a single study,

insulin-like growth factor (IGF-1) was found to slow the progression of ALS modestly; because this effect was not confirmed in a second trial, IGF-1 is not routinely available as an ALS treatment at this time. Clinical trials of several other agents are in progress, including brain-derived neurotrophic factor, glial-derived neurotrophic factor, the anti-glutamate compound topiramate, and creatine. Creatine has proven to be beneficial in SOD-1 transgenic ALS mice, perhaps by augmenting intracellular ATP stores. In a single study in France, vitamin E was beneficial in sporadic ALS. It is also modestly beneficial in the ALS mice and thus is now used empirically by many individuals with ALS. On the basis of successful animal experiments, trials of neural stem therapy of the spinal cord are also being developed in ALS.

In the absence of a primary therapy for ALS, a variety of rehabilitative aids may substantially assist ALS patients. Foot-drop splints facilitate ambulation by avoiding tripping on a floppy foot and obviating excessive hip flexion. Finger-extension splints can potentiate grip. Respiratory support may be life-sustaining. For patients electing against long-term ventilation by tracheostomy, positive-pressure ventilation by mouth or nose provides transient (several weeks) relief from hypercarbia and hypoxia. Also extremely beneficial for some patients is a respiratory device (In-exsufflator, Emerson) that produces an artificial cough. This is highly effective in clearing airways and preventing aspiration pneumonia. When bulbar disease prevents normal chewing and swallowing, gastrostomy is uniformly helpful, restoring normal nutrition and hydration. Fortunately, an increasing variety of speech synthesizers are now available to augment speech when there is advanced bulbar palsy. Because they facilitate oral communication and may be effective for telephone use, such devices are helpful in preserving patient autonomy.

In contrast to ALS, several of the disorders (Table 365-2) that bear some clinical resemblance to ALS are treatable; for this reason, a careful search for such forms of secondary motor neuron disease is warranted.

SELECTED DISORDERS OF THE LOWER MOTOR NEURON

In the varieties of motor neuron disease grouped under this heading, the peripheral motor neurons are affected without evidence of involvement of the corticospinal motor system (Table 365-1).

X-Linked Spinobulbar Muscular Atrophy (Kennedy's Disease) This is an X-linked lower motor neuron disorder in which progressive weakness and wasting of limb and bulbar muscles begins in males in midadult life and is conjoined with androgen insensitivity manifested by gynecomastia and reduced fertility (Chap. 335). In addition to gynecomastia, which may be subtle, two findings distinguishing this disorder from ALS are the absence of signs of pyramidal tract disease (spasticity) and the presence of a subtle sensory neuropathy in some patients. The underlying molecular defect is an expanded trinucleotide repeat (-CAG-) in the first exon of the androgen receptor gene on the X chromosome; this may be readily screened from DNA from blood. An inverse correlation appears to exist between the number of -CAG- repeats and the age of onset of the disease (Chap. 359).

Adult Tay-Sach's Disease Several reports have described adult-onset, predominantly

lower motor neuropathies arising from deficiency of the enzymeb-hexosaminidase (hex A). These tend to be distinguishable fromALSbecause they are very slowly progressive; dysarthria and radiographically evident cerebellar atrophy may be prominent. In rare cases, spasticity may also be present, although it is generally absent (Chap. 349).

Spinal Muscular Atrophy TheSMAs are a family of selective lower motor neuron diseases of early onset. Despite some phenotypic variability (largely in age of onset), the defect in the majority of families with SMA is genetically linked to a locus on the proximal long arm of chromosome 5. The affected gene at this locus is a putative motor neuron survival protein (SMN, for survival motor neuron) that is important in the formation and trafficking of RNA complexes across the nuclear membrane. All types of SMA are transmitted as traits. Neuropathologically these disorders are characterized by extensive loss of large motor neurons; muscle biopsy reveals evidence of denervation atrophy. Several clinical forms are described.

Infantile SMA (SMA I, Werdnig-Hoffmann Disease) has the earliest onset and most rapidly fatal course. In some instances it is apparent even before birth, as indicated by decreased fetal movements late in the third trimester. Though alert, afflicted infants are weak and floppy (hypotonic) and lack muscle stretch reflexes. Death generally ensues within the first year of life. When the family history is unclear, it is difficult in the early weeks and months to distinguishSMA I from benign congenital hypotonia. An electromyogram is often particularly helpful as SMA I usually demonstrates fulminant denervation; in congenital hypotonia the electromyogram is often myopathic or normal.

Chronic childhood SMA (SMA II) begins later in childhood and evolves with a more slowly progressive course. *Juvenile SMA (*SMAIII, Kugelberg-Welander disease) manifests during late childhood and runs a slow, indolent course. Unlike most denervating diseases, in this chronic disorder weakness is greatest in the proximal muscles; indeed, the pattern of clinical weakness can suggest a primary myopathy such as limb-girdle dystrophy. Electrophysiologic and muscle biopsy evidence of denervation distinguish SMA III from the myopathic syndromes.

Multifocal Motor Neuropathy with Conduction Block In this disorder lower motor neuron function is regionally and chronically disrupted by remarkably focal blocks in conduction. Many patients have elevated serum titers of mono- and polyclonal antibodies to ganglioside G_{M1}; it is hypothesized that the antibodies produce selective, focal, paranodal demyelination of motor neurons.MMN is not typically associated with corticospinal signs. In contrast toALS, MMN may respond dramatically to therapy such as intravenous immunoglobulin or chemotherapy; it is thus imperative that MMN be excluded when considering a diagnosis of ALS.*A detailed discussion of this condition can be found in Chap. 378.*

Other Forms of Lower Motor Neuron Disease In individual families, other syndromes characterized by selective lower motor neuron dysfunction in anSMA-like pattern have been described. There are rare X-linked and autosomal dominant forms of apparent SMA. There is anALSvariant of juvenile onset, the Fazio-Londe syndrome, which involves mainly the musculature innervated by the brainstem. A component of lower motor neuron dysfunction is also found in degenerative disorders such as Machado-Joseph disease and the related olivopontocerebellar degenerations (Chap.

SELECTED DISORDERS OF THE UPPER MOTOR NEURON

Primary Lateral Sclerosis This exceedingly rare disorder arises sporadically in adults in mid- to late life. ClinicallyPLS is characterized by progressive spastic weakness of the limbs, preceded or followed by spastic dysarthria and dysphagia, indicating combined involvement of the corticospinal and corticobulbar tracts. Fasciculations, amyotrophy, and sensory changes are absent; neither electromyography nor muscle biopsy shows denervation. On neuropathologic examination there is selective loss of the large pyramidal cells in the precentral gyrus and degeneration of the corticospinal and corticobulbar projections. The peripheral motor neurons and other neuronal systems are spared. The course of PLS is variable; while long-term survival is documented, the course may be as aggressive as inALS, with approximately 3-year survival from onset to death. Early in its course, PLS raises the question of multiple sclerosis or other demyelinating diseases such as adrenoleukodystrophy as diagnostic considerations. A myelopathy suggestive of PLS is infrequently seen with infection with the human T cell leukemia virus (HTLV-I) (Chap. 368). The clinical course and laboratory testing will distinguish these possibilities.

Familial Spastic Paraplegia In its pure form,FSP is usually transmitted in families as an autosomal dominant trait; most adult-onset cases are dominantly inherited. It arises in the third or fourth decade and is characterized by progressive spastic weakness beginning in the distal lower extremities. Patients with FSP typically have long survival, presumably because respiratory function is spared. Late in the illness there may be urinary urgency and incontinence and sometimes fecal incontinence; sexual function tends to be preserved. In pure forms of FSP, ataxia, posterior column sensory loss, and amyotrophy are absent or minimal; however, in some patients, minor sensory changes (impaired vibration and position sense) may be observed in late stages. Some family members may show isolated spasticity without other clinical symptoms. Neuropathologically, in FSP there is degeneration of the corticospinal tracts, which appear nearly normal in the brainstem but show increasing atrophy at more caudal levels in the spinal cord. It is now apparent that defects at several different loci underlie both dominantly and recessively inherited forms of FSP (Table 365-2). An infantile-onset form of X-linked, recessive FSP arises from mutations in the gene for proteolipid protein. This is an example of rather striking allelic variation, as most other mutations in the same gene cause not FSP but Pelizaeus-Merzbacher disease, a disorder ofCNSmyelin. Defects in two other genes encoding the proteins "spastin" and "paraplegin" have recently been associated, respectively, with dominantly and recessively inherited FSP. The latter gene is of particular interest as it has homology to metalloproteases that are important in mitochondrial function in yeast.

Rarely,FSP may arise concomitantly with significant involvement of other regions of the nervous system. Thus, it has been described concurrently with amyotrophy, mental retardation, mental retardation with skin thickening, optic atrophy, and sensory neuropathy. In some cases there is loss of fibers in the ascending posterior columns and the spinocerebellar tracts, features reminiscent of Friedreich's ataxia. These complicated forms of FSP emphasize the challenge inherent in classifying the neurodegenerative disorders; there may be considerable overlap of the clinical

phenotypes in diseases otherwise classified as distinct. Fortunately, it is likely that increasingly available genetic testing will clarify these nosologic difficulties.

WEB SITES

Several web sites provide valuable information on ALS including those offered by the Muscular Dystrophy Association (www.mdausa.org), the Amyotrophic Lateral Sclerosis Association (www.alsa.org), and the World Federation of Neurology (www.wfnals.org).

(Bibliography omitted in Palm version)

366. DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM - *John W. Engstrom, Joseph B. Martin*

Rapid adjustments in vital physiologic mechanisms critical to survival are accomplished by the autonomic nervous system (ANS). The importance of this regulation is emphasized by the extent and severity of disability resulting from compromised ANS function. This chapter describes the clinical manifestations, diagnosis, and treatment of ANS disorders. *The functional anatomy and relevant pharmacology of the sympathetic and parasympathetic components of the ANS are discussed in Chap. 72. Hypothalamic disorders that cause disturbances in homeostasis are discussed in Chaps. 17 and 328.*

CLINICAL MANIFESTATIONS

Classification Disorders of the ANS may result from central nervous system (CNS) or peripheral nervous system (PNS) causes (Table 366-1). In many instances, the clinical signs and symptoms are due to interruption of a reflex arc controlling autonomic responses. The interruption can occur in the afferent limb, CNS processing centers, or efferent limb of the reflex arc. For example, a lesion of the medulla produced by a posterior fossa tumor can impair blood pressure (BP) responses to postural changes and result in orthostatic hypotension. Hypotension can also be caused by lesions of the spinal cord or peripheral vasomotor nerve fibers (diabetes mellitus). Diagnosis of the site of reflex interruption is dependent on the clinical context, ANS tests, and neuroimaging. Important elements of the clinical context include the presence or absence of CNS signs (pathophysiology and prognosis differ), association with sensory or motor polyneuropathy, family history, and pathologic findings. Some syndromes do not fit easily into any classification scheme because little is known about etiology, pathology, or treatment.

Symptoms of Autonomic Dysfunction The clinical manifestations of autonomic lesions are influenced by the organ involved, the normal balance of sympathetic-parasympathetic innervation, the nature of the underlying illness, and the severity and stage of progression. *Impotence* often heralds autonomic failure in men and may precede other symptoms by more than a decade (Chap. 51). A decrease in the frequency of spontaneous early morning erections may occur months before loss of nocturnal penile tumescence and development of total impotence. *Bladder dysfunction* may appear early in men and women, particularly in those with CNS involvement. Brain and spinal cord disease above the level of the lumbar spine results first in urinary frequency and small bladder volumes, and eventually in incontinence (*upper motor neuron* or *spastic bladder*). Disease of PNS autonomic nerve fibers to and from the bladder results in large bladder volumes, urinary frequency, and overflow incontinence (*lower motor neuron bladder* or *flaccid bladder*). Measurement of bladder volume (postvoid residual) is a useful bedside test for distinguishing between upper and lower motor neuron bladder dysfunction. *Gastrointestinal autonomic dysfunction* typically presents as severe constipation. Diarrhea occurs occasionally (as in diabetes mellitus) due to rapid transit of contents or uncoordinated small bowel motor activity, or on an osmotic basis from bacterial overgrowth associated with small bowel stasis. Impaired glandular secretory function may cause difficulty with food intake due to decreased salivation or eye irritation due to decreased lacrimation. Occasionally, temperature elevation and vasodilation can result from *anhidrosis* because sweating is normally

important for heat dissipation ([Chap. 17](#)).

Orthostatic hypotension (OH) (also called "postural hypotension") is the most disabling feature of autonomic dysfunction. OH can cause a variety of symptoms, including dimming or loss of vision, lightheadedness, diaphoresis, diminished hearing, pallor, and weakness. Syncope results when the drop in[BP](#)impairs cerebral perfusion. Other manifestations of impaired cardiovascular control from baroreflex dysfunction include supine hypertension, a heart rate that is fixed regardless of posture, and postprandial hypotension. The most common causes of OH are not neurologic in origin ([Table 366-2](#)) and must be distinguished from neurogenic etiologies ([Table 366-1](#)).*Neurocardiogenic and cardiac syncope are considered in [Chap. 20](#).*

Approach to the Patient

The most common, clinically significant autonomic disorders present with symptoms of[OH](#). The first step in the evaluation of symptomatic orthostasis is the exclusion of treatable causes. The history should include a review of current medications which may cause OH (e.g., diuretics, antihypertensives, antidepressants, phenothiazines, ethanol, narcotics, insulin, barbiturates, andb-adrenergic and calcium channel blockers). Exaggerated responses to medications may be the first sign of an underlying autonomic disorder. The history may reveal a potential underlying cause for symptoms (e.g., diabetes, Parkinson's disease) or may reveal specific underlying mechanisms (e.g., cardiac pump failure, reduced intravascular volume). Inappropriate or extreme venous pooling may contribute to symptomatic OH. The relationship of symptoms to meals (splanchnic shunting of blood), or standing on awakening in the morning (due to relative intravascular volume depletion) should be sought.

Physical examination includes measurement of supine and standing pulse and[BP](#), with a period of at least 2 min between positions. Sustained drops in systolic (>20 mmHg) or diastolic (>10 mmHg) BP after standing for at least 2 min that are not associated with an increase in pulse rate of>15 beats per minute suggest an autonomic deficit. In nonneurogenic causes of OH, the BP drop is accompanied by a compensatory increase in heart rate of >15 beats per minute. The requirement that the hypotension is sustained differentiates autonomic failure from sluggish baroreceptor responses that are common in the elderly. Other common signs of[ANS](#)dysfunction include supine hypertension or postprandial hypotension. Neurologic evaluation should include a mental status examination (to exclude neurodegenerative disorders), cranial nerve examination (to detect the impaired downgaze found with progressive supranuclear palsy), motor examination (for Parkinson's disease and parkinsonian syndromes), and sensory examination (for polyneuropathies). In patients without a clear initial diagnosis, follow-up neurologic evaluations performed over years may reveal an evolution of neurologic findings that makes it possible to reach a specific diagnosis.

Disorders of autonomic function should be considered in the differential diagnosis of patients with symptoms of altered sweating (hyperhidrosis or hypohidrosis), constipation, impotence, or bladder dysfunction (urinary frequency, hesitancy, or incontinence). An initial practical approach to the patient with[OH](#) or autonomic symptoms is summarized in[Table 366-3](#).

Autonomic Testing (See also [Chap. 357](#)) Autonomic function tests are helpful when the history and physical examination findings are inconclusive, when detection of subclinical involvement is important to evaluate the extent and severity of abnormalities, or to monitor the effects of therapy. Both physiologic and pharmacologic tests are available to assess the functional characteristics of the ANS. Commonly used physiologic tests assess autonomic aspects of cardiovascular function. These tests are noninvasive and provide quantitative and regional data about autonomic function. Pharmacologic tests can elucidate pathophysiologic abnormalities and guide the development of rational therapy.

HEART RATE VARIATION WITH DEEP BREATHING This is a test of parasympathetic influence on cardiovascular function. Results are influenced by the subject's posture, rate and depth of respiration [5 to 6 breaths per minute and a forced vital capacity (FVC)>1.5 L are optimal], age, medications, and hypocapnea. Interpretation of results requires comparison of test data with results from normal individuals collected under the same test conditions. For example, the lower limit of normal heart rate variation with deep breathing in persons younger than 20 years is >15 to 20 beats/min, but for persons over age 60 it is 5 to 8 beats/min. Heart rate variation with deep breathing (respiratory sinus arrhythmia) is abolished by the administration of atropine.

VALSALVA RESPONSE This response assesses integrity of the afferent limb, central processing, and efferent limb of the baroreceptor reflex ([Table 366-4](#)). The response is obtained with the subject sitting or supine. A constant expiratory pressure of 40 mmHg is maintained for 15 s while changes in heart rate and beat-to-beat BP are measured. There are four phases of BP and heart rate response to the Valsalva maneuver. Phases I and III are mechanical and related to changes in intrathoracic and intraabdominal pressure. In early phase II, reduced stroke volume and venous return results in a fall in BP, reflex tachycardia, and increased total peripheral resistance. Increased total peripheral resistance arrests the BP drop approximately 5 to 8 s after the onset of the maneuver. Late phase II begins with a progressive rise in BP toward baseline. Venous return and cardiac output return to normal in phase IV. Persistent peripheral arteriolar vasoconstriction results in a temporary BP overshoot and phase IV bradycardia (mediated by the baroreceptor reflex).

Autonomic function during the Valsalva maneuver can be measured in several ways. The *Valsalva ratio* is calculated from heart rate changes during the maneuver and is defined as the maximum phase II tachycardia divided by the minimum phase IV bradycardia. The ratio reflects the integrity of the entire baroreceptor reflex arc and of sympathetic efferents to blood vessels; sympathetic efferent function is assessed in the phase II BP response and the BP overshoot. Test results depend on the age and posture of the subject, the expiratory pressure, the duration of expiration, the FVC, and medications. Noninvasive recording of beat-to-beat BP changes provides a direct measure of sympathetic efferent input to blood vessels during phases II and IV that does not depend on the presence of a normal baroreceptor reflex arc.

SUDOMOTOR FUNCTION The capacity to produce sweat can be assessed quantitatively or qualitatively. Sweating is induced by release of acetylcholine from sympathetic postganglionic fibers. The *quantitative sudomotor axon reflex test* (QSART) is a measure of regional autonomic function mediated by acetylcholine-induced

sweating. A reduced or absent response indicates a lesion of the postganglionic sudomotor axon. For example, sweating may be reduced in the legs as a result of peripheral neuropathy (e.g., in diabetes) before other signs of autonomic dysfunction emerge. The *thermoregulatory sweat test* (TST) is a *qualitative* measure of regional sweat production in response to an elevation of body temperature. An indicator powder placed on the anterior body surface changes color with sweat production during temperature elevation. The pattern of color changes is a measure of regional sweat secretion. The pattern of sweat abnormality may suggest a peripheral or central cause for the deficit. For example, a unilateral decrease over half the body suggests a central lesion. Measurement of galvanic skin responses in the limbs after an induced electrical potential is another qualitative test for detecting the presence or absence of sweating. The response is simple to measure, but habituation occurs.

ORTHOSTATIC BLOOD PRESSURE RECORDINGS Beat-to-beatBPmeasurements determined in supine, 80° tilt, and tilt-back positions are useful to quantitate orthostatic failure of BP control. It is important to allow a 20-min period of supine rest before assessing changes in BP during tilting. The test can be useful for the evaluation of patients with unexplained syncope and to detect vagally mediated syncope.

COLD PRESSOR TEST The cold pressor test assesses sympathetic function. The individual immerses one hand in ice water (1° to 4°C) andBP is measured at 30 s and 1 min. The systolic and diastolic pressures normally rise by 10 to 20 mmHg. The afferent pathway is spinothalamic and thus is distinct from the afferent limb of the baroreceptor reflex arc. When spinothalamic pathways are intact, an abnormal response indicates an abnormality of autonomic central processing or sympathetic efferent function. When the response to the cold pressor test is normal and the Valsalva response is abnormal, the lesion is located in the afferent limb of the baroreceptor reflex arc.

PHARMACOLOGIC TESTS Pharmacologic assessments can help localize an autonomic defect to theCNS or the PNS. The test is controlled for time of day, position of the patient, level of patient activity, and food intake. Measures should be taken to minimize patient stress. Measurement of plasma levels of neurotransmitter metabolites andBPresponses to infused drugs helps to distinguish between central and peripheral causes of autonomic dysfunction (Table 366-5); however, these studies are not routine clinical tools.

SPECIFIC SYNDROMES OF ANS DYSFUNCTION

Multiple System Atrophy Multiple system atrophy (MSA) is an uncommon entity that comprises several overlapping clinical syndromes, including striatonigral degeneration (Shy-Drager syndrome), progressive supranuclear palsy (Chap. 363), and olivopontocerebellar atrophy (Chap. 364). The clinical syndrome can include various combinations of symptoms of autonomic dysfunction (OH, impotence, bladder and bowel dysfunction, and defective sweating), as well as additional symptoms ofCNSdisease such as rigidity, tremor, loss of associative movements, or abnormal eye movements. Most patients present with autonomic dysfunction alone, and other neurologic manifestations usually develop within 5 years. Patients with the striatonigral variant exhibit a form of parkinsonism in which bradykinesia and rigidity are more prominent than tremor. Patients with either a pure cerebellar syndrome or striatonigral

degeneration may also develop pyramidal tract involvement. Some patients have features of both subtypes.

These disorders progress relentlessly to death 7 to 10 years after onset. Pharmacologic differences distinguishMSA from peripheral causes of autonomic failure (Table 366-4). Neuropathologic changes include primary neuronal degeneration with loss of neurons and gliosis in manyCNSregions, including the brainstem, the cerebellum, the striatum, and the intermediolateral cell column of the thoracolumbar spinal cord.ANSabnormalities are also associated with Parkinson's disease and Huntington's disease.

Spinal Cord Lesions Spinal cord lesions from any cause may result in focal autonomic deficits or autonomic hyperreflexia. Descending pathways from the brain normally modulate organized patterns of sympathetic activity and modulate segmental autonomic reflexes. Spinal cord transection or hemisection may be attended by autonomic hyperreflexia affecting bowel, bladder, sexual, temperature-regulation, or cardiovascular functions. Dangerous increases or decreases in body temperature may result from inability to experience the sensory accompaniments of heat or cold exposure below the level of the injury. Quadriparetic patients exhibit both supine hypertension andOH after upward tilting. Markedly increased autonomic discharge can be elicited by bladder pressure or stimulation of the skin or muscles; suprapubic palpation of the bladder, catheter insertion, catheter obstruction, or urinary infection are common and correctable precipitants. This phenomenon, termed autonomic dysreflexia, affects 85% of patients with a traumatic spinal cord lesion above the C6 level. In patients with supine hypertension,BP can be lowered by tilting the head upward. Vasodilator drugs may be used to treat acute elevations in BP. Clonidine is used prophylactically to reduce the hypertension resulting from bladder stimulation. Sudden, dramatic increases in BP can lead to intracranial hemorrhage and death.

Peripheral Nerve and Neuromuscular Junction Disorders Peripheral neuropathies (Chap. 377) are the most common cause of chronic autonomic insufficiency. Neuropathies that affect small myelinated and unmyelinated fibers of the sympathetic and parasympathetic nerves occur in diabetes mellitus, amyloidosis, chronic alcoholism, porphyria, and Guillain-Barre syndrome. Neuromuscular junction disorders include botulism and Lambert-Eaton syndrome.

Diabetes Mellitus Autonomic involvement in diabetes may begin at any stage in the disease (Chap. 333) and often presents with asymptomatic abnormalities in vagal function that can be detected as reduced heart rate variation with deep breathing. Loss of small myelinated and unmyelinated nerve fibers in the splanchnic distribution, carotid sinus, and vagus nerves is characteristic. Widespread enteric neuropathy can cause profound disturbances in gut motility (gastroparesis), nausea and vomiting, malnutrition, achlorhydria, and bowel incontinence. Other symptoms may include impotence, urinary incontinence, pupillary abnormalities, andOH. Typical symptoms and signs of hypoglycemia may fail to appear because damage to the sympathetic innervation of the adrenal gland can result in a lack of epinephrine release. Insulin excess may also cause profound hypotension. Autonomic dysfunction may lengthen the QT interval and enhance the risk of sudden death. Hyperglycemia appears to be one risk factor for autonomic involvement. Biochemical and pharmacologic studies in diabetic neuropathy

are compatible with autonomic failure localized to the PNS [low supine plasma norepinephrine (NE) levels and exaggerated pressor responsiveness].

Amyloidosis Autonomic neuropathy occurs in both sporadic and familial forms of amyloidosis (Chap. 319). Although patients usually present with a distal painful neuropathy accompanied by sensory loss, autonomic insufficiency can precede the development of the polyneuropathy. Death is usually due to cardiac or renal impairment. Postmortem studies reveal amyloid deposition in many organs, including two sites that contribute to autonomic failure: intraneural blood vessels and autonomic ganglia. Pathologic examination reveals a loss of unmyelinated and myelinated nerve fibers.

Alcoholic Neuropathy Abnormal parasympathetic vagal and efferent sympathetic function occurs in individuals with chronic alcoholism. Pathologic changes can be demonstrated in the parasympathetic (vagus) and sympathetic fibers and in ganglia. Impotence is a major problem, but concurrent gonadal hormone abnormalities may obscure the parasympathetic component to this symptom. Clinical symptoms of autonomic failure generally appear when the polyneuropathy is severe. OH may also be prominent in Wernicke's encephalopathy (Chap. 376). Autonomic involvement may contribute to the high mortality rates associated with alcoholism (Chap. 387).

Porphyria Although each of the porphyrias can cause autonomic dysfunction, the condition is most extensively documented in the acute intermittent type (Chap. 346). Autonomic symptoms include tachycardia, sweating, urinary retention, and hypertension or, less commonly, hypotension. Other prominent symptoms include anxiety, abdominal pain, nausea, and vomiting. Abnormal autonomic function can occur both during acute attacks and during remissions. Elevated catecholamine levels during acute attacks correlate with the degree of tachycardia and hypertension.

Guillain-Barre syndrome BP fluctuations and arrhythmias can be severe (Chap. 378). It is estimated that 2 to 10% of seriously ill patients with Guillain-Barre syndrome suffer fatal cardiovascular collapse. Abnormal sweating, sphincter disturbance, and pupillary dysfunction also occur. Demyelination has been described in the vagus and glossopharyngeal nerves, the sympathetic chain, and the white rami communicantes. The presence of autonomic involvement is not clearly related to the severity of motor or sensory involvement.

Botulism The toxin binds presynaptically to cholinergic nerve terminals and, after uptake into the cytosol, blocks acetycholine release by digesting key proteins involved in neurotransmitter release. Manifestations of this blockade consist of motor paralysis and autonomic disturbances, including blurred vision, dry mouth, nausea, unreactive or sluggishly reactive pupils, constipation, and urinary retention (Chap. 144).

Pure Autonomic Failure (PAF) This sporadic syndrome consists of postural hypotension, impotence, bladder dysfunction, and defective sweating. The disorder begins in the middle decades and occurs in women more than in men. The symptoms can be disabling, but the disease does not shorten life span. The clinical and pharmacologic characteristics suggest a primary involvement of postganglionic sympathetic neurons. There is a severe reduction in the density of neurons within sympathetic ganglia, resulting in low supine plasma NE levels and noradrenergic

supersensitivity ([Table 366-5](#)). The clinical diagnosis may be difficult in early stages because patients may present with isolated[OH](#), raising a question of PAF, but they later develop signs of multiple system atrophy (discussed above).

Postural Orthostatic Tachycardia Syndrome (POTS) This syndrome is characterized by symptomatic orthostatic intolerance (*not*[OH](#)) and an increase in heart rate to >120 beats per minute or by 30 beats per minute with standing. The condition affects young adult women most commonly, but it can occur over a wide age range. Associated symptoms include light-headedness, shortness of breath, and exercise intolerance. The pathogenesis is unclear in most cases; hypovolemia, venous pooling, impaired brainstem regulation, or b-receptor supersensitivity may play a role. In one affected individual, a mutation in the[NE](#)transporter resulting in impaired NE clearance from synapses was responsible. Only one-fourth of patients eventually resume their usual daily activities. Expansion of fluid volume and postural training are initial approaches to treatment. If the response to treatment is inadequate, then fludrocortisone, phenobarbital, beta blockers, and clonidine have been used with some success.

Postprandial Hypotension The importance of postprandial hypotension (PPH) among healthy elderly persons, hypertensive patients, and elderly patients in nursing homes has probably been underestimated. Abnormally reduced peripheral vasoconstriction in response to shunting of blood to the splanchnic circulation after a meal contributes to PPH. The wisdom of administering cardiovascular medications that have hypotensive effects at mealtimes to healthy and hypertensive elderly patients is questionable. PPH is also associated with diabetes, Parkinson's disease, renal failure treated with hemodialysis, cardiovascular disease, paraplegia, and autonomic failure.

Inherited Disorders Riley-Day syndrome (familial dysautonomia) is an autosomal recessive disorder of infants and children that occurs among Ashkenazi Jews. The defective gene, located on the long arm of chromosome 9, has not been identified. Decreased tearing, hyperhidrosis, reduced sensitivity to pain, areflexia, absent fungiform papillae on the tongue, and labile[BP](#) may be present. Episodic abdominal crises and fever are common. Increased sensitivity to intraocular methacholine and absent axon flare response to intradermal histamine injection are useful diagnostic markers. Normal resting plasma[NE](#)levels that do not increase on standing are consistent with an afferent lesion. Pathologic examination of nerves reveals a loss of small myelinated and unmyelinated nerve fibers.

Primary Hyperhidrosis This syndrome presents with excess sweating of the palms of the hands and soles of the feet. The disorder affects 0.6 to 1.0% of the population; the etiology is unclear (there may be a genetic component). While not dangerous, the condition can be socially embarrassing (e.g., shaking hands) or disabling (e.g., inability to write without soiling the paper). Onset of symptoms is usually in adolescence; the condition tends to improve with age. Topical antiperspirants (e.g., Drysol) are occasionally helpful. T2 ganglionectomy or sympathectomy is successful in>90% of patients with palmar hyperhidrosis. The advent of endoscopic transaxillary T2 sympathectomy has lowered the complication rate of the procedure. The most common complication is compensatory hyperhidrosis, which improves spontaneously over months; other potential complications include recurrent hyperhidrosis (16%), Horner's syndrome (<2%), gustatory sweating, wound infection, hemothorax, and intercostal

neuralgia. Local injection of botulinum toxin has been used to block cholinergic, post-ganglionic sympathetic fibers to sweat glands in patients with palmar hyperhidrosis; however, the technique is limited by the need for repetitive injections (the effect usually lasts 4 months before waning), pain with injection, the high cost of botulinum toxin, and the possibility of temporary intrinsic hand muscle weakness. Tap water iontophoresis has been successful for some patients.

Miscellaneous The importance of autoimmunity in the pathogenesis of autonomic failure has been underestimated; autoantibodies against acetylcholine receptors in autonomic ganglia have been found in some patients with acute pandysautonomia and paraneoplastic autonomic neuropathy. Other conditions associated with autonomic failure include infections, poisoning (organophosphates), malignancy, and aging. Disorders of the hypothalamus can affect autonomic function and produce abnormalities in temperature control, satiety, sexual function, and circadian rhythms (Chap. 328).

Reflex Sympathetic Dystrophy and Causalgia The failure to identify a primary role of the ANS in the pathogenesis of these disorders has resulted in a change of nomenclature. *Complex regional pain syndrome* (CRPS) *types I* and *II* are now used in place of reflex sympathetic dystrophy (RSD) and causalgia, respectively.

CRPS type I is a regional pain syndrome that usually develops after tissue trauma. Examples of associated trauma include myocardial infarction, minor shoulder or limb injury, and stroke. *Allodynia* (the perception of a nonpainful stimulus as painful), *hyperpathia* (an exaggerated pain response to a mildly painful stimulus), and spontaneous pain occur; these symptoms are unrelated to the severity of the initial trauma and are not confined to the distribution of a single peripheral nerve. CRPS type II is a regional pain syndrome that develops after injury to a peripheral nerve. Spontaneous pain initially develops within the territory of the affected nerve but eventually may spread outside the nerve distribution.

Pain is the primary clinical feature of CRPS. Vasomotor abnormalities, sudomotor abnormalities, or focal edema may occur alone or in combination, but must be present for diagnosis. Limb pain syndromes that do not meet these criteria are best classified as "limb pain -- not otherwise specified (NOS)". In CRPS, localized sweating (increased resting sweat output) and changes in blood flow may produce temperature differences between affected and unaffected limbs.

CRPS type I (RSD) has classically been divided into three clinical phases but is now considered to be more variable than previously thought. Phase I consists of pain and swelling in the distal extremity occurring within weeks to 3 months after the precipitating event. The pain is diffuse, spontaneous, and either burning, throbbing, or aching in quality. The involved extremity is warm and edematous, and the joints are tender. Increased sweating and hair growth are present. In phase II (3 to 6 months after onset), thin, shiny, cool skin appears. After an additional 3 to 6 months (phase III), atrophy of the skin and subcutaneous tissue plus flexion contractures complete the clinical picture.

Therapy for both types of CRPS is unsatisfactory. The desire to provide relief for these severely disabling pain syndromes has produced a variety of surgical and medical treatments with conflicting reports of efficacy. Clinical trials suggest that early

mobilization with physical therapy or a brief course of steroids may be helpful for CRPS type I. The long-term results of this treatment are unclear. Other medical treatments have included the use of adrenergic blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers, phenytoin, opioids, and calcitonin. Stellate ganglion blockade is a commonly used invasive therapeutic technique. Although stellate ganglion blocks often provide temporary pain relief, the efficacy of repetitive blocks is uncertain.

TREATMENT

Management of autonomic failure is usually limited to alleviating the disability caused by symptoms. Treatment of the primary disorder does not generally improve autonomic function. The history and examination are key to the identification of easily reversible conditions (Table 366-3).

OHis often severely disabling but may be mild. Neurogenic OH should be treated only if symptoms are present that limit activities of daily living. Nonpharmacologic interventions can be helpful. Patients should avoid sodium depletion or dehydration by maximizing salt intake (eating salty foods) and deliberately drinking at least 2 to 2.5 L/d of water. Sleeping in a head-up tilt position reduces nocturnal diuresis, morning postural hypotension and hypovolemia, and minimizes supine hypertension. Patients are often advised to sit with legs dangling over the edge of the bed for several minutes before attempting to stand in the morning. Isotonic exercise is desirable, but vigorous exercise or prolonged recumbency should be avoided. Circumstances that accentuate vasodilation (alcohol intake, high ambient temperature) may precipitate severe hypotension. Nonprescription medicines containing sympathomimetics must be used carefully because they may cause severe hypertension in the setting of autonomic failure accompanied by denervation supersensitivity. Compressive garments are of questionable value.

Most patients require pharmacologic therapy for the management ofOH. Fludrocortisone is the initial drug of choice; at doses between 0.1 mg/d and 0.3 mg bid orally, it enhances renal sodium conservation and increases the sensitivity of arterioles to norepinephrine. Susceptible patients may develop fluid overload, congestive heart failure, supine hypertension, or hypokalemia; with chronic administration, potassium supplements are often necessary. Sustained elevations of supineBP above 200/110 should be avoided.

OHof moderate severity can be treated with a combination of fludrocortisone and thea$_1$-receptor agonist midodrine. Midodrine is well absorbed when given orally and causes arteriolar and venous constriction withoutCNS or cardiac stimulation. It is administered orally 30 to 45 min before meals at an initial dose of 5 mg tid, increasing to a maximum of 10 mg q4h. Side effects include pruritus, uncomfortable piloerection, and supine hypertension.

OHwith a postprandial component may respond to several measures. Frequent, small, low-carbohydrate meals may diminish splanchnic shunting of blood after meals and reducePPH. Prostaglandin inhibitors (ibuprofen or indomethacin) taken with meals can prevent PPH. Caffeine (250 mg or two cups of coffee) can be given once per day,

usually in the morning. The somatostatin analogue octreotide can be useful in the treatment of postprandial syncope by inhibiting the release of gastrointestinal peptides that have vasodilator and hypotensive effects. The dose ranges from 25 ug subcutaneously bid to 100 to 200 ug subcutaneously tid. Despite the lack of a pressor effect, octreatide may also be useful for preventing the PPH that occurs in normal elderly patients.

OH accompanied by diarrhea may respond to thea$_2$agonist clonidine; coincident causes of nonneurogenicOH must be excluded before this treatment is begun because the risk of associated hypotension is significant. Initial doses are 0.1 to 0.2 mg orally every morning; the dose is gradually increased if drowsiness, dry mouth, constipation, supine hypertension, or hypotension are not dose-limiting. Octreotide may also be useful for some patients with this condition.

OH associated with anemia may respond to erythropoietin. One study found that systolicBPincreased by 20 mmHg and orthostatic symptoms improved with normalization of the hematocrit. Erythropoietin is administered subcutaneously at doses of 25 to 75 U/kg three times per week. The hematocrit increases after 2 to 6 weeks. A weekly maintenance dose is usually necessary. The increased intravascular volume that accompanies the rise in hematocrit can exacerbate supine hypertension.

Many patients withANSfailure exhibit exaggerated sensitivity to various drugs. Compounds with hypotensive actions should generally be avoided. For example, anticholinergic agents are a better initial choice than dopaminergic compounds for parkinsonism. Anesthetic management poses unique problems since these patients may have abnormal baroreceptor reflexes, impaired sympathetic innervation of peripheral arterioles, exaggerated pharmacologic responses, abnormal fluid balance, or adrenal medullary insufficiency. More important than the choice of anesthetic is awareness by the physician of the implications that autonomic failure may have for peri- and postoperative monitoring and management.

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367. COMMON DISORDERS OF THE CRANIAL NERVES - *M. Flint Beal*, *Stephen L. Hauser*

Symptoms and signs of cranial nerve pathology are common in internal medicine. They often develop in the context of a widespread neurologic disturbance, and in such situations cranial nerve involvement may represent the initial manifestation of the illness. In other disorders, involvement is largely restricted to one or several cranial nerves; these distinctive disorders are reviewed in this chapter. Disorders of ocular movement are discussed inChap 28; disorders of smell, taste, and hearing inChap 29; and vertigo and disorders of vestibular function inChap 21.

DISORDERS OF FACIAL SENSATION

The trigeminal (fifth cranial) nerve supplies sensation to the skin of the face and anterior half of the head (Fig. 367-1). Its motor part innervates the masseter and pterygoid masticatory muscles.

TRIGEMINAL NEURALGIA (TIC DOULOUREUX)

The most striking disorder of trigeminal nerve function is tic douloureux, a condition characterized by excruciating paroxysms of pain in the lips, gums, cheek, or chin and, very rarely, in the distribution of the ophthalmic division of the fifth nerve. The disorder occurs almost exclusively in middle-aged and elderly persons. The pain seldom lasts more than a few seconds or a minute or two but may be so intense that the patient winces, hence the term *tic*. The paroxysms recur frequently, both day and night, for several weeks at a time. Another characteristic feature is the initiation of pain by stimuli applied to certain areas on the face, lips, or tongue ("trigger zones") or by movement of these parts. *Objective signs of sensory loss cannot be demonstrated.* The adequate stimulus to a trigger zone for precipitating an attack is a tactile one and possibly tickle, rather than a noxious or thermal stimulus. Usually a spatial and temporal summation of impulses is necessary to trigger an attack, which is followed by a refractory period of up to 2 or 3 min.

The *diagnosis* of this disorder rests on these strict clinical criteria, and the condition must be distinguished from other forms of facial and cephalic neuralgia and pain arising from diseases of the jaw, teeth, or sinuses (Chap. 15). Tic douloureux is usually without assignable cause; in typical cases, neuroimaging studies are not necessary. On occasion, when trigeminal neuralgia develops in a younger adult, it may be due to a plaque of multiple sclerosis at the root entry zone of the fifth nerve in the pons. Very rarely it occurs with herpes zoster or a tumor. To a degree that remains uncertain, pain of tic douloureux may be caused by a redundant or tortuous blood vessel in the posterior fossa, causing an irritative lesion of the nerve or its root. Usually, however, lesions such as aneurysms, neurofibromas, or meningiomas affecting the nerve produce a loss of sensation (trigeminal neuropathy, see below).

TREATMENT

Drug therapy with carbamazepine is the initial treatment of choice and is effective in approximately 50 to 75% of patients. Carbamazepine should be started as a single daily

dose of 100 mg taken with food, and increased gradually (by 100 mg daily every 1 to 2 days) until substantial (>50%) pain relief is achieved. Most patients require a maintenance dose of 200 mg qid. Doses >1200 mg daily provide no additional benefit. Dizziness, imbalance, sedation, and rare cases of agranulocytosis are the most important side effects of carbamazepine. If treatment is effective, it is usually continued for approximately 1 month and then tapered as tolerated. If carbamazepine is not well tolerated or is ineffective, phenytoin, 300 to 400 mg daily, can be tried. Baclofen may also be administered, either alone or in combination with carbamazepine or phenytoin. The initial dose is 5 to 10 mg tid, gradually increasing as needed to 20 mg qid.

If drug treatment fails, surgical therapy should be offered. The most widely applied procedure creates a heat lesion of the trigeminal (gasserian) ganglion or nerve, a method termed *radiofrequency thermal rhizotomy*. Injection of glycerol in Meckel's cave is a method preferred by some surgeons. Either procedure produces short-term relief in >95% of patients; however, long-term studies indicate that pain recurs in a substantial percentage of treated patients in some series. Complications and morbidity are infrequent in experienced hands. These procedures result in partial numbness of the face and carry a risk of corneal denervation with secondary keratitis when used for the rare instances of first-division trigeminal neuralgia.

A third treatment, microvascular decompression, requires a suboccipital craniectomy, a major procedure requiring several days of hospitalization. It has an 80% efficacy rate, but the pain may recur, and, in a small number of cases, there is damage to the eighth or seventh nerve.

TRIGEMINAL NEUROPATHY

A variety of diseases in addition to tic douloureux may affect the trigeminal nerve (Table 367-1). Most present with sensory loss on the face or with weakness of the jaw muscles. Deviation of the jaw on opening indicates weakness of the pterygoids on the side to which the jaw deviates. Tumors of the middle cranial fossa (meningiomas), of the trigeminal nerve (schwannomas), or of the base of the skull (metastatic tumors) may cause a combination of motor and sensory signs. Lesions in the cavernous sinus can affect the first and second divisions of the trigeminal nerve, and lesions of the superior orbital fissure can affect the first (ophthalmic) division. The accompanying corneal anesthesia increases the risk of ulceration (neurokeratitis).

Loss of sensation over the chin (mental neuropathy) can be the only manifestation of systemic malignancy. Rarely, an idiopathic form of trigeminal neuropathy is observed. It is characterized by feelings of numbness and paresthesias, sometimes bilaterally, with loss of sensation in the territory of the trigeminal nerve but without weakness of the jaw. Recovery is the rule, but the symptoms may be troublesome for many months, or even years. Leprosy may involve the trigeminal nerves.

Tonic spasm of the masticatory muscles, known as *trismus*, is symptomatic of tetanus (Chap. 143). It may also occur as an idiosyncratic reaction in patients treated with phenothiazine drugs; lesser degrees may be associated with disease of the pharynx, temporomandibular joint, teeth, and gums.

DISORDERS OF THE FACIAL NERVE

The seventh cranial nerve supplies all the muscles concerned with facial expression. The sensory component is small (the nervus intermedius); it conveys taste sensation from the anterior two-thirds of the tongue and probably cutaneous impulses from the anterior wall of the external auditory canal. The motor nucleus of the seventh nerve lies anterior and lateral to the abducens nucleus. After leaving the pons, the seventh nerve enters the internal auditory meatus with the acoustic nerve. The nerve continues its course in its own bony channel, the facial canal, and exits from the skull via the stylomastoid foramen. It then passes through the parotid gland and subdivides to supply the facial muscles.

A complete interruption of the facial nerve at the stylomastoid foramen paralyzes all muscles of facial expression. The corner of the mouth droops, the creases and skin folds are effaced, the forehead is unfurrowed, and the eyelids will not close. Upon attempted closure of the lids, the eye on the paralyzed side rolls upward (Bell's phenomenon). The lower lid sags also, and the punctum falls away from the conjunctiva, permitting tears to spill over the cheek. Food collects between the teeth and lips, and saliva may dribble from the corner of the mouth. The patient complains of a heaviness or numbness in the face, but sensory loss is rarely demonstrable and taste is intact.

If the lesion is in the middle ear portion, taste is lost over the anterior two-thirds of the tongue on the same side. If the nerve to the stapedius is interrupted, there is hyperacusis (painful sensitivity to loud sounds). Lesions in the internal auditory meatus may also affect the adjacent auditory and vestibular nerves, causing deafness, tinnitus, or dizziness. Intrapontine lesions that paralyze the face usually affect the abducens nucleus as well, and often the corticospinal and sensory tracts.

If the peripheral facial paralysis has existed for some time and recovery of motor function is incomplete, a continuous diffuse contraction of facial muscles may appear. The palpebral fissure becomes narrowed, and the nasolabial fold deepens. Attempts to move one group of facial muscles may result in contraction of all of them (associated movements, or *synkinesis*). Facial spasms may develop and persist indefinitely, being initiated by every facial movement (*hemifacial spasm*). This condition may represent a transient or permanent sequela to a Bell's palsy but may also be due to an irritative lesion of the facial nerve (e.g., an acoustic neuroma, an aberrant artery that compresses the nerve and is relieved by surgery, or a basilar artery aneurysm). However, in the most common form of hemifacial spasm, the cause and pathology are unknown. Anomalous regeneration of the seventh nerve fibers may result in other troublesome phenomena. If fibers originally connected with the orbicularis oculi come to innervate the orbicularis oris, closure of the lids may cause a retraction of the mouth, or if fibers originally connected with muscles of the face later innervate the lacrimal gland, anomalous tearing ("crocodile tears") may occur with any activity of the facial muscles, such as eating. Yet another unusual facial synkinesia is one in which jaw opening causes a closure of the eyelids on the side of the facial palsy (jaw-winking).

BELL'S PALSY

The most common form of facial paralysis is idiopathic, i.e., *Bell's palsy*. The incidence rate of this disorder is about 23 per 100,000 annually, or about 1 in 60 or 70 persons in a lifetime. The pathogenesis of the paralysis is unproven, but an association with herpes simplex virus type 1 DNA in endoneurial fluid and posterior auricular muscle has been documented.

Clinical Manifestations The onset of Bell's palsy is fairly abrupt, maximal weakness being attained by 48 h as a general rule. Pain behind the ear may precede the paralysis for a day or two. Taste sensation may be lost unilaterally, and hyperacusis may be present. In some cases there is mild cerebrospinal fluid (CSF) lymphocytosis. Magnetic resonance imaging (MRI) may reveal swelling and uniform enhancement of the geniculate ganglion and facial nerve, and, in some cases, entrapment of the swollen nerve in the temporal bone is noted. Fully 80% of patients recover within a few weeks or months. Electromyography may be of some prognostic value; evidence of denervation after 10 days indicates that there has been axonal degeneration and that there will be a long delay (3 months, as a rule) before regeneration occurs and that it may be incomplete. The presence of incomplete paralysis in the first week is the most favorable prognostic sign.

Differential Diagnosis There are many other causes of facial palsy that must be considered in the differential diagnosis of idiopathic Bell's palsy. Tumors that invade the temporal bone (carotid body, cholesteatoma, dermoid) may produce a facial palsy, but the onset is insidious and the course progressive. The *Ramsay Hunt syndrome*, presumably due to herpes zoster of the geniculate ganglion, consists of a severe facial palsy associated with a vesicular eruption in the pharynx, external auditory canal, and other parts of the cranial integument; often the eighth cranial nerve is affected as well. *Acoustic neuromas* frequently involve the facial nerve by local compression. Infarcts, demyelinating lesions of multiple sclerosis, and tumors are the common pontine lesions that interrupt the facial nerve fibers; other signs of brainstem involvement are usually present. Bilateral facial paralysis (facial diplegia) occurs in *Guillain-Barre syndrome* (Chap. 378) and also in a form of sarcoidosis known as *uveoparotid fever* (*Heerfordt syndrome*). Lyme disease is a frequent cause of facial palsies in endemic areas. The *Melkersson-Rosenthal syndrome* consists of a rarely encountered triad of recurrent facial paralysis, recurrent -- and eventually permanent -- facial (particularly labial) edema, and less constantly, plication of the tongue; its cause is unknown. Leprosy frequently involves the facial nerve, and facial neuropathy may also occur in diabetes mellitus.

All these forms of nuclear or peripheral facial palsy must be distinguished from the supranuclear type. In the latter, the frontalis and orbicularis oculi muscles are involved less than those of the lower part of the face, since the upper facial muscles are innervated by corticobulbar pathways from both motor cortices, whereas the lower facial muscles are innervated only by the opposite hemisphere. In supranuclear lesions there may be a dissociation of emotional and voluntary facial movements, and often some degree of paralysis of the arm and leg or an aphasia (in dominant hemisphere lesions) is conjoined.

Laboratory Evaluation The diagnosis of Bell's palsy can usually be made clinically in patients with (1) a typical presentation, (2) no risk factors or preexisting symptoms for

other causes of facial paralysis, (3) absence of cutaneous lesions of herpes zoster in the external ear canal, and (4) a normal neurologic examination with the exception of the facial nerve. Particular attention to the eighth cranial nerve, which courses near to the facial nerve in the pontomedullary junction and in the temporal bone, and to other cranial nerves is essential. In atypical or uncertain cases, an erythrocyte sedimentation rate, testing for diabetes mellitus, a Lyme titer, chest x-ray for possible sarcoidosis, or MRI scanning may be indicated.

TREATMENT

Symptomatic measures include (1) the use of paper tape to depress the upper eyelid during sleep and prevent corneal drying, and (2) massage of the weakened muscles. A course of glucocorticoids, given as prednisone 60 to 80 mg daily during the first 5 days and then tapered over the next 5 days, appears to shorten the recovery period and modestly improve the functional outcome. In one double-blind study, patients treated within 3 days of onset with both prednisone and acyclovir (400 mg five times daily for 10 days) had a better outcome than patients treated with prednisone alone.

OTHER FACIAL DISORDERS

Facial hemiatrophy occurs mainly in females and is characterized by a disappearance of fat in the dermal and subcutaneous tissues on one side of the face. It usually begins in adolescence or early adult years and is slowly progressive. In its advanced form, the affected side of the face is gaunt, and the skin is thin, wrinkled, and rather brown. The facial hair may turn white and fall out, and the sebaceous glands become atrophic. The muscles and bones are not involved as a rule. Sometimes the atrophy becomes bilateral. The condition is a form of lipodystrophy. Treatment is cosmetic, consisting of transplantation of skin and subcutaneous fat.

Facial myokymia refers to a fine rippling activity of the facial muscles; it may be caused by a plaque of multiple sclerosis. *Blepharospasm* is an involuntary recurrent spasm of both eyelids that occurs in elderly persons as an isolated phenomenon or with varying degrees of spasm of other facial muscles. Severe, persistent cases of blepharospasm or hemifacial spasm can be treated by local injection of botulinus toxin into the orbicularis oculi; the spasms are relieved for 3 to 4 months, and the injections can be repeated.

GLOSSOPHARYNGEAL NERVE DISORDERS

GLOSSOPHARYNGEAL NEURALGIA

This form of neuralgia resembles trigeminal neuralgia in many respects but is much less common. The pain is intense and paroxysmal; it originates in the throat, approximately in the tonsillar fossa. In some cases the pain is localized in the ear or may radiate from the throat to the ear because of involvement of the tympanic branch of the glossopharyngeal nerve. Spasms of pain may be initiated by swallowing. There is no demonstrable sensory or motor deficit. Cardiac symptoms -- bradycardia, hypotension, and fainting -- have been reported. A trial of carbamazepine or phenytoin is the recommended therapy, but if that is unsuccessful, division of the glossopharyngeal

nerve near the medulla is the definitive treatment. Percutaneous rhizotomy of glossopharyngeal and vagal fibers in the jugular foramen alleviates pain in some patients.

Very rarely, herpes zoster involves the glossopharyngeal nerve. Glossopharyngeal neuropathy in conjunction with vagus and accessory nerve palsies may also occur with a tumor or aneurysm in the posterior fossa or in the jugular foramen. Hoarseness due to vocal cord paralysis, some difficulty in swallowing, deviation of the soft palate to the intact side, anesthesia of the posterior wall of the pharynx, and weakness of the upper part of the trapezius and sternocleidomastoid muscles make up the syndrome (Table 367-2, jugular foramen syndrome).

DISORDERS OF THE VAGUS NERVE

DYSPHAGIA AND DYSPHONIA

Complete interruption of the intracranial portion of one vagus nerve results in a characteristic paralysis. The soft palate droops ipsilaterally and does not rise in phonation. There is loss of the gag reflex on the affected side, as well as of the "curtain movement" of the lateral wall of the pharynx, whereby the faucial pillars move medially as the palate rises in saying "ah." The voice is hoarse and slightly nasal, and the vocal cord lies immobile midway between abduction and adduction. There may also be a loss of sensibility at the external auditory meatus and the posterior pinna.

The pharyngeal branches of both vagi may be affected in diphtheria; the voice has a nasal quality, and regurgitation of liquids through the nose occurs during the act of swallowing.

The vagus nerve may be involved at the meningeal level by neoplastic and infectious processes and within the medulla by tumors, vascular lesions (e.g., the lateral medullary syndrome of Wallenberg), and motor neuron disease. This nerve may be involved by the inflammatory lesion of herpes zoster. Polymyositis and dermatomyositis, which cause hoarseness and dysphagia by direct involvement of laryngeal and pharyngeal muscles, may be confused with diseases of the vagus nerves. Also, dysphagia is a symptom in some patients with myotonic dystrophy. *See Chap. 40 for discussion of nonneurologic forms of dysphagia.*

The recurrent laryngeal nerves, especially the left, are most often damaged as a result of intrathoracic disease. Aneurysm of the aortic arch, an enlarged left atrium, and tumors of the mediastinum and bronchi are much more frequent causes of an isolated vocal cord palsy than are intracranial disorders.

When confronted with a case of laryngeal palsy, the physician must attempt to determine the site of the lesion. If it is intramedullary, there are usually other signs, such as ipsilateral cerebellar dysfunction, loss of pain and temperature sensation over the ipsilateral face and contralateral arm and leg, and an ipsilateral Horner syndrome. If the lesion is extramedullary, the glossopharyngeal and spinal accessory nerves are frequently involved (see jugular foramen syndrome, Table 367-2). If it is extracranial in the posterior laterocondylar or retroparotid space, there may be a combination of ninth,

tenth, eleventh, and twelfth cranial nerve palsies and a Horner syndrome (Table 367-2). If there is no sensory loss over the palate and pharynx and no palatal weakness or dysphagia, the lesion is below the origin of the pharyngeal branches, which leave the vagus nerve high in the cervical region; the usual site of disease is then the mediastinum.

DISORDERS OF THE ACCESSORY NERVE

Isolated involvement of the accessory, or eleventh cranial, nerve can occur anywhere along its route, resulting in partial or complete paralysis of the sternocleidomastoid and trapezius muscles. More commonly, involvement occurs in combination with deficits of the ninth and tenth cranial nerves in the jugular foramen or after exit from the skull (Table 367-2). An idiopathic form of accessory neuropathy, akin to Bell's palsy, has been described, and it may be recurrent in some cases. Most but not all patients recover.

DISORDERS OF THE HYPOGLOSSAL NERVE

The twelfth cranial nerve supplies the ipsilateral muscles of the tongue. The nucleus of the nerve or its fibers of exit may be involved by intramedullary lesions such as tumor, poliomyelitis, or most often motor neuron disease. Lesions of the basal meninges and the occipital bones (platybasia, invagination of occipital condyles, Paget's disease) may compress the nerve in its extramedullary course or in the hypoglossal canal. Isolated lesions of unknown cause can occur. Atrophy and fasciculation of the tongue develop weeks to months after interruption of the nerve.

MULTIPLE CRANIAL NERVE PALSIES

Several cranial nerves may be affected by the same disease process. In this situation, the main clinical problem is to determine whether the lesion lies within the brainstem or outside it. Lesions that lie on the surface of the brainstem are characterized by involvement of adjacent cranial nerves (often occurring in succession) and late and rather slight involvement of the long sensory and motor pathways and segmental structures lying within the brainstem. The opposite is true of intramedullary, intrapontine, and intramesencephalic lesions. The extramedullary lesion is more likely to cause bone erosion or enlargement of the foramens of exit of cranial nerves. The intramedullary lesion involving cranial nerves often produces a crossed sensory or motor paralysis (cranial nerve signs on one side of the body and tract signs on the opposite side).

Involvement of multiple cranial nerves outside the brainstem is frequently the result of diabetes or trauma (sudden onset), localized infections such as herpes zoster (acute onset), infectious and noninfectious causes of meningitis (Chap. 374) or granulomatous diseases such as Wegener's granulomatosis (subacute onset), Behcet's disease, or tumors and enlarging saccular aneurysms (chronic development). Of the tumors, lymphomas, neurofibromas, meningiomas, chordomas, cholesteatomas, carcinomas, and sarcomas have all been observed to involve a succession of lower cranial nerves. Owing to their anatomic relationships, the multiple cranial nerve palsies form a number of distinctive syndromes, listed inTable 367-2. Sarcoidosis is the cause of some cases of multiple cranial neuropathy, and chronic glandular tuberculosis (scrofula) the cause of

a few others. Midline granuloma of the nasopharynx may also affect multiple cranial nerves, as do nasopharyngeal tumors, platybasia, basilar invagination of the skull, and the adult Chiari malformation. A purely motor disorder without atrophy always raises the question of myasthenia gravis (Chap. 380). Guillain-Barre syndrome commonly affects the facial nerves bilaterally (facial diplegia). In the Fisher variant of the Guillain-Barre syndrome, oculomotor paresis occurs with ataxia and areflexia in the limbs (Chap. 378). Wernicke encephalopathy can cause a severe ophthalmoplegia combined with other brainstem signs.

The *cavernous sinus syndrome* is a distinctive and frequently life-threatening disorder. It often presents as orbital or facial pain; orbital swelling and chemosis due to occlusion of the ophthalmic veins; fever; oculomotor neuropathy affecting the third, fourth, and sixth cranial nerves; and trigeminal neuropathy affecting the ophthalmic (V_1) and occasionally the maxillary (V_2) divisions of the trigeminal nerve. Cavernous sinus thrombosis, often secondary to infection from orbital cellulitis (frequently *Staphylococcus aureus*), a cutaneous source on the face, or sinusitis (especially with mucormycosis in diabetic patients), is the most frequent cause; other etiologies include aneurysm of the carotid artery, a carotid-cavernous fistula (orbital bruit may be present), meningioma, nasopharyngeal carcinoma or other tumor, or an idiopathic granulomatous disorder (Tolosa-Hunt syndrome). Due to the anatomy of the cavernous sinus (Fig. 367-2) the syndrome may extend to become bilateral. Early diagnosis is essential, especially in cases due to infection, and treatment depends upon the underlying etiology. In infectious cases, prompt administration of broad-spectrum antibiotics, drainage of any abcess cavities, and identification of the offending organism is essential. Anticoagulant therapy may benefit cases of primary thrombosis. Repair or occlusion of the carotid artery may be required for treatment of fistulas or aneurysms. The Tolosa-Hunt syndrome generally responds to glucocorticoids.

An idiopathic form of multiple cranial nerve involvement on one or both sides of the face is occasionally seen (see Juncos and Beal). The syndrome consists of a subacute onset of boring facial pain, followed by paralysis of motor cranial nerves. The clinical features overlap those of the Tolosa-Hunt syndrome and appear to be due to idiopathic inflammation of the dura mater, which may be visualized byMRI. The syndrome is frequently responsive to glucocorticoids.

ACKNOWLEDGEMENT

(Bibliography omitted in Palm version)

368. DISEASES OF THE SPINAL CORD - *Stephen L. Hauser*

Diseases of the spinal cord are frequently devastating. They can produce quadriplegia, paraplegia, and sensory deficits far beyond the damage they would inflict elsewhere in the nervous system because the spinal cord contains, in a small cross-sectional area, almost the entire motor output and sensory input systems of the trunk and limbs. Many spinal cord diseases are reversible if recognized and treated at an early stage (Table 368-1); thus, they are among the most critical of neurologic emergencies. The efficient use of diagnostic procedures, guided by a working knowledge of the relevant anatomy and clinical features of common spinal cord diseases, is often the key to a successful outcome.

Approach to the Patient

Spinal Cord Anatomy Relevant to Clinical Signs The spinal cord is a thin, tubular extension of the central nervous system contained within the bony spinal canal. It originates at the medulla and continues caudally to terminate at the filum terminale, a fibrous extension of the conus medullaris that terminates at the coccyx. The adult spinal cord is approximately 18 inches long, oval or round in shape, and enlarged in the cervical and lumbar regions, where neurons that innervate the upper and lower extremities, respectively, are located. The white matter tracts containing ascending sensory and descending motor pathways are located peripherally, whereas nerve cell bodies are clustered in an inner region shaped like a four-leaf clover that surrounds the central canal (anatomically an extension of the fourth ventricle). The membranes that cover the spinal cord -- the pia, arachnoid, and dura -- are continuous with those of the brainstem and cerebral hemispheres.

The spinal cord is somatotopically organized, consisting of 31 segments, each containing an exiting ventral motor root and entering dorsal sensory root (Fig. 368-1). During embryologic development, growth of the cord lags behind that of the vertebral column, and in the adult the spinal cord ends at approximately the first lumbar vertebral body. The lower spinal nerves take an increasingly downward course to exit via the appropriate intervertebral foramina. The first seven pairs of cervical spinal nerves exit above the same-numbered vertebral bodies, whereas all the subsequent nerves exit below the same-numbered vertebral bodies; this situation is due to the presence of eight cervical spinal cord segments but only seven cervical vertebrae. The approximate relationship between spinal cord segments and the corresponding vertebral bodies is shown in Table 368-2. These relationships assume importance for localization of lesions that cause spinal cord compression; a T10 spinal cord level, for example, indicates involvement of the cord adjacent to the seventh or eighth thoracic vertebral body.

LEVEL OF THE LESION The presence of a *level* below which sensory, motor, and/or autonomic function is disturbed is a hallmark of spinal cord disease. A sensory level is sought by asking the patient to identify as sharp a pinprick stimulus or as cool a cold stimulus (a dry tuning fork after immersion in cold water) applied to the low back and sequentially moved up toward the neck on each side. In general, a sensory level to pinprick or temperature, indicating damage to the spinothalamic tract, is located one to two segments below the actual level of a unilateral spinal cord lesion, but it may be at the level of the lesion when bilateral. That is because sensory fibers enter the cord at

the dorsal root, synapse in the dorsal horn, and then ascend ipsilaterally for several segments before crossing just anterior to the central canal to join the opposite spinothalamic tract. Lesions that disrupt descending corticospinal and bulbospinal tracts cause paraplegia or quadriplegia, with increased muscle tone, exaggerated deep tendon reflexes, and extensor plantar signs. Such lesions also typically produce autonomic disturbances, with disturbed sweating and bladder, bowel, and sexual dysfunction. A sweat level may be determined by drawing a spoon up the torso. There will be little resistance to movement of the spoon along the dry, nonsweating skin; at the level at which sweating begins, resistance will suddenly increase.

The uppermost level of a spinal cord lesion is often localized by attention to *segmental signs* corresponding to disturbed motor or sensory innervation by an individual cord segment. A band of altered sensation (hyperalgesia or hyperpathia) at the upper end of the sensory disturbance, fasciculations or atrophy in muscles innervated by one or several segments, or a single diminished or absent deep tendon reflex may be noted. These signs may also occur with focal root or peripheral nerve disorders; thus, segmental signs are most useful when they occur with other signs of cord disease. With severe and acute transverse lesions, the limbs may be flaccid rather than spastic (so-called spinal shock). This state may last for several days, rarely for weeks, and may be initially mistaken for extensive damage to many segments of the cord (as in ascending necrotic myelopathy associated with cancer) or as polyneuropathy. Brief clonic or myoclonic movements of the limbs often precede paralysis in acute transverse lesions, particularly those due to cord infarction.

PATTERNS OF SPINAL CORD DISEASE The location of the major ascending and descending pathways of the spinal cord are shown in Fig. 368-1. Most fiber tracts -- including the posterior columns and the spinocerebellar and pyramidal tracts -- travel ipsilateral to the side of the body they innervate. As noted above, afferent fibers mediating pain and temperature sensation are unusual in that they ascend contralaterally as the spinothalamic tract. The anatomic relationships of these various fiber tracts and nuclei produce distinctive clinical syndromes that are pathognomonic of spinal cord disease and that often provide clues to the underlying disease process.

Brown-Sequard hemicord syndrome This syndrome consists of ipsilateral weakness (pyramidal tract) and loss of joint position and vibratory sense (posterior column), with contralateral loss of pain and temperature sense (spinothalamic tract) below the lesion. The sensory level for pain and temperature is one or two levels below the lesion. Segmental signs, such as radicular pain, muscle atrophy, or loss of a deep tendon reflex, when they occur, are unilateral. Pure examples of hemicord syndromes are rare; partial or bilateral forms are more common. Partial syndromes may involve the dorsal (posterior) quadrant, producing ipsilateral loss of vibration and position sense, or ventral (anterior) quadrant with ipsilateral paralysis and contralateral loss of pain and temperature sense.

Central Cord Syndrome The central cord syndrome results from disorders of gray matter nerve cells and crossing spinothalamic tracts near the central canal. In the cervical cord, the central cord syndrome produces arm weakness out of proportion to leg weakness and a "dissociated" sensory loss consisting of loss of pain and temperature sense in a cape distribution over the shoulders, lower neck, and upper trunk with intact light touch,

joint position, and vibration sense. Trauma, syringomyelia, tumors, and anterior spinal artery ischemia are common causes of the central cord syndrome.

Anterior two-thirds syndrome This syndrome results from extensive bilateral disease of the spinal cord that spares the posterior columns. All spinal cord functions -- motor, sensory and autonomic -- are lost below the level of the lesion, with the striking exception of intact vibration and position sensation. The etiology is vascular, either thromboembolism of the anterior spinal artery or compression of this vessel by mass lesions within the spinal canal.

Intramedullary and Extramedullary Syndromes The diagnosis of spinal cord disorders frequently requires that intramedullary processes, which arise within the substance of the cord, be distinguished from extramedullary processes that compress the spinal cord or its vascular supply. Distinguishing features are relative and serve only as rough guides to clinical decision making. With extramedullary lesions, radicular pain is often prominent, and there is early sacral sensory loss (lateral spinothalamic tract) and spastic weakness in the legs (corticospinal tract) due to the superficial location of these fibers in the lateral spinal cord, which renders them susceptible to external compression. Intramedullary lesions tend to produce poorly localized burning pain rather than radicular pain and spare sensation in the perineal and sacral areas; corticospinal tract signs may appear late. With extramedullary lesions, the distinction between extradural and intradural masses is important, as the former are generally malignant and the latter benign; a long duration of symptoms favors an intradural origin.

SPECIFIC LOCALIZING SIGNS

Cervical cord High cervical cord lesions are frequently life-threatening, producing quadriplegia and weakness of respiratory muscles innervated by the phrenic nerve (C3-C5). There is diaphragmatic paralysis, and breathing is possible only by use of accessory muscles of respiration. Extensive lesions near the junction of the cervical cord and medulla are usually fatal owing to involvement of adjacent medullary centers, which results in vasomotor and respiratory collapse. Partial lesions in this area, generally due to trauma, may interrupt decussating pyramidal tract fibers destined for the legs, which cross below those of the arms, resulting in a "crural paresis" of the lower limbs. Compressive lesions near the foramen magnum may produce weakness of the ipsilateral shoulder and arm followed by weakness of the ipsilateral leg, then the contralateral leg, and finally the contralateral arm; the patient may complain of suboccipital pain spreading to the neck and shoulders. Lesions at C4-C5 produce quadriplegia with preserved respiratory function. At the midcervical (C5-C6) level, there is relative sparing of shoulder muscles and loss of biceps and brachioradialis reflexes. Lesions at C7 spare the biceps but produce weakness of finger and wrist extensors and loss of the triceps reflex. Lesions at C8 paralyze finger and wrist flexion, and the finger flexor reflex is lost. In general, cervical cord disorders are best localized by the pattern of weakness that ensues, whereas sensory deficits have less localizing value. A Horner's syndrome (miosis, ptosis, and facial hypohidrosis) may also occur ipsilateral to cervical cord lesions at any level.

Thoracic cord Lesions of the thoracic cord are best localized by identification of a sensory level on the trunk. Sensory dermatomes of the body are shown in Fig. 23-2;

useful markers are at the nipples (T4) and umbilicus (T10). Weakness of the legs and disturbances of bladder, bowel, or sexual function may also accompany damage to the thoracic cord. The abdominal wall musculature, supplied by the lower thoracic cord, is observed during movements of respiration or coughing or by asking the patient to interlock the fingers behind the head in the supine position and attempt to sit up. Lesions at T9-T10 paralyze the lower, but spare the upper, abdominal muscles, resulting in upward movement of the umbilicus when the abdominal wall contracts (Beevor's sign) and in loss of lower, but not upper, superficial abdominal reflexes (Chap. 356). With unilateral lesions, attempts to contract the abdominal wall produce movement of the umbilicus to the normal side; superficial abdominal reflexes are absent on the involved side. Midline back pain is a useful localizing sign in the thoracic region.

Lumbar cord The lumbar and sacral cord segments progressively decrease in size, and focal lesions of these segments are less easily localized than in cervical and thoracic regions. Lesions at L2-L4 paralyze flexion and adduction of the thigh, weaken leg extension at the knee, and abolish the patellar reflex. Lesions at L5-S1 paralyze movements of the foot and ankle, flexion at the knee, and extension of the thigh, and abolish the ankle jerk (S1). A cutaneous reflex useful in localization of lumbar cord disease is the cremasteric reflex (Chap. 356), which is segmentally innervated at L1-L2.

Sacral Cord/Conus Medullaris The conus medullaris is the tapered caudal termination of the spinal cord, comprising the lower sacral and single coccygeal segments. Isolated lesions of the conus medullaris spare motor and reflex functions in the legs. The conus syndrome is distinctive, consisting of bilateral saddle anesthesia (S3-S5), prominent bladder and bowel dysfunction (urinary retention and incontinence with lax anal tone), and impotence. The bulbocavernosus (S2-S4) and anal (S4-S5) reflexes are absent (Chap. 356). Muscle strength is largely preserved. Lesions of the conus medullaris must be distinguished from those of the cauda equina, the cluster of nerve roots derived from the lower cord as they descend to their exits in the intervertebral foramina. Cauda equina lesions are characterized by severe low back or radicular pain, asymmetric leg weakness or sensory loss, variable areflexia in the lower extremities, and relative sparing of bowel and bladder function. Mass lesions in the lower spinal canal may produce a mixed clinical picture in which elements of both cauda equina and conus medullaris syndromes coexist. *Cauda equina syndromes are discussed in Chap. 16.*

ACUTE AND SUBACUTE SPINAL CORD DISEASES

Acute and subacute spinal cord disorders are commonly due to extramedullary compression (tumor, infection, spondylosis, or trauma), infarction or hemorrhage, or inflammation. In this category are some of the most dangerous -- and treatable -- disorders in clinical practice. Early recognition is the key to successful management. Epidural compression due to malignancy often presents with warning signs, generally neck or back pain, bladder disturbances, or sensory symptoms, that precede the development of paralysis. Infarction, hemorrhage, or spinal subluxation is more likely to produce sudden "strokelike" myelopathy without antecedent symptoms.

NEOPLASTIC SPINAL CORD COMPRESSION

Neoplasms of the spinal canal may be extramedullary (epidural or intradural) or

intramedullary. In adults, most neoplasms are epidural in origin, resulting from metastases to the adjacent vertebral body, spinous or transverse process, or pedicle. Vertebral metastases are essentially bone-marrow metastases, and the propensity of solid tumors to metastasize to the vertebral column probably reflects the high percentage of bone marrow located in the axial skeleton of older individuals. Retroperitoneal neoplasms (especially lymphomas or sarcomas) may enter the spinal canal through the intervertebral foramina; typically they produce radicular pain and other signs of root involvement prior to cord compression. Almost any malignant tumor can metastasize to the spinal canal, although breast, lung, prostate, kidney, lymphoma, and plasma cell dyscrasia are particularly frequent. The thoracic cord is most commonly involved; exceptions are metastases from prostate and ovarian cancer, which occur disproportionately in the sacral and lumbar vertebrae, perhaps resulting from spread through Batson's plexus, a network of veins along the anterior surface of the spinal cord in the epidural space.

Pain is the initial symptom; it may be either aching and localized or sharp and radiating in quality. Pain indicates displacement of pain-sensitive structures, especially periosteum and meninges. The pain worsens with movement, coughing, or sneezing and may awaken patients at night. The recent onset of back pain, particularly if in the thoracic spine (which is uncommonly involved by spondylosis), should prompt consideration of vertebral metastasis. Rarely, pain is mild or absent. Pain typically precedes signs of cord compression by weeks or even months, but once cord compression occurs, it is always progressive and may advance rapidly. Therapy is effective only if administered early, when signs of cord dysfunction are mild or absent; therapy will not reverse a complete paralysis that has been present for>48 h. These realities highlight the importance of prompt recognition and efficient management of these lesions.

Plain radiographs of the spine and radionuclide bone scans have only a limited role in diagnosis because they fail to identify 15 to 20% of metastatic vertebral lesions and may miss paravertebral masses that reach the epidural space by growth through the intervertebral foramina. Magnetic resonance imaging (MRI) provides excellent anatomic resolution of the site and extent of the tumor (Fig. 368-2); at most centers, MRI has largely replaced computed tomography (CT) and myelography in the diagnosis of epidural masses. MRI can often distinguish between malignant lesions and other masses -- epidural abscess, tuberculoma, or epidural hemorrhage, among others -- that present in a similar fashion. Vertebral metastases are usually hypointense relative to a normal bone marrow signal on T1-weighted MRI scans; after the administration of gadolinium, contrast enhancement may "normalize" the appearance of the tumor by increasing its intensity to that of normal bone marrow. In contrast to infection, vertebral metastases typically do not cross the disk space. Nonetheless, it can be difficult to distinguish between infection and malignancy by MRI.

Because imaging resources are scarce, and both cancer and back pain are common, it is important to convey to the radiologist an estimate of the urgency of the imaging procedure requested. If signs of spinal cord involvement are present, imaging should be obtained on an emergency basis. If there are radicular symptoms but no evidence of myelopathy, it is usually safe to defer imaging for 24 to 48 h. With back or neck pain only, imaging studies should be obtained within a few days. Finally, up to 40% of

patients who present with symptomatic disease at one level are found to have asymptomatic epidural disease elsewhere; thus, the entire spine should be imaged in all patients with epidural malignancy.

TREATMENT

Management includes glucocorticoids to reduce interstitial edema, local radiotherapy (initiated as early as possible) to the symptomatic lesion, and specific therapy for the underlying tumor type. Glucocorticoids (dexamethasone, 40 mg daily) can be administered before the imaging study if the clinical suspicion is strong and continued at a lower dose (20 mg daily in divided doses) until radiotherapy (a total of 3000 cGy administered in 15 daily fractions) is completed. Radiotherapy appears to be as effective as surgery, even for classically radioresistant metastases. Biopsy of the epidural mass is usually unnecessary in patients with known preexisting cancer, but biopsy is indicated if a history of underlying cancer is lacking. Surgery, either decompression or vertebral body resection, should be considered when signs of cord compression worsen despite radiotherapy, when the maximum tolerated dose of radiotherapy has been delivered previously to the site, or when a vertebral compression fracture contributes to cord compression. A good response to radiotherapy can be expected in individuals who are ambulatory at presentation; new weakness is prevented, and some recovery of motor function occurs in approximately half of treated patients. Fixed motor deficits -- paraplegia or quadriplegia -- do not usually respond to either radiotherapy or surgery.

In contrast to tumors of the epidural space, most intradural mass lesions are slow-growing and benign. Meningiomas and neurofibromas account for most of these lesions, with occasional cases representing chordoma, lipoma, dermoid, or sarcoma. Meningiomas (Fig. 368-3) are often located posterior to the thoracic cord or near the foramen magnum, although they can arise from the meninges anywhere along the spinal canal. Neurofibromas are benign tumors of the nerve sheath that typically arise near the posterior root; when multiple, neurofibromatosis (Chap. 370) is the likely etiology. Symptoms usually begin with radicular sensory symptoms followed by an asymmetric, progressive spinal cord syndrome. Therapy is surgical resection.

Primary intramedullary tumors of the spinal cord are uncommon. They typically present as central cord or hemicord syndromes, often in the cervical region; there may be poorly localized burning pain in the extremities and sparing of sacral sensation. In adults, most of these lesions are either ependymomas, hemangioblastomas, or low-grade astrocytomas (Fig. 368-4). Complete resection of an intramedullary ependymoma is often possible with microsurgical techniques. Debulking of an intramedullary astrocytoma can also be helpful, as these are often slowly growing lesions; the value of adjunctive radiotherapy is uncertain. Secondary (metastatic) intramedullary tumors are rare.

SPINAL CORD INFARCTION

The spinal cord is supplied by three arteries that course vertically over its surface, a single anterior spinal artery, and paired posterior spinal arteries. At each segment, paired penetrators branching from the anterior spinal artery supply the anterior two-thirds of the spinal cord; the posterior spinal arteries, which often become less

distinct below the midthoracic level, supply the posterior columns. Rostrally, the spinal arteries arise from the vertebral arteries. During embryogenesis, arterial feeders arise at each segmental level, but most involute before birth; generally, between three and eight major feeders remain, arising from the vertebral, subclavian, intercostal (off the aorta), iliac, and sacral arteries. In addition to the vertebral arteries, in adults, anterior spinal artery feeders often occur at C6, at an upper thoracic level, and at T11-L2 (artery of Adamkiewicz). Feeders from the aorta are more likely to arise from the left side.

Spinal cord ischemia can occur at any level. The signs are determined by the level of the lesion and by the individual vascular anatomy, including areas of watershed flow and potential for anastomosis. The anterior spinal artery is discontinuous in some individuals, increasing the importance of feeders to the lower cord. With systemic hypotension, cord infarction occurs at the level of greatest ischemic risk, often T3-T4, and also at boundary zones between the anterior and posterior spinal artery territories. The latter may result in an acute -- or more commonly progressive -- syndrome of weakness and spasticity with little sensory change resembling amyotrophic lateral sclerosis (ALS).

Acute infarction in the territory of the anterior spinal artery produces paraplegia or quadriplegia, dissociated sensory loss affecting pain and temperature sense but sparing vibration and position sense, and loss of sphincter control. Onset may be sudden and dramatic or progressive over minutes or hours. Sharp midline or radiating back pain localized to the area of ischemia is frequently noted. Partial infarction of one anterior hemicord (hemiplegia or monoplegia and crossed pain and temperature loss) may also occur. Areflexia due to spinal shock is often present initially; with time, hyperreflexia and spasticity appear.

The acute onset of pain, sparing of posterior column function, and sharply demarcated spinal cord level distinguish anterior spinal artery infarction from epidural spinal cord compression, in which pain is often chronic, posterior column sense is impaired, and a cord level is indistinct. An exception to this rule is when epidural tumors compress or invade vascular structures, resulting in an anterior spinal artery syndrome. Infarction in the territory of the posterior spinal arteries, resulting in loss of posterior column function, also occurs and may be underrecognized as a cause of loss of position and vibration sense.

Spinal cord infarction is associated with aortic atherosclerosis, dissecting aortic aneurysm (chest or back pain with diminished pulses in legs), or hypotension from any cause. Cardiogenic emboli, vasculitis related to collagen vascular disease, and surgical clipping of aortic aneurysms are other predisposing conditions. Occasional cases develop either during pregnancy or after acute back trauma or exercise that by an unknown mechanism leads to embolism of nucleus pulposus material into spinal vessels. In a substantial number of cases, no cause can be found, and thromboembolism in arterial feeders is suspected.

MRIis often normal but is useful to exclude other causes of acute myelopathy, in particular epidural compression, spinal cord hemorrhage (hematomyelia), infectious myelitis, or transverse myelitis. Lumbar puncture is indicated whenever the underlying cause has not been clarified by MRI. Other useful laboratory studies include a

sedimentation rate to search for an underlying vasculitis, Venereal Disease Research Laboratories test, and evaluation for aortic or cardiac disease or for a hypercoagulable state.

Therapy is directed at treatment of any predisposing condition. In cord infarction due to presumed thromboembolism, anticoagulation is probably not indicated, with the exception of the unusual transient ischemic attack or incomplete infarction with a stuttering or progressive course.

EPIDURAL HEMATOMA

Hemorrhage into the epidural (or subdural) space can compress the spinal cord or roots. Presenting symptoms are the acute onset of focal or radicular pain followed by variable signs of a spinal cord or conus medullaris disorder. Trauma, tumor, or blood dyscrasias are predisposing conditions. Rare cases complicate lumbar puncture or epidural anesthesia, sometimes in association with use of low-molecular-weight heparin. Epidural hematoma can also occur on an idiopathic basis.MRIconfirms the clinical suspicion and can delineate the extent of the bleed. Extrinsic spinal cord compression from any cause is a medical emergency, and appropriate treatment consists of prompt recognition, reversal of any underlying clotting disorder, and emergency surgical decompression. Surgery may be followed by substantial recovery, especially in patients with some preservation of motor function preoperatively. Because of the risk of hemorrhage, lumbar puncture should be avoided whenever possible in patients with thrombocytopenia or other coagulopathies (including those due to therapeutic anticoagulation) until the underlying bleeding disorder is reversed.

HEMATOMYELIA

Hemorrhage into the substance of the spinal cord is rare. It may result from trauma, an intraparenchymal vascular malformation (see below), vasculitis due to polyarteritis nodosa or lupus erythematosus, bleeding disorders, or spinal cord infection or neoplasm. Hematomyelia presents as an acute painful transverse myelopathy. With large lesions, extension into the subarachnoid space may occur, resulting in subarachnoid hemorrhage (Chap. 361). Diagnosis is best made byMRI. Therapy is supportive, and surgical intervention is generally not useful. An exception is hematomyelia due to an underlying vascular malformation; in such cases, selective spinal angiography may be indicated, followed by acute surgical intervention to evacuate the clot and remove the underlying vascular lesion.

EPIDURAL ABSCESS

Spinal epidural abscess presents as a clinical triad of pain, fever, and rapidly progressive weakness. Prompt recognition of this distinctive and treatable medical emergency will in most cases prevent severe and permanent sequelae. Epidural abscesses can form anywhere along the spinal canal. Pain is almost always present, either midline along the spine or radicular in type. The duration of pain prior to presentation is generally two weeks or less, but in some chronic cases it may be several months or longer. Fever is common, often accompanied by an elevated white blood cell count or sedimentation rate. As the abscess expands, spinal cord injury results from

venous congestion and thrombosis, thrombophlebitis of the epidural space, spinal artery disease, or cord compression. Once weakness and other signs of myelopathy appear, progression is often rapid, although it may be gradual.

Risk factors include impaired immune status (diabetes mellitus, renal failure, alcoholism, malignancy), intravenous drug abuse, and infections of the skin or other tissues. Two-thirds of epidural infections result from hematogenous spread from the skin (furunculosis), soft tissue (pharyngeal or dental abscesses), or deep viscera (bacterial endocarditis). One-third result from direct extension of a local infection to the subdural space; examples of local predisposing conditions are vertebral osteomyelitis, decubitus ulcers, or iatrogenic complications of lumbar puncture, epidural anesthesia, or spinal surgery.

Most cases are due to *Staphylococcus aureus*; gram-negative bacilli, *Streptococcus*, anaerobes, and fungi can also cause epidural abscesses. Tuberculosis from an adjacent vertebral source remains an important cause in the underdeveloped world. As the population ages and the number of immunosuppressed individuals increases, an increase in the incidence of spinal epidural abscess (currently 2 per 1000 hospital admissions) has been noted.

MRIscans (Fig. 368-5) localize the abscess and exclude a primary intraparenchymal lesion, for example, transverse myelitis or hematomyelia. Lumbar puncture is often not required but may be indicated if encephalopathy or other clinical signs raise the question of associated meningitis, which is present in fewer than 25% of cases. In such situations, the level of the tap should be planned carefully to minimize the risk of inducing either meningitis by passage of the needle through infected tissue or herniation from decompression below an area of obstruction to the flow of cerebrospinal fluid (CSF). A high cervical tap is often the safest approach. CSF abnormalities in subdural abscess consist of pleocytosis with a preponderance of polymorphonuclear cells, an elevated protein level, and a reduced glucose level. Blood cultures are positive in <25% of cases.

TREATMENT

Treatment is emergency decompressive laminectomy with debridement combined with long-term antibiotic treatment. Surgical evacuation prevents development of paralysis and may improve or reverse paralysis in evolution, but it is unlikely to improve deficits of more than several days duration. Antibiotics should be started empirically before surgery, modified on the basis of culture results, and usually continued for at least 4 weeks. If surgery is contraindicated or if there is a fixed paraplegia or quadriplegia that is unlikely to improve following surgery, long-term administration of systemic and oral antibiotics can be used; in such cases, coverage may be guided by results of positive blood cultures. However, paralysis may develop or progress during antibiotic therapy; thus, initial surgical management remains the treatment of choice.

TRANSVERSE MYELITIS

Transverse myelitis is an acute or subacute, generally monophasic, inflammatory disorder of the spinal cord. The initial symptom is focal neck or back pain, followed by

various combinations of paresthesias, sensory loss, motor weakness, and sphincter disturbance evolving within hours to several days. There may be mild sensory symptoms only, or a devastating functional transection of the cord. Partial forms may selectively involve posterior columns, anterior spinothalamic tracts, or one hemicord. Dysesthesias may begin in the feet and ascend either symmetrically or asymmetrically, earlier in one leg than in the other; these symptoms may initially raise a question of Guillain-Barre syndrome, but involvement of the trunk with a sharply demarcated spinal cord level indicates the myelopathic nature of the process. In severe cases, areflexia indicating spinal shock may be present, but hyperreflexia soon supervenes; persistent areflexic paralysis indicates necrosis over multiple segments of the spinal cord.

Up to 40% of cases are associated with an antecedent infection or recent vaccination. Many infectious agents have been implicated, including influenza, measles, varicella, rubeola, mumps, and Epstein-Barr virus and cytomegalovirus, as well as *Mycoplasma*. As in the related disorder acute disseminated encephalomyelitis (Chap. 371), transverse myelitis often begins as the patient appears to be recovering from the infection, and infectious agents have not been isolated from the nervous system of affected individuals. These features suggest that transverse myelitis results from an autoimmune response triggered by infection and not from direct infection of the spinal cord.

Multiple sclerosis (MS) (see below) may present initially as transverse myelitis. MS-associated transverse myelitis usually is not associated with an antecedent infection or vaccination. Devic's disease (Chap. 371) is a demyelinating disorder that presents as transverse myelitis associated with optic neuritis that is typically bilateral. Transverse myelitis, at times recurrent, has also been associated with systemic lupus erythematosus and other collagen-vascular diseases, Sjogren's syndrome, and Behcet's disease; sarcoidosis may produce a subacute transverse myelopathy with severe cord swelling.

MRIfindings consist of variable swelling of the cord and diffuse or multifocal areas of abnormal bright signal on T2-weighted sequences, often extending over several cord segments. Contrast enhancement, indicating disruption in the blood-brain barrier associated with perivenous inflammation, is present in acute cases. MRI is also useful to exclude cord compression. A brain MRI should be obtained in all cases to assess the likelihood that the transverse myelitis represents an initial attack ofMS. A normal scan indicates that the risk of evolution to MS is low -- approximately 5% over 3 to 5 years; by contrast, the finding of multiple periventricular T2-bright lesions indicates a risk of 50% or greater over the same time period.CSF may be normal, but more often there is pleocytosis, with up to several hundred mononuclear cells per microliter; in severe or rapidly evolving cases, polymorphonuclear cells may be present. CSF protein levels are normal or at most mildly elevated; oligoclonal banding is a variable finding but, when present, is associated with future evolution to MS.

There are no prospective trials of therapy. Intravenous methylprednisolone (500 mg qd for 3 days) followed by oral prednisone (1 mg/kg per day for several weeks, then gradual taper) is used for treatment of moderate to severe symptoms.

ACUTE INFECTIOUS MYELOPATHIES

These inflammatory disorders result from direct invasion of the spinal cord by infectious agents. Bacterial etiologies are rare; almost any pathogenic species may be responsible and in one recent review *Listeria monocytogenes* was most frequently identified. Poliomyelitis is the prototypic virus that produces acute infection of the spinal cord. Herpes zoster is currently the most common viral cause of acute myelitis; cytomegalovirus, herpes simplex virus type 1, Epstein-Barr virus, and rabies virus have been identified in occasional cases. Herpes simplex virus type 2 may produce a recurrent sacral myelitis, which could be mistaken for MS, in association with outbreaks of genital herpes.*Viral infections of the spinal cord are discussed in Chap. 373.*

Schistosomiasis (Chap. 222) is an important cause of parasitic myelitis worldwide. The myelitis is intensely inflammatory and granulomatous in nature, caused by a local response to tissue-digesting enzymes produced by ova from the parasite. Toxoplasmosis (Chap. 217) can cause a focal myelopathy, and this diagnosis should be considered in patients with AIDS owing to the high frequency of nervous system toxoplasmosis in this population.

CHRONIC MYELOPATHIES

SPONDYLITIC MYELOPATHY

Neck and shoulder pain with stiffness are early symptoms; pressure on nerve roots results in radicular arm pain, most often in a C5 or C6 distribution. Compression of the cervical cord produces a slowly progressive spastic paraparesis, at times asymmetric, and often accompanied by paresthesias in the feet and hands. Vibratory sense is frequently diminished in the legs, and occasionally there is a sensory level for vibration on the upper thorax. Coughing or straining often produces leg weakness or radiating arm or shoulder pain. Dermatomal sensory loss in the arms, atrophy of intrinsic hand muscles, increased deep tendon reflexes in the legs, and extensor plantar responses are common. Urinary urgency or incontinence occurs in advanced cases. Reflexes in the arms are often diminished at some level, often the biceps (C5-C6). In individual cases, radicular, myelopathic, or combined signs may predominate. The diagnosis should be considered in cases of progressive cervical myelopathy, paresthesias of the feet and hands, or wasting of the hands. Spondylitic myelopathy is also one of the most common causes of gait difficulty in the elderly.

Diagnosis is best made by MRI. Extrinsic compression is appreciated on axial views, and T2-weighted sequences may reveal abnormal areas of high signal intensity within the cord adjacent to the site of compression. Definitive therapy consists of surgical relief of the compression, generally by posterior laminectomy. When that is not feasible, an anterior approach with resection of the protruded disc material may be required.*Cervical spondylosis and related degenerative diseases of the spine are discussed in Chap. 16.*

VASCULAR MALFORMATIONS

Although uncommon, vascular malformations are important lesions because they represent a treatable cause of progressive myelopathy. Arteriovenous malformations (AVMs) are most often located posteriorly, within the dura or along the surface of the

cord, at or below the midthoracic level. The typical presentation is a middle-aged man with a progressive myelopathy. The myelopathy may worsen slowly or rapidly or may have periods of apparent remission with superimposed worsenings resemblingMS. Acute deterioration due to hemorrhage into the spinal cord or subarachnoid space may also occur. At presentation, most patients have sensory, motor, and bladder disturbances. The motor disorder may predominate and produce a mixture of upper and lower motoneuron signs, simulatingALS. Pain, either dysesthesias or radicular pain, is also common. Other symptoms suggestive of AVM include intermittent claudication (symptoms that appear with exercise and are relieved by rest), or an effect of posture, menses, or fever on symptoms. A rare AVM syndrome presents as a progressive thoracic myelopathy with paraparesis developing over weeks or several months, associated with abnormally thick, hyalinized vessels (Foix-Alajouanine syndrome).

AVMslocated at cervical or upper thoracic levels are distinctive; they occur equally in males and females, tend to be located anterior rather than posterior to the cord, often have an intramedullary component to the malformation, and may bleed (see "Hematomyelia," above).

Examination of the skin overlying the spine may reveal a vascular lesion, lipoma, or area of altered pigmentation, all clues to a spinal cordAVM. Bruits are rare but should be sought at rest or after exercise. High-resolutionMRI with contrast administration detects most AVMs (Fig. 368-6). A small number of AVMs not detected by MRI may be visualized byCTmyelography as enlarged vessels along the surface of the cord. Definitive diagnosis requires selective spinal angiography, which will also define the vascular feeders and extent of the malformation. Embolization with occlusion of the major feeding vessels may stabilize a progressive neurologic deficit or produce a gradual recovery.

RETROVIRUS-ASSOCIATED MYELOPATHIES

The myelopathy associated with the human T cell lymphotropic virus type I (HTLV-I) presents as a slowly progressive spastic paraparesis with variable sensory and bladder disturbance. The myelopathy is typically thoracic. Approximately half of patients have back or leg pain. Signs may be asymmetric, may lack a well-defined sensory level, and may spare upper extremity function, although hyperreflexia in the arms is common. Onset is generally insidious, and the tempo of progression is variable, but most patients are nonambulatory within 10 years of onset. This presentation may resemble primary progressiveMS or a thoracicAVM. Diagnosis is made by demonstration ofHTLV-I-specific antibody in serum by enzyme-linked immunosorbent assay (ELISA), confirmed by radioimmunoprecipitation or Western blot analysis of specific antibody directed against protein products of the viral *gag* and *env* genes. There is no effective treatment; symptomatic therapy for spasticity and bladder symptoms may be helpful. *HTLV-I infections of the nervous system are discussed in Chap. 373.*

A progressive myelopathy may also occur in AIDS, characterized by vacuolar degeneration of the posterior and lateral tracts resembling subacute combined degeneration (see below).

SYRINGOMYELIA

Syringomyelia is a cavitary expansion of the spinal cord that may produce a progressive myelopathy. Syrinxes commonly occur in the lower cervical/high thoracic region or in the high cervical region, where they may extend rostrally to the medulla or pons (syringobulbia); any region of the spinal cord may be involved. More than half of all cases are associated with Chiari malformations. In the Chiari type 1 malformation, the cerebellar tonsils protrude through the foramen magnum and into the cervical spinal canal; when this abnormality is associated with protrusion of meninges (meningocele) or meninges and cord (meningomyelocele) through a spinal canal that has incompletely closed, it is designated a Chiari type 2 (or Arnold-Chiari) malformation. Acquired cases are often associated with trauma, inflammatory spinal cord disorders such as transverse myelitis, chronic arachnoiditis due to tuberculosis or other etiologies, or spinal cord tumors. Occasional cases are idiopathic.

Syringomyelia has been proposed to result from interference with the normal outflow of CSF from the fourth ventricle to the subarachnoid space due to obstruction of the foramina of Luschka and Magendie. This blockage leads to downward pressure on the cervical spinal cord and progressive syrinx formation. However, syringomyelia may occur without foraminal obstruction, indicating that other factors, for example interference with normal upward CSF flow in the spinal canal, may also be important. Syrinxes associated with Chiari type 1 malformations generally communicate freely with the subarachnoid space, and the syrinx fluid resembles normal CSF; by contrast, in many acquired cases the syrinx cavities do not communicate, and the fluid is proteinaceous.

The classic presentation is a central cord syndrome with dissociated sensory loss and areflexic weakness in the upper limbs. The sensory deficit consists of loss of pain and temperature sensation which is "suspended" over the nape of the neck, shoulders, and upper arms in a cape distribution or is in the hands; vibration and position sensation is largely preserved. Most cases begin asymmetrically with unilateral sensory loss. Muscle wasting in the lower neck, shoulders, arms, and hands with asymmetric or absent reflexes reflects extension of the cavity to the anterior horns. As the lesion enlarges, spasticity and weakness of the legs, bladder and bowel dysfunction, and, in some cases, a Horner's syndrome appear. Thoracic kyphoscoliosis is a frequent additional finding. Some patients develop numbness and sensory loss on the face from damage to the descending tract of the trigeminal nerve (C2 level or above). With Chiari malformations, cough headache, and neck, arm, or facial pain are common. Syringobulbia may present as palatal or vocal cord paralysis, dysarthria, horizontal or vertical nystagmus, episodic dizziness, and/or tongue weakness.

Symptoms typically begin insidiously in adolescence or early adulthood, progress irregularly, and may undergo spontaneous arrest for several years. Onset or sudden deterioration may follow trauma, neck manipulation or extension, or severe cough. Symptoms of syringobulbia may progress rapidly.

MRIscans accurately identify syrinx cavities and associated spinal cord enlargement (Fig. 368-7). In all cases, MRI scans of the brain and the entire spinal cord should be obtained to delineate the full extent of the syrinx, assess posterior fossa structures, and determine whether hydrocephalus is present. If a Chiari malformation is not found, a

contrast-enhanced MRI scan should be obtained to search for abnormal enhancement from an associated spinal cord tumor.

TREATMENT

Treatment is surgical. Syringomyelia associated with tonsillar herniation is treated with posterior fossa decompression, generally consisting of suboccipital craniectomy, upper cervical laminectomy, and placement of a dural graft. If obstruction of fourth ventricular outflow is present, flow is reestablished by enlargement of the opening. If the syrinx cavity is large, some surgeons recommend direct decompression of the fluid cavity, but the added benefit of this procedure is uncertain, and morbidity may occur. With Chiari malformations, shunting of hydrocephalus should generally precede any attempt to correct the syrinx. Surgical results are often excellent, with stabilization of the neurologic deficit in most cases; some patients have improvement postoperatively. Syringomyelia secondary to trauma or infection is treated with a decompression and drainage procedure in which a small shunt is inserted between the syrinx cavity and the subarachnoid space. Finally, syringomyelia due to an intramedullary spinal cord tumor is managed by resection of the tumor if feasible; decompression of the cyst cavity may produce temporary relief, but recurrence is common.

MULTIPLE SCLEROSIS

Spinal cord involvement is common in MS. It may develop acutely as an exacerbation in a patient with known MS or appear as the presenting manifestation of the disease (see "Transverse Myelitis," above). Chronic progressive myelopathy is the most frequent cause of disability in both primary progressive and secondary progressive forms of MS. Involvement is typically asymmetric, producing motor, sensory, and bladder/bowel disturbances. Diagnosis is facilitated by identification of earlier attacks that may not be initially recalled by the patient; by MRI, CSF and evoked response testing; and by exclusion of other conditions. The diagnosis may be particularly difficult to establish in patients with primary progressive MS. Therapy with interferon b or glatiramer acetate is indicated for many patients with MS-related myelopathy that is not due to primary progressive MS. *MS is discussed in Chap. 371.*

SUBACUTE COMBINED DEGENERATION (VITAMIN B$_{12}$DEFICIENCY)

This treatable myelopathy presents with parasthesias in the hands and feet, early loss of vibration and position sensation, and a progressive spastic and ataxic weakness. Loss of reflexes due to a superimposed peripheral neuropathy, present in many patients, is an important diagnostic clue. Optic atrophy and irritability and other mental changes may be prominent in advanced cases and on occasion are the presenting symptoms (megaloblastic madness). The myelopathy of subacute combined degeneration tends to be diffuse rather than focal; signs are generally symmetric and reflect predominant involvement of the posterior and lateral tracts. The diagnosis is confirmed by the finding of a low serum B$_{12}$concentration, elevated levels of homocysteine and methylmalonic acid in uncertain cases, and a positive Schilling test (Chap. 75).

TABES DORSALIS

Tabes dorsalis and meningovascular syphilis of the spinal cord are presently rare but must be considered in the differential diagnosis of spinal cord syndromes, in particular those that arise in individuals infected with HIV. The most common symptoms of tabes are characteristic fleeting and repetitive, lancinating pains, which occur mostly in the legs and less commonly in the back, thorax, abdomen, arms, and face. Ataxia of the legs and gait due to loss of position sense occurs in half of patients. Paresthesias, bladder disturbances, and acute abdominal pain with vomiting (visceral crisis) occur in 15 to 30% of patients. The cardinal signs of tabes are loss of reflexes in the legs, impaired position and vibratory sense, Romberg's sign, and bilateral Argyll Robertson pupils, which fail to constrict to light but react with accommodation.

FAMILIAL SPASTIC PARAPLEGIA

Occasional cases of progressive myelopathy occur on a familial basis. Most present with progressive spasticity and weakness in the legs. Sphincter disturbances and mild degrees of sensory loss may also be present. On examination, a sharply defined spinal cord level is not detected, in contrast to many focal spinal cord disorders. In some families, whose condition is referred to as "complicated" familial spastic paraplegia, additional neurologic signs, for example, nystagmus, ataxia, or optic atrophy, occur. Onset may be as early as the first year of life or as late as middle adulthood. The genetic basis of several forms of familial spastic paraplegia is now known (Table 368-3). No disease-modifying therapy exists.

ADRENOMYELONEUROPATHY

This X-linked disorder, a variant of adrenoleukodystrophy, most commonly presents as a progressive spastic paraparesis beginning in early adulthood; some patients also have a mild peripheral neuropathy. Affected males usually have a history of adrenal insufficiency beginning in childhood. Rare heterozygous females may also present with adult-onset myelopathy. Diagnosis is usually made by demonstration of elevated levels of very long chain fatty acids in plasma and in cultured fibroblasts. The responsible gene, located at Xq17-28, encodes a protein involved in peroxysomal transport. Steroid replacement is indicated if hypoadrenalism is present, and bone marrow transplantation has been attempted for this condition without clear evidence of efficacy.

OTHER CHRONIC MYELOPATHIES

Primary lateral sclerosis (Chap. 365) is characterized by progressive spasticity with weakness, often accompanied by dysarthria and dysphonia. Sensory function is spared. The disorder resembles ALS, but there is no evidence of a lower motor neuron disturbance. Toxic causes include (1) lathyrism due to ingestion of chick peas containing the excitotoxin b-*N*-oxalylaminoalanine (BOAA) and seen primarily in the undeveloped world, and (2) nitrous oxide inhalation producing a myelopathy identical to subacute combined degeneration. Systemic lupus erythematosus (Chap. 311) and Sjogren's syndrome (Chap. 314) have both been associated with progressive myelopathy. Cancer-related causes include chronic paraneoplastic myelopathy (Chap. 101) or radiation injury (Chap. 370). Finally, in some patients the etiology of a chronic myelopathy may not be determined initially. A cause can ultimately be identified in most

idiopathic cases and thus periodic reassessment is essential.

*Traumatic spinal cord lesions are discussed in Chap. 369.

MEDICAL REHABILITATION OF SPINAL CORD DISORDERS

The prospects for significant recovery from an acute spinal cord lesion fade after approximately 4 months. There are currently no effective means to promote repair of injured spinal cord tissue; promising experimental approaches include the use of factors that influence reinnervation by axons of the corticospinal tract or nerve graft bridges that promote reinnervation across spinal cord lesions. The disability associated with irreversible spinal cord damage is determined primarily by the level of the lesion and by whether the disturbance in function is complete or incomplete (Table 368-4). Even a complete high cervical cord lesion may be compatible with a productive life. Development of a rehabilitation plan framed by realistic expectations, and attention to the neurologic, medical, and psychological complications that commonly arise, are primary goals of treatment.

The usual symptoms associated with medical illnesses may be lacking, because of the destruction of afferent pain pathways in the cord. Unexplained fever, worsening of spasticity, or deterioration in neurologic function should prompt search for an underlying cause such as infection, thrombophlebitis, or an intraabdominal pathology; these etiologies are far more likely to be responsible than primary neurologic events such as meningitis, secondary syringomyelia, or chronic arachnoiditis. The loss of normal thermoregulation and inability to maintain normal body temperature can produce recurrent fever (*quadriplegic fever*), although most episodes of fever are due to infection of the urinary tract, lung, skin, or bone.

Bladder dysfunction generally results from loss of supraspinal innervation of the detrusor muscle of the bladder wall and the sphincter musculature. Detrusor spasticity is treated with anticholinergic drugs (oxybutinin, 2.5 to 5 mg qid) or tricyclic antidepressants with anticholinergic properties (imipramine, 25 to 200 mg/d). Failure of the sphincter muscle to relax during bladder emptying (urinary dyssynergia) may be managed with the a-adrenergic blocking agent terazosin hydrochloride (1 to 2 mg tid or qid), with intermittent catheterization, or, if that is not feasible, by use of a condom catheter in men or a permanent indwelling catheter. Surgical options include the creation of an artificial bladder by isolating a segment of intestine that can be catheterized intermittently (enterocystoplasty) or can drain continuously to an external appliance (urinary conduit). Bladder areflexia due to acute spinal shock or conus lesions is best treated by catheterization.

Bladder dysfunction predisposes the patient to urinary tract infection. Bacteriuria due to asymptomatic colonization is extremely common and is generally not treated. Prophylaxis with antiseptics or antibiotics is of little value. Urinary tract infections may present only as foul-smelling urine or a change in voiding pattern; the development of high fever or other systemic signs often indicates pyelonephritis. Bowel regimens and disimpaction are necessary in most patients to ensure at least biweekly evacuation and avoid colonic distention or obstruction.

High cervical cord lesions cause various degrees of mechanical respiratory failure requiring artificial ventilation. In cases of incomplete respiratory failure, chest physical therapy is useful, and a negative-pressure cuirass may alleviate atelectasis, particularly if the major lesion is below C4. With severe respiratory failure, tracheal intubation, followed by tracheotomy, provides tracheal access for ventilation and suctioning. Phrenic nerve pacing may be useful in some patients with lesions at C5 or above.

Patients with acute cord injury are at high risk for venous thrombosis and pulmonary embolism. During the first two weeks, use of calf-compression devices and anticoagulation with heparin (5000 U subcutaneously every 12 h) or warfarin (INR, 2 to 3) are recommended. In cases of persistent paralysis, anticoagulation should probably be continued for 3 months.

Prophylaxis against decubitus ulcers should involve frequent changes in position in a chair or bed, the use of special mattresses, and cushioning of areas where pressure sores often develop, such as the sacral prominence and heels. Early treatment of ulcers with careful cleansing, surgical or enzyme debridement of necrotic tissue, and appropriate dressing and drainage may prevent infection of adjacent soft tissue or bone.

Spasticity (Chap. 22) is often a late manifestation of spinal cord disease, occurring weeks or even months after the initial insult. Stretching exercises are useful to maintain mobility of joints. Drug treatment is effective but may result in reduced function, as some patients use their spasticity as an aid to stand, transfer, or walk. Baclofen (15 to 240 mg/d in divided doses) is the most effective drug available; it acts by facilitating GABA-mediated inhibition of motor reflex arcs. Diazepam acts by a similar mechanism and is useful for leg spasms that interrupt sleep (2 to 4 mg at bedtime). For nonambulatory patients, the direct muscle inhibitor dantrolene (25 to 100 mg qid) may be used, but it is potentially hepatotoxic. In severe cases, intrathecal baclofen administered via an implanted pump, botulinum toxin injections, or dorsal rhizotomy may be required to control spasticity.

Paroxysmal autonomic hyperreflexia may occur following lesions above the major splanchnic sympathetic outflow at T6. Headache, flushing, and diaphoresis above the level of the lesion, and hypertension with bradycardia or tachycardia, are the major symptoms. The trigger is typically a noxious stimulus -- for example, bladder or bowel distention, a urinary tract infection, or a decubitus ulcer -- below the level of the cord lesion. Ascending sensory fibers are thought to activate, via interneurons, sympathetic neurons of the intermediolateral nuclei in the thoracic spinal cord, producing vasoconstriction, tachycardia, and systemic hypertension. Reflex pathways, activated by carotid and aortic baroreceptors and projecting to the central nervous system via the vagus and glossopharyngeal nerves, then inhibit sympathetic activity above the cord lesion, producing vasodilation, but below the lesion descending pathways are blocked and sympathetic hyperactivity continues. Treatment consists of removal of offending stimuli; ganglionic blocking agents (mecamylamine, 2.5 to 5 mg) or other short-acting antihypertensive drugs are useful in some patients (see review by Colachis).

(Bibliography omitted in Palm version)

369. TRAUMATIC INJURIES OF THE HEAD AND SPINE - *Allan H. Ropper*

Head injuries are frequent in industrialized countries and affect many individuals in the prime of life. Almost 10 million head injuries occur annually in the United States alone, about 20% of which are serious enough to cause brain damage. Among men under 35 years, accidents, usually motor vehicle collisions, are the chief cause of death, and >70% of these involve head injury. Minor head injuries are so common that almost all physicians encounter patients requiring immediate care or suffering from various sequelae. Traumatic spinal cord injuries often occur in conjunction with head injury. The two are best considered together in the context of trauma to the nervous system.

A recent decline in mortality from head and spinal cord injuries can be attributed mainly to the use of seat belts and motorcycle helmets and the development of ambulance systems with trained personnel. In addition, a systematic approach to the evaluation of patients with head and spine trauma, beginning at the scene of the accident, has contributed to the improvement in outcome. Also, the wide availability of computed tomography (CT) and magnetic resonance imaging (MRI) has contributed to advances in diagnosis and intensive care treatment and an understanding of the pathologic lesions that are produced by trauma.

TYPES OF HEAD INJURIES

SKULL FRACTURES

A blow to the skull causes a fracture if the elastic tolerance of the bone is exceeded. Intracranial lesions accompany two-thirds of skull fractures, and the presence of a skull fracture increases manyfold the chances of an underlying subdural or epidural hematoma. Consequently, fractures are important primarily as markers of the site and severity of injury. They are also the cause of cranial nerve injuries and the source of entry pathways to the cerebrospinal fluid (CSF) for bacteria (meningitis), air (pneumocephalus), and leakage of CSF.

Fractures are classified as *linear*, *basilar*, *compound*, or *depressed*. Linear fractures, which are most often associated with subdural or epidural hematomas, account for 80% of all skull fractures. They are usually oriented from the point of impact toward the base of the skull. Basilar skull fractures are often extensions of adjacent fractures over the convexity of the skull but may occur independently owing to stresses on the floor of the middle cranial fossa or occiput. They are usually located parallel to the petrous bone or along the sphenoid bone toward the sella turcica and ethmoidal groove. Although most are uncomplicated, basilar skull fractures can causeCSFleakage, pneumocephalus, and cavernous-carotid fistulas. Hemotympanum (blood behind the tympanic membrane), delayed ecchymosis over the mastoid process (Battle's sign), or periorbital ecchymosis ("racoon sign") all signify fracture of the basilar skull. Because routine x-ray examination may fail to disclose basilar fractures, they should be suspected if these clinical signs are present. CSF may leak through the cribriform plate or the adjacent sinus and manifest as a watery discharge from the nose (CSF rhinorrhea). Persistent rhinorrhea and recurrent meningitis are indications for surgical repair of torn dura underlying the fracture. The precise site of the leak is often difficult to determine, but useful diagnostic tests include the instillation of water-soluble contrast into the CSF followed byCT with

the patient in various positions, and injection of radionuclide compounds or fluorescein into the CSF with an assessment of uptake of these compounds by absorptive nasal pledgets. The site of an intermittent leak is rarely delineated, and most resolve spontaneously. Sellar fractures, even ones associated with serious neuroendocrine dysfunction, are sometimes radiologically occult. Fractures of the dorsum sella may cause sixth or seventh nerve palsies or optic nerve damage. An air-fluid level in the sphenoid sinus suggests a fracture of the sellar floor.

Petrous bone fractures, especially those oriented along the long axis of the bone, may be associated with facial palsy, disruption of ear ossicles, and CSF otorrhea. Transverse petrous fractures are less common; they almost always damage the cochlea or labyrinths and often the facial nerve. External bleeding from the ear is usually from local abrasion of the external canal but can also result from petrous fracture.

Fractures of the frontal bone are often depressed, involving the frontal and paranasal sinuses and the orbits; permanent anosmia results if the olfactory filaments in the cribriform plate are disrupted. Depressed skull fractures are typically compound, but they are often neurologically asymptomatic because the impact energy is dissipated in breaking the bone; however, some are associated with brain contusions and focal neurologic signs caused by damage to the underlying cortical area. Prompt debridement and exploration of compound fractures are required in order to avoid infection.

CRANIAL NERVE INJURIES

The cranial nerves likely to be injured with head trauma include the olfactory, optic, oculomotor, and trochlear nerves; the first and second branches of the trigeminal nerve; and the facial and auditory nerves. Anosmia and an apparent loss of taste (actually a loss of perception of aromatic flavors, with elementary tastes retained) occur in ~10% of persons with serious head injuries, particularly with falls on the back of the head. This sequela results from displacement of the brain and shearing of the olfactory nerve filaments and may occur in the absence of a fracture. Recovery is the rule, leaving residual hyposmia, but if bilateral anosmia persists for several months, the prognosis is poor. Fractures of the sphenoid bone may rarely bruise or transect the optic nerve, resulting in unilateral partial or complete blindness and an unreactive pupil, usually equal in size to that of the other side and with a preserved consensual light response. Partial optic nerve injuries from closed trauma result in blurring of vision, central or paracentral scotomas, or sector defects. Direct orbital injury may cause short-lived blurred vision for close objects and pupillary paralysis because of reversible iridoplegia. Diplopia limited to downward gaze, which suggests trochlear nerve damage, occurs as an isolated problem after minor injury and can develop after a delay of several days; it may also result from fracture of the lesser wing of the sphenoid bone. The diplopia is corrected if the head is tilted away from the affected eye. Direct facial nerve injury by a basal fracture is present immediately in 3% of severe injuries; it may also be delayed 5 to 7 days. Fractures through the petrous bone, particularly the less common transverse type, are liable to produce this injury. Delayed facial palsy, the mechanism of which is unknown, has a good prognosis. Injury to the eighth cranial nerve from a fracture of the petrous bone causes loss of hearing, vertigo, and nystagmus immediately after injury. Deafness from nerve injury must be distinguished from that due to rupture of the eardrum, blood in the middle ear, or disruption of the ossicles from fracture through the

middle ear. A high-tone hearing loss occurs with direct cochlear concussion.

SEIZURES

Convulsions are surprisingly uncommon immediately after a head injury, but a brief period of tonic extensor posturing or a few clonic movements of the limbs just after the moment of impact may occur. However, the superficial cortical scars that evolve from contusions are highly epileptogenic and may later manifest as seizures, even after many years (Chap. 360). The severity of injury determines the risk of future seizures. It has been estimated that 17% of individuals with brain contusion, subdural hematoma, or prolonged loss of consciousness will develop a seizure disorder and that this risk extends for an indefinite period of time, whereas the risk is only 2% after mild injury; the majority of convulsions in the latter group occur within 5 years of injury.

CONCUSSION

Concussion refers to an immediate but transient loss of consciousness that is associated with a short period of amnesia and described as the experience or appearance of being dazed or "star struck." It typically occurs after a blunt impact that creates a sudden deceleration of the cranium and a movement of the brain within the skull. Severe concussion may precipitate a brief convulsion or autonomic signs such as facial pallor, bradycardia, faintness with mild hypotension, or sluggish pupillary reaction, but most patients are neurologically normal. Higher primates are particularly susceptible to concussion; in contrast, billy goats, rams, and woodpeckers can tolerate impact velocity and deceleration 100-fold greater than that experienced by humans. The mechanism of loss of consciousness in concussion is believed to be a transient electrophysiologic dysfunction of the reticular activating system in the upper midbrain caused by rotation of the cerebral hemispheres on the relatively fixed brainstem (Chap. 24).

Gross and light-microscopic changes in the brain are usually absent following concussion, but biochemical and ultrastructural changes, such as mitochondrial ATP depletion and local disruption of the blood-brain barrier, suggest that complex abnormalities occur.CT andMRIscans are usually normal; however, approximately 3% of patients will be found to have an intracranial hemorrhage of some type.

The amnesia of concussion typically follows at least a few moments of unresponsiveness, but rarely there is no loss of consciousness. The memory loss spans the time of, and moments before, mild impact injuries but may encompass previous weeks (rarely months) in cases of more severe trauma. The extent of retrograde amnesia has been suggested as a rough measure of the severity of injury. Any anterograde amnesia is usually brief and disappears rapidly in alert patients. Memory is regained in an orderly way from the most distant to recent memories, with islands of amnesia occasionally remaining in severe cases. The mechanism of peritraumatic amnesia is not known. Hysterical posttraumatic amnesia is not uncommon and should be suspected when inexplicable abnormalities of behavior occur, such as recounting events that cannot be recalled on later testing, a bizarre affect that emulates the lay notion of amnesia or psychosis (Ganser syndrome), forgetting one's own name, or a persistent anterograde deficit that is excessive in comparison with the degree of injury.

A single, uncomplicated head injury only infrequently produces permanent neurobehavioral changes in patients who are free of preexisting psychiatric problems and substance abuse. However, there has been increasing attention to minor problems in memory and concentration that may have an anatomic correlate in small shearing or other microscopic lesions (see below).

CONTUSION, BRAIN HEMORRHAGE, AND SHEARING LESIONS

A surface bruise of the brain, or *contusion*, consists of varying degrees of petechial hemorrhage, edema, and tissue destruction. Contusions and deeper hemorrhages result from mechanical forces that displace the hemispheres forcefully relative to the skull by deceleration of the brain against the inner skull, either under a point of impact (coup lesion) or, as the brain swings back, in the antipolar area (contrecoup lesion). Trauma sufficient to cause prolonged unconsciousness usually produces some degree of contusion. Because the motion of the hemispheres brings them into contact with the prominences of the sphenoid and other frontal basal bones, blunt impact, as from an automobile dashboard or from falling forward while drunk, typically causes contusions on the orbital surfaces of the frontal lobes and the anterior and basal portions of the temporal lobes. With lateral forces, as from the doorframe of a car, the contusions are situated on the lateral convexity of the hemispheres. In both instances there may be obverse contrecoup contusions.

Contusions are visible on CT and MRI scans, appearing early as inhomogeneous hyperdensities on CT and as hyperintensities on MRI; the signal changes reflect small scattered areas of cortical and subcortical blood and localized brain edema (Fig. 369-1); there is also some degree of subarachnoid bleeding, which may be detected by scans or lumbar puncture. Confluent, roughly spherical contusions can be distinguished from cerebral hemorrhages by their involvement of the cortical surface. Contusions may acquire a surrounding ringlike contrast enhancement after a week that may be mistaken for tumor or abscess. Glial and macrophage reactions begin within 2 days and result years later in scarred, hemosiderin-stained depressions on the surface (*plaques jaunes*) that are one source of posttraumatic epilepsy.

The clinical signs produced by contusions vary with their location and size; a hemiparesis or gaze preference, similar to the signs of a middle cerebral artery stroke, is fairly typical. Large bilateral contusions produce coma with extensor posturing. Contusions limited to the frontal lobes produce an abulic-taciturn state and those in the temporal lobe may cause an aggressive, combative, or delirous syndrome, described below. The secondary effects of progressive edema are the most threatening aspect of contusion injury and lead to coma and signs of secondary brainstem compression (pupillary enlargement).

Deep hemorrhages in the central white matter may result from confluent contusions in the depths of a sulcus. However, ganglionic, diencephalic, and other deep hematomas due to torsion or shearing forces in the brain occur independently of surface damage. Large single hemorrhages after minor trauma may bring to attention a bleeding diathesis or cerebrovascular amyloidosis in the elderly. For unexplained reasons, deep cerebral hemorrhages may not develop until several days after severe injury. Sudden

neurologic deterioration in a comatose patient or an unexplained rise in intracranial pressure (ICP) should therefore prompt investigation with a CT scan.

Another type of deep white matter lesion consists of widespread acute disruption, or "shearing," of axons at the time of impact. Characteristically there are small areas of tissue disruption in the corpus callosum and dorsolateral pons, but these areas may not be appreciated in scans. The presence of widespread axonal damage of both hemispheres, a state called *diffuse axonal injury*, has been proposed as the explanation of persistent coma or vegetative state, but small ischemic-hemorrhagic lesions in the midbrain and low diencephalon are as often the cause. Only severe shearing lesions that contain blood are visualized by CT, usually in the corpus callosum and centrum semiovale (Fig. 369-2); however, within days of the injury, MRI scan demonstrates such lesions throughout the white matter, especially with the use of gradient echo MRI sequences.

On occasion, especially in children, cranial trauma causes diffuse brain swelling within a few hours after injury, even though CT may not reveal focal contusions or hemorrhages. The swelling creates a mass effect with disastrous consequences. Swelling is likely due to microvascular disruption and greatly increased cerebral blood flow. Episodes of moderate hypotension after the injury may play a role in this complication.

Residual symptoms and signs of primary or secondary compressive brainstem hemorrhages or ischemic lesions include cerebellar tremor, pupillary enlargement, eye movement abnormalities, and the "locked-in" syndrome (Chap. 24).

SUBDURAL AND EPIDURAL HEMATOMAS

Hemorrhages beneath the dura (subdural) or between the dura and skull (epidural) may be associated with contusions and other injuries, making it difficult to determine their relative contribution to the clinical state. However, subdural and epidural hematomas more often occur as the sole manifestation of injury, and each has characteristic clinical and radiologic features. Because the mass effect and the rise in ICP caused by these hemorrhages may be life threatening, it is imperative that they be identified immediately by CT or MRI scan and evacuated when appropriate.

Acute Subdural Hematoma These lesions become symptomatic minutes or hours after injury. Up to one-third of patients have a lucid interval before coma supervenes, but most are drowsy or comatose from the moment of injury. Direct cranial trauma is not required for acute subdural hemorrhage to occur; acceleration forces alone, as from whiplash, are adequate, especially in the elderly and those taking anticoagulant medications. A unilateral headache and slightly enlarged pupil on the same side are frequently but not invariably found. Stupor or coma, a hemiparesis, and unilateral pupillary enlargement are the typical signs of larger hematomas; pupillary dilation is contralateral to the hematoma in 5 to 10%. In an acutely deteriorating patient with diminished alertness and with pupillary enlargement, burr (drainage) holes or an emergency craniotomy are appropriate, at times even without prior radiographic confirmation of subdural hematoma. Small subdural hematomas may be asymptomatic and usually do not require therapy. A more subacute syndrome from subdural hematoma occurs days to weeks after injury with drowsiness, headache, confusion, or

mild hemiparesis; it is seen in alcoholics and in the elderly. Chronic subdural hematoma is described below.

Most subdural hematomas appear as crescentic collections over the convexity of the hemisphere and are located over the frontotemporal region, less often in the inferior middle fossa or over the occipital poles (Fig. 369-3). The degree of midline shift is disproportionately greater than the apparent size of the clot in any one axialCT scan, but the guidelines relating shift to the level of consciousness outlined inChap. 24remain useful. Less common instances of interhemispheric, posterior fossa, or bilateral convexity clots are difficult to diagnose clinically, although drowsiness and the signs expected for each region can be detected (Chap 25). Larger clots are thought to be primarily venous in origin, though additional arterial bleeding sites are often found; some large clots, when explored surgically, appear to be exclusively arterial.

Acute Epidural Hematoma Epidural hematomas evolve more rapidly than subdural hematomas and are therefore more treacherous. They occur in up to 10% of severe trauma cases and are less often associated with underlying cortical damage than are subdural hematomas. Most patients are unconscious when first seen. A "lucid interval" of several minutes to hours before coma supervenes is said to be most characteristic of epidural hemorrhage, although it is not common, and epidural hemorrhage by no means is the only cause of this temporal profile.

An epidural hematoma located over the convexity of either lateral temporal lobe is explained by its origin from a torn dural vessel, most commonly the middle meningeal artery, which is transected by a fracture of the squamous portion of the temporal bone. Frontal, inferior temporal, or occipitoparietal epidural hematomas are less frequent, occurring when fractures disrupt branches of the middle meningeal artery. The hematoma strips the tightly attached dura from the inner table of the skull, producing a characteristic lenticular shaped clot onCT(Fig. 369-4). Epidural hematomas may be less frequent in the elderly because of the tighter attachment of dura to skull that occurs with aging. Posterior fossa epidural hematomas are rare and difficult to detect clinically; most result from surgery in that region, such as resection of an acoustic schwannoma.

Chronic Subdural Hematoma A history of trauma may or may not be elicited; 20 to 30% of patients recall no head injury, particularly the elderly and those with a bleeding diathesis. The causative injury may be trivial (striking the head against the branch of a tree, a sudden stop in a car, or minor head contact during a fall or faint) and is often forgotten because it was remote. Headaches (common but not invariable), slowed thinking, change in personality, a seizure, or a mild hemiparesis emerges weeks or months afterwards. The headache may fluctuate in severity, sometimes with positional changes. Many chronic subdural hematomas are bilateral and produce perplexing clinical syndromes. The initial clinical impression is of a stroke, brain tumor, drug intoxication, depression, or a dementing illness because drowsiness, inattentiveness, and incoherence of thought are more prominent than focal signs such as hemiparesis. Patients with undetected small bilateral subdural hematomas seem to have a low tolerance for surgery, anesthesia, and drugs that depress the nervous system, remaining drowsy or confused for long periods postoperatively. Occasionally a chronic hematoma causes brief episodes of hemiparesis or aphasia that are indistinguishable from transient ischemic attacks.

Skull x-rays are usually normal except for a shift of the calcified pineal body to one side or an occasional unexpected fracture. In very long-standing cases the irregular calcification of membranes that surround the collection may be appreciated.CTperformed without contrast infusion shows a low-density mass over the convexity of the hemisphere (Fig. 369-5), but between 2 to 6 weeks after the initial bleeding the clot appears isodense compared to adjacent brain. Bilateral chronic hematomas may fail to be detected because of the absence of lateral tissue shifts; this circumstance is suggested by a "hypernormal" CT scan with fullness of the cortical sulci and small ventricles in an older patient. CT with contrast demonstrates the vascular fibrous capsule surrounding the clot;MRI can reliably identify either a subacute or chronic clot. Lumbar puncture is not recommended for diagnosis because of the risk of worsening tissue shifts but, if performed, shows xanthochromia of the spinal fluid and a variable number of red blood cells. Chronic subdural hematomas can expand gradually and clinically resemble tumors of the brain.

Clinical observation and serial imaging are reasonable in patients with few symptoms and small subdural collections. Treatment with glucocorticoids alone is sufficient in some cases, but surgical evacuation is more often successful. The fibrous membranes that grow from the dura and encapsulate the region require surgical resection to prevent recurrent fluid accumulation. Small hematomas are largely resorbed, leaving only the organizing membranes, which become calcified after many years.

PENETRATING INJURIES, COMPRESSIONS, AND LACERATIONS

Tangential scalp wounds from bullets are capable of producing neurologic signs or delayed seizures because small hemorrhages or contusions arise even in the absence of missile penetration. Bullets entering the brain cause considerable damage because of their tremendous kinetic energy. A cylindrical area of necrosis surrounds the bullet track, but the nature of injury differs for different projectiles. Soft civilian bullets typically shatter on impact and leave a track of metallic fragments with moderate parenchymal damage, whereas military bullets, because of their high velocity and energy, disrupt tissue at great distances from the track and produce massive brain destruction. All of these penetrating injuries cause a rapid increase inICP for several minutes, followed by a drop depending on the volume of secondary hemorrhage and the degree of developing edema. Infection is a risk mainly from shell fragments, shrapnel, grenades, and mines, because such small projectiles carry surface bacteria and dirt into the brain. Most neurosurgeons administer systemic antibiotics prophylactically and perform local debridement for all types of penetrating injuries. Aneurysms may form as a result of disruption of vessel walls from the shock wave of the passing projectile; facial-orbital entrance wounds have the highest incidence of this complication. The aneurysms have an unpredictable course, but most that rupture do so in the first month. The prognosis for survival after missile injuries is good if consciousness is preserved and poor if coma is present from the outset.

In civilian practice, intracranial foreign bodies such as knives, picks, studgun staples, or high-speed tool bits may be missed unless skull x-rays are taken after what are seemingly minor penetrating injuries. Surgical removal of the object, debridement, and extensive exploration for hemorrhage and necrotic tissue are required.

TRAUMATIC VASCULAR DISSECTION AND OCCLUSION

The kinetic energy of minor or more severe head or neck trauma can produce dissection of the internal carotid or vertebral arteries by stripping the intima or the media. Chiropractic neck manipulation accounts for some cases. Severe blunt impacts to the neck can initiate a dissection several centimeters above the origins of the internal carotid or vertebral arteries. There is usually local neck pain over the affected carotid artery, a Horner's syndrome, and headache over the ipsilateral anterior cranium. Some patients with carotid dissection subsequently have large middle cerebral artery strokes with hemiplegia after a period of fluctuating hemiparesis. In drowsy or comatose patients, evidence of dissection or subsequent stroke is difficult to determine, but its presence is suggested by unexplained hemiplegia, unilateral miosis, or appearance of cerebral infarction on CT scan.

Traumatic vertebral artery dissection causes vertigo, vomiting, suboccipital or supraorbital headache, and other signs of lateral medullary or cerebellar ischemia. These symptoms may be attributed erroneously to vestibular concussion. In comatose patients, the only indication may be inferior cerebellar infarction on imaging studies. Vasospasm from traumatic subarachnoid blood may also be involved in the development of infarction after head injury.

Cavernous sinus arteriovenous fistulas are rare but serious complications in patients who survive severe head injury. The problem is first evident as a self-audible bruit (many are also audible to the examiner), proptosis, conjunctival injection, or visual impairment. Angiography shows early filling of the cavernous sinus and its draining tributaries. The fistula enlarges, causing increasingly severe local changes around the eye and orbit and decreased chances of visual recovery. About 10%, mostly small fistulas, resolve spontaneously. Many surgical approaches have been tried, including ligation of the carotid artery and direct obliteration of the fistula or cavernous sinus, but a detachable balloon that is delivered by an intravascular catheter has proved most successful.

INTRACRANIAL PRESSURE AND CEREBRAL BLOOD FLOW

Raised ICP arising from contusion, hematoma, and subsequent progressive edema accounts for at least 50% of deaths after head injury; outcome is inversely related to the level of ICP. Aggressive treatment of raised ICP in modern intensive care units is believed to contribute to improved survival after severe head injury, but many other factors pertain, and the role of direct monitoring of ICP to guide therapy, while favored in many centers, is still uncertain.

For several minutes to an hour after acute head injury, cerebral blood flow increases in most patients, although metabolic demands and oxygen consumption of the cerebrum are diminished. Autoregulation -- the ability of the cerebral vasculature to maintain a constant blood flow in response to decreased or increased perfusion pressure -- is impaired globally and even more so in damaged regions. The rise in cerebral blood volume caused by the failure of autoregulation is thought to account for approximately two-thirds of the rise in ICP after severe head injury. The blood-brain barrier also

becomes more permeable in contused regions, promoting edema formation. Resting ICP is spontaneously interrupted by rises in ICP, termed *plateau waves*, which arise as a result of a loss of cerebrovascular tone and a resultant increase in cerebral blood volume. Plateau waves may be precipitated by iatrogenic maneuvers such as suctioning, physical therapy, excess fluid administration, or pain but also by mild, often unnoticed hypotension that causes cerebrovascular dilation. Signs of clinical deterioration, such as pupillary enlargement, may occur after plateau waves; occasionally, brain death ensues. Other secondary systemic phenomena after severe head injury, particularly hypotension and hypoxia, cause brain damage and greatly alter outcome.*The regulation of ICP and its relationship to cerebral blood flow (CBF) are discussed in Chap. 376.*

CLINICAL SYNDROMES AND TREATMENT OF HEAD INJURY

MINOR INJURY

The patient who is fully alert and attentive after head injury but who has one or more symptoms of headache, faintness, nausea, a single episode of emesis, difficulty with concentration, or slight blurring of vision has a good prognosis with little risk of subsequent deterioration. Such patients have usually sustained a concussion and are expected to have a brief amnestic epoch. Children and young adults are particularly prone to drowsiness, vomiting, and irritability, which is sometimes delayed for several hours after apparently minor injuries. Occasionally, vasovagal syncope occurs several minutes to an hour after the injury and may cause undue concern. Constant generalized or frontal headache is common in the days following trauma; it may be migrainous (throbbing and hemicranial) in nature. After several hours of observation, patients with this category of injury may be accompanied home and observed by a family member or friend. Most patients with a minor syndrome do not have a skull fracture on skull x-ray or hemorrhage onCT. The decision to perform these tests depends largely on clinical signs suggesting that the impact was severe (e.g., prolonged concussion, periorbital or mastoid hematoma, repeated vomiting), on the seriousness of other bodily injuries, and on the degree of surveillance that can be expected at home. Persistent severe headache and repeated vomiting in the context of normal alertness and no focal neurologic signs are usually benign, but radiologic studies should be obtained and observation in the hospital is justified.

INJURY OF INTERMEDIATE SEVERITY

Patients who are not comatose but who have persistent confusion, behavioral changes, subnormal alertness, extreme dizziness, or focal neurologic signs such as hemiparesis should be admitted to the hospital and soon thereafter have aCT scan. Usually a contusion or hematoma is found. The clinical syndromes most common in this group, in addition to postconcussive headache, dizziness, and vomiting, include (1) delirium with a disinclination to be examined or moved, expletive speech, and resistance if disturbed (anterior temporal lobe contusions); (2) a quiet, disinterested, slowed mental state (abulia) with dull facial appearance and irascibility (inferior frontal and frontopolar contusions); (3) a focal deficit such as aphasia or mild hemiparesis (due to subdural hematoma or convexity contusion, or, less often, carotid artery dissection); (4) confusion with inattention, poor performance on simple mental tasks, and fluctuating or slightly

erroneous orientation (associated with several types of injuries, including the first two described above as well as medial frontal contusions and interhemispheric subdural hematoma); (5) repetitive vomiting, nystagmus, drowsiness, and unsteadiness (usually labyrinthine concussion, but occasionally due to a posterior fossa subdural hematoma or vertebral artery dissection); and (6) diabetes insipidus (damage to the median eminence or pituitary stalk). It needs to be emphasized that intermediate-grade injuries are often complicated by drug or alcohol intoxication.

Clinical observation is necessary to detect increasing drowsiness, change in respiratory pattern, or pupillary enlargement and to ensure restriction of free water (unless there is diabetes insipidus). Asymmetry in limb posture, limb movement, or gaze preference suggests a subdural or epidural hematoma or large contusion. Most patients in this category improve over several days. During the first week, the state of alertness, memory, and other cognitive performance often fluctuate, and irascibility or agitation is common. Behavioral changes are worst at night, as with most other encephalopathies, and may be treated with small doses of antipsychotic medications. Subtle abnormalities of attention, intellect, spontaneity, and memory tend to return to normal weeks or months after the injury, sometimes surprisingly abruptly; persistent losses in cognition are discussed below.

SEVERE INJURY

Patients who are comatose from the onset require immediate neurologic attention and often resuscitation. After intubation, with care taken to avoid deforming the cervical spine, the depth of coma, pupillary size and reactivity, limb movements, and Babinski responses are assessed. As soon as vital functions permit and cervical spine x-rays and a CT scan have been obtained, the patient should be transported to a critical care unit. The finding of an epidural or subdural hematoma or large intracerebral hemorrhage is an indication for prompt surgery and intracranial decompression in otherwise salvageable patients. Subsequent treatment is probably best guided by direct measurement of ICP but may proceed on a presumptive basis using clinical status and CT scan as guides. All potential exacerbating factors must be eliminated. Hypoxia, hyperthermia, hypercarbia, awkward head positions, and high mean airway pressures from mechanical ventilation all increase cerebral blood volume and ICP. Many, but not all, patients will have lower ICP when the head and trunk are elevated. Active management of raised ICP includes hyperosmolar dehydration with 20% mannitol (0.25 to 1 g/kg every 3 to 6 h), preferably using directly measured ICP as a guide. Otherwise, a serum osmolality of ~300 mosmol/L is desirable. It is customary to restrict free water administration in order to maintain high serum osmolarity, but there is no rationale for a reduction in the total volume of fluids administered if they are iso- or hyperosmolar, e.g., normal saline. Induced hypocarbia to an initial level of 28 to 33 mmHg P_{CO_2} is rapidly effective in reducing ICP, but its duration of effect is limited and its use has fallen out of favor, perhaps excessively so.

Persistently raised ICP after inception of this conservative therapy generally indicates a poor outcome. Although the addition of high-dose barbiturates may further lower ICP, there is no beneficial effect on overall outcome. In many instances, barbiturates cause a parallel reduction in ICP and BP without a net improvement in cerebral perfusion. Systolic BP should be maintained >100 mmHg by vasopressor agents, if necessary.

Mean BP levels>110 to 120 mmHg may exaggerate brain edema, but some neurosurgeons allow the BP to rise above normal on the basis that this may abort plateau waves. A conventional approach to extreme hypertension utilizes diuretics and b-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, or intermittent doses of barbiturates. A number of other antihypertensive drugs, including some calcium channel blockers and nitrates, are said to be relatively contraindicated because they may raise ICP. Antacids administered by nasogastric tube or direct-acting drugs are utilized to keep gastric pH >3.5 and prevent gastrointestinal bleeding as described below. The use of large doses of glucocorticoids in severe head injury does not improve outcome. Several studies suggest that early nutritional support results in faster neurologic recovery from head injury. If the patient remains comatose, it is worthwhile to repeat the CT or MRI scan to exclude a delayed surface or intracerebral hemorrhage. Intensive care salvages some critically ill head-injured patients by concentrating efforts on simple treatments that avoid medical complications, particularly pneumonia and sepsis and preventable increases in ICP.

SYSTEMIC DERANGEMENTS RESULTING FROM SEVERE HEAD TRAUMA

Injuries outside the cranium should be searched for at the outset, because they are likely to be forgotten if not initially noted. In particular, associated spinal, long bone, and abdominal injuries may cause delayed difficulties in management. Over half of patients who persist in coma for 24 h after head injury develop *abnormalities of electrolytes or fluid balance*. Diabetes insipidus should be suspected if urine output increases and urine specific gravity is low (Chap. 329). Replacement of water losses suffices for mild cases, but vasopressin may be required. Secretion of aldosterone and antidiuretic hormone (vasopressin, AVP) in response to stress favor the retention of sodium and free water, respectively. The latter usually predominates, leading to mild hypervolemic hyponatremia, but this is obscured if osmotic dehydrating agents have been used.

Some patients with head injuries suffer *hypoxia* acutely after injury without obvious pulmonary infiltrates. Aspiration pneumonia presents a great risk; lung injury from aspirated gastric contents, infection, and atelectasis may combine to produce the adult respiratory distress syndrome (ARDS) and severe arteriovenous shunting (Chap. 265). ARDS also occurs owing to disseminated intravascular coagulopathy, fat embolism, or, rarely, "neurogenic" pulmonary edema (see below). The effect of positive end-expiratory pressure (PEEP) on ICP is complex, but PEEP should not be withheld if necessary for oxygenation. *Atelectasis* is common in all poorly responsive patients and is treated with chest physical therapy and adequate ventilator tidal volumes. *Pulmonary embolism* is also a major threat to bedridden patients, and intermittent pneumatic calf compression or modest doses of subcutaneous heparin may be useful prophylaxis. The latter has not predisposed to intracerebral or gastrointestinal bleeding. Early recognition of deep leg vein thrombosis and aggressive treatment by occlusion of the inferior vena cava may prevent later emboli.

Patients with severe long bone injuries are subject to widespread *cerebral fat embolism*. For uncertain reasons, this complication is seen less often than previously, perhaps because of better fluid replacement. In the typical case, head injury is a minor part of the overall trauma; nonetheless, severe cranial injury masks the syndrome. Several days after the bone fractures occur, restlessness, delirium or drowsiness progressing to coma

in severe cases, seizures, generalized brain edema, and hypoxia develop. About half the patients have retinal and punctate conjunctival hemorrhages or fat that is visible in retinal vessels. A petechial rash (prominent in the anterior axillary folds and supraclavicular fossae), diffuse interstitial infiltrates on the chest x-ray, fat in the urine, and/or renal failure occur in some patients. Severe reduction in arterial oxygen content is common from widespread lung injury (ARDS). Cerebral fat embolism causes a cerebral purpura, mainly in the white matter, due to capillary occlusion by fat globules. There is evidence that patients in whom this complication is recognized and treated early have a better prognosis. Massive doses of glucocorticoids and administration of positive-pressure ventilation with high end-expiratory pressures have been claimed to be useful.

Most patients with severe head injuries develop gastric erosions, but only a few have clinically significant hemorrhages. *Gastrointestinal bleeding* usually occurs in the first days to 1 week after injury. Unlike the majority of patients in shock or with stress ulceration, head-trauma patients often have elevated gastric acidity. Prophylactic treatment with gastric coating agents as discussed above, with H$_2$receptor blockers, or with frequent antacid administration probably reduces gastric hemorrhage in other stress states and is commonly used in head trauma.

Acute head trauma may cause transient apnea and cardiac arrest. In the absence of overwhelming brain damage, recovery from the arrest is the rule. Subsequently, a sympathoadrenal discharge or raisedICPcauses *systemic hypertension*, either with the classically associated bradycardia of the Cushing response or, almost as frequently, with tachycardia. Cardiac arrhythmias are common, most notably sinus bradycardia, supraventricular tachycardias, nodal rhythm, and heart block. T-wave inversion and alterations in the ST segment may simulate subendocardial ischemia. In some instances these changes are due to cardiac muscle contusion.

Neurogenic pulmonary edema is a form of respiratory failure in which the alveoli fill with fluid, as in congestive heart failure, but left ventricular end-diastolic pressure is normal after the infiltrates are established. The nature of this pulmonary vascular leak is not settled, but it may be the result of a sudden shift of intravascular volume from the systemic to the pulmonary circulation or there may be a direct cerebral neurogenic influence on the pulmonary microvasculature. The alveolar capillary leak may continue despite a return of pulmonary vascular pressure to normal.

Many patients demonstrate a mild *coagulopathy*, and 5 to 10% have various degrees of disseminated intravascular coagulation, a harbinger of poor outcome. There is a correlation between the severity of injury and the level of increased fibrin degradation products in blood, and one cause of the coagulopathy may be the release of highly thromboplastic material from damaged brain tissue.

PROGNOSIS

Extensive work by Jennet's group in Glasgow and by the Traumatic Coma Data Bank has provided data on the outcome in severe head injury. Verbal output, eye opening, and the best motor response of the limbs have been found to be predictive of outcome and are summarized using the "Glasgow Coma Scale" (Table 369-1). Over 85% of

patients with aggregate scores of 3 or 4 die within 24 h. However, a number of patients with slightly higher scores but a poor initial prognosis, including absent pupillary light responses, survive, suggesting that an initially aggressive approach is justified in most patients. Patients <20 years, particularly children, may make remarkable recoveries after having grave early neurologic signs. In one large study of severe head injury, 55% of children had a good outcome at 1 year, compared with 21% of adults. Older age, increasedICP, hypoxia and hypotension, and CT scan evidence of compression of the cisterns surrounding the brainstem and shift of midline structures are all poor prognostic signs. Delayed evacuation of large intracerebral clots is also associated with a poor prognosis.

Evoked potentials have prognostic value in head injury, similar to their use in ischemic-hypoxic brain injury, and their accuracy in predicting a poor outcome probably exceeds that of purely clinical methods. The results obtained from somatosensory evoked potentials are clearest, with the bilateral absence of cortical potentials (more caudal potentials present) predicting death or a vegetative state in over 90% of patients. A normal or mildly abnormal test, however, does not reliably predict a good functional outcome.

NEUROPSYCHOLOGICAL OUTCOME AFTER HEAD INJURY

A structural basis has been sought for the posttraumatic nervous instability termed the *postconcussion syndrome*, which consists of fatigue, dizziness, headache, and difficulty in concentration after mild or moderate injury. Most instances are difficult to distinguish from asthenia and depression. However, with intermediate-grade injury there is probably a substantial incidence of difficulty with attention and memory as well as other subtle cognitive deficits. Based on experimental models, some investigators believe that subtle axonal shearing lesions or biochemical alterations account for these symptoms despite normal findings on brain imaging, evoked potentials, and electroencephalogram. In moderate and severe trauma, neuropsychological changes are found routinely, but some of these deficits identified in formal testing are not important in daily functioning. Test scores tend to improve rapidly during the first 6 months after injury, then more slowly for years.

SPINAL CORD TRAUMA

Approximately 10,000 patients a year in the United States, mostly young and otherwise healthy, become paraplegic or quadriplegic because of spinal cord injuries; there are an estimated 200,000 quadriplegics in the nation. Most spinal cord injuries in civilian life result from fracture or dislocation of the surrounding vertebral column. Vertical compression with flexion is the main mechanism of injury in the thoracic cord, and hyperextension or flexion is the main cause of injury in the cervical cord. Preexisting spondylosis, a congenitally narrowed spinal canal, hypertrophied ligamentum flavum (Chap. 16), and instability of the apophyseal joints from diseases such as rheumatoid arthritis predispose to severe spinal cord damage even after minor degrees of injury.

PATHOPHYSIOLOGY AND PATHOLOGY OF SPINAL CORD INJURY

Considerable spinal cord damage results from secondary phenomena that arise in the

minutes and hours following injury. Even when a complete transverse myelopathy is evident immediately after impact, some secondary changes and the resultant damage may be reversible. The immediate compression of the cord causes pericapillary hemorrhages that coalesce and enlarge, particularly in the gray matter. Infarction of gray matter and early white matter edema are evident within 4 hours of experimental blunt injury. Eight hours after injury, there is global infarction at the traumatized level, and only at this point does necrosis of white matter and paralysis below the level of the lesion become irreversible. The necrosis and central hemorrhages enlarge to occupy one or two levels above and below the point of primary impact. Gliosis progresses over several months, and the affected regions may cavitate, causing a syringomyelic syndrome.

A large number of interventions for acute spinal compression injury have been of uncertain benefit, but high doses of methylprednisolone (typically 30 mg/kg followed by 5.4 mg/kg hourly for 23 h) administered within 8 hours of injury is associated with a slightly improved outcome. The critical factor for recoverable function is the time from injury to the institution of any therapy.

MANAGEMENT OF SPINAL CORD INJURY SYNDROMES

Any patient with an injury that involves the spine or head potentially has an associated instability of the spinal column. The care of such patients begins at the scene of the accident: the neck should be immobilized, and care should be taken during transport and during the physical and radiologic examinations to prevent extension or rotation of the neck and torsion-rotation of the thoracic spine. Intubation, if necessary, can be accomplished by a blind nasotracheal technique or over an endoscope in order to avoid neck extension. High thoracic or cervical cord transection causes hypotension and bradycardia because of a functional sympathectomy (sometimes corroborated by bilateral ptosis and miosis -- Horner's syndrome), which responds to infusion of crystalloid or colloid.

The neurologic assessment in the awake patient with possible spinal injury focuses on neck or back pain, diminished limb power, a sensory level on the trunk, and on deep tendon reflexes, which are usually absent below the level of acute cord injury. The level of injury can be approximated from the upper dermatome of sensory loss. Injuries above C5 cause quadriplegia and respiratory failure. At C5 and C6 the biceps are weak, whereas the deltoid and the supra- and infraspinatus are spared. C7 injuries cause weakness of the triceps, wrist extensors, and forearm pronators. Injuries at T1 and below cause paraplegia. Compression in the lower thoracic and lumbar spine causes a conus medullaris or cauda equina syndrome. Cauda equina injuries are usually incomplete, involving peripheral nerves rather than spinal cord, and therefore are surgically remediable for longer periods after injury than spinal cord compression. In a comatose patient, absent reflexes, especially with small pupils or paradoxical breathing and hypotension, signify a high cervical cord injury. *The principles of spinal cord localization are considered in detail in Chap. 368.*

Reversible and preventable causes of spinal cord compression must be detected and surgically remedied. These include dislocation of a vertebral body, or an unstable vertebral fracture that can lead to misalignment and cord compression in the future.

Treatment of fractures through the pedicles, facets, or vertebral bodies varies; some fractures heal with immobilization and time, usually 2 to 3 months, while others require surgical fusion to ensure stability. Many traumatic myelopathies have no clearly associated fracture or dislocation, but there is generally rupture of the supporting ligaments that has produced transient cord compression during the impact. If x-rays suggest any aberration in the position of vertebrae, then realignment should generally be undertaken quickly. CT or MRI exam is the most useful for demonstrating spinal misalignment and fractures. The role of myelography is not as compelling as it was in the past, but many neurosurgeons choose to instill a few drops of water-soluble contrast medium into the spinal subarachnoid space to demonstrate a block to the flow of CSF by CT or conventional myelography. Decompression within 2 hours of severe injury may lead to some recovery of spinal cord function. With incomplete myelopathies, especially if the limbs are becoming progressively weaker, early realignment is performed even many hours after injury. The surgical approaches to decompressing the spinal column depend on the specific nature of the injury. In complete transverse myelopathies beyond 6 to 12 hours after injury, decompressive laminectomies are usually unsuccessful in restoring function.

Atlantoaxial dislocation can cause immediate death from respiratory failure, an event that may occur unexpectedly even without other neurologic signs. Rheumatoid arthritis predisposes to this injury. Atlantooccipital dislocations occur predominantly in children and are almost always fatal. "Jefferson's fractures" are burst fractures of the ring of the atlas resulting from a force descending on the vertex of the skull, as in diving accidents; they are usually asymptomatic. "Hangman's fractures" are produced by hyperextension and longitudinal distraction of the upper cervical spine, as occurs with penal hanging or striking the chin on a steering wheel in a head-on collision. These are usually fractures through the pedicles of C2 with subluxation anteriorly of C2 on C3. Traction reduction and prolonged immobilization usually allow proper healing.

Hyperflexion dislocation of the cervical vertebrae commonly causes quadriplegia. Occasionally, a markedly displaced injury is unassociated with neurologic dysfunction, presenting only with neck pain. Any degree of subluxation must be considered as potentially unstable.

Compression fracture of the cervical spine can cause neurologic damage if a bone fragment is driven backward (burst fracture) into the spinal cord. "Teardrop fractures" with crushing of a vertebral body, leaving a fragment of bone anteriorly, are usually associated with ligamentous disruption and spinal instability. Single compression fractures of the thoracic spine are usually stable because the thoracic cage provides support, but they may be associated with anterior spinal cord compression and require decompression and stabilization with the insertion of metal rods.

Mild *cervical hyperextension* injuries may cause only disruption of supporting ligamentous structures and can be well tolerated. More severe injuries cause vertebral displacement and cord compression. The "central cord syndrome" is produced by brief compression of the cervical cord and disruption of the central gray matter. It usually occurs in patients with an already narrow spinal canal, either congenitally or from cervical spondylosis. There is weakness of the arms with pinprick loss over the arms and shoulders, and relative sparing of leg power and sensation on the trunk and legs.

Abnormality of bladder function is variable. The prognosis for recovery is good.

Thoracolumbar fracture is produced by impact in the high or middle back, usually while the patient is bent over. Impingement on the spinal canal results in a complex combination of cauda equina and conus medullaris dysfunction. Purely lumbar fractures with displacement of a vertebral body produce cauda equina compression. Surgical decompression is usually recommended, even with severe neurologic deficits, because there is considerable potential for recovery of the nerve roots of the cauda.

The subsequent care of patients with spinal cord injury is best undertaken in specialized centers. *General principles of medical and urologic management are discussed in Chap. 368.*

(Bibliography omitted in Palm version)

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370. PRIMARY AND METASTATIC TUMORS OF THE NERVOUS SYSTEM - *Stephen M. Sagar, Mark A. Israel*

Malignant primary tumors of the central nervous system (CNS) occur in approximately 18,000 individuals and account for an estimated 13,300 deaths in the United States annually, a mortality rate of 5 per 100,000. An almost equal number of benign tumors of the CNS were diagnosed, with a much lower mortality rate. Glial tumors account for 50 to 60% of primary brain tumors, meningiomas account for about 25%, schwannomas for about 10%, and all other CNS tumors for the remainder. An increase in the frequency of diagnosis of malignant gliomas in the elderly has been reported in recent years. It is unclear if this change represents a true increased incidence or is the result of more frequent use of modern neuroimaging techniques.

Brain and vertebral metastases from systemic tumors are more prevalent than primary CNS tumors. About 15% of patients who die of cancer (80,000 individuals each year in the United States) have symptomatic brain metastases; an additional 5% suffer spinal cord involvement. These tumors, therefore, pose a major problem in the management of systemic cancer.

BRAIN TUMORS

Approach to the Patient

Clinical Features Brain tumors usually present with one of three syndromes: (1) subacute progression of a focal neurologic deficit; (2) seizure; or (3) nonfocal neurologic disorder such as headache, dementia, personality change, or gait disorder. The presence of systemic symptoms such as malaise, weight loss, anorexia, or fever suggests a metastatic rather than a primary brain tumor.

Progressive focal neurologic deficits result from compression of neurons and white matter tracts by expanding tumor and surrounding edema. Less commonly, a brain tumor may present with a stroke-like onset of focal neurologic deficit. Although this presentation may be caused by hemorrhage into the tumor, often no hemorrhage can be demonstrated and the mechanism is obscure. Tumors frequently associated with hemorrhage include high-grade astrocytomas and metastatic melanoma and choriocarcinoma.

Seizures may result from disruption of cortical circuits. Tumors that invade or compress the cerebral cortex, even small meningiomas, are more likely to be associated with seizures than subcortical neoplasms. Nonfocal neurologic dysfunction usually reflects increased intracranial pressure, hydrocephalus, or diffuse tumor spread. Tumors in some areas of the brain may produce subtle deficits; for example, frontal lobe tumors may present with personality change, dementia, or depression.

Headache may result from focal irritation or displacement of pain-sensitive structures (Chap. 15) or from a generalized increase in intracranial pressure. A headache that worsens rather than abates with recumbency is suggestive of a mass lesion. The headache of increased intracranial pressure has a characteristic pattern. Early on, these headaches are usually holocephalic and episodic, occurring more than once a day.

They typically develop rapidly over several minutes, persist for 20 to 40 min, and subside quickly. They may awaken the patient from a sound sleep, generally 60 to 90 min after retiring, or may be precipitated by coughing, sneezing, or straining. Vomiting may occur with severe headaches. As elevated intracranial pressure becomes sustained, the headache becomes continuous but varying in intensity. Elevated intracranial pressure may cause papilledema (Chap. 28), although it is often not present in patients over 55 years old.

Infrequent but characteristic brain tumor presentations include anosmia from a meningioma arising along the cribiform plates and olfactory tracts and unilateral hearing loss from schwannomas of the eighth cranial nerve. Asymptomatic brain tumors, most often meningiomas, are commonly discovered incidentally on imaging studies obtained for unrelated purposes.

The Karnofsky performance scale is useful in assessing and following patients with brain tumors (Chap. 79). A score ³70 indicates that the patient is ambulatory and independent in self-care activities; it has often been taken as a level of function justifying aggressive therapy.

Laboratory Examination Primary brain tumors typically do not produce serologic abnormalities such as an elevated sedimentation rate or tumor-specific antigens associated with systemic cancers. In contrast, metastases to the nervous system, depending on the type and extent of the primary tumor, may be associated with systemic signs of malignancy (Chap. 83). Lumbar puncture may precipitate brain herniation in patients with mass lesions, and should be performed only in patients with suspectedCNSinfection or meningeal metastasis. Findings in the cerebrospinal fluid (CSF) of patients with primary and metastatic nervous system tumors may include raised opening pressure, elevated protein level, and a mild lymphocytic pleocytosis. Astrocytomas that extend to the ventricular surface, or the rupture of an epidermoid cyst, can occasionally produce an intense CSF inflammatory reaction simulating infectious meningitis. The CSF rarely contains malignant cells, with the important exceptions of leptomeningeal metastases, primary CNS lymphoma and primitive neuroectodermal tumors, including medulloblastoma.

Neuroimaging Computed tomography (CT) and magnetic resonance imaging (MRI) reveal mass effect and contrast enhancement. Mass effect reflects the volume of neoplastic tissue as well as surrounding edema. Brain tumors typically produce a vasogenic pattern of edema, with accumulation of excess water in white matter. The normal blood-brain barrier results from tight junctions between endothelial cells that prevent entry of most charged molecules into the nervous system. Contrast enhancement reflects a breakdown of the blood-brain barrier within the tumor, permitting leakage of contrast agent. Low-grade gliomas typically do not exhibit contrast enhancement.

Positron emission tomography (PET) and single-photon emission tomography (SPECT) have ancillary roles in the imaging of brain tumors, primarily in distinguishing tumor recurrence from tissue necrosis that can occur after irradiation (see below). Electroencephalography (EEG) has a role in the evaluation of patients with possible seizures. Functional imaging with PET,MRI, or magnetoencephalography may be of use

in surgical or radiosurgical planning to define the anatomic relationship of the tumor to critical brain regions such as the primary motor cortex.

TREATMENT

Symptomatic Glucocorticoids decrease the volume of edema surrounding brain tumors and improve neurologic function; dexamethasone (12 to 20 mg/d in divided doses orally or intravenously) is used because it has relatively little mineralocorticoid activity.

Tumors that involve the cerebral cortex or hippocampus may produce epilepsy. Anticonvulsants are therefore used therapeutically and prophylactically; phenytoin, carbamazepine, and valproic acid are equally effective (Chap. 360). If the tumor is subcortical in location, prophylactic anticonvulsants are unnecessary.

Gliomas are associated with an increased risk for deep vein thrombosis and pulmonary embolism, probably because these tumors secrete procoagulant factors into the systemic circulation. Whether this risk extends to other brain tumors is unknown. Even though hemorrhage within gliomas is a frequent histopathologic finding, patients with gliomas appear to be at no increased risk for symptomatic intracranial bleeding following treatment with an anticoagulant. Prophylaxis with low-dose subcutaneous heparin should be considered for patients with gliomas who have lower limb immobility, which places them at risk for deep venous thrombosis.

PRIMARY BRAIN TUMORS

ETIOLOGY

Exposure to ionizing radiation is the only well-documented environmental risk factor for the development of brain tumors. A number of hereditary syndromes are associated with an increased risk of brain tumors (Table 370-1). Genes that contribute to the development of brain tumors, as well as other malignancies, fall into two general classes, *tumor-suppressor genes* and *proto-oncogenes* (Chap. 81). Whereas germ line mutations of tumor suppressor genes are rare, somatic mutations are almost invariably found in malignant tumors, including brain tumors. Likewise, the over-expression of proto-oncogenes is frequent in brain tumors as well as systemic malignancies. Moreover, cytogenetic analysis often reveals characteristic changes. In astrocytic tumors, DNA is commonly lost on chromosomes 10p, 17p, 13q, and 9. Oligodendrogliomas frequently have deletions of 1p and 19q. In meningiomas portions of 22q, which contains the gene for neurofibromatosis type 2, are often lost. Less frequently there is evidence of amplification of specific genes, for example *EGFR* in some astrocytomas.

The particular constellation of genetic alterations varies among individual gliomas, even those that are histologically indistinguishable. Moreover, gliomas are genetically unstable, genetic abnormalities tend to accumulate with time, and these changes correspond with increasingly aggressive malignant behavior. There appear to be at least two genetic routes for the development of malignant glioma (Fig. 370-1). One route involves the progression, generally over years, from a low grade astrocytoma with early deletions of chromosome 17 and inactivation of the p53 gene to a malignant glioma with

additional chromosomal deletions. The second route is characterized by the de novo appearance of a malignant glioma with amplification of the *EGFR* gene and an intact p53 gene. In both pathways, inactivation of the *PTEN* gene as a result of the loss of chromosome 10 occurs frequently.

ASTROCYTOMAS

Tumors derived from astrocytes are the most common primary intracranial neoplasms (Fig. 370-2). Their neuropathologic appearance is highly variable. The most widely used histologic grading system is the World Health Organization (WHO) four-tiered grading system. Grade I is reserved for special histologic variants of astrocytoma that have an excellent prognosis after surgical excision. These include *juvenile pilocytic astrocytoma*, *subependymal giant cell astrocytoma* (which occurs in patients with tuberous sclerosis), and *pleiomorphic xanthoastrocytoma*. At the other extreme is grade IV, *glioblastoma multiforme*, a clinically aggressive tumor. *Astrocytoma* (grade II) and *anaplastic astrocytoma* (grade III) are intermediate. The histologic features associated with higher grade are hypercellularity, nuclear and cytoplasmic atypia, endothelial proliferation, mitotic activity, and necrosis. Endothelial proliferation and necrosis are especially robust predictors of aggressive behavior.

A limitation of all grading schemes, especially when applied to a single biopsy, is that astrocytic tumors are histologically variable from region to region, and their histopathology may change with time. It is common for low-grade astrocytomas to progress over time to a higher histopathologic grade and a more aggressive clinical course.

Quantitative measures of mitotic activity also correlate with prognosis. The proliferation index can be determined by immunohistochemical staining with antibodies to the proliferating cell nuclear antigen (PCNA) or with a monoclonal antibody termed *Ki-67*, which recognizes a histone protein expressed in proliferating but not quiescent cells. These measures provide estimates of DNA synthesis and correlate with malignant clinical behavior of the tumor.

The overall prognosis is poor. In a representative Finnish population, the median survival was 93.5 months for patients with grade I or II astrocytomas, 12.4 months for patients with grade III (anaplastic astrocytoma), and 5.1 months for patients with grade IV (glioblastoma) tumors. In the United States, the median survival of patients with high-grade brain tumors is approximately 12 months. In addition to histopathology, features that correlate with poor prognosis include age over 65 and a poor functional status, as defined by the Karnofsky performance scale (see Table 79-2).

Low-Grade Astrocytoma Low-grade astrocytomas are more common in children than adults. Pilocytic astrocytoma, named for its characteristic spindle-shaped cells, is the most common childhood brain tumor. It frequently occurs in the cerebellum. Typically, this tumor is cystic and well demarcated from adjacent brain. Complete surgical excision usually produces long-term, disease-free survival.

The optimal management of other low-grade astrocytomas, termed fibrillary astrocytomas, is controversial. For patients who are symptomatic from mass effect or

poorly controlled epilepsy, surgical excision can relieve symptoms. For patients who are asymptomatic or minimally symptomatic at presentation, a diagnostic biopsy should be performed and, when surgically feasible, the tumor may be resected. The indications for postoperative radiation therapy are uncertain. In many centers, when only a biopsy or partial resection is possible, postoperative external beam radiation therapy is administered, whereas it is not used if a gross total tumor resection can be achieved. Other centers reserve radiation therapy for tumor recurrence or progression, at which time the tumor may display a more malignant phenotype. No role for chemotherapy in the management of low-grade astrocytoma has been defined.

High-Grade Astrocytoma The large majority of astrocytomas arising in adults are high grade, supratentorial, and do not have a clearly defined margin. Neoplastic cells migrate away from the main tumor mass and infiltrate adjacent brain, often tracking along white matter pathways. Imaging studies do not indicate the full extent of the tumor. These tumors are eventually fatal, although prolonged survival occurs in a few patients. Longer survival correlates with younger age, better performance status, and greater extent of surgical resection. Late in their course, gliomas, especially those located in the posterior fossa, can metastasize along CSF pathways to the spine. Metastases outside the CNS are rare.

High-grade astrocytomas are managed with glucocorticoids, surgery, radiation therapy, and chemotherapy. Dexamethasone is generally administered at the time of diagnosis and continued for the duration of radiation therapy. After completion of radiotherapy, the dose of dexamethasone is tapered to the lowest tolerated dose.

Because astrocytomas infiltrate adjacent normal brain, total surgical excision is not possible. Surgery is indicated to obtain tissue for pathologic diagnosis and to control mass effect. Moreover, retrospective studies indicate that the extent of tumor resection correlates with survival, at least in younger patients. Therefore, accessible astrocytomas are resected aggressively in patients younger than 65 years old who are in good general medical condition.

Postoperative radiation therapy prolongs survival and improves quality of life, although the duration of benefit is only a few months. Treated with dexamethasone alone following surgery, the mean survival of patients under 65 years of age with glioblastoma is 7 to 9 months. Survival is prolonged to 11 to 13 months with radiation therapy. Focal brain irradiation is less toxic and is as effective as whole-brain radiation for the treatment of primary glial tumors. Radiation is generally administered to the tumor mass, as defined by contrast enhancement on a CT or MRI scan, plus a 3- to 4-cm margin. A total dose of 5000 to 7000 cGy is administered in 25 to 35 equal fractions, 5 days per week.

The roles of stereotaxic radiosurgery and interstitial brachytherapy in glioma treatment are uncertain. *Stereotaxic radiosurgery* is the administration of a focused high dose of radiation to a precisely defined volume of tissue in a single treatment, usually using the gamma knife. Stereotaxic radiosurgery can potentially achieve tumor ablation without surgery. A major limitation of stereotaxic radiosurgery is that it can be used for only relatively small tumors, generally less than 3 cm in maximum diameter. *Interstitial brachytherapy*, the implantation of radioactive beads into the tumor mass, is generally

reserved for tumor recurrence because of its associated toxicity -- in particular, necrosis of adjacent brain tissue.

Chemotherapy is marginally effective and is often used as an adjuvant following surgery and radiation therapy. Nitrosoureas, including carmustine (BCNU) and lomustine (CCNU), are the most effective available agents. Since a typical glioma infiltrates normal brain where the blood-brain barrier is relatively intact, lipid-soluble agents such as the nitrosoureas, which cross the blood-brain barrier, may reach more malignant cells than water-soluble agents. Experimental approaches include intraarterial infusion of chemotherapy, the implantation of chemotherapy-releasing wafers or injection of chemotherapeutic agents into the tumor resection cavity, administration of chemotherapy after disruption of the blood-brain barrier, and intensive chemotherapy regimens supported by autologous bone marrow transplantation.

Gliomatosis cerebri is a rare form of astrocytoma in which there is diffuse infiltration of the brain by malignant astrocytes without a focal enhancing mass. It generally presents as a multifocalCNSsyndrome or a more generalized disorder including dementia, personality change, or seizures. Neuroimaging studies are often nonspecific, and biopsy is required to establish the diagnosis. Gliomatosis is treated with whole-brain radiation therapy and, in selected patients, with systemic chemotherapy.

OLIGODENDROGLIOMAS

Oligodendrogliomas have a more benign course and are more responsive to cytotoxic treatment than astrocytomas. Five-year survival is greater than 50%, and 10-year survival is 25 to 34%.

Oligodendrogliomas occur chiefly in supratentorial locations; in adults about 30% contain areas of calcification (Fig. 370-3). Many gliomas contain mixtures of cells with astrocytic and oligodendroglial features. If this mixed histology is prominent, the tumor is termed a *mixed glioma* or an *oligoastrocytoma*. The greater the oligodendroglial component, the more benign the clinical course. As a rule, oligodendrogliomas are less infiltrative than astrocytomas, permitting more complete surgical excision. The histologic features of mitoses, necrosis, and nuclear atypia are associated with a more aggressive clinical course. If these features are prominent, the tumor is termed an *anaplastic oligodendroglioma*.

The optimal management of oligodendrogliomas has not been defined. Surgery, at minimum a stereotaxic biopsy, is necessary to establish a diagnosis. Many oligodendrogliomas are amenable to gross total surgical resection. In addition, oligodendrogliomas may respond dramatically to systemic combination chemotherapy with procarbazine, lomustine and vincristine (PCV). Oligodendrogliomas with deletions of chromosomes 1p and 19q typically respond to PCV, but only about 25% of oligodendrogliomas lacking these genetic markers respond to chemotherapy. Chemotherapy may be used as the initial treatment, and residual tumor can be surgically excised or treated with stereotaxic radiosurgery. An alternative approach is to first excise the accessible tumor mass, then administer systemic chemotherapy and finally, employ stereotaxic radiosurgery or external beam radiation for residual tumor.

EPENDYMOMAS

In adults ependymomas are typically located in the spinal canal, especially in the lumbosacral region, arising from the filum terminale of the spinal cord. These tumors often have a myxopapillary histology, with a papillary arrangement of cells and mucin production. In children, ependymomas occur within the ventricles, most often the fourth ventricle, and may exhibit diagnostic ependymal rosettes. Ependymomas with histologic signs of malignancy, including cellular atypia, frequent mitotic figures, or a high labeling index, virtually always recur after surgical resection. Imaging with CT or MRI scans reveals ependymomas as uniformly enhancing masses that are relatively well demarcated from adjacent neural tissue. Ependymomas may metastasize via CSF pathways: brain tumor metastases that spread to the spinal cord by this means are termed *drop metastases*.

Following the gross total excision of an ependymoma, the prognosis is excellent. The 5-year disease-free survival is >80%. However, many ependymomas cannot be totally excised, and postoperative focal external beam radiation or stereotaxic radiosurgery is used. Whether focal radiation is adequate or whether the entire neuraxis needs to be irradiated is not resolved.

GERMINOMAS

These tumors most commonly present during the second decade of life, generally at sites within or adjacent to the third ventricle including the pineal region. Germinomas are the most frequent variety of *germ cell tumor*, a tumor type arising in midline structures and including *teratoma*, yolk sac tumor (*endodermal sinus tumor*), *embryonal carcinoma*, and *choriocarcinoma*. Germinomas of the CNS may be benign but are more often aggressive and invasive. Due to their location, patients frequently present with hypothalamic-pituitary dysfunction including diabetes insipidus, visual field deficits, disturbances of memory or mood, or hydrocephalus (Chap. 328). Neuroimaging demonstrates germinomas to be uniformly enhancing masses with or without well-defined borders. The treatment of choice is complete surgical resection. For unresectable tumors, a stereotaxic biopsy is performed for diagnosis, and focal radiation is the primary therapy. When the extent of disease or very young age precludes radiotherapy as primary treatment, platinum-based chemotherapy may decrease tumor size and facilitate subsequent radiation therapy of residual disease or recurrent tumor. Prognosis depends on the histology and surgical resectability of the tumor. Germinomas are generally radiosensitive and chemosensitive, and 5-year survival is >85%.

MEDULLOBLASTOMAS AND PRIMITIVE NEUROECTODERMAL TUMORS (PNET)

These highly cellular malignant tumors are thought to arise from neural precursor cells. Medulloblastomas of the posterior fossa are the most frequent malignant brain tumor of children. If the tumor is not disseminated at presentation, the prognosis is generally favorable; subsets of pediatric patients have >70% survival rates at 5 years, although <50% of all children with medulloblastoma survive to adulthood. PNET is a term applied to tumors histologically indistinguishable from medulloblastoma but occurring either in adults or supratentorially in children. In adults, >50% present in the posterior fossa, but these tumors frequently disseminate along CSF pathways.

If possible, these tumors should be surgically excised, although outcome is not related to the extent of surgery. In adults, surgical excision of a PNET should be followed by chemotherapy and irradiation of the entire neuraxis, with a boost in radiation dose to the primary tumor. Aggressive treatment can result in prolonged survival, although half of adult patients relapse within 5 years of treatment.

CNS LYMPHOMA

Primary CNS Lymphoma These are B cell malignancies of intermediate to high grade that present within the neuraxis without evidence of systemic lymphoma. They occur most frequently in immunocompromised individuals, specifically organ transplant recipients or patients with AIDS (Chap. 309), but the incidence of primary CNS lymphoma is increasing in both immunocompetent and immunocompromised patients. In immunocompromised patients, CNS lymphomas are invariably associated with Epstein-Barr virus (EBV) infection of the tumor cells. Chromosomal translocations involving the c-*myc* gene occur in EBV-associated lymphomas outside the CNS (Chap. 112) but not in primary CNS lymphoma.

In immunocompetent patients, neuroimaging studies most often reveal a uniformly enhancing mass lesion. In immunocompromised patients, primary CNS lymphoma is likely to be multicentric and exhibit ring enhancement or to arise in the meninges (Fig. 370-4). Stereotaxic needle biopsy can be used to establish the diagnosis. Leptomeningeal involvement is present in approximately 15% of patients at presentation and in 50% at some time during the course of the illness. Moreover, the disease extends to the eyes in up to 15% of patients. Therefore, a slit-lamp examination and, if indicated, anterior chamber paracentesis or vitreous biopsy is necessary before radiation therapy to define radiation ports.

The prognosis of primary CNS lymphoma is poor compared to histologically similar lymphoma occurring outside the CNS. Many patients experience a favorable clinical and radiographic response to glucocorticoids that may be dramatic; however, it is invariably transient and relapse occurs within weeks. Radiotherapy has been the mainstay of treatment, but systemic combination chemotherapy including high-dose methotrexate is also effective. Intrathecal chemotherapy with methotrexate should also be used if leptomeningeal disease is present. Despite aggressive therapy, >90% of patients develop recurrent CNS disease. Historically, the survival of immunocompetent patients with CNS lymphoma has been approximately 18 months, and may now be longer with the use of systemic chemotherapy. In organ transplant recipients, reversal of the immunosuppressed state can improve outcome. Survival with AIDS-related primary CNS lymphoma is very poor, generally £3 months; pretreatment performance status, the degree of immunosuppression, and the extent of CNS dissemination at diagnosis all appear to influence outcome.

Secondary CNS Lymphoma Secondary CNS lymphoma almost always occurs in association with progressive systemic disease in adults with B cell lymphoma or B cell leukemia who have tumor involvement of bone, bone marrow, testes, or the cranial sinuses. Leptomeningeal lymphoma is usually detectable with contrast-enhanced CT or gadolinium-enhanced MRI of the brain and spine or by CSF examination. Treatment

consists of systemic chemotherapy, intrathecal chemotherapy, and CNS irradiation. It is usually possible to effectively suppress the leptomeningeal disease, although the overall prognosis is determined by the course of the systemic lymphoma.

PITUITARY ADENOMAS See[Chap. 328](#)**.**

MENINGIOMAS

Meningiomas are derived from mesoderm, probably from cells giving rise to the arachnoid granulations. These tumors are usually benign and attached to the dura. They may invade the skull but only infrequently invade the brain. Meningiomas most often occur along the sagittal sinus, over the cerebral convexities, in the cerebellar-pontine angle, and along the dorsum of the spinal cord. They are more frequent in women than men, with a peak incidence in middle age.

Meningiomas may be found incidentally on a[CT](#) or[MRI](#) scan or may present with a focal seizure, a slowly progressive focal deficit, or symptoms of raised intracranial pressure. The radiologic image of a dural-based, extra-axial mass with dense, uniform contrast enhancement is essentially diagnostic, although a dural metastasis must also be considered ([Fig. 370-5](#)). A meningioma may have a "dural tail," a streak of dural enhancement flanking the main tumor mass; however, this finding may be present with other dural tumors.

Total surgical resection of benign meningiomas is curative. If a total resection cannot be achieved, local external beam radiotherapy reduces the recurrence rate to <10%. For meningiomas that are not surgically accessible, targeted radiosurgery with the gamma knife or heavy particle radiation should be considered. Small asymptomatic meningiomas incidentally discovered in older patients can safely be followed radiologically; these tumors grow at an average rate of approximately 0.24 cm in diameter per year and only rarely become symptomatic.

Rare meningiomas invade the brain or have histologic evidence of malignancy such as nuclear pleomorphism and cellular atypia. A high mitotic index is also predictive of aggressive behavior. *Hemangiopericytoma*, although not strictly a meningioma, is a meningeal tumor with an especially aggressive behavior. Meningiomas with features of aggressiveness and hemangiopericytomas, even if totally excised by gross inspection, frequently recur and should receive postoperative radiotherapy. Chemotherapy has no proven benefit.

SCHWANNOMAS

These tumors are also called *neuromas*, *neurinomas*, or *neurolemmomas*. They arise from Schwann cells of nerve roots, most frequently in the eighth cranial nerve (vestibular schwannoma, formerly termed acoustic schwannoma). The fifth cranial nerve is the second most frequent site; however, schwannomas may arise from any cranial or spinal root except the optic and olfactory nerves, which are myelinated by oligodendroglia rather than Schwann cells. Neurofibromatosis (NF) type 2 (see below) strongly predisposes to vestibular schwannoma. Schwannomas of spinal nerve roots are also seen in these patients as well as patients with NF type 1.

Eighth nerve schwannomas typically arise from the vestibular division of the nerve. Because the vestibular system adapts to slow destruction of the eighth nerve, vestibular schwannomas characteristically present as progressive unilateral hearing loss rather than with dizziness or other vestibular symptoms. Unexplained unilateral hearing loss always merits evaluation, including audiometry and either brainstem auditory evoked potentials or an MRI scan (Chap. 29). As a vestibular schwannoma grows, it can compress the cerebellum, pons, or facial nerve, producing associated symptoms. With rare exceptions schwannomas are histologically and clinically benign. They appear as dense and uniformly enhancing neoplasms on MRI (Fig. 370-6). Vestibular schwannomas enlarge the internal auditory canal, an imaging feature that helps distinguish them from other cerebellopontine angle masses.

Whenever possible, schwannomas should be surgically excised. When the tumors are small, it is usually possible to preserve hearing in the involved ear. In the case of large tumors, the patient is usually deaf at presentation; nonetheless, surgery is indicated to prevent further compression of posterior fossa structures. Gamma knife treatment is also effective for schwannoma but is equivalent in cost and complication rate to surgery. Moreover, the long-term consequences of stereotaxic radiosurgery, including the possibility of secondary radiation-induced neoplasms, are unknown.

OTHER BENIGN BRAIN TUMORS

Epidermoid tumors are cystic tumors with proliferative epidermal cells at the periphery and more mature epidermal cells towards the center of the cyst. The mature cells desquamate into the liquid center of the cyst. Epidermoid tumors are thought to arise from embryonic epidermal rests within the cranium. They occur extraaxially near the midline, in the middle cranial fossa, the suprasellar region, or the cerebellopontine angle. Epidermoid cysts are well-demarcated lesions that are amenable to complete surgical excision. Postoperative radiation therapy is unnecessary.

Dermoid cysts are thought to arise from embryonic rests of skin tissue trapped within the CNS during closure of the neural tube. The most frequent locations are in the midline supratentorially or at the cerebellopontine angle. Histologically, they are composed of all elements of the dermis, including epidermis, hair follicles, and sweat glands; they frequently calcify. Treatment is surgical excision.

Craniopharyngiomas are thought to arise from remnants of Rathke's pouch, the mesodermal structure from which the anterior pituitary gland is derived (Chap. 328). Craniopharyngiomas typically present as suprasellar masses. Histologically, craniopharyngiomas resemble epidermoid tumors; they are usually cystic, and in adults 80% are calcified. Because of their location, they may present as growth failure in children, endocrine dysfunction in adults, or visual loss in either age group. Treatment is surgical excision; postoperative external beam radiation or stereotaxic radiosurgery is added if total surgical removal cannot be achieved.

Colloid cysts are benign tumors of unknown cellular origin that occur within the third ventricle and can obstruct CSF flow. *Rare benign primary brain tumors* include neurocytomas, subependymomas, and pleomorphic xanthoastrocytomas. Surgical

excision of these neoplasms is the primary treatment and can be curative.

NEUROCUTANEOUS SYNDROMES

This group of genetic disorders, also known as the *phakomatoses*, produces a variety of developmental abnormalities of skin along with an increased risk of nervous system tumors (Table 370-1). These disorders are inherited as autosomal dominant conditions with variable penetrance.

NEUROFIBROMATOSIS TYPE 1 (VON RECKLINGHAUSEN'S DISEASE) (FIG. 370-CD1)

NF1 is characterized by cutaneous *neurofibromas*, pigmented lesions of the skin called *cafe au lait spots*, freckling in non-sun exposed areas such as the axilla, hamartomas of the iris termed Lisch nodules, and pseudoarthrosis of the tibia. Neurofibromas are benign peripheral nerve tumors composed of proliferating Schwann cells and fibroblasts. They present as multiple, palpable, rubbery, cutaneous tumors. They are generally asymptomatic; however, if they grow in an enclosed space, e.g., the intervertebral foramen, they may produce a compressive radiculopathy or neuropathy. Aqueductal stenosis with hydrocephalus, scoliosis, short stature, hypertension, epilepsy, and mental retardation may also occur.

Mutation of the *NF1* gene on chromosome 17 causes von Recklinghausen's disease. The *NF1* gene is a tumor suppressor gene; it encodes a protein, *neurofibromin*, which modulates signal transduction through the *ras* GTPase pathway. Patients with NF1 are at increased risk of developing nervous system neoplasms, including plexiform neurofibromas, optic gliomas, ependymomas, meningiomas, astrocytomas, and pheochromocytomas. Neurofibromas may undergo secondary malignant degeneration and become sarcomas.

NEUROFIBROMATOSIS TYPE 2

NF2 is characterized by the development of bilateral vestibular schwannomas in >90% of individuals who inherit the gene. Patients with NF2 also have a predisposition for the development of meningiomas, gliomas, and schwannomas of cranial and spinal nerves. In addition, a characteristic type of cataract, juvenile posterior subcapsular lenticular opacity, occurs in NF2. Multiple cafe au lait spots and peripheral neurofibromas occur rarely.

In patients with NF2, vestibular schwannomas usually present with progressive unilateral deafness early in the third decade of life. Bilateral vestibular schwannomas are generally detectable by MRIat that time (Fig. 370-6). Surgical management, designed to treat the underlying tumor and preserve hearing as long as possible, is difficult.

The *NF2* gene on chromosome 22q codes for a protein called *neurofibromin 2*, *schwannomin*, or *merlin*, with homology to a family of cytoskeletal proteins that includes moesin, ezrin, and radixin.

TUBEROUS SCLEROSIS (BOURNEVILLE'S DISEASE)

Tuberous sclerosis is characterized by cutaneous lesions, seizures, and mental retardation. The cutaneous lesions include adenoma sebaceum (facial angiofibromas, Fig. 370-CD2), ash leaf-shaped hypopigmented macules (best seen under ultraviolet illumination with a Wood's lamp) (Fig. 370-CD3), shagreen patches (yellowish thickenings of the skin over the lumbosacral region of the back), and depigmented nevi. On neuroimaging studies, the presence of subependymal nodules, which may be calcified, is characteristic. Patients inheriting the tuberous sclerosis gene are at increased risk of developing ependymomas and childhood astrocytomas, of which >90% are *subependymal giant cell astrocytomas*. These are benign neoplasms that may develop in the retina or along the border of the lateral ventricles. They may obstruct the foramen of Monro and produce hydrocephalus. Rhabdomyomas of the myocardium and angiomyomas of the kidney, liver, adrenals, and pancreas may also occur.

Treatment is symptomatic. Anticonvulsants for seizures, shunting for hydrocephalus, and behavioral and educational strategies for mental retardation are the mainstays of management. Severely affected individuals generally die before age 30.

Mutations at both 9q(TSC-1) and 16p(TSC-2) are associated with tuberous sclerosis. The mutated genes code for *tuberins*, proteins that modulate the GTPase activity of other cellular proteins.

VON HIPPEL-LINDAU SYNDROME

This syndrome consists of retinal, cerebellar, and spinal hemangioblastomas, which are slowly growing cystic tumors. Hypernephroma, renal cell carcinoma, pheochromocytoma, and cysts of the kidneys, pancreas, epididymis, or liver may also occur. Erythropoietin production by hemangioblastomas may result in polycythemia. The von Hippel-Lindau (VHL) tumor suppressor gene on chromosome 3p encodes a protein that appears to suppress transcription elongation by RNA polymerase II.

TUMORS METASTATIC TO BRAIN

MECHANISMS OF BRAIN METASTASES

The large majority of brain metastases disseminate by hematogenous spread. The anatomic distribution of brain metastases generally parallels regional cerebral blood flow, with a predilection for the gray matter-white matter junction and for the border zone between middle cerebral and posterior cerebral artery distributions. The lung is the most common origin of brain metastases; both primary lung cancer and cancers metastatic to the lung can metastasize to the brain. Breast cancer has a propensity to metastasize to the cerebellum and the posterior pituitary gland. This propensity could be explained by patterns of retrograde venous flow from the thorax into the skull or by an especially hospitable environment for breast cancer cells provided by the cerebellum and pituitary (the "seed and soil" hypothesis).

Lung cancer (adenocarcinoma and small cell lung cancer), breast cancer (especially ductal carcinoma), gastrointestinal malignancies, and melanoma are common tumors

that metastasize to brain (Table 370-2). Certain less common tumors have a special propensity to metastasize to brain, including germ cell tumors and thyroid cancer. By contrast, prostate cancer, ovarian cancer, and Hodgkin's disease rarely metastasize to the brain. Moreover, breast cancer that metastasizes to bone tends not to metastasize to the brain. Therefore, the cellular environment of the brain is hospitable to only a subset of systemic cancers. Parenchymal spinal cord metastases are rare.

EVALUATION OF METASTASES FROM KNOWN CANCER

On MRI scans brain metastases typically appear as well-demarcated, approximately spherical lesions that are hypointense or isointense relative to brain on T1-weighted images and bright on T2-weighted images. They invariably enhance with gadolinium, reflecting extravasation of gadolinium through tumor vessels that lack a blood-tumor barrier (Fig. 370-7). Small metastases often enhance uniformly. Larger metastases typically produce ring enhancement surrounding a central mass of nonenhancing necrotic tissue that develops as the metastasis outgrows its blood supply. Metastases are surrounded by variable amounts of edema. Blood products may also be seen, reflecting hemorrhage of abnormal tumor vessels.

The radiologic appearance of a brain metastasis is not specific. The differential diagnosis of ring-enhancement lesions includes brain abscess, radiation necrosis, toxoplasmosis, granulomas (tuberculosis, sarcoidosis), demyelinating lesions, primary brain tumors, primary CNS lymphoma, stroke, hemorrhage, and trauma. Contrast-enhanced CT scanning is less sensitive than MRI for the detection of brain metastases. Cytologic examination of the CSF is not indicated, since intraparenchymal brain metastases almost never shed cells into CSF. Measuring CSF levels of tumor markers such as carcinoembryonic antigen (CEA) is rarely helpful in management.

BRAIN METASTASES WITHOUT A KNOWN PRIMARY TUMOR

In general hospital populations, up to one-third of patients presenting with brain metastases do not have a known underlying cancer. These patients generally present with either a seizure or a progressive neurologic deficit. Neuroimaging studies demonstrate one or multiple ring-enhancement lesions. In individuals who are not immunocompromised and not at risk for brain abscesses, this radiologic pattern is most likely due to brain metastasis.

Diagnostic evaluation begins with a search for the primary tumor. Blood tests should include CEA and liver function tests. A careful examination of the skin for melanoma and the thyroid gland for masses should be carried out. A CT scan of the chest, abdomen, and pelvis should be obtained. If these are all negative, further imaging studies, including bone scan, other radionuclide scans, and upper and lower gastrointestinal barium studies, are unlikely to be productive. The search for a primary cancer most often discloses lung cancer, particularly small cell lung cancer, or melanoma. In 30% of patients no primary tumor can be identified even after extensive evaluation.

A tissue diagnosis is essential. If a primary tumor is found, it will usually be more accessible to biopsy than a brain lesion. If a single brain lesion is found in a surgically accessible location, if a primary tumor is not found, or if the primary tumor is in a

location difficult to biopsy, the brain metastasis should be biopsied or resected.

TREATMENT

Once a systemic cancer metastasizes to the brain it is, with rare exception, incurable. Therapy is therefore palliative, designed to prevent disability and suffering and, if possible, to prolong life. Published outcome studies have focused on survival as the primary end point, leaving questions regarding quality of life unanswered. There is, however, widespread agreement that glucocorticoids, anticonvulsants, and radiation therapy improve the quality of life for many patients. The roles of surgery and chemotherapy are less well established.

General Measures High-dose glucocorticoids frequently ameliorate symptoms of brain metastases. Improvement is often dramatic, occurs within 6 to 24 h, and is sustained with continued administration, although the toxicity of glucocorticoids is cumulative. Therefore, if possible, a more definitive therapy for metastases should be instituted to permit withdrawal of glucocorticoid therapy. One-third of patients with brain metastases have one or more seizures. Anticonvulsants are empirically used for seizure prophylaxis when supratentorial metastases are present.

Specific Measures

Radiation Therapy Radiation is the primary treatment for brain metastases. Since multiple microscopic deposits of tumor cells throughout the brain are likely to be present in addition to metastases visualized by neuroimaging studies, whole-brain irradiation is usually used. Its benefit has been established in controlled studies, but no clear dose response has been shown. Usually, 30-37.5 Gy is administered in 10 to 15 fractions; an additional dose ("boost") of focal irradiation to a single or large metastasis may also be administered.

Surgery Up to 40% of patients with brain metastases have only a single tumor mass identified by CT. Accessible single metastases are usually surgically excised as a palliative measure. If the systemic disease is under control, total resection of a single brain lesion has been demonstrated to improve survival and minimize disability. Survival appears to be improved if surgery is followed by whole-brain irradiation.

Chemotherapy Brain metastases of certain tumors, including breast cancer, small cell lung cancer, and germ cell tumors, are often responsive to systemic chemotherapy. Although metastases frequently do not respond as well as the primary tumor, dramatic responses to systemic chemotherapy or hormonal therapy may occur in some cases. In patients who are neurologically stable, two to four cycles of systemic chemotherapy may be administered initially to reduce tumor mass and render the residual tumor more amenable to radiation therapy. Even if a complete radiologic remission is achieved from chemotherapy, whole-brain irradiation should then be administered.

Experimental Therapies These include stereotaxic radiosurgery, gene therapy, immunotherapy, intraarterial chemotherapy, and chemotherapy administered following osmotic disruption of the blood-brain barrier.

LEPTOMENINGEAL METASTASES

Leptomeningeal metastases are also called *carcinomatous meningitis*, *meningeal carcinomatosis*, and, in the cases of specific tumors, *leukemic meningitis* or *lymphomatous meningitis.* Clinical evidence of leptomeningeal metastases is present in 8% of patients with metastatic solid tumors; at necropsy, the prevalence is as high as 19%. Among solid tumors, adenocarcinomas of the breast and lung and melanoma are most often responsible (Table 370-2). In one-quarter of patients the systemic cancer is under control; thus effective control of leptomeningeal disease can improve the quality and duration of life.

Pathologically, three patterns of tumor involvement may be seen: (1) a diffuse coating of the leptomeninges by a thin layer of tumor cells, (2) nodular growth of macroscopic tumor metastases in meninges and on nerve roots, or (3) plaque-like metastases in the leptomeninges with many cells shed into the subarachnoid space and extension of tumor into Virchow-Robin spaces. Leptomeningeal metastases may coexist with parenchymal CNS metastases.

Cancer usually metastasizes to the meninges via the bloodstream. Alternatively, a superficially located parenchymal metastasis may shed cells directly into the subarachnoid space. Some tumors, including squamous cell carcinoma of the skin and some non-Hodgkin's lymphomas, have a propensity to grow along peripheral nerves and may seed the meninges by that route.

CLINICAL FEATURES

Leptomeningeal metastases present with signs and symptoms at multiple levels of the nervous system, most often in a setting of known systemic malignancy. Encephalopathy is frequent, and cranial neuropathy or spinal radiculopathy from nodular nerve root compression is characteristic. Hydrocephalus results from obstruction of CSF outflow in the posterior fossa. Focal neurologic deficits from coexisting intraparenchymal metastases may occur.

LABORATORY EVALUATION

Leptomeningeal metastases are diagnosed by cytologic demonstration of malignant cells in the CSF, by MRI demonstration of nodular tumor deposits in the meninges or diffuse meningeal enhancement (Fig. 370-8), or by meningeal biopsy. CSF findings are usually those of an inflammatory meningitis, consisting of lymphocytic pleocytosis, elevated protein levels, and normal or low CSF glucose. A complete MRI examination of the neuraxis may demonstrate hydrocephalus due to obstruction of CSF pathways and identify nodular meningeal metastases.

TREATMENT

In selected patients, intrathecal chemotherapy and focal external beam radiotherapy to sites of leptomeningeal disease are the mainstays of management. Although the prognosis of leptomeningeal metastases is poor, approximately 20% of patients aggressively treated for leptomeningeal metastases can expect a sustained response of

approximately 6 months. Intrathecal therapy exposes meningeal tumor to high concentrations of chemotherapy with minimal systemic toxicity. Methotrexate can be safely administered intrathecally and is effective against leptomeningeal metastases from a variety of solid tumors and lymphoma; ara-C and thio-TEPA are alternative agents. Intrathecal chemotherapy may be administered either by repeated lumbar puncture or through an indwelling Ommaya reservoir, which consists of a catheter in one lateral ventricle attached to a reservoir implanted under the scalp. If there is a question of patency of CSF pathways, a radionuclide flow study may be performed.

Large deposits of tumor on the meninges or along nerve roots are unlikely to respond to intrathecal chemotherapy, as the barrier to diffusion is too great. Therefore, external beam radiation is employed. Hydrocephalus is treated with a ventriculoperitoneal shunt, although seeding of the peritoneum by tumor is a risk.

MALIGNANT SPINAL CORD COMPRESSION

Spinal cord compression from solid tumor metastases usually results from expansion of a vertebral metastasis into the epidural space. Primary tumors that frequently metastasize to bone include lung, breast, and prostate cancer. Back pain is usually the first symptom and is prominent at presentation in 90% of patients. The pain is typically dull, aching, and may be associated with localized tenderness. If a nerve root is compressed, radicular pain is also present. The neurologic signs that accompany spinal cord compression are determined by the spinal level of the lesion; the thoracic cord is most often affected. Weakness, sensory loss, and autonomic dysfunction (urinary urgency and incontinence, fecal incontinence, and sexual impotence in men) are the hallmarks of spinal cord compression. Once signs of spinal cord compression appear, they tend to progress rapidly. It is thus essential to recognize and treat this devastating complication of malignancy at the earliest possible time in order to prevent irreversible neurologic deficits. *Diagnosis and management are discussed in Chap. 368.*

METASTASES TO THE PERIPHERAL NERVOUS SYSTEM

Systemic cancer may compress or invade peripheral nerves. Compression of the brachial plexus may occur by direct extension of Pancoast's tumors (cancer of the apex of the lung) or by extension of local lymph node metastases of breast or lung cancer or lymphoma. The lumbosacral plexus may be compressed by the retroperitoneal spread of prostate or ovarian cancer or lymphoma. Skull metastases may compress cranial nerve branches as they pass through the skull, and pituitary metastases may extend into the cavernous sinus. The epineurium generally provides an effective barrier to invasion of the peripheral nerves by solid tumors, but certain tumors characteristically invade and spread along peripheral nerves. Squamous cell carcinoma of the skin may spread along branches of the trigeminal nerve and extend intracranially. Non-Hodgkin's lymphoma may be neurotrophic and cause a syndrome resembling mononeuropathy multiplex. Focal external beam radiation may reduce pain, prevent irreversible loss of peripheral nerve function, and possibly restore function.

In patients with cancer who have brachial or lumbosacral plexopathy, it may be difficult to distinguish tumor invasion from radiation injury. High radiation dose or the presence of myokymia (rippling contractions of muscle) suggests radiation injury, whereas pain

suggests tumor. Radiographic imaging studies may be equivocal, and surgical exploration is sometimes required.

COMPLICATIONS OF THERAPY

RADIATION TOXICITY

The nervous system is vulnerable to delayed injury by therapeutic radiation. The mechanism of injury is unknown, but radiation-induced free radical production is probably contributory. Histologically, there is demyelination, hyaline degeneration of small arterioles, and eventually brain infarction and necrosis. However, radiation injury can occur without vasculopathy, suggesting that ischemia is a late manifestation and does not account entirely for the tissue damage.

Radiation injury to the brain is classified by the time of its occurrence. *Acute radiation injury* occurs during or immediately after therapy. It is rarely seen with current protocols of external beam radiation but may occur after stereotaxic radiosurgery. Manifestations include headache, sleepiness, and worsening of preexisting neurologic deficits. *Early delayed radiation injury* occurs within 4 months of therapy. It is associated with an increased white matter T2 signal on MRI scans. In children, the *somnolence syndrome* is a common form of early delayed radiation injury in which somnolence and ataxia develop after whole-brain irradiation. Irradiation of the cervical spine may cause Lhermitte's phenomenon, an electricity-like sensation evoked by neck flexion (Chap. 368). Acute and early delayed radiation injury are steroid-responsive and self-limited disorders and do not appear to increase the risk of late radiation injury.

Late delayed radiation injury produces permanent damage to the nervous system. It occurs more than 4 months (generally 8 to 24 months) after completion of therapy; onset 15 years after therapy has been described. After whole-brain irradiation, progressive dementia can occur, sometimes accompanied by gait apraxia. White matter signal abnormalities are present on MRI studies (Fig. 370-9). Following focal brain irradiation, radiation necrosis occurs within the radiation field, producing a contrast-enhanced mass, frequently with ring enhancement. MRI or CT scans are often unable to distinguish radiation necrosis from recurrent tumor, but PET or SPECT scans may demonstrate that glucose metabolism is increased in tumor tissue but decreased in radiation necrosis. Biopsy is frequently required to establish the correct diagnosis. Peripheral nerves, including the brachial and lumbosacral plexuses, may also develop late delayed radiation injury over a time span similar to that observed in the CNS.

If untreated, radiation necrosis of the CNS may act as an expanding mass lesion, although it may resolve spontaneously or after steroid treatment. Progressive radiation necrosis is best treated with surgical resection if the patient has a life expectancy of at least 6 months and a good Karnofsky performance score. There are anecdotal reports that anticoagulation with heparin or coumadin may be beneficial. Radiation injury also accelerates the development of atherosclerosis in large arteries, but an increase in the risk of stroke becomes significant only years after radiation treatment.

Endocrine dysfunction frequently follows exposure of the hypothalamus or pituitary gland to therapeutic radiation. Growth hormone is the pituitary hormone most sensitive

to radiation therapy, and thyroid-stimulating hormone is the least sensitive; ACTH, prolactin, and the gonadotropins have an intermediate sensitivity.

Development of a second neoplasm is another risk of therapeutic radiation that generally occurs many years after radiation exposure. Depending on the irradiated field, the risk of gliomas, meningiomas, sarcomas, and thyroid cancer is increased.

COMPLICATIONS OF CHEMOTHERAPY

Chemotherapy regimens used to treat primary brain tumors have generally included a nitrosourea and are well tolerated. Infrequently, nitrosoureas and other drugs used to treat CNS neoplasms cause altered mental states (e.g., confusion, depression), ataxia, and seizures. Chemotherapy for systemic malignancy is a more frequent cause of nervous system toxicity. Cisplatin commonly produces tinnitus and high-frequency bilateral hearing loss, especially in younger patients. At cumulative doses>450 mg/m$_2$, cisplatin can produce a symmetric, large fiber axonal predominantly sensory neuropathy; paclitaxel (Taxol) produces a similar picture. Fluorouracil and high-dose cytosine arabinoside can cause cerebellar dysfunction that resolves after discontinuation of therapy. Vincristine, which is commonly used to treat lymphoma, may cause an acute ileus and is frequently associated with development of a progressive distal, symmetric sensory-motor neuropathy with foot drop and paresthesias.

(Bibliography omitted in Palm version)

371. MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES - *Stephen L. Hauser, Donald E. Goodkin*

The demyelinating diseases occupy a unique place in neurology owing to their frequency; tendency to strike young adults; diversity of manifestations; and range of fundamental questions in neurobiology, immunology, virology, and genetics that arise regarding their pathogenesis. These disorders share features of inflammation and selective destruction of central nervous system (CNS) myelin; the peripheral nervous system (PNS) is spared. No specific tests for the demyelinating diseases exist, and diagnosis is based on recognition of the distinctive clinical patterns of CNS injury they produce.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is characterized by (1) a relapsing-remitting or progressive course and (2) a pathologic triad of CNS inflammation, demyelination, and gliosis (scarring). Lesions of MS are classically said to be *disseminated* in time and space. MS affects approximately 350,000 Americans and 1.1 million individuals worldwide. In Western societies, MS is second only to trauma as a cause of neurologic disability arising in early to middle adulthood. Current evidence indicates that MS is an autoimmune disease that develops in genetically susceptible individuals who have resided in certain permissive environments. Manifestations of MS vary from a benign illness to a rapidly evolving and incapacitating disease requiring profound adjustments in life-style and goals for patients and their families. Complications from MS affect multiple body systems; hence, a multidisciplinary approach is recommended to optimize clinical care.

PATHOGENESIS

Anatomy MS derives its name from the multiple scarred areas visible on macroscopic examination of the brain. These lesions, termed *plaques*, are sharply demarcated gray or pink areas easily distinguished from surrounding white matter. Plaques vary in size from 1 or 2 mm to several centimeters. The acute MS lesion, rarely found at autopsy, consists of perivenular cuffing by inflammatory mononuclear cells, predominantly T lymphocytes and macrophages, which also infiltrate white matter tissue and appear to orchestrate demyelination. At sites of inflammation, the blood-brain barrier is disrupted but the vessel wall itself is preserved, distinguishing the MS lesion from vasculitis. In some inflammatory lesions, a distinctive pattern of myelin damage, termed *vesicular demyelination*, can be appreciated. This change consists of dissolution of the multilamellated compact myelin sheaths that surround axon cylinders and their reconstitution as a lattice-like network of myelin membrane fragments. Myelin-specific autoantibodies (see "Immunology," below) are bound to the vesiculated myelin membranes, at least in some patients; these autoantibodies are thought to promote demyelination and stimulate macrophages and microglial cells (specialized CNS phagocytes of bone marrow origin) that scavenge the myelin debris. As lesions evolve, astrocytes proliferate extensively (gliosis). Oligodendrocytes, the myelin-producing cells, also proliferate initially in most MS lesions, but these cells are often destroyed as the infiltration and gliosis progress. Surviving oligodendrocytes or those that newly differentiate from a precurser pool may partially remyelinate naked

axons, resulting in *shadow plaques*. MS lesions may enlarge by gradual concentric outward growth; some chronic plaques display histologic gradations of increasing acuity from the center to the lesion edge.

The correspondence between number and size of plaques ("plaque burden") and the severity of clinical symptoms is imprecise. Hence, an extensive plaque burden may be associated with mild symptoms; or, conversely, seemingly minor pathologic changes may be present in some severely disabled individuals. Occasional cases either are clinically silent or produce "nonspecific" isolated symptoms such as facial pain, and evidence of MS is found unexpectedly at autopsy.

Recent ultrastructural studies of MS lesions suggest that different underlying pathologies may be present in different patients. Heterogeneity has been identified both in terms of the fate (i.e., death or survival) of oligodendrocytes in plaques and by the presence or absence of antibody and complement deposition. In primary progressive MS (PPMS; see below), a distinctive oligodendroglial cytopathy has been reported based on examination of a limited number of cases; if confirmed, this finding would suggest that PPMS is a unique disorder. Finally, although selective demyelination with sparing of axon cylinders is the hallmark of MS, partial or total axonal destruction, and in extreme cases cavitation, may also occur. The extent of axonal loss appears to correlate with irreversible neurologic disability. Axonal loss and cavitation are particularly prominent in the subtype of MS known as neuromyelitis optica or Devic's syndrome (see below).

Physiology Demyelination may have either negative or positive effects on axonal conduction. *Negative conduction abnormalities* consist of slowed axonal conduction, variable conduction block that occurs in the presence of high- but not low-frequency volleys of impulses, or complete conduction block. Conduction block in demyelinated fibers may also occur in response to raised temperature or metabolic derangements. The mechanism of conduction block appears to involve a hyperpolarization of the resting axon potential due to the exposure of voltage-dependent potassium channels that are normally buried underneath the myelin sheath. *Positive conduction abnormalities* include generation of ectopic impulses, spontaneously or after mechanical deformation, and abnormal "crosstalk" between demyelinated axons. Variable conduction block may explain the fluctuations in function that vary from hour to hour and from day to day in many patients and the characteristic worsening that is associated with fever or exercise. Ectopic impulse generation or "crosstalk" might give rise to Lhermitte's symptom, paroxysmal symptoms, or paresthesias (see below). Experimental therapies designed to alleviate conduction abnormalities in MS have included the use of calcium channel blockers to reduce the threshold for impulse generation and pharmacologic blockade (with 4-aminopyridine) of potassium channels.

Epidemiology MS is approximately twice as common in females as in males. In both sexes, the incidence rises steadily from adolescence to age 35 and declines gradually thereafter. The mean age of onset is slightly later in men than in women, due in part to a relative overrepresentation of males in PPMS, which has a later mean age of onset. MS beginning as early as age two years or as late as the eighth decade of life is rare but well documented. Various epidemiologic observations, summarized below, support of the role of an environmental exposure of some type in MS.

Location and Risk MS is primarily a disease of individuals living in temperate climates. The prevalence increases with increasing distance from the equator; this finding appears to be true in both the northern and southern hemispheres. Prevalence rates and north-south gradients are generally similar in North America and Europe. The highest known prevalence (250 per 100,000) occurs in the Orkney islands, located north of the mainland of Scotland, and MS is also common throughout Scandinavia and northern Europe. Numerous studies also suggest that location influences MS risk. For example, the prevalence of MS is low in Japan (2 per 100,000) but moderate (15 per 100,000) in Japanese Americans.

Changes in prevalence Studies from the United States, Europe, and Australia suggest that the prevalence of MS may have increased during the twentieth century, however these findings could represent an artifact due to improved detection of cases in the modern era.

Reported clusters Several possible point epidemics of MS have been described, the most convincing of which occurred in the Faeroe Islands off the coast of Denmark after the British occupation during World War II.

GENETIC CONSIDERATIONS

An inherent genetic susceptibility to MS exists, as summarized by the following observations:

Risk in Different Ethnic Groups The prevalence of MS differs among ethnic groups that reside in the same environment. In the United States, the prevalence of MS is higher in Caucasians than in other racial groups, consistent with observations in other parts of the world.

Familial Aggregation First-, second-, and third-degree relatives of patients with MS are at increased risk for the disease. Siblings of affected individuals have a lifetime risk of ~5%, whereas the risk to parents or children of affected individuals is somewhat lower. Studies of adoptees, half-siblings, and spouses of patients with MS strongly indicate that familial aggregation is primarily determined by shared genetic, and not environmental, factors.

Twin Studies The most compelling evidence for a genetic effect on MS is derived from twin studies, which demonstrate concordance rates of ~30% in monozygotic twins and 5% in dizygotic twins (similar to the risk in nontwin siblings).

The inheritance of MS cannot be explained with a simple genetic model. A single-gene hypothesis is at odds with concordance estimates in twin and family studies and with the observed nonlinear decrease in disease risk as the genetic distance from the MS proband is increased. It is likely that susceptibility is determined by multiple independent genetic loci (polygenic inheritance), each with a relatively small contribution to the overall risk. It is also possible that different genetic causes of susceptibility to MS (genetic heterogeneity) may exist. Linkage and association studies have identified the major histocompatibility complex (MHC) on chromosome 6 as one genetic determinant for MS. This complex encodes the histocompatibility antigens (the HLA system) that

present peptide antigens to T cells. The class II (HLA-D) region of the MHC is most strongly associated with MS, and susceptibility appears to result from the presence of the DR2 allele and its corresponding haplotype, defined by molecular criteria as DRB1*1501, DQA1*0102, DQB1*0602. Other genetic regions implicated in MS susceptibility include loci on chromosomes 3, 5, 16, and 19.

Immunology MS appears to be an autoimmune disease mediated, at least in part, by T lymphocytes. Evidence in support of this concept is derived from analogy to the laboratory model experimental allergic encephalomyelitis (EAE) and from direct studies of the immune system of MS patients.

Autoreactive T Lymphocytes Myelin basic protein (MBP) is an important T cell antigen in EAE and probably also in human MS. In patients with MS but not in unaffected individuals activated MBP-reactive T cells can be identified in the peripheral blood. In cerebrospinal fluid (CSF), the frequency of T cells reactive against MBP (and other myelin proteins) is also higher in patients with MS than in unaffected individuals. Direct evidence that MBP-reactive T cells are present in MS lesions has also been suggested by sequence analysis of the antigen-binding domain of T cell receptor molecules cloned from plaque tissue. The susceptibility gene DR2 may influence the immune response to MBP because it binds with high affinity to a fragment of MBP spanning amino acids 89 to 101; this region of MBP appears to be immunodominant for T cell responses in DR2-positive individuals.

Autoantibodies Increasing evidence suggests that autoantibodies play some role in MS, probably acting in concert with a pathogenic T cell response. In EAE, autoantibodies directed against myelin oligodendrocyte glycoprotein (MOG), a quantitatively minor myelin protein, were found to mediate MS-like demyelinating lesions; and recently anti-MOG antibodies were also detected in actively demyelinating MS lesions. MOG is thus a good candidate as a humoral autoantigen in MS. Evidence of an abnormal humoral immune response is present in the CSF of patients with MS. Membrane attack complexes can be detected in the CSF, suggesting a role for complement-mediated antibody damage. Elevated levels of immunoglobulin are easily measured and are characteristic of CSF in MS. Oligoclonal antibody -- derived from expansion of a small number of different molecules -- is also present in most cases. Oligoclonal immunoglobulin is also detected in other chronic inflammatory responses, including infections, and thus is not specific to MS. It is synthesized locally, and the specific pattern is unique to each patient. Attempts to identify an antigen against which most oligoclonal immunoglobulin is directed have been unsuccessful.

Cytokines Numerous cytokines and chemokines have been detected in brain, CSF, and peripheral blood of patients with MS, and it is probable that these molecules regulate many of the cellular interactions that operate in this disease (Chap. 305). By analogy to EAE $T_H 1$ cytokines that regulate cellular immunity, including interleukin (IL) 2, tumor necrosis factor (TNF) a, and interferon (IFN)g have traditionally been thought to be central to MS pathogenesis. TNF-a or IFN-g may contribute directly to tissue damage by injuring oligodendrocytes or the myelin membrane. Unfortunately, treatment strategies designed to blunt the $T_H 1$ response have thus far not been successful in treating MS. Furthermore, a recent clinical trial with a humanized antibody to TNF-a appeared to worsen MS. The identification of autoantibodies in MS suggests that $T_H 2$ cytokines

(including IL-4, IL-5, and IL-10) may play a pathogenic role in MS, and may explain why the results of TH1-based approaches have been disappointing.

Triggers Magnetic resonance imaging (MRI) scans indicate that many patients with relapsing forms of MShave bursts of multifocal inflammation that occur approximately monthly, or 7 to 10 times more frequently than clinical attacks. This finding suggests the presence of a large reservoir of subclinical disease in MS. Bursts appear to be associated with the migration of activated T cells from the peripheral blood across the blood-brain barrier and into brain; the triggers responsible for these bursts are not known. Patients may experience relapses after nonspecific upper respiratory infections, suggesting that molecular mimicry between viruses and myelin antigens may trigger attacks, or that some viruses may function as superantigens capable of activating disease-inducing T cells in MS (Chap. 305).

Microbiology As noted above, epidemiologic evidence supports the role of an environmental exposure inMS. MS risk also correlates with high socioeconomic status, which may reflect improved sanitation and delayed initial exposures to infectious agents. Some viruses, e.g., poliomyelitis and measles viruses, produce neurologic sequelae more frequently when the age of initial infection is delayed. The most widely studied experimental model of virus-induced demyelinating disease is infection with Theiler virus, a murine coronavirus similar to measles virus and canine distemper virus. Infection with some Theiler strains produces a chronic infection of oligodendrocytes with multifocal perivascular lymphocytic infiltration and demyelination, closely resembling lesions of MS.

In patients withMS, high antibody titers have been reported in serum andCSFagainst many viruses, including measles, herpes simplex, varicella, rubella, Epstein-Barr, and influenza C and some parainfluenza strains. Furthermore, numerous viruses and bacteria (or their genomic sequences) have been recovered from MS tissues and fluids. The most recent claims have involved human herpes virus type 6 (HHV-6) and chlamydia pneumoniae. A causal role for any infectious agent in MS remains unproven.

CLINICAL MANIFESTATIONS

The onset ofMS may be abrupt or insidious. Symptoms may be severe or seem so trivial that a patient may not seek medical attention for months or years. Initial symptoms are commonly one or more of the following: weakness or diminished dexterity in one or more limbs, a disturbance of gait, optic neuritis, sensory disturbance, diplopia, and ataxia (Table 371-1).

Weakness of the limbs may manifest as fatigue, disturbance of gait, or loss of dexterity. Initially, weakness may be detected only after physical exertion. Weakness is frequently accompanied by pyramidal signs including increased motor tone (spasticity), hyperreflexia, an extensor plantar response, and an absent superficial abdominal reflex. Occasionally, a tendon reflex may be lost (simulating a peripheral nerve lesion) if afferent fibers of the motor reflex arc are disrupted by a lesion in the dorsal root entry zone.

Optic neuritis generally presents as diminished acuity, dimness, or color desaturation in

the central field of vision. These symptoms may be mild or progress over hours or days to severe visual loss, or rarely to complete loss of light perception. Visual symptoms are generally monocular but may occur bilaterally. Periorbital pain frequently precedes or accompanies diminished visual acuity and may be aggravated by eye movement. An afferent pupillary response (Fig. 28-2) may be detected by a swinging flashlight test. Funduscopic examination may be normal or reveal swelling of the optic disc (papillitis). Venous sheathing of retinal vessels, due to the transendothelial migration of lymphocytes, is occasionally present. Pallor of the optic disc (optic atrophy) commonly follows an episode of optic neuritis. Uveitis occurs rarely.

Visual blurring in MS may result from optic neuritis or diplopia. These two causes are distinguished by asking the patient to cover each eye sequentially and observing whether the visual difficulty clears. *Diplopia* may result from an internuclear ophthalmoplegia (INO) or extraocular muscle weakness of the sixth (or rarely the third or fourth) cranial nerves. An INO consists of impaired or slowed adduction of one eye from a lesion in the ipsilateral medial longitudinal fasciculus. This tract connects the sixth cranial nerve nucleus with the contralateral third nerve nucleus. Prominent nystagmus is often observed in the abducting eye, along with a small skew deviation. An INO can resemble an isolated medial rectus palsy. Convergence is often preserved in INO, helping to differentiate between these two entities. The finding of bilateral INO is highly suggestive of MS. Other common gaze disturbances in MS include a horizontal gaze palsy due to an ipsilateral lesion in the abducens nucleus or the paramediam pontine reticular formation, a "one and a half" syndrome from a horizontal gaze palsy plus an INO, and acquired pendular nystagmus.

Sensory symptoms commonly include paresthesias (tingling, "pins and needles," or painful burning) or hypesthesia (numbness or a "dead" feeling). Complaints of unpleasant feelings of "swollen," "wet,", "raw", or "tightly wrapped" body parts are common. Sensory symptoms often begin in a focal area of a limb, the torso, or the head and spread over hours or days to adjacent ipsilateral or contralateral areas of the body. Involvement of the trunk with a "cord level" is diagnostically helpful because it identifies the spinal cord and not the PNS as the origin of the sensory symptoms.

Ataxia of gait and limbs reflects demyelination in the cerebellum or cerebellar pathways. In advanced MS cerebellar dysarthria (scanning speech) is common. The true extent of cerebellar involvement may be uncertain when motor and sensory deficits coexist.

Bladder dysfunction manifests as urgency or hesitancy in voiding, incomplete emptying, or incontinence. Constipation is also common. One or more of these symptoms occurs at some time in most patients with MS and may be present at onset. Fecal urgency or bowel incontinence occur less commonly.

Cognitive dysfunction may be recognized early or late in the course of MS. Cognitive deficits most commonly include memory loss, impaired attention, problem-solving difficulties, slowed information processing, and difficulties in shifting between cognitive tasks. Impaired judgment and emotional liability may be evident. These symptoms impair activities of daily living in as many as 20% of patients.

Depression is experienced by ~60% of patients during the course of the illness. Suicide

is 7.5-fold more common than in age-matched controls.

Fatigue occurs in most patients with MS. It may be maximum during mid-afternoon or continuous throughout the day. Symptoms of fatigue include generalized motor weakness, limited ability to concentrate or read, lassitude, and sleepiness.

Heat sensitivity is experienced as the appearance of new symptoms or the worsening of preexisting symptoms on exposure to heat. For example, transient visual blurring may become apparent during a hot shower or with physical exercise. It is a common phenomenon for symptoms of MS to worsen transiently, sometimes in a dramatic fashion, during the course of a febrile illness (see pseudoexacerbation, below).

Ancillary Symptoms *Lhermitte's symptom* is the sensation of a momentary electric current or shock evoked by neck flexion, other neck movements, or cough. The symptom typically radiates down the spine into the legs, but it may radiate into the arms or be provoked by movements of the lumbar spine. Lhermitte's symptom is not specific to MS; it also occurs with other spinal cord disorders, including cervical spondylosis.

Paroxysmal symptoms are brief and stereotypic. Tonic spasms consist of an unpleasant tingling or other sensation association with tonic contraction of a limb, face, or trunk. Other paroxysmal symptoms include dysarthria and ataxia, diplopia, transient unilateral paralysis, hemifacial spasm, paresthesias, and pain. Attacks may be momentary or persist for ³30 s. They generally begin in clusters, occurring many times throughout the day, and the patient may identify precipitating factors such as hyperventilation or particular movements.

Trigeminal neuralgia, a lancinating facial pain, may also occur; features that suggest MS rather than an idiopathic etiology (Chap. 367) include onset before 50 years of age, bilateral occurrence, objective facial sensory loss, and constant rather than paroxysmal pain.

Facial weakness may resemble idiopathic Bell's palsy; however, facial weakness due to MS is generally not associated with ipsilateral loss of taste sensation or retroauricular pain (Chap. 367).

Facial myokymia, or chronic flickering contractions of the facial musculature, are also common. The movements commonly involve the orbicularis oculus muscle and appear under the eye. Facial myokymia may arise from lesions of the corticobulbar tracts or brainstem course of the facial nerve.

Vertigo may appear suddenly and in dramatic fashion with gait unsteadiness and vomiting, resembling acute labyrinthitis. A brainstem rather than end-organ origin of vertigo is suggested by the presence of coexisting trigeminal or facial nerve involvement, vertical nystagmus, or nystagmus that is unaccompanied by latency of onset, direction reversal, or fatigue (Chap. 21). Hearing loss may also occur but is uncommon.

DISEASE COURSE

Approximately 85% of patients with MS experience an abrupt onset of symptoms and signs at disease onset. Thereafter, the clinical course may be characterized by acute episodes of worsening (exacerbations or relapses), gradual progression of disability, or combinations of both. Four clinical patterns are recognized by international consensus. Patients with *relapsing-remitting MS* (RRMS) experience relapses with or without complete recovery and are clinically stable between these episodes (Fig. 371-1, A and B). Approximately 50% of patients with RRMS convert to *secondary progressive MS* (SPMS) within 10 years of disease onset. The secondary progressive phase is characterized by gradual progression of disability with or without superimposed relapses (Fig. 371-1, C and D). In contrast, patients with *primary progressive MS* (PPMS) experience gradual progression of disability from onset without superimposed relapses (Fig. 371-1, E and F). Approximately 10% of patients with MS experience this clinical pattern. Patients with *progressive relapsing MS* experience gradual progression of disability from disease onset later accompanied by one or more relapses; this clinical pattern affects ~5% of patients (Fig. 371-1G).

DIAGNOSIS

There is no definitive diagnostic test. Diagnostic criteria for clinically definite MS require documentation of two or more episodes of symptoms and two or more signs that reflect pathology in anatomically noncontiguous white matter tracts of the CNS (Table 371-2). Symptoms must last more than one day and occur as distinct episodes that are separated by 28 or more days. At least one of the two required signs must be present on neurological examination. The second may be documented as an abnormal paraclinical test, either brain or spinal cord MRI, or visual, auditory, or somatosensory evoked electrical response. In patients who experience gradual progression of disability for 6 or more months without superimposed relapses, documentation of intrathecal IgG may be used to support the diagnosis.

DIAGNOSTIC TESTS

Magnetic Resonance Imaging Widespread availability of brain and spinal cord MRI has revolutionized the diagnosis and management of MS. Disease-related changes are detected by MRI (Fig. 371-2) in >95% of patients who otherwise meet diagnostic criteria for definite MS (Table 371-2). An increase in vascular permeability, detected by leakage of the intravenous contrast agent gadolinium DPTA into the brain, appears to be a very early event in the formation of new MS lesions and perhaps is a marker of inflammation. Gadolinium enhancement persists for 2 to 8 weeks; and the residual mixture of edema, inflammation, demyelination, axonal loss, and gliosis in the MS plaque remains visible as a focal area of hyperintensity on spin-echo (T2-weighted) and proton-density images. Lesions often appear to extend outward from the ventricular surface, corresponding to a pattern of perivenous demyelination that is observed pathologically in MS (Dawson's fingers). Lesions are also commonly found within the brainstem, corpus callosum, cerebellum, and spinal cord. Lesions of the anterior corpus callosum are particularly useful diagnostically because this site is usually spared in cerebrovascular disease. Specific criteria for the use of MRI in support of a diagnosis of MS have been proposed (Table 371-2).

The correlation between the total volume of T2-weighted signal abnormality -- the

"lesion burden" -- and clinical measures of disability is poor. Approximately one-third of hyperintense T2-weighted lesions appear hypointense on T1-weighted imaging sequences. These "black holes" provide more specific imaging markers of irreversible demyelination and axonal loss that correlate more robustly with clinical measures of disability. The correlation between MRI measures and clinical status is even stronger with emerging imaging techniques, including magnetization transfer imaging and proton-magnetic resonance spectroscopic imaging, which can distinguish irreversible demyelination and axonal loss from reversible edema and inflammation.

Evoked Responses Evoked response testing may detect slowed or absent conduction in visual, auditory, somatosensory, or motor pathways (Chap. 357). These tests use computer averaging techniques to record the electrical response evoked in the nervous system after repetitive sensory stimuli. One or several evoked responses are abnormal in 80 to 90% of patients with MS. Abnormalities in evoked responses occur with a variety of neurologic disorders that disrupt pathways being measured; thus, they are not specific to MS. Testing is of diagnostic value when it provides evidence of a subclinical second lesion in a patient who manifests only one abnormality on neurologic examination (Table 371-2).

Cerebrospinal Fluid (CSF) CSF abnormalities consist of abnormally increased levels of intrathecally synthesized IgG, oligoclinal banding, and mononuclear cell pleocytosis. Various formulas are used to distinguish intrathecally synthesized IgG from serum IgG that may have entered the CNS passively across a disrupted blood-brain barrier. One formula expresses the ratio of IgG to albumin in the CSF divided by the ratio in the serum ("the CSF IgG index"). Oligoclonal banding of CSF IgG is detected by agarose gel electrophoresis techniques. Two or more oligoclonal bands are found in 75 to 90% of patients with MS. Oligoclonal banding may be absent at the onset of MS, and in individual patients the number of bands present may increase with time. It is important that paired serum samples be studied to exclude a systemic origin of the oligoclonal bands.

Other CSF abnormalities also occur but are less specific for MS. In one large series, CSF mononuclear pleocytosis (>5 cells/uL) was present in 25% of patients with MS. CSF cell counts are generally <20/uL in patients with MS, and counts >50/uL are unusual but may occur with acute myelopathy. Pleocytosis of >75 cells/uL or a finding of polymorphonuclear leukocytes in CSF makes the diagnosis of MS unlikely. Pleocytosis is more common in young patients with relapsing-remitting MS than in older patients with progressive forms of MS. The total CSF protein content is usually normal or only slightly increased. A protein elevation>100 mg/dL is rare and should prompt consideration of alternative diagnosis such as an infection or tumor.

DIFFERENTIAL DIAGNOSIS

Numerous diagnostic formulas have been proposed for MS (Table 371-2); although useful, they cannot replace sound clinical judgment. No single clinical sign or test is diagnostic of MS. The diagnosis is usually easily made in a young adult with relapsing and remitting symptoms referable to different areas of CNS white matter. The possibility of an alternate diagnosis should be considered when (1) symptoms are localized exclusively to the posterior fossa, craniocervical junction, or spinal cord; (2) the patient

is younger than 15 or older than 60 years; (3) the clinical course is progressive from onset; and (4) the patient has never experienced visual, sensory or bladder symptoms. Diagnosis may also be difficult in patients with a rapid or even explosive onset suggesting a cerebrovascular accident, or mild symptoms only and a normal neurologic examination. In such situations, the patient should be questioned carefully for a history of prior attacks that may not be recalled initially. Rarely, a mass lesion resulting from intense inflammation and swelling may occur in MS and may mimic a primary or metastatic tumor.

Examination reveals evidence of neurologic disease in most patients. Abnormal signs are often more widespread than expected from the interview. For example, a patient with MS may present with symptoms in one leg and signs in both. This type of finding is helpful when it permits exclusion of a single focal lesion as the source of a patient's symptoms. Conversely, the presence of features that are uncommon or rare in MS should call the diagnosis into question. These include aphasia, extrapyramidal syndromes suggesting parkinsonism, chorea, isolated dementia, amyotrophy with fasciculations, peripheral neuropathy, fever, headache, seizures, or coma.

Systemic lupus erythematosus (SLE) rarely produces a relapsing or progressive disorder that mimics MS; other manifestations of SLE are usually present (Chap. 311). Behcet's syndrome may produce a chronic illness with optic neuropathy and myelopathy but more often presents as an acute or subacute multifocal CNS disorder (Fig. 371-CD1); characteristic oral and genital lesions, uveitis, and an elevated ESR are distinguishing features (Chap. 316). Relapsing-remitting CNS syndromes have also been described in Sjogren's syndrome. Sarcoidosis may produce cranial nerve palsies (especially of the seventh cranial nerve), progressive optic atrophy, or myelopathy (Chap. 318). Systemic involvement helps to distinguish these conditions from MS. Lyme borreliosis (Fig. 371-CD2) may involve the optic nerve, brainstem, or spinal cord in the absence of characteristic rash, fever, or meningoradiculitis (Chap. 176). Other chronic infections, including meningovascular syphilis and infection with HIV, may need to be considered. HTLV type I-associated myelopathy (HAM; tropical spastic paraparesis) is characterized by back pain, progressive spasticity affecting predominantly the lower limbs, and bladder symptoms (Chap. 373). Diagnosis is based on identification of specific antibody to HTLV-I in serum and CSF and by direct virus isolation. Infection with the HTLV-II retrovirus may cause a progressive myelopathy similar to that caused by HTLV-I.

As noted above, the acute onset of a focal CNS disturbance in a previously healthy individual may suggest a stroke or migraine. Progressive focal deficits should always prompt consideration of a compressive lesion. Primary CNS lymphoma may produce single or multiple lesions that contrast-enhance on MRI and may resemble acute lesions of MS. A progressive or relapsing brainstem disturbance may be due to a vascular malformation in the posterior fossa. Pontine glioma is distinguished from MS by its tendency to produce progressive deficits that involve contiguous structures. Chiari malformations presenting in adulthood may cause cerebellar ataxia, nystagmus, and spastic weakness of the limbs; headache, lower cranial nerve palsies, and a syringomyelic syndrome are useful distinguishing features. Progressive myelopathies may result from cervical spondylosis, spinal cord tumor, or arteriovenous malformation (Chap. 368).

A positive family history, neurologic signs suggesting diffuse symmetric demyelination, and lack of characteristicCSFchanges raise the possibility of a metabolic or genetic condition that may mimicMS. Subacute combined degeneration due to vitamin B12deficiency may produce an MS-like syndrome in the absence of megaloblastic anemia (Chap. 368). Uncommon genetic disorders that may mimic MS include Krabbe's disease, metachromatic leukodystrophy, methylenetetrahydrofolate reductase deficiency, biotinidase deficiency, adrenomyeloneuropathy, familial spastic paraparesis, spinocerebellar ataxia, mitochondrial encephalopathy with lactic acidosis and stroke (MELAS), Leber's disease, and subacute necrotizing encephalomyelopathy (Leigh's disease).

PROGNOSIS

Most patients withMSexperience progressive disability. Fifteen years after diagnosis, fewer than 20% of patients with MS have no functional limitation, 50 to 60% require assistance when ambulating, 70% are limited or unable to perform major activities of daily living, and 75% are not employed. In 1998, it was estimated that the total annual economic burden of MS in the United States exceeded 6.8 billion. The following clinical and brainMRIfeatures may confer a more favorable prognosis: presentation with isolated optic neuritis or sensory symptoms, complete recovery from a first attack, age of onset younger than 40 years, female sex, relapsing-remitting clinical course, and fewer than two relapses in the first year of illness. In general, patients who experience minimal neurologic impairment 5 years after the first symptoms are least likely to be severely disabled 10 to 15 years later. By comparison, patients with persistent truncal ataxia, severe action tremor, or a disease course that is progressive from the onset are more likely to experience progression of disability.

In patients who experience an initial attack of monosymptomatic optic neuritis, brainstem signs, or myelopathy, brainMRIprovides useful prognostic information. If the brain MRI reveals multiple T2-weighted lesions, the risk of developing definiteMSwithin a 10-year period of follow-up is 70 to 80%. Conversely, if the brain MRI is normal, <10% of patients will experience a second episode of symptoms consistent with MS within 10 years.

TREATMENT

The treatment ofMS may be divided into two categories: (1) treatments designed to modify the disease process and (2) symptomatic management. Longitudinal scoring of the functional consequences of MS is essential for treatment decisions. The Kurtzke Expanded Disability Status Score (EDSS) is the most widely used measure of neurologic impairment in MS (Table 371-3).

Disease Modifying Therapies forRRMS(Fig. 371-3) Three treatment options for patients with RRMS are approved for use in the United States: (1)IFN-b1b (Betaseron), (2) IFN-b1a (Avonex), and (3) glatiramer acetate (Copaxone). Each of these treatments is also prescribed for patients withSPMS who experience frequent exacerbations because this clinical pattern cannot be distinguished reliably from RRMS with incomplete recovery from exacerbations. In Phase III clinical trials, recipients of IFN-b1b, IFN-b1a, and glatiramer acetate experienced ~30% fewer clinical

exacerbations and significantly fewer newMRIlesions compared to placebo recipients. IFN-b1b and IFN-b1a also convincingly delayed time to onset of sustained progression of disability. Furthermore, IFN-b1a was found to delay the development of clinically definite MS in patients who experience a single episode of demyelination and have MRI findings indicating prior subclinical disease.

Treatment effects withIFN-b1b and IFN-b1a may be mediated by down regulating (1) expression ofMHCmolecules on the surface of antigen-presenting cells, (2) actions of proinflammatory cytokines, and (3) expression of vascular endothelial adhesion molecules and matrix metalloproteinases that mediate trafficking of activated lymphocytes and macrophages into theCNS. Glatiramer acetate, a synthetic polypeptide designed to resembleMBP, may act by (1) inducing antigen-specific suppressor T cells as a result of shared determinants between copolymer 1 and MBP and (2) binding to MHC molecules on the surface of antigen-presenting cells.

IFN-b1b, 8.0 million international units (MIU), is administered by subcutaneous injection every other day. IFN-b1a, 6.0 MIU, is administered by intramuscular injection once every week. Glatiramer acetate, 20 mg, is administered by subcutaneous injection every day. IFN-b1b, IFN-b1a and glatiramer acetate are generally well tolerated. Erythematous reactions at the injection site are common with IFN-b1b and glatiramer acetate. Transient flu-like symptoms frequently occur at the beginning of IFN-b treatment; these symptoms, which usually resolve within several months, can be managed with ibuprofen, acetaminophen or other analgesic medications. Approximately 15% of glatiramer acetate recipients experience one or more episodes of flushing, chest tightness, dyspnea, palpitations, and anxiety after injection. This systemic reaction is unpredictable, self-limited, and generally lasts <1 h. Approximately 40% of IFN-b1b recipients and 5 to 25% of IFN-b1a recipients develop neutralizing antibodies within 12 months of initiating therapy. Data suggest that neutralizing antibodies may degrade clinical efficacy, but this relationship is not apparent in all patients. The clinical usefulness of commercially available tests for neutralizing antibodies is unclear.

In the United States, ~90% of treated patients withRRMSreceive one of the interferons as first-line therapy, and the remaining 10% receive glatiramer acetate. Irrespective of the agent chosen, treatment should probably be discontinued in patients who continue to experience frequent clinical exacerbations or gradual progression of disability for³6 months. It is unknown whether patients who fail to respond adequately to treatment with any one of these interventions will respond more favorably to another; thus, it is reasonable to try a second agent (Fig. 371-3). The value of combination therapy is also unknown at this time.

Disease Modifying Therapies forSPMSIFN-b1b (Betaferon) and mitoxantrone (novantrone) were each shown to reduce annual exacerbation rates andMRIactivity and delay time to onset of sustained progression of disability in patients with SPMS. Applications for approval of use of these drugs are filed in the United States. IFN-b1b is currently approved for treatment of SPMS in Canada and Europe. IFN-b1b, 8.0 MIU, is administered subcutaneously every other day. Mitoxantrone, 12 mg/m2, is administered by intravenous infusion every third month. It may act as a T and B cell immunosuppressant and an enhancer of suppressor cell function. Mitoxantrone may cause mild nausea, slight hair thinning, leukopenia, thrombocytopenia and irreversible

amennorhea. Dose-related cardiac toxicity is of concern, and treatment with mitoxantrone should be considered only in patients with normal ventricular ejection fractions; periodic echocardiograms are advised if cumulative doses of mitoxantrone exceed 100 mg/m2.

Other Off-Label Treatment Options for RRMS and SPMS *Azathioprine*, 2 to 3 mg/kg body weight, is administered orally each day. This drug modestly reduces annual exacerbation rates in patients with RRMS and SPMS. Its effect on sustained progression of disability is less convincing

Methotrexate, 7.5 mg, is administered orally once each week. This drug, when administered for up to 2 years, modestly reduces disease activity in patients with SPMS as assessed by MRI and standardized tests of manual dexterity. An important practical advantage of methotrexate is the simplicity of a weekly oral dosing schedule.

Cyclophosphamide (CTX) reduces progression of disability in patients with SPMS when compared to ACTH. However, this observation has not been convincingly demonstrated in a placebo-controlled trial. Some investigators advocate pulse CTX therapy for young adults with aggressive forms of MS who fail to respond to approved treatment options.

Intravenous immunoglobulin (IVIg), 0.15 to 0.20 g/kg body weight, administered monthly for up to 2 years convincingly reduced annual exacerbation rates, but its effects on disability and MRI activity were not investigated. At higher doses, 1g/kg body weight daily for 2 days every 6 months, IVIg significantly reduced new MRI activity. Use of this treatment will probably be limited because of its high cost, questions about optimal dose, and uncertainty about the effect of long-term treatment on disability.

Methylprednisolone administered in bimonthly cycles at high doses modestly delays time to onset of sustained progression of disability.

2-Chlorodeoxyadenosine (2-CDA, cladribine) significantly reduces MRI activity in patients with SPMS. However, significant clinical benefits were not observed during 12 months of therapy in a Phase III clinical trial. In the absence of convincing clinical benefit, it is unlikely that 2-CDA will be commonly prescribed.

Disease-Modifying Therapies for PPMS No approved therapies for PPMS exist at this time. The results of ongoing trials of IFN-b1a, glatiramer acetate, and mitoxantrone in PPMS are awaited.

Therapy for Exacerbations The severity and duration of acute exacerbations of MS are reduced by treatment with glucocorticoids. Although methylprednisolone (MePDN) is most commonly prescribed, there is no consensus for the optimal dose and route of administration. Clinical exacerbations that impair activities of daily living can be treated with MePDN, 1000 mg, administered intravenously each day for 3 days followed by oral prednisone, 60 mg daily for 5 days, then tapering by 10 mg each day thereafter. A similar approach is employed for treatment of initial attacks of demyelinating disease. With the exception of severe attacks that jeopardize patient safety, treatment can generally be administered in an outpatient setting. Physical and occupational therapy should be prescribed when impaired mobility or decreased manual dexterity impair

activities of daily living.

Common side effects of short-term glucocorticoid therapy include fluid retention, potassium loss, weight gain, gastric disturbances, acne, and emotional lability. Salt and fluid retention are managed with a low-salt, potassium-rich diet and avoidance of potassium-wasting diuretics. In patients who have heart disease or require concurrent diuretic therapy, oral potassium supplementation is advised. Lithium carbonate (300 mg orally bid) may provide effective prophylaxis for patients who experience emotional lability and insomnia associated with glucocorticoid therapy. For patients with a history of peptic ulcer disease, cimetidine (400 mg bid) or ranitidine (150 mg bid) is advised.

In one small controlled trial, plasma exchange (7 treatments given over 2 weeks) was effective in some patients with unusually fulminant attacks of demyelination unresponsive to glucocorticoids.

When patients experience an acute deterioration, it is important to consider whether this change reflects new disease activity or a "pseudoexacerbation" resulting from an adverse reaction to therapy, increased ambient temperature, fever, or an infection. In such instances treatment with glucocorticoids is contraindicated. Pseudoexacerbations generally resolve within 48 h after initiating appropriate treatment.

Other Therapeutic Claims Purported therapies of no proven value include megadose vitamins, calcium orotate, bee stings, cow colostrum, hyperbaric oxygen, procarin, and chelation. Patients should be discouraged from seeking out costly or potentially hazardous therapies carried out by well-meaning but naive practitioners. Although preliminary data suggest potential roles for HHV-6 and chlamydia pneumonia inMS, these reports are unconfirmed, and treatment with gancyclovir or antibiotics is not currently recommended. The National Multiple Sclerosis Society web site is the best source for information on therapeutic options for MS.

Symptomatic Therapy *Spasticity* with stiffness, flexor spasms, and clonus can be disabling and painful. Acute worsening of spasticity may occur with underlying infection (frequently of the urinary tract), obstipation, bedsores, other painful lesions, or injuries. Although the mechanisms are poorly understood, spasticity may also worsen followingIFN-btherapy. These potential precipitants should be considered and treated specifically. All medications for spasticity have limited efficacy and may produce symptomatic worsening in patients who rely upon spasticity to provide leg strength necessary for effective ambulation. Baclofen (15 to 80 mg/d in divided doses) is the most useful drug available. In refractory cases, baclofen administered orally in higher doses (up to 240 mg/d) or intrathecally via an indwelling catheter may be effective. Tizanidine (2 to 8 mg tid) and diazepam (1 to 2 mg bid or tid) are particularly effective for painful nocturnal spasms, but daytime use is often limited by excessive somnolence. Cyclobenzaprine hydrochloride (5 to 10 mg bid or tid), clonazepam (0.5 to 1.0 mg tid, including a bedtime dose), and clonidine hydrochloride (0.1 to 0.2 mg tid, including a bedtime dose) may be useful for patients who otherwise fail to respond. Dantrolene may produce unacceptable weakness, and its use is usually reserved for nonambulatory patients. A course of glucocorticoids may be given in exceptional cases where other agents have failed, but benefits seldom last more than 2 to 3 weeks.

Pain, including trigeminal neuralgia and painful dysesthesias, may respond to carbamazepine (100 to 1200 mg/d in divided, escalating doses), gabapentin (300-3600 mg/d), dilantin (300-400 mg/d), amitriptyline (25-150 mg/d), or baclofen (10-80 mg/d). In patients with unilateral leg pain, it may be difficult to distinguish dysesthesias due to MS from radiculopathy due to lumbar disk disease; nonsurgical therapy is justified in the absence of convincing signs of nerve root compression.

Paroxysmal symptoms respond to carbamazepine (up to 1200 mg in divided doses), gabapentin (100 to 600 mg tid), or acetazolamide (125 to 250 mg tid). Although no treatment for tremor is satisfactory, slight improvement is occasionally seen with clonazepam (0.5 to 1.0 mg bid or tid), primidone (125 to 250 mg bid or tid), ondansetron (4 to 8 mg bid or tid), and isoniazid (up to 1200 mg in divided doses). Stereotaxic thalamotomy may be considered in cases of disabling tremor in which a unilateral reduction in symptoms is required, but the general experience with this procedure has been disappointing.

Because specific symptoms of *bladder dysfunction* correlate poorly with physiologic findings, urodynamic evaluation is often required. The pathophysiology of abnormal micturition also may change over time in MS. Bladder hyperreflexia is treated with anticholinergics: oxybutynin (5 mg bid or tid), tolterodine (1 to 2 mg bid), or propantheline (7.5 to 15 mg qid). Urinary retention due to bladder hyporeflexia may respond to the cholinergic drug bethanecol (10 to 50 mg tid or qid). Dyssynergia between detrusor and external sphincter muscles may be treated effectively with a combination of anticholinergic medication to decrease bladder contractions and intermittent catheterization. Terazosin hydrochloride (1 to 5 mg at bedtime) ameliorates dyssynergia but may result in urinary incontinence. Supravesical urinary diversion or a chronic indwelling catheter may be required in cases of severe bladder disturbance. Ascorbic acid may reduce the risk of urinary tract infections.

Bowel dysfunction, including constipation and urge incontinence, can be ameliorated by regimentation of bowel function with laxatives and enemas. A low-fiber diet to decrease bulk may be advised for incontinence. *Erectile dysfunction* in males is often treated effectively with sildenafil citrate (50 to 100 mg po prn). Those who fail to respond may benefit from papaverine and phentolamine injections in the corpora cavernosa. Implantation of a penile prosthesis is generally undertaken only for those who fail to respond to other treatment options. Women may experience vaginismus, which may respond to antispasticity medications, or decreased vaginal lubrication leading to dyspareunia, which may be treated effectively with water soluble lubricants.

Afternoon *fatigue* may be reduced by a shift to an early work schedule or a regular afternoon nap. Amantadine (100 mg bid), pemoline (37.5 mg bid), or fluoxetine hydrochloride (20 mg qd or bid) may prove useful in some patients with disabling fatigue. *Emotional lability* often responds to amitriptyline (25 to 75 mg/d) or fluoxetine (20 mg/d). It is essential to be vigilant for clinical evidence of *depression*, since the risk of suicide is increased in patients with MS. Occupational counseling and other support services may assist patients and their families in coping with the effects of the disease. Health maintenance should be emphasized, including stress reduction, a balanced diet, avoidance of rapid change in weight, and adequate rest. Although there is little evidence linking vaccination with relapses of MS, it is prudent to avoid unnecessary

immunizations. Swimming is an ideal form of exercise for many patients because of the buoyant support and hypothermia that is achieved.

Pregnancy may affect the course of MS. Compared with nonpregnant MS patients, pregnant patients experience fewer attacks during gestation but more attacks in the first 3 months after parturition. The two effects appear to be roughly similar in magnitude; thus, no effect of pregnancy on disability or on the overall disease course has been identified. Although it has been hypothesized that high levels of prolactin induced in the postpartum period and maintained by breast feeding result in immune stimulation that predisposes to relapses of MS, studies indicate no effect of breast feeding on attack frequency in the postpartum period. The advisability of childbearing should be determined primarily by the patient's physical state and available social support.

CLINICAL VARIANTS OF MS

Neuromyelitis optica (Devic's syndrome) is characterized by separate attacks of acute optic neuritis and myelitis. Optic neuritis may be unilateral or bilateral and precede or follow an attack of myelitis by days, months, or years. Respiratory failure may result from cervical cord lesions. CSF neutrophil counts >50/uL are reported to occur in as many as 20% of patients. In contrast to patients with MS, patients with Devic's syndrome do not experience brainstem, cerebellar, and cognitive involvement, and the brain MRI is normal. Characteristically, MRI demonstrates a transiently enhancing focal region of swelling and cavitation that extends over three or more spinal cord segments. In contrast to MS, histopathology of these lesions may reveal areas of necrosis and thickening of blood vessel walls. Thus, it remains uncertain whether Devic's syndrome is a variant of MS or a separate entity. The role of disease-modifying therapies for MS has not been rigorously studied in patients with Devic's syndrome. This syndrome is unusual in Caucasians but appears to be more common in Asians. The 5-year survival rate in the Mayo Clinic series was ~70%.

Acute MS (Marburg's variant) is a rare acute fulminant process that generally ends in death from brainstem involvement within one year. There are no remissions. Diagnosis can be established only at postmortem examination; widespread demyelination, axonal loss, edema, and macrophage infiltration are characteristic, and discrete plaques may also be seen. In contrast to postinfectious encephalomyelitis (see below), this disorder does not follow exanthematous infection or vaccination. It has been suggested that acute MS may be associated with an immature form of myelin that is more susceptible to breakdown. As with Devic's syndrome, it is unclear whether this syndrome represents an extreme form of MS or another disease altogether.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

In contrast to MS, acute disseminated encephalomyelitis (ADEM) is distinguished by a monophasic course and a frequent association with antecedent immunization (postvaccinal encephalomyelitis) or infection (postinfectious encephalomyelitis). The pathologic hallmark of ADEM is the presence of widely scattered small foci of perivenular inflammation and demyelination. In its most explosive form, acute hemorrhagic leukoencephalitis, lesions are vasculitic and hemorrhagic, and the clinical course is devastating.

Postvaccinal encephalomyelitis may follow the administration of smallpox and certain rabies vaccines. Postinfectious encephalomyelitis is most frequently associated with the viral exanthems of childhood. Natural infection with measles virus is the most common antecedent (1 in 1000 cases). Worldwide, measles encephalomyelitis remains a common illness, but in developed countries use of the live measles vaccine has dramatically reduced its incidence. An ADEM-like illness rarely follows vaccination with live measles vaccine (1 to 2 in 10_6 immunizations). ADEM is now most frequently associated with varicella (chickenpox) infections (1 in 4000 to 10,000 cases). It also may follow infection with rubella, mumps, influenza, parainfluenza, and infectious mononucleosis viruses and with *Mycoplasma*. Some patients may have a nonspecific upper respiratory infection or no known antecedent illness.

An autoimmune response to MBP can be detected in the CSF from many patients with ADEM. This response has been most clearly established after rabies vaccination and infection with measles virus. With measles infection, the induction of immune responses to a variety of CNS antigens may occur, but only the response to MBP correlates with the development of ADEM. Many cases of postvaccinal encephalomyelitis may result from sensitization with brain material that contaminates the viral vaccines. Attempts to demonstrate direct viral invasion of the CNS have been unsuccessful. The molecular mechanism responsible for virus-induced triggering of an autoimmune response to MBP is not known but may include molecular mimicry due to antigens shared between the virus and host determinants or to virus-mediated CNS injury with secondary sensitization to MBP.

CLINICAL MANIFESTATIONS

The severity of ADEM varies. In severe cases, the onset is abrupt, and progression is rapid (hours to days). In postinfectious ADEM, the neurologic syndrome generally begins late in the course of the viral illness as the exanthem is fading. Fever reappears, and headache, meningismus, and lethargy progressing to coma may develop. Seizures are common. Signs of disseminated neurologic disease are consistently present. Motor findings may include hemiparesis or quadriparesis and extensor plantar responses. Tendon reflexes may be lost initially, later to become hyperactive. Variable degrees of sensory loss and of brainstem involvement may occur. In ADEM due to complications from chickenpox, cerebellar involvement is often prominent. CSF protein is modestly elevated (50 to 150 mg/dL). Lymphocytic pleocytosis, generally £200 cells per microliter, occurs in 80% of patients. Occasional patients have higher counts or a mixed polymorphonuclear-lymphocytic pattern during the initial days of the illness. Transient CSF oligoclonal banding has been reported. MRI may reveal extensive gadolinium enhancement of white matter in brain and spinal cord.

DIAGNOSIS

The diagnosis is easily established when there is a history of recent vaccination or exanthematous illness. In severe cases with predominantly cerebral involvement, acute encephalitis due to infection with herpes simplex or other viruses may be difficult to exclude. In the absence of a specific viral prodrome or of immunization, it may not be possible to distinguish ADEM from acute MS. The simultaneous onset of disseminated

symptoms and signs indicating optic nerve, brain, and spinal cord involvement is common in ADEM and rare in MS. Similarly, meningismus, drowsiness or coma, or seizures suggest ADEM. Optic nerve involvement is generally bilateral in ADEM and unilateral in MS, and transverse myelopathy is usually complete in the former and partial in the latter. The CSF protein level is normal in most patients with MS; lymphocyte counts are rarely>50 cells/uL, and polymorphonuclear leukocytes are not present. MRI findings that may support a diagnosis of ADEM include extensive and relatively symmetric white matter abnormalities and diffuse gadolinium enhancement of all abnormal areas, indicating active disease and a monophasic course.

TREATMENT

Therapy consists of intravenous methylprednisolone as employed for exacerbations of MS. Uncontrolled studies have found ACTH and plasmapheresis also to be of benefit. Occasional patients show evidence of relapse shortly after termination of therapy, and for them, reinstitution of therapy may be useful. The prognosis reflects the severity of the underlying acute illness. Measles encephalomyelitis is associated with a mortality rate of 5 to 20%, and most survivors have permanent neurologic sequelae. Children who recover may have persistent seizures and behavioral and learning disorders.

(Bibliography omitted in Palm version)

372. BACTERIAL MENINGITIS AND OTHER SUPPURATIVE INFECTIONS - *Karen L. Roos, Kenneth L. Tyler*

ACUTE BACTERIAL MENINGITIS

DEFINITION

Bacterial meningitis is an acute purulent infection within the subarachnoid space. It is associated with a central nervous system (CNS) inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure, and stroke. The meninges, the subarachnoid space, and the brain parenchyma are all involved in the inflammatory reaction; as such, *meningoencephalitis* is the more accurate descriptive term.

EPIDEMIOLOGY

Bacterial meningitis is the most common form of suppurative intracranial infection, with an annual incidence >2.5 cases/100,000 population. The epidemiology of bacterial meningitis has changed in recent years. Currently, the organisms most commonly responsible for community-acquired bacterial meningitis are *Streptococcus pneumoniae* (~50%), *Neisseria meningitidis* (~25%), group B streptococci (~10%), and *Listeria monocytogenes* (~10%). *Haemophilus influenzae* was once the most common cause of bacterial meningitis in the United States. The incidence of *H. influenzae* meningitis declined precipitously following the introduction of the *H. influenzae* type b (Hib) vaccine in 1987, and *H. influenzae* now accounts for <10% of bacterial meningitis cases. There have also been major changes in the epidemiology of pneumococcal disease, with the global emergence and increasing prevalence of penicillin- and cephalosporin-resistant strains of *S. pneumoniae*. As of 1998, ~44% of clinical isolates of *S. pneumoniae* in the United States had intermediate or high levels of resistance to penicillin. In the past several years, there has been an increase in the incidence of meningococcal infections on college campuses and an increase in the incidence of meningococcal disease in North America and Europe due to the emergence of a virulent strain of serogroup C, serotype 2a *N. meningitidis*. An increasing incidence of *N. meningitidis* strains with moderate or relative resistance to penicillin and a decreased susceptibility to ampicillin has been reported worldwide, but the clinical significance of these strains is still unknown. Annual meningitis epidemics, caused primarily by the serogroup A meningococcus, continue to occur in the meningitis belt of sub-Saharan Africa. Epidemics due to the serogroup B meningococcus continue to occur in Europe, Latin America, and New Zealand. Group B streptococcus or *S. agalactiae* was previously responsible for meningitis predominantly in neonates, but it has been reported with increasing frequency in individuals >50 years, particularly those with underlying diseases. *L. monocytogenes* has emerged as an important cause of bacterial meningitis in the elderly and in individuals with impaired cell-mediated immunity.

ETIOLOGY

S. pneumoniae (Chap. 140) is the most common cause of meningitis in adults >20 years. There are a number of predisposing conditions that increase the risk of pneumococcal meningitis, the most important of which is pneumococcal pneumonia.

Additional risk factors include coexisting acute or chronic otitis media, alcoholism, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, and head trauma with basilar skull fracture and cerebrospinal fluid (CSF) rhinorrhea.

N. meningitidis (Chap. 146) accounts for nearly 60% of bacterial meningitis cases in children and young adults between the ages of 2 and 20. The nasopharynx is initially colonized by this organism, resulting in either an asymptomatic carrier state or invasive meningococcal disease. The risk of invasive disease following nasopharyngeal colonization depends on both bacterial virulence factors and host immune defense mechanisms, including the host's capacity to produce antimeningococcal antibodies and to lyse meningococci by both the classic and alternative complement pathways. Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infections.

Enteric gram-negative bacilli are the causative organisms of meningitis that is associated with chronic and debilitating diseases such as diabetes, cirrhosis or alcoholism, and chronic urinary tract infections and following neurosurgical procedures, particularly craniotomy or craniectomy.

Resistance to infection with *L. monocytogenes* requires effective cell-mediated immunity. As a result, elderly individuals and those with impaired cell-mediated immunity due to organ transplantation, pregnancy, malignancy, chronic illness, or immunosuppressive therapy are all at increased risk for listerial meningitis. Infection is acquired by ingesting foods contaminated by this organism. Foodborne human listerial infection has been reported from contaminated coleslaw, milk, deli meat, and soft cheeses.

The frequency of *H. influenzae* type b meningitis in children has declined dramatically since the introduction of the Hib conjugate vaccine, although rare cases of Hib meningitis in vaccinated children have been reported. More frequently, *H. influenzae* causes meningitis in unvaccinated children and adults.

Staphylococcus aureus and coagulase-negative staphylococci are predominant organisms causing meningitis that follows invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus, or occurs as a complication of the use of subcutaneous Ommaya reservoirs for the administration of intrathecal chemotherapy.

PATHOPHYSIOLOGY

The most common bacteria that cause meningitis, *S. pneumoniae* and *N. meningitidis*, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. Bacteria are transported across epithelial cells in membrane-bound vacuoles to the intravascular space or invade the intravascular space by creating separations in the apical tight junctions of columnar epithelial cells. Once the bacteria gain access to the bloodstream, they are able to avoid phagocytosis by neutrophils and classic complement-mediated bactericidal activity because of the presence of a polysaccharide capsule. Once in the bloodstream, bacteria can reach the intraventricular choroid plexus. Infection of choroid plexus epithelial cells allows bacteria direct access to

the CSF. Some bacteria, such as *S. pneumoniae*, can adhere directly to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses. Normal CSF contains few white blood cells (WBCs) and relatively small amounts of complement proteins and immunoglobulins. The paucity of the latter two prevents effective opsonization of bacteria, an essential prerequisite for bacterial phagocytosis by neutrophils. Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate.

A critical event in the pathogenesis of bacterial meningitis is the inflammatory reaction induced by the invading bacteria. Many of the neurologic manifestations and complications of bacterial meningitis result from the immune response to the invading pathogen rather than from direct bacteria-induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy.

The lysis of bacteria with the subsequent release of cell-wall components into the subarachnoid space is the initial step in the induction of the inflammatory response and the formation of a purulent exudate in the subarachnoid space (Fig. 372-1). Bacterial cell-wall components, such as the lipopolysaccharide (LPS) molecules of gram-negative bacteria and teichoic acid and peptidoglycans of *S. pneumoniae*, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, and CSF leukocytes. In experimental models of meningitis, cytokines including tumor necrosis factor (TNF) and interleukin (IL) 1 are present in CSF within 1 to 2 h of intracisternal inoculation of LPS. This cytokine response is quickly followed by an increase in CSF protein concentration and leukocytosis. Chemokines (cytokines that induce chemotactic migration in leukocytes) and a variety of other proinflammatory cytokines are also produced and secreted by leukocytes and tissue cells that are stimulated by IL-1 and TNF. In addition, bacteremia and the inflammatory cytokines induce the production of excitatory amino acids, reactive oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that can induce death of brain cells.

Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF and IL-1 act synergistically to increase the permeability of the blood-brain barrier, resulting in induction of vasogenic edema and the leakage of serum proteins into the subarachnoid space (Fig. 372-1). The subarachnoid exudate of proteinaceous material and leukocytes obstructs the flow of CSF through the ventricular system and diminishes the resorptive capacity of the arachnoid granulations in the dural sinuses, leading to obstructive and communicating hydrocephalus and concomitant interstitial edema.

Inflammatory cytokines upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, which allows for leukocytes to adhere to vascular endothelial cells and to subsequently migrate into the CSF. The adherence of leukocytes to capillary endothelial cells increases the permeability of blood vessels, allowing for the leakage of plasma proteins into the CSF, which adds to the inflammatory exudate. Neutrophil degranulation results in the release of toxic metabolites that contribute to

cytotoxic edema, cell injury, and death. Contrary to previous beliefs, CSF leukocytes probably do little to contribute to the clearance of CSF bacterial infection.

During the very early stages of meningitis there is an increase in cerebral blood flow, soon followed by a decrease in cerebral blood flow and a loss of cerebrovascular autoregulation. Cerebral perfusion pressure (CPP) is defined as the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP), i.e., CPP= MAP - ICP. CPP is protected by cerebrovascular autoregulation, which dilates or constricts cerebral resistance vessels in response to alterations in CPP, due to changes in either the MAP or the ICP. Loss of cerebrovascular autoregulation means that any increase in systemic blood pressure leads to an increase in cerebral blood flow and ICP. Conversely, a decrease in mean systemic arterial pressure, for example, associated with septic shock, results in a decrease in cerebral blood flow and subsequent cerebral ischemia and infarction. The cerebrovascular complications of bacterial meningitis include not only a loss of autoregulation but also narrowing of the large arteries at the base of the brain due to encroachment on the vessel by the purulent exudate in the subarachnoid space and infiltration of the arterial wall by inflammatory cells with intimal thickening (vasculitis); this may result in ischemia and infarction, obstruction of branches of the middle cerebral artery by thrombosis, thrombosis of the major cerebral venous sinuses, and thrombophlebitis of the cerebral cortical veins. The combination of interstitial, vasogenic, and cytotoxic edema leads to raised ICP and coma. Cerebral edema, either focal or generalized, can lead to cerebral herniation (see below). Focal or diffuse cerebral edema is the most likely cause of meningitis-associated brain herniation; however, hydrocephalus and dural sinus or cortical vein thrombosis may also play a role.

CLINICAL PRESENTATION

Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity ("stiff neck"). Each of these signs and symptoms occurs in>90% of cases. Alteration in mental status occurs in >75% of patients and can vary from lethargy to coma. Nausea, vomiting, and photophobia are also common complaints. Nuchal rigidity is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion. Kernig's and Brudzinski's signs are also classic signs of meningeal irritation. Kernig's sign is elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed; attempts to passively extend the leg elicit pain when meningeal irritation is present. Brudzinski's sign is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees.

Seizures occur as part of the initial presentation of bacterial meningitis or during the course of the illness in up to 40% of patients. Focal seizures are usually due to focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage, or focal edema. Generalized seizure activity and status epilepticus are due to fever, hyponatremia, or cerebral anoxia or, less commonly, as a result of toxicity from antimicrobial agents.

The rash of meningococcemia begins as a diffuse erythematous maculopapular rash

resembling a viral exanthem, but the skin lesions of meningococcemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles.

Raised ICP is an expected complication of bacterial meningitis and is the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mmH$_2$O, and 20% have opening pressures >400 mmH$_2$O. Signs of increased ICP include a deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations). The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases.

DIAGNOSIS

When the clinical presentation is suggestive of bacterial meningitis, blood cultures should be immediately obtained and empirical antimicrobial therapy initiated without delay. The diagnosis of bacterial meningitis is made by examination of the CSF (Table 372-1). The need for cranial magnetic resonance imaging (MRI) or computed tomography (CT) prior to lumbar puncture remains a controversial issue and must be dealt with on a case-by-case basis. In a patient with a normal level of consciousness and a neurologic examination with no evidence of papilledema or focal deficits, it is safe to perform lumbar puncture without prior neuroimaging studies. If lumbar puncture is delayed in order to obtain neuroimaging studies, empirical antibiotic therapy should be initiated after blood cultures are obtained. Antibiotic therapy for several hours prior to lumbar puncture will not significantly alter the CSF white blood cell count or glucose concentration, nor is it likely to sterilize the CSF so that the organism cannot be identified on Gram's stain. Increased ICP should be treated in patients with clinical signs of increased pressure, and lumbar puncture performed with a 22- or 25-gauge needle. Only a minimum amount of CSF need be removed for analysis; ~3.5 mL of CSF is sufficient to obtain a cell count (1.0 mL), glucose and protein concentrations (1.0 mL), latex particle agglutination (LA) tests (0.5 mL), and Gram's stain and bacterial cultures (1.0 mL). If possible, an additional 0.5 to 1.0 mL should be saved. Preadministration of mannitol and hyperventilation further decrease the risk of herniation in patients with elevated ICP.

The classic CSF abnormalities in bacterial meningitis are: (1) polymorphonuclear leukocytosis (>100 cells per microliter in 90%), (2) decreased glucose concentration [<2.2 mmol/L (<40 mg/dL) and/or CSF/serum glucose ratio of <0.4 in ~60%], (3) increased protein concentration [>0.45 g/L (>45 mg/dL) in 90%], and (4) increased opening pressure (>180 mmH$_2$O in 90%). CSF bacterial cultures are positive in >80% of patients, and CSF Gram's stain demonstrates organisms in >60%.

Opening pressure should be measured with the patient in the lateral recumbent position. In adults, the normal opening pressure is <180 mmH$_2$O, and the normal white blood cell count is <5 mononuclear cells (lymphocytes and monocytes) per microliter. Polymorphonuclear neutrophils (PMNs) are not found in cell counts of normal CSF; however, rare PMNs can be found in concentrated CSF specimens, such as those

analyzed for cytology. CSF glucose concentrations<2.2 mmol/L (<40 mg/dL) are abnormal, and a CSF glucose concentration of zero can be seen in bacterial meningitis. Use of the CSF/serum glucose ratio corrects for hyperglycemia that may mask a relative decrease in the CSF glucose concentration. The CSF glucose concentration is low when the CSF/serum glucose ratio is <0.6. A CSF/serum glucose ratio<0.40 is highly suggestive of bacterial meningitis but may also be seen in other conditions, including carcinomatous meningitis and rare cases of viral meningitis. It takes at least 30 min, and more likely several hours, for CSF glucose concentration to reach equilibrium with blood glucose concentrations; therefore, administration of 50 mL of 50% glucose (D50) prior to lumbar puncture, as commonly occurs in emergency room settings, is unlikely to alter CSF glucose concentration significantly unless more than a few hours have elapsed between glucose administration and lumbar puncture.

TheLA test for the detection of bacterial antigens of *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b, group B streptococcus, and *Escherichia coli* K1 strains in theCSF is very useful for making a rapid diagnosis of bacterial meningitis, especially in patients who have been pretreated with antibiotics and in whom CSF Gram's stain and culture are negative. The CSF LA test has a *specificity* of 95 to 100% for *S. pneumoniae* and *N. meningitidis*, so a positive test is virtually diagnostic of bacterial meningitis by these organisms. However, the *sensitivity* of the CSF LA test is only 70 to 100% for detection of *S. pneumoniae* and 33 to 70% for detection of *N. meningitidis* antigens, so a negative test does not exclude infection by these organisms. The Limulus amebocyte lysate assay is a rapid diagnostic test for the detection of gram-negative endotoxin in CSF, and thus for making a diagnosis of gram-negative bacterial meningitis. The test has a specificity of 85 to 100% and a sensitivity approaching 100%. Thus, a positive Limulus amebocyte lysate assay occurs in virtually all patients with gram-negative bacterial meningitis, but false-positives may occur. CSF polymerase chain reaction (PCR) tests are not as useful in the diagnosis of bacterial meningitis as they are in the diagnosis of viral CNS infections. A CSF PCR test has been developed for detecting DNA from bacteria in CSF, but its sensitivity and specificity need to be better characterized before its role in diagnosis can be defined.

Almost all patients with bacterial meningitis will ultimately have neuroimaging studies performed.MRI is preferred overCTbecause of its superiority in demonstrating areas of cerebral edema and ischemia. In patients with bacterial meningitis, diffuse meningeal enhancement is often seen after the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in anyCNSdisease associated with increased blood-brain barrier permeability.

Petechial skin lesions, if present, should be biopsied. The rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the organism on Gram's stain.

DIFFERENTIAL DIAGNOSIS

Foremost in the differential diagnosis of bacterial meningitis is viral meningoencephalitis, specifically herpes simplex virus (HSV) encephalitis (Chaps. 182,373). The clinical presentation of HSV encephalitis includes headache, fever, altered consciousness, focal neurologic deficits (e.g., dysphasia, hemiparesis), and

focal or generalized seizures. Features that distinguish herpes encephalitis from bacterial meningitis include the findings on CSF studies, neuroimaging, and electroencephalogram (EEG). The classic CSF profile in patients with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, as contrasted with the PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. MRI abnormalities other than meningeal enhancement are not seen in uncomplicated bacterial meningitis. Patients with HSV encephalitis frequently have MRI abnormalities, including increased signal within the orbitofrontal and medial temporal lobes and insular cortex on T2-weighted and FLAIR images. There is a distinctive EEG pattern in HSV encephalitis consisting of periodic, stereotyped, sharp-and-slow wave complexes originating in one or both temporal lobes and repeating at regular intervals of 2 to 3 s. The periodic complexes are typically noted between the second and the fifteenth day of the illness and are present in two-thirds of pathologically proven cases of HSV encephalitis.

The clinical presentation of encephalitis caused by arthropod-borne viruses (Chap. 198) can also resemble that of bacterial meningitis. Another consideration is rickettsial disease (Chap. 177). Rocky Mountain spotted fever (RMSF) is transmitted by a tick bite and caused by the bacteria *Rickettsia rickettsii*. The disease may resemble bacterial meningitis because of its common presentation with high fever, prostration, myalgia, headache, and nausea and vomiting. Most patients develop a characteristic rash within 96 h of the onset of symptoms. The rash is initially a diffuse erythematous maculopapular rash that may be difficult to distinguish from that of meningococcemia. It progresses to a petechial rash, then to a purpuric rash, and, if untreated, to skin necrosis or gangrene. The color of the lesions changes from bright red to very dark red, then yellowish-green to black. The rash typically begins in the wrist and ankles, and then spreads distally and proximally within a matter of a few hours and involves the palms and soles. Diagnosis is made by immunofluorescent staining of skin biopsy specimens.

Focal suppurative CNS infections (see below), including subdural and epidural empyema and brain abscess, should also be considered. The presence of focal features in a patient with suspected bacterial meningitis should prompt immediate neuroimaging studies; MRI is preferable to CT and is extremely sensitive and specific for diagnosis.

Among noninfectious CNS processes, subarachnoid hemorrhage (SAH; Chap. 361) is generally the major consideration. A classic presentation of SAH is the explosive onset of a severe headache or a sudden transient loss of consciousness followed by a severe headache. Nuchal rigidity and vomiting are frequently present and contribute to the resemblance between SAH and meningitis. CT scan is a sensitive indicator of the presence of SAH and usually allows for prompt diagnosis, although occasional patients with suspected SAH have a normal CT scan. In these patients a lumbar puncture is indicated, and the presence of grossly bloody CSF allows SAH to be immediately distinguished from bacterial meningitis.

TREATMENT

Empirical antimicrobial therapy (Table 372-2) Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy within 60 min of a patient's arrival in

the emergency room. Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF Gram's stain and culture are known. *S. pneumoniae* (Chap. 140) and *N. meningitidis* (Chap. 146) are the most common etiologic organisms of community-acquired bacterial meningitis. Due to the emergence of penicillin- and cephalosporin-resistant *S. pneumoniae*, empirical therapy of community-acquired bacterial meningitis in children and adults should include a third-generation cephalosporin (e.g., ceftriaxone or cefotaxime) and vancomycin. Ceftriaxone or cefotaxime provide good coverage for susceptible *S. pneumoniae*, group B streptococci, and *H. influenzae* and adequate coverage for *N. meningitidis*. Ampicillin should be added to the empirical regimen for coverage of *L. monocytogenes* in individuals under three months of age, those over age 55, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancies, or immunosuppressive therapy. In hospital-acquired meningitis, and particularly meningitis following neurosurgical procedures, staphylococci and gram-negative organisms including *Pseudomonas aeruginosa* are the most common etiologic organisms. In these patients, empirical therapy should include a combination of vancomycin and ceftazidime. Ceftazidime should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients, as *P. aeruginosa* may be the meningeal pathogen, and ceftazidime is the only cephalosporin with adequate activity against *P. aeruginosa* in the CNS.

Specific antimicrobial therapy (Table 372-3)

Meningococcal meningitis Although ceftriaxone and cefotaxime provide adequate empirical coverage for *N. meningitidis*, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. Isolates of *N. meningitidis* with moderate resistance to penicillin have been identified, but patients infected with these strains have still been successfully treated with penicillin. CSF isolates of *N. meningitidis* should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of intravenous antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 h for 2 days in adults and 10 mg/kg every 12 h for 2 days in children >1 year). Rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of ciprofloxacin (750 mg), one dose of azithromycin (500 mg), or one IM dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions either through kissing or by sharing toys, beverages, or cigarettes.

Pneumococcal meningitis Antimicrobial therapy of pneumococcal meningitis is initiated with a third-generation cephalosporin (ceftriaxone or cefotaxime) and vancomycin (Tables 372-2 and 372-3). All CSF isolates of *S. pneumoniae* should be tested for sensitivity to penicillin and the third-generation cephalosporins. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly. For *S. pneumoniae* meningitis, an isolate of *S. pneumoniae* is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC)< 0.06 ug/mL, to have intermediate resistance when the MIC is 0.1 to 1.0 ug/mL, and to be highly resistant when the MIC> 1.0 ug/mL. Isolates of *S. pneumoniae* that have cephalosporin MICs £ 0.5 ug/mL are considered sensitive to the cephalosporins (cefotaxime,

ceftriaxone, cefepime). Those with MICs of 1 ug/mL are considered to have intermediate resistance, and those with MICs ³ 2 ug/mL are considered resistant. Penicillin-resistant strains of *S. pneumoniae* are more common than cephalosporin-resistant strains of *S. pneumoniae*. For meningitis due to pneumococci with cefotaxime or ceftriaxone MICs£ 0.5 ug/mL, treatment with cefotaxime or ceftriaxone is usually adequate. If the MIC is ³1 ug/mL, vancomycin is the antibiotic of choice. Rifampin can be added to vancomycin for its synergistic effect but is inadequate as monotherapy because resistance develops rapidly when it is used alone.

Patients with *S. pneumoniae* meningitis should have a repeat lumbar puncture performed 24 to 36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24 to 36 h of antibiotic therapy should be considered presumptive evidence of antibiotic resistance. Patients with penicillin- and cephalosporin-resistant strains of *S. pneumoniae* who do not respond to intravenous vancomycin alone may benefit from the addition of intraventricular vancomycin. The intraventricular route of administration is preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration. A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis.

L. monocytogenes **meningitis** Meningitis due to this organism is treated with ampicillin for at least 3 weeks (Table 372-3). Gentamicin is often added (2 mg/kg loading dose then 5.1 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim [10 to 20 (mg/kg)/d] and sulfamethoxazole [50 to 100 (mg/kg)/d] given every 6 h may provide an alternative in penicillin-allergic patients.

Staphylococcal meningitis Meningitis due to susceptible strains of *S. aureus* or coagulase-negative staphylococci is treated with nafcillin (Table 372-3). Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. In these patients, the CSF should be monitored during therapy. If the CSF is not sterilized after 48 h of intravenous vancomycin therapy, then either intrathecal or intraventricular vancomycin, 20 mg once daily, can be added.

Gram-negative bacillary meningitis The third-generation cephalosporins, cefotaxime, ceftriaxone, and ceftazidime, are equally efficacious for the treatment of gram-negative bacillary meningitis, with the exception of meningitis due to *P. aeruginosa*, which should be treated with ceftazidime (Table 372-3). A 3-week course of intravenous antibiotic therapy is recommended for meningitis due to gram-negative bacilli.

Newer antibiotics Cefepime is a broad-spectrum fourth-generation cephalosporin with in vitro activity similar to that of cefotaxime or ceftriaxone against *S. pneumoniae* and *N. meningitidis* and greater activity against *Enterobacter* spp. and *P. aeruginosa*. The dose of cefepime is 2 g intravenously every 12 h in adults. In clinical trials, cefepime has been demonstrated to be equivalent to cefotaxime in the treatment of pneumococcal and meningococcal meningitis, but its efficacy in bacterial meningitis caused by penicillin- and cephalosporin-resistant pneumococcal organisms, *Enterobacter* spp., and *P. aeruginosa* has not been established. Meropenem is a carbapenem antibiotic structurally related to imipenem, but reportedly with less seizure proclivity than

imipenem. Meropenem is highly active in vitro against *L. monocytogenes*, has been demonstrated to be effective in cases of meningitis caused by *P. aeruginosa*, and shows good activity against penicillin-resistant pneumococci. In experimental pneumococcal meningitis, meropenem was comparable to ceftriaxone and inferior to vancomycin in sterilizing CSF cultures. The dose of meropenem is 1 to 2 g intravenously every 8 h for adults. The number of patients with bacterial meningitis enrolled in clinical trials of meropenem has not been sufficient to definitively assess the epileptogenic potential of this antibiotic. Firm recommendations regarding the use of cefepime and meropenem in bacterial meningitis await more clinical experience.

Adjunctive therapy The release of bacterial cell-wall components by bactericidal antibiotics leads to the production of the inflammatory cytokines IL-1 and TNF in the subarachnoid space (Fig. 372-1). Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1 and TNF at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the blood-brain barrier. The rationale for giving dexamethasone 20 min before antibiotic therapy is that dexamethasone inhibits the production of TNF by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Dexamethasone does not alter TNF production once it has been induced. The results of clinical trials of dexamethasone therapy in children, predominantly with meningitis due to *H. influenzae* and *S. pneumoniae*, have demonstrated its efficacy in decreasing meningeal inflammation and neurologic sequelae such as the incidence of sensorineural hearing loss. Evidence for efficacy of dexamethasone in other types of bacterial meningitis remains much more limited. The American Academy of Pediatrics recommends the consideration of dexamethasone for bacterial meningitis in infants and children ^{3}2 months. The recommended dose is 0.6 mg/kg per day in four divided doses given intravenously for the first 2 days of antibiotic therapy or 0.8 mg/kg per day in two divided doses given for 2 days. The first dose of dexamethasone should be administered before or at least with the first dose of antibiotic.

The role of dexamethasone in the treatment of bacterial meningitis in adults remains uncertain. In a single clinical trial, dexamethasone was demonstrated to reduce the incidence of mortality in adults from pneumococcal meningitis. Other clinical trials of dexamethasone therapy in adults with bacterial meningitis are in progress. The suggested dose of dexamethasone is 0.6 mg/kg per day in four divided doses for the first 2 to 4 days of antimicrobial therapy. For the reasons cited earlier, dexamethasone should ideally be given 20 min before, or not later than simultaneous with, the first dose of antibiotics. It is unlikely to be of significant benefit if started ^{3}6h after antimicrobial therapy has been initiated. Dexamethasone may decrease the penetration of vancomycin into CSF, and it delays the sterilization of CSF in experimental models of *S. pneumoniae* meningitis. As a result, its potential benefit should be carefully weighed when vancomycin is the antibiotic of choice. The third-generation cephalosporins and rifampin penetrate the CSF extremely well, even in the presence of dexamethasone, and may provide an alternative when adjunctive dexamethasone is being used to treat *S. pneumoniae* meningitis.

Increased Intracranial Pressure Emergency treatment of increased ICP includes elevation of the patient's head to 30 to 45°, intubation and hyperventilation (Pa_{CO_2} 25 to 30 mmHg), and mannitol. Patients with increased ICP should be managed in an

intensive care unit. In these patients, accurate ICP measurements are best obtained with an ICP monitoring device. *Increased intracranial pressure is discussed in detail in Chap. 376.*

PROGNOSIS

Mortality is 3 to 7% for meningitis caused by *H. influenzae*, *N. meningitidis*, or group B streptococci; 15% for that due to *L. monocytogenes*; and 20% for *S. pneumoniae*. In general, the risk of death from bacterial meningitis is significantly associated with (1) decreased level of consciousness on admission, (2) onset of seizures within 24 h of admission, (3) signs of increased ICP, (4) young age (infancy) and age >50, (5) the presence of comorbid conditions including shock and/or the need for mechanical ventilation, and (6) delay in the initiation of treatment. Decreased CSF glucose concentration [<2.2 mmol/L (<40 mg/dL)] and markedly increased CSF protein concentration [>3 g/L (>300 mg/dL)] have been predictive of increased mortality and poorer outcomes in some series. Moderate or severe sequelae occur in ~25% of survivors of bacterial meningitis, although the exact incidence varies with the infecting organism. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

BRAIN ABSCESS

DEFINITION

A brain abscess is a focal, suppurative process within the brain parenchyma; it begins in an area of devitalized brain tissue as a localized area of cerebritis and develops into a collection of pus surrounded by a well-vascularized capsule.

EPIDEMIOLOGY

A bacterial brain abscess is a relatively uncommon intracranial infection, with an incidence of approximately 1 in 100,000 persons per year. Predisposing conditions include paranasal sinusitis, otitis media, and dental infections. Brain abscess is an extremely uncommon complication of these common infections, reflecting the efficiency with which they are treated with oral antimicrobial therapy, thereby minimizing the risk of subsequent intracranial spread of infection. In most modern series, a significant percentage of brain abscesses are not caused by classic pyogenic bacteria, but rather by *Toxoplasmi gondii*, *Aspergillus* spp., *Nocardia* spp., *Mycobacteria* spp., and fungi such as *Cryptococcus neoformans*. This distribution reflects the importance of brain abscesses in hosts whose immune systems are compromised, whether from HIV infection, organ transplantation, cancer, or immunosuppressive therapy. In Latin America and in immigrants from Latin America, the most common cause of brain abscess is *Taenia solium* (neurocysticercosis). The discussion that follows is limited to bacterial brain abscess; the other etiologies are discussed elsewhere.

ETIOLOGY

A brain abscess may develop (1) by direct spread from a contiguous cranial site of infection, such as paranasal sinusitis, otitis media, mastoiditis, or dental infection; (2)

following head trauma or a neurosurgical procedure; or (3) as a result of hematogenous spread from a remote site of infection. In 20 to 30% of cases no obvious primary source of infection is apparent (cryptogenic brain abscess).

Abscesses that develop as a result of direct spread of infection from the frontal, ethmoidal, or sphenoidal sinuses and those that occur due to dental infections are usually located in the frontal lobes. The most common pathogens in brain abscesses associated with paranasal sinusitis are microaerophilic and anaerobic streptococci, *Haemophilus* spp., *Bacteroides* spp. (non-*fragilis*), and *Fusobacterium* spp. The most common pathogens in brain abscess from dental infections are streptococci and *Prevotella* and *Porphyromonas* (formerly *Bacteroides*) spp.

The majority of brain abscesses associated with otitits media and mastoiditis occur in the temporal lobe and cerebellum and are caused by streptococci, *Bacteroides* spp. (including *B. fragilis*), *P. aeruginosa*, and Enterobacteriaceae. A brain abscess that is the result of hematogenous spread of infection from a site elsewhere in the body can occur anywhere in the brain but tends to form primarily in areas supplied by the middle cerebral artery (i.e., posterior frontal or parietal lobes). Metastatic abscesses are usually located at the interface of the gray-white matter and are often multiple. The microbiology of these brain abscesses is dependent on the primary source of infection. For example, brain abscesses that develop as a complication of infective endocarditis are often due to viridans streptococci or *S. aureus*; those that follow pyogenic lung infection are often due to *Streptococcus*, *Actinomyces*, or *Fusobacterium* species; those resulting from urinary sepsis are often caused by Enterobacteriaceae or *Pseudomonas aeruginosa*; and those associated with an intraabdominal source are frequently caused by *Streptococcus* spp., Enterobacteriaceae, or anaerobes. Abscesses that follow penetrating head trauma are frequently due to *S. aureus*, *Clostridium* spp., or Enterobacteriaceae, and those following a neurosurgical procedure are usually due to staphylococci, Enterobacteriaceae, or *P. aeruginosa*. Congenital cardiac malformations that produce a right-to-left shunt, such as tetralogy of Fallot, and atrial and ventricular septal defects allow bloodborne bacteria to bypass the pulmonary capillary bed and reach the brain. The decreased arterial oxygenation and saturation from the right-to-left shunt and polycythemia may cause focal areas of cerebral ischemia, thus providing a nidus for microorganisms that bypassed the pulmonary circulation to multiply and form an abscess. Streptococci are the most common pathogens in this setting.

PATHOGENESIS AND HISTOPATHOLOGY

Results of experimental models of brain abscess formation suggest that for bacterial invasion of brain parenchyma to occur, there must be preexisting or concomitant areas of ischemia, necrosis, or hypoxia in brain tissue. The intact brain parenchyma is relatively resistant to infection. Once bacteria have established infection, brain abscess formation evolves through four stages, regardless of the infecting organism. The early cerebritis stage (days 1 to 3) is characterized by a perivascular infiltration of inflammatory cells, which surround a central core of coagulative necrosis. Marked edema surrounds the lesion at this stage. In the late cerebritis stage (days 4 to 9), pus formation leads to enlargement of the necrotic center, which is surrounded at its border by an inflammatory infiltrate of macrophages and fibroblasts. A thin capsule of fibroblasts and reticular fibers gradually develops, and the surrounding area of cerebral

edema becomes more distinct than in the previous stage. The third stage, early capsule formation (days 10 to 13), is characterized by the formation of a capsule that is better developed on the cortical than on the ventricular side of the lesion. This stage correlates with the appearance of a ring-enhancing capsule on neuroimaging studies. The final stage, late capsule formation (day 14 and beyond), is defined by a well-formed necrotic center surrounded by a dense collagenous capsule. The surrounding area of cerebral edema has regressed, but marked gliosis with large numbers of reactive astrocytes has developed outside the capsule. This gliotic process may contribute to the development of seizures as a sequelae of brain abscess.

CLINICAL PRESENTATION

A brain abscess presents as an expanding intracranial mass lesion, rather than as an infectious process. The most common symptom is headache, occurring in >75% of patients. The headache is often characterized as a constant, dull, aching sensation, either hemicranial or generalized, and it becomes progressively more severe and refractory to therapy. Fever is present in only 50% of patients at the time of diagnosis and is typically low-grade. Thus the absence of fever should not exclude the diagnosis. The new onset of focal or generalized seizure activity is a presenting sign in 25 to 30% of patients. In most large series, a focal neurologic deficit is part of the initial presentation in>60% of patients.

The clinical presentation of a brain abscess depends on its location and on the presence of raisedICP, which develops as edema surrounds the evolving abscess. Hemiparesis is the most common localizing sign of a frontal lobe abscess. A temporal lobe abscess may present with a disturbance of language (dysphasia) or an upper homonymous quadrantanopia. Nystagmus and ataxia are signs of a cerebellar abscess. The earliest signs of increased ICP in a patient with a brain abscess are papilledema, nausea and vomiting, and drowsiness or confusion. Meningismus is not present unless the abscess has ruptured into the ventricle or the infection has spread to the subarachnoid space.

DIAGNOSIS

The diagnosis of a brain abscess is made by neuroimaging studies.CT has the advantage of greater feasibility in acutely ill patients, butMRI is better for demonstrating abscesses in the early (cerebritis) stages and is superior to CT for identifying abscesses in the posterior fossa. Cerebritis appears on MRI as an area of low-signal intensity on T1-weighted images with irregular postgadolinium enhancement and as an area of increased signal intensity on T2-weighted images. Cerebritis is often not visualized by CT scan. As the abscess matures, the appearance of the lesion changes. On a contrast-enhanced CT scan, a mature brain abscess appears as a focal area of hypodensity surrounded by ring enhancement. On T1-weighted MRI, a mature brain abscess has the characteristics demonstrated inFig. 372-2. On T2-weighted MRI, there is a hyperintense central area of pus surrounded by a well-defined hypointense capsule and a hyperintense area of edema.

The microbiologic diagnosis is made by Gram's stain and culture of abscess material obtained by stereotactic needle aspiration. Lumbar puncture should not be performed in

patients with known or suspected focal intracranial infections such as abscess or empyema; CSF analysis contributes nothing to diagnosis or therapy, and lumbar puncture increases the risk of herniation.

Additional laboratory studies that may provide clues to the diagnosis of brain abscess in patients with a CNS mass lesion include the peripheral white blood cell count and erythrocyte sedimentation rate; the latter will be elevated in about 60% of patients, and about 50% will have a peripheral leukocytosis.

DIFFERENTIAL DIAGNOSIS

Conditions that can cause headache, fever, focal neurologic signs, and seizure activity include brain abscess, subdural empyema, bacterial meningitis, viral meningoencephalitis, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis. In unusual cases, tumors and, more rarely, cerebral infarction or hematoma can have an MRI or CT appearance resembling brain abscess.

TREATMENT

Empirical therapy of a brain abscess depends on the source of infection (Table 372-4) and typically includes a third-generation cephalosporin (e.g., cefotaxime) and metronidazole (Table 372-3 for antibiotic dosages). Patients with multiple abscesses, which suggest the possibility of hematogenous spread, or those who develop abscesses following head trauma should have nafcillin added to this regimen for coverage of staphylococci. Patients who develop abscesses following neurosurgical procedures should be treated with vancomycin plus ceftazidime (in place of cefotaxime) for coverage of both staphylococci and *P. aeruginosa*.

Aspiration and drainage of the abscess under stereotactic guidance are beneficial for both diagnosis and therapy. Empirical antibiotic coverage can be modified based on the results of Gram's stain and culture of the abscess contents (Table 372-4). Complete excision of a bacterial abscess via craniotomy or craniectomy is generally reserved for multiloculated abscesses or those in which stereotactic aspiration is unsuccessful. Antibiotic therapy alone is generally not optimal for treatment of brain abscess and should be reserved for patients whose abscesses cannot be surgically aspirated or otherwise drained, for selected patients with multiple abscesses, and in patients whose condition is too tenuous to allow performance of a neurosurgical procedure. All patients should receive a minimum of 6 to 8 weeks of parenteral antibiotic therapy. The role, if any, of supplemental oral antibiotic therapy following completion of a standard course of parenteral therapy has never been adequately studied.

In addition to surgical drainage and antibiotic therapy, patients should receive prophylactic anticonvulsant therapy because of the high risk of focal or generalized seizures. Anticonvulsant therapy is continued for at least 3 months after resolution of the abscess, and decisions regarding withdrawal are then based on the EEG. If the EEG is abnormal, anticonvulsant therapy should be continued. If the EEG is normal, anticonvulsant therapy can be slowly withdrawn, with close follow-up and repeat EEG after the medication has been discontinued.

Glucocorticoids should not be given routinely to patients with brain abscesses. Intravenous dexamethasone therapy (10 mg every 6 h) is usually reserved for patients with substantial periabscess edema and associated mass effect and increased ICP. Dexamethasone should be tapered as rapidly as possible to avoid delaying the natural process of encapsulation of the abscess.

Serial CT or MRI scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess. More frequent studies (e.g., weekly) are probably warranted in the subset of patients who are receiving antibiotic therapy alone. A small amount of enhancement may remain for months after the abscess has been successfully treated.

PROGNOSIS

Bacterial abscess can be successfully treated in the majority of patients. Seizures, however, are a common complication and occur in as many as 70% of patients.

SUBDURAL EMPYEMA

DEFINITION

A subdural empyema (SDE) is a collection of pus between the dura and arachnoid membranes (Fig. 372-3).

EPIDEMIOLOGY

SDE is a rare intracranial infection. Sinusitis is the most common predisposing condition and typically involves the frontal sinuses, either alone or in combination with the ethmoid and maxillary sinuses. Sinusitis-associated empyema has a striking predilection for young males, possibly reflecting sex-related differences in sinus anatomy and development. SDE may also develop as a complication of head trauma or following neurosurgical drainage of a subdural hematoma. Secondary infection of a subdural effusion may also result in empyema, although secondary infection of hematomas, in the absence of a prior neurosurgical procedure, is rare.

ETIOLOGY

Aerobic and microaerophilic streptococci and anaerobic bacteria are the most common causative organisms of sinusitis-associated SDE. Staphylococci and gram-negative bacilli are often the etiologic organisms when SDE follows neurosurgical procedures or head trauma. SDE should be distinguished from subdural effusions that, especially in infants and children, may complicate bacterial meningitis. Subdural effusions are sterile collections of protein-rich fluid that result from increased permeability of the thin-walled capillaries and veins in the inner layer of the dura.

PATHOPHYSIOLOGY

Sinusitis-associated SDE develops as a result of either retrograde spread of infection from septic thrombophlebitis of the mucosal veins draining the sinuses or contiguous

spread of infection to the brain from osteomyelitis in the posterior wall of the frontal or other sinuses. SDE may also develop from direct introduction of bacteria into the subdural space as a complication of a neurosurgical procedure. The evolution of SDE can be extremely rapid because the subdural space is a large compartment that offers few mechanical barriers to the spread of infection. In patients with sinusitis-associated SDE, suppuration typically begins in the upper and anterior portions of one cerebral hemisphere and then extends posteriorly. SDE is often associated with other intracranial infections including epidural empyema (40%), cortical thrombophlebitis (35%), and intracranial abscess or cerebritis (>25%). Cortical venous infarction produces necrosis of underlying cerebral cortex and subcortical white matter, with focal neurological deficits and seizures (see below).

CLINICAL PRESENTATION

A patient with SDE typically presents with fever and a progressively worsening headache. Patients may also have signs and symptoms related to sinusitis or other primary sites of intracranial infection. As the infection progresses, focal neurologic deficits, seizures, and signs of increased ICP commonly occur. Headache is the most common complaint at the time of presentation; initially it is localized to the side of the subdural infection but then becomes more severe and generalized. Contralateral hemiparesis or hemiplegia is the most common focal neurologic deficit and can occur from the direct effects of the SDE on the cortex or as a consequence of venous infarction. Seizures begin as partial motor seizures that then become secondarily generalized. Seizures may be due to the direct irritative effect of the SDE on the underlying cortex or result from cortical venous infarction (see above). In untreated SDE, the increasing mass effect and increase in ICP cause progressive deterioration in consciousness, leading ultimately to coma.

DIAGNOSIS

Neuroimaging has greatly facilitated the diagnosis of SDE. MRI (Fig. 372-4) is superior to CT in identifying SDE and any associated intracranial infections. The administration of gadolinium greatly improves diagnosis by enhancing the rim of the empyema and allowing the empyema to be clearly delineated from the underlying brain parenchyma. Cranial MRI is also extremely valuable in identifying sinusitis, other focal CNS infections, cortical venous infarction, cerebral edema, and cerebritis.

CSF examination should be avoided in all patients with SDE as it adds no useful information and is associated with the risk of cerebral herniation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the combination of headache, fever, focal neurologic signs, and seizure activity that progresses rapidly to an altered level of consciousness includes SDE, bacterial meningitis, viral encephalitis, brain abscess, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis.

TREATMENT

Emergent neurosurgical evacuation of the empyema, either through burr-hole drainage

or craniotomy, is the definitive step in the management of this infection. Empirical antimicrobial therapy should include a combination of a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone), vancomycin, and metronidazole (Tables 372-3 and 372-4 for dosages). Parenteral antibiotic therapy should be continued for a minimum of 4 weeks. Specific diagnosis of the etiologic organisms is made based on Gram's stain and culture of fluid obtained via either burr holes or craniotomy; the initial empirical antibiotic coverage should be modified accordingly.

PROGNOSIS

Prognosis is influenced by the level of consciousness of the patient at the time of hospital presentation, the size of the empyema, and the speed with which therapy is instituted. Long-term neurologic sequelae, which include seizures and hemiparesis, occur in up to 50% of cases.

EPIDURAL ABSCESS

DEFINITION

Cranial epidural abscess is a suppurative infection occurring in the potential space between the inner skull table and the dura (Fig. 372-5).

ETIOLOGY AND PATHOPHYSIOLOGY

A cranial epidural abscess develops as a complication of a craniotomy or compound skull fracture or as a result of spread of infection from the frontal sinuses, middle ear, mastoid, or orbit. An epidural abscess may develop contiguous to an area of osteomyelitis, when craniotomy is complicated by infection of the wound or bone flap, or as a result of direct infection of the epidural space. Infection in the frontal sinus, middle ear, mastoid, or orbit can reach the epidural space through retrograde spread of infection from septic thrombophlebitis in the emissary veins that drain these areas or by way of direct spread of infection through areas of osteomyelitis. Unlike the subdural space, the epidural space is really a potential rather than an actual compartment. The dura is normally tightly adherent to the inner skull table, and infection must dissect the dura away from the skull table as it spreads. As a result, epidural abscesses are often smaller than SDEs. Cranial epidural abscesses, unlike brain abscesses, only rarely result from hematogenous spread of infection from extracranial primary sites. The bacteriology of a cranial epidural abscess is similar to that of SDE (see above). The etiologic organisms of an epidural abscess that arises from frontal sinusitis, middle ear infections, or mastoiditis are usually streptococci or anaerobic organisms. Staphylococci or gram-negative organisms are the usual cause of an epidural abscess that develops as a complication of craniotomy or compound skull fracture.

CLINICAL PRESENTATION

Patients typically present with severe hemicranial headache and persistent fever. The diagnosis should always be suspected when these symptoms occur following recent head trauma or neurosurgery or in the setting of frontal sinusitis, mastoiditis, or otitis media.

DIAGNOSIS

CranialMRI is the procedure of choice to demonstrate a cranial epidural abscess. The sensitivity ofCT is limited by the presence of signal artifacts arising from the bone of the inner skull table. On MRI, an epidural abscess appears as a lentiform or crescent-shaped fluid collection that is hyperintense compared toCSF on T2-weighted images. On T1-weighted images, the fluid collection has a signal intensity that is intermediate between that of brain tissue and CSF. Following the administration of gadolinium, a significant enhancement of the dura is seen on T1-weighted images.

TREATMENT

Immediate neurosurgical drainage is indicated. Empirical antimicrobial therapy, pending the results of Gram's stain and culture of the purulent material obtained at surgery, should include a combination of penicillin, a third-generation cephalosporin, nafcillin or vancomycin, and metronidazole (Tables 372-2 and372-3). When the organism has been identified, antimicrobial therapy can be modified accordingly. Antibiotics should be continued for at least 3 weeks after surgical drainage.

SUPPURATIVE THROMBOPHLEBITIS

DEFINITION

Suppurative intracranial thrombophlebitis is septic venous thrombosis of cortical veins and sinuses. This may occur as a complication of bacterial meningitis,SDE, epidural abscess, or infection in the skin of the face, paranasal sinuses, middle ear, or mastoid.

ANATOMY AND PATHOPHYSIOLOGY

The cerebral veins and venous sinuses have no valves; therefore, blood within them can flow in either direction. The superior sagittal sinus is the largest of the venous sinuses (Fig. 372-6). It receives blood from the frontal, parietal, and occipital superior cerebral veins and the diploic veins, which communicate with the meningeal veins. Bacterial meningitis is a common predisposing condition for septic thrombosis of the superior sagittal sinus. The diploic veins, which drain into the superior sagittal sinus, provide a route for the spread of infection from the meninges, especially in cases where there is purulent exudate near areas of the superior sagittal sinus. Infection can also spread to the superior sagittal sinus from nearbySDE or epidural abscess. Dehydration from vomiting, hypercoagulable states, and immunologic abnormalities, including the presence of circulating antiphospholipid antibodies, also contribute to cerebral venous sinus thrombosis. Thrombosis may extend from one sinus to another, and often at autopsy thrombi of different histologic ages can be detected in several sinuses. Thrombosis of the superior sagittal sinus is often associated with thrombosis of superior cortical veins and small parenchymal hemorrhages.

The superior sagittal sinus drains into the transverse sinuses (Fig. 372-6). The transverse sinuses also receive venous drainage from small veins from both the middle ear and mastoid cells. The transverse sinus becomes the sigmoid sinus before draining

into the internal jugular vein. Septic transverse/sigmoid sinus thrombosis can be a complication of acute and chronic otitis media or mastoiditis. Infection spreads from the mastoid air cells to the transverse sinus via the emissary veins or by direct invasion. The cavernous sinuses are inferior to the superior sagittal sinus at the base of the skull. The cavernous sinuses receive blood from the facial veins via the superior and inferior ophthalmic veins. Bacteria in the facial veins enter the cavernous sinus via these veins. Bacteria in the sphenoid and ethmoid sinuses can spread to the cavernous sinuses via the small emissary veins. The sphenoid and ethmoid sinuses are the most common sites of primary infection resulting in septic cavernous sinus thrombosis.

CLINICAL MANIFESTATIONS

Septic thrombosis of the superior sagittal sinus presents as headache, nausea and vomiting, confusion, and focal or generalized seizures. There may be a rapid development of stupor and coma. Weakness of the lower extremities with bilateral Babinski signs or hemiparesis is often present. When superior sagittal sinus thrombosis occurs as a complication of bacterial meningitis, nuchal rigidity and Kernig's and Brudzinski's signs may be present.

The oculomotor nerve, the trochlear nerve, the abducens nerve, the ophthalmic and maxillary branches of the trigeminal nerve, and the internal carotid artery all pass through the cavernous sinus. The symptoms of *septic cavernous sinus thrombosis* are fever, headache, frontal and retroorbital pain, and diplopia. The classic signs are ptosis, proptosis, chemosis, and extraocular dysmotility due to deficits of cranial nerves III, IV, and VI. Hypo- or hyperesthesia of the ophthalmic and maxillary divisions of the fifth cranial nerve and a decreased corneal reflex may be detected. There may be evidence of dilated, tortuous retinal veins and papilledema.

Headache and earache are the most frequent symptoms of *transverse sinus thrombosis*. A transverse sinus thrombosis may also present with Gradinego's syndrome characterized by otitis media, sixth nerve palsy, and retroorbital or facial pain. Sigmoid sinus and internal jugular vein thrombosis may present with neck pain.

DIAGNOSIS

The diagnosis of septic venous sinus thrombosis is suggested by an absent flow void within the affected venous sinus on MRI and confirmed by magnetic resonance venography or the venous phase of cerebral angiography. The diagnosis of thrombophlebitis of intracerebral and meningeal veins is suggested by the presence of intracerebral hemorrhage but requires cerebral angiography for definitive diagnosis.

TREATMENT

Septic venous sinus thrombosis is usually treated with antibiotics and hydration. The choice of antimicrobial therapy is based on the bacteria responsible for the predisposing or associated condition. Anticoagulation with dose-adjusted heparin has been reported to be beneficial in patients with aseptic venous sinus thrombosis; it is also used in the treatment of septic venous sinus thrombosis complicating bacterial meningitis in patients who are worsening despite antimicrobial therapy and intravenous fluids. The presence

of a small intracerebral hemorrhage from septic thrombophlebitis is not an absolute contraindication to heparin therapy. Successful management of aseptic venous sinus thrombosis has been reported with urokinase therapy and with a combination of intrathrombus recombinant tissue plasminogen activator (rtPA) and intravenous heparin, but there is yet no reported experience with these therapies in septic venous sinus thrombosis.

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373. VIRAL MENINGITIS AND ENCEPHALITIS - *Kenneth L. Tyler*

Hundreds of viruses have been reported to produce acute infection and injury to the central or peripheral nervous systems. Many aspects of the clinical characteristics of these diseases are determined by whether the infection is limited primarily to the meninges (*meningitis*) or extends to involve the parenchyma of the brain (*encephalitis*), spinal cord (*myelitis*), or nerve roots (*radiculitis*). In some cases more than one of these areas can be involved simultaneously (meningoencephalitis, myeloradiculitis, etc.). Viruses can also produce chronic or persistent infections of the central nervous system (CNS). *Infections caused by HIV are discussed in Chap. 309, human T cell leukemia virus (HTLV) types I and II in Chap. 368, and prions in Chap. 375.*

ACUTE VIRAL INFECTIONS

VIRAL MENINGITIS

Clinical Manifestations The syndrome of viral meningitis consists of fever, headache, and meningeal irritation coupled with an inflammatory cerebrospinal fluid (CSF) profile (see below). Fever may be accompanied by malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. It is not uncommon to see a mild degree of lethargy or drowsiness. The presence of more profound alterations in consciousness, such as stupor, coma, or marked confusion, should prompt consideration of alternative diagnoses. Similarly, seizures, cranial nerve palsies, or other focal neurologic signs or symptoms suggests parenchymal involvement and is not typical of uncomplicated viral meningitis. The headache associated with viral meningitis is usually frontal or retroorbital and often associated with photophobia and pain on moving the eyes. Nuchal rigidity is present in most cases but may be mild and present only near the limit of neck anteflexion. Evidence of severe meningeal irritation, such as Kernig's and Brudzinski's signs (Chap. 372), is generally absent.

Etiology Enteroviruses account for 75 to 90% of aseptic meningitis cases in most series (Table 373-1). Viruses belonging to the *Enterovirus* genus are members of the family Picornaviridae and include the coxsackieviruses, echoviruses, polioviruses, and human enteroviruses 68 to 71. Using a variety of diagnostic techniques includingCSFpolymerase chain reaction (PCR) tests, culture, and serology, a specific viral cause can be found in 75 to 90% of cases of viral meningitis. CSF cultures are positive in 30 to 70% of patients, the frequency of isolation depending on the specific viral agent. Approximately two-thirds of culture-negative cases of aseptic meningitis have a specific viral etiology identified by CSF PCR testing (see below).

Epidemiology The exact incidence of viral meningitis in the United States is impossible to determine since most cases go unreported to public health authorities. In temperate climates, there is a substantial increase in cases during the summer and early fall months, reflecting the seasonal predominance of enterovirus and arthropod-borne encephalitis virus ("arbovirus") infections, with a peak monthly incidence of about 1 reported case per 100,000 population. The dramatic seasonal predilections of some viruses causing meningitis provide a valuable but not always infallible clue to diagnosis (Table 373-2).

Laboratory Diagnosis

CSF *examination* The most important laboratory test in the diagnosis of meningitis is examination of the CSF. The typical profile in cases of viral meningitis is a lymphocytic pleocytosis (25 to 500 cells per microliter), a normal or slightly elevated protein level [0.2 to 0.8 g/L (20 to 80 mg/dL)], a normal glucose level, and a normal or mildly elevated opening pressure (100 to 350 mm H_2O). Organisms *are not* seen on Gram's or acid-fast stained smears or india ink wet mounts of CSF. Rarely, polymorphonuclear neutrophils (PMNs) may predominate in the first 48 h of illness, especially in patients with infections due to echovirus 9 or Eastern equine virus. However, the presence of a persisting PMN pleocytosis should always prompt consideration of bacterial meningitis or parameningeal infections. The total CSF cell count in viral meningitis is typically 25 to 500/uL, although cell counts of several thousand per microliter are occasionally seen, especially with infections due to lymphocytic choriomeningitis virus (LCMV) and mumps virus. The CSF glucose level is typically normal in viral infections, although it may be decreased in 10 to 30% of cases due to mumps as well as in cases due to LCMV. Rare instances of decreased CSF glucose concentration occur in cases of meningitis due to echoviruses and other enteroviruses, herpes simplex virus (HSV) type 2, and varicella-zoster virus (VZV). As a rule, a lymphocytic pleocytosis with a low glucose level should suggest fungal, listerial, or tuberculous meningitis or noninfectious disorders (e.g., sarcoid, neoplastic meningitis).

A number of tests measuring levels of various CSF proteins, enzymes, and mediators, including C-reactive protein, lactic acid, lactate dehydrogenase, neopterin, quinolinate, interleukin (IL) 1b, IL-6, soluble IL-2 receptor, b_2-microglobulin, and tumor necrosis factor (TNF), have been proposed as potential discriminators between viral and bacterial meningitis or as markers of specific types of viral infection (e.g., infection with HIV), but are of limited general use.

Polymerase Chain Reaction Amplification of Viral Nucleic Acid Amplification of viral-specific DNA or RNA from CSF using PCR amplification has become the single most important method for diagnosing CNS viral infections. HSV DNA is frequently amplified from the CSF of patients with herpes simplex encephalitis (HSV-1) and recurrent lymphocytic meningitis (HSV-2), even when standard culture techniques are negative. PCR is also used routinely to diagnose CNS viral infections caused by enteroviruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and VZV. Genomic amplification and detection of enteroviral (coxsackie-, polio-, echo-, enterovirus) RNA in the CSF of patients with meningitis is now the diagnostic procedure of choice for this group of viruses.

CSF culture The overall results of CSF culture for the diagnosis of viral infection are disappointing (Table 373-3), presumably because of the generally low concentration of infectious virus present and the need to customize isolation procedures for individual viruses. For viral isolation, 2 mL of CSF should be brought promptly to the microbiology laboratory, where it should be refrigerated and processed as speedily as possible. CSF specimens for viral isolation should never be stored in a-20°C freezer since viruses are often unstable at this temperature, and most freezers have "frostfree" warm-up cycles that are detrimental to viral stability. Storage for>24 h is probably best done in a-70°C freezer.

Other Sources for Viral Isolation Viruses may also be isolated from sites and body fluids other than CSF, including throat swabs, stool, blood, and urine. Enteroviruses and adenoviruses may be found in feces; arboviruses, some enteroviruses, and LCMV, in blood; mumps and CMV, in urine; and enteroviruses, mumps, and adenoviruses, in throat washings. During enteroviral infections, viral shedding in stool may persist for several weeks. The presence of enterovirus in stool is not diagnostic and may result from residual shedding from a previous enteroviral infection; it also occurs in some asymptomatic individuals during enteroviral epidemics.

Serologic Studies For some viruses, such as the arboviruses, serologic studies remain an important diagnostic tool but are less useful for viruses such as HSV, VZV, CMV, and EBV for which the prevalence of antibody seropositivity in the general population is high. Diagnosis of viral infection can be made by documenting seroconversion between acute-phase and convalescent sera (typically obtained after 2 to 4 weeks), or by demonstrating the presence of virus-specific IgM antibodies. Antiviral antibodies may be measured in CSF (see below). The timing of the antibody response often means that serologic data are useful mainly for the retrospective establishment of a specific diagnosis, and their value in initial diagnosis and management is limited. Most viral infections of the CNS are associated with intrathecal synthesis of antiviral antibody. This results in an elevation in the ratio of antibody in CSF compared to serum (CSF/serum antibody index).

Agarose electrophoresis or isoelectric focusing of CSF g-globulins may reveal the presence of oligoclonal bands. These bands have been found in association with a number of viral infections, including infections with HIV, HTLV type I, VZV, mumps, subacute sclerosing panencephalitis (SSPE), and progressive rubella panencephalitis. The associated antibodies are often directed against viral proteins. The finding of oligoclonal bands may be of some diagnostic utility, since typically they are not seen with arbovirus, enterovirus, or HSV infections. Oligoclonal bands are also encountered in certain noninfectious neurologic diseases (e.g., multiple sclerosis) and may be found in nonviral infections (e.g., syphilis, Lyme borreliosis).

Other Laboratory Studies All patients with suspected viral meningitis should have a complete blood count and differential; liver function tests; and measurement of the erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), and plasma levels of electrolytes, glucose, creatinine, creatine kinase, aldolase, amylase, and lipase. Abnormalities in specific test results may suggest particular etiologic diagnoses. Magnetic resonance imaging (MRI), computed tomography (CT), electroencephalography (EEG), evoked response studies, electromyography (EMG), and nerve conduction studies are not necessary in most cases. They are best used selectively when atypical presentations or unusual features present diagnostic problems.

Differential Diagnosis The most important issue in the differential diagnosis is the exclusion of nonviral causes that can mimic viral meningitis. The major categories of disease that should always be considered and excluded are (1) bacterial meningitis and other infectious meningidities (e.g., *Mycoplasma*, *Listeria*, *Brucella*, *Coxiella*, and *Rickettsia*); (2) parameningeal infections or partially treated bacterial meningitis; (3)

nonviral infectious meningitides where cultures may be negative (e.g., fungal, tuberculous, parasitic, or syphilitic disease); (4) neoplastic meningitis; and (5) meningitis secondary to noninfectious inflammatory diseases such as sarcoid, Behcet's disease, and the uveomeningitic syndromes.

Specific Viral Etiologies Enteroviruses (Chap. 193) are the most common cause of viral meningitis (>75% of cases with etiology identified) and should be considered the leading candidates when a typical case occurs in the summer months, especially in a child (<15 years) (Table 373-4). However, despite their summer prevalence, sporadic cases of enteroviralCNSinfection are seen year-round. The physical examination should include a careful search for exanthemata, hand-foot-mouth disease, herpangina, pleurodynia, myopericarditis, and hemorrhagic conjunctivitis, which may be stigmata of enterovirus infections.PCRamplification of enteroviral RNA fromCSF has become the diagnostic procedure of choice for these infections.

Arbovirus infections typically occur in the summer months, have clear geographic localization, and occur in epidemics, all factors reflecting the ecology of their transmission through infected insect vectors (Fig. 373-1);Table 373-6;Chap. 198). Arboviral meningitis should be considered when clusters of meningitis cases occur in a restricted geographic region during the summer or early fall. A history of tick exposure or travel or residence in the appropriate geographic area should suggest the possibility of Colorado tick fever virus or Powassan virus infection, although nonviral diseases producing meningitis (e.g., Lyme disease) or headache with meningismus (e.g., Rocky Mountain spotted fever) may also present this way.

HSV-2 meningitis (Chap. 182) occurs in approximately 25% of women and 11% of men at the time of an initial (primary) episode of genital herpes. Of these patients, 20% go on to have recurrent attacks of meningitis. In some series, HSV-2 has been the most important cause of aseptic meningitis in adults, especially women, and overall it is probably second only to enteroviruses as a cause of viral meningitis. Although HSV-2 can be cultured fromCSFduring a first episode of meningitis, cultures are invariably negative during recurrent episodes of HSV-2 meningitis. Diagnosis depends on amplification of HSV-2 DNA from CSF byPCR. Almost all cases of recurrent HSV meningitis are due to HSV-2, although rare cases due to HSV-1 have been reported. Most cases of benign recurrent lymphocytic meningitis, including those meeting accepted diagnostic criteria for Mollaret's meningitis, appear to be due to HSV. Genital lesions may not be present, and most patients give no history of genital herpes. CSF cultures are negative, although HSV DNA can be amplified from CSF by PCR during attacks of meningitis but not during symptom-free intervals.

VZV meningitis should be suspected in the presence of concurrent chickenpox or shingles. However, it is important to recognize that in some series up to 40% ofVZVmeningitis cases have been reported to occur in the absence of rash. The frequency of VZV as a cause of meningitis is extremely variable, ranging from as low as 3% to as high as 20% in different series. The frequency would be expected to decline with the increasing utilization of the live attenuated varicella vaccine (Varivax) in children. In addition to meningitis, encephalitis (see below), and shingles (see below), VZV can also produce acute cerebellar ataxia. This typically occurs in children and presents with the abrupt onset of limb and truncal ataxia. A similar syndrome occurs

less commonly in association with EBV and enteroviral infection. PCR has rapidly become a major tool in the diagnosis of VZV CNS infections. In patients with negative CSF PCR results, the diagnosis of VZV CNS infection can be made by the demonstration of VZV-specific intrathecal antibody synthesis and/or the presence of VZV CSF IgM antibodies, or by positive CSF cultures.

EBV infections may also produce aseptic meningitis, with or without accompanying evidence of the infectious mononucleosis syndrome. The diagnosis may be suggested by the finding of atypical lymphocytes in the CSF or an atypical lymphocytosis in peripheral blood. The demonstration of IgM antibody to viral capsid antigen (VCA), antibody to the diffuse (D) component of early antigen (EA), or subsequently a rising titer of antibody to nuclear antigen (EBNA) are indicative of acute EBV infection. EBV is almost never cultured from CSF, but EBV DNA can be amplified from CSF in many patients with EBV-associated CNS infections. HIV-infected patients with primary CNS lymphoma may have a positive CSF PCR for EBV DNA even in the absence of meningoencephalitis.

HIV meningitis should be suspected in any patient with known or identified risk factors for HIV infection. Aseptic meningitis is a common manifestation of primary exposure to HIV and occurs in 5 to 10% of cases. In some patients, seroconversion may be delayed for several months; however, detection of the presence of HIV genome by PCR or p24 protein establishes the diagnosis. HIV can be cultured from CSF in some patients. Cranial nerve palsies, most commonly involving cranial nerves V, VII, or VIII, are more common in HIV meningitis than in other viral infections. *For further discussion of HIV infection see Chap. 309.*

Mumps (Chap. 196) should be considered when meningitis occurs in the late winter or early spring, especially in males (male/female ratio 3:1). With the widespread use of the live attenuated mumps vaccine in the United States since 1967, the incidence of mumps meningitis has fallen by >95%. Rare cases of mumps vaccine-associated meningitis have been reported, but they are not usually seen after vaccination with the attenuated Jeryl-Lynn strain of virus used in the United States. The presence of orchitis, oophoritis, parotitis, pancreatitis, or elevations in serum lipase and amylase are suggestive but can be found with other viruses, and their absence does not exclude the diagnosis. Clinical meningitis occurs in 5% of patients with parotitis, but only 50% of patients with meningitis have associated parotitis. Mumps infection confers lifelong immunity, so a documented history of previous infection excludes this diagnosis. The presence of hypoglycorrhachia (10 to 30%) may be an additional diagnostic clue, once other causes have been excluded (see above). Up to 25% of patients may have a PMN-predominant CSF pleocytosis, and CSF abnormalities may persist for months. Diagnosis is typically made by isolation of virus from CSF and/or demonstration of seroconversion between acute-phase and convalescent sera.

LCMV infection (Chap. 198) should be considered when aseptic meningitis occurs in the late fall or winter, and in individuals with a history of exposure to house mice (*Mus musculus*), pet or laboratory rodents (e.g., hamsters), or their excreta. Some patients have an associated rash, pulmonary infiltrates, alopecia, parotitis, orchitis, or myopericarditis. Laboratory clues to the diagnosis of LCMV, in addition to the clinical findings noted above, may include the presence of leukopenia, thrombocytopenia, or

abnormal liver function tests. Some cases present with a marked CSF pleocytosis (>1000 cells per microliter) and hypoglycorrachia (<30%).

TREATMENT

In the usual case of viral meningitis, treatment is symptomatic, and hospitalization is not required. Exceptions include patients with deficient humoral immunity, neonates with overwhelming infection, and patients in whom the clinical or CSF profile suggests the possibility of a bacterial or other nonviral cause of infection. Patients with suspected bacterial meningitis should receive appropriate empirical therapy pending culture results (Chap. 372). Patients usually prefer to rest undisturbed in a quiet, darkened room. Analgesics can be used to relieve headache, which is often reduced by the initial diagnostic lumbar puncture. Antipyretics may help to reduce fever, which rarely exceeds 40°C. Hyponatremia may develop as a result of inappropriate vasopressin secretion (SIADH), so fluid and electrolyte status should be monitored. Repeat lumbar puncture is indicated only in patients whose fever and symptoms fail to resolve after a few days or if there is doubt about the initial diagnosis.

Oral or intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or -2 and in cases of severe EBV or VZV infection. Data concerning treatment of HSV, EBV, and VZV meningitis are extremely limited. Seriously ill patients should probably receive intravenous acyclovir (30 mg/kg per day in three divided doses) for 7 days. Oral acyclovir (800 mg, five times daily), famciclovir (500 mg, tid), or valacyclovir (1000 mg, tid) for a week may be tried in less severely ill patients, although data on efficacy are lacking. Patients with HIV meningitis should receive highly active antiretroviral therapy (Chap. 309).

Patients with viral meningitis who are known to have deficient humoral immunity (e.g. X-linked agammaglobulinemia), and who are not already receiving either intramuscular g-globulin or intravenous immunoglobulin (IVIG), should be treated with these agents. Intraventricular administration of immunoglobulin through an Ommaya reservoir has been tried in some patients with chronic enteroviral meningitis who have not responded to intramuscular or intravenous immunoglobulin.

An experimental drug, pleconaril (Viropharma Inc., VP 63843), has shown efficacy against a variety of enteroviral infections and has good oral bioavailability and excellent CNS penetration. Ongoing clinical trials in patients with enteroviral meningitis suggest that pleconaril decreases the duration of symptoms compared to placebo. Since most cases of enteroviral CNS infection are benign and self-limited, the indications for pleconaril therapy need to be better defined. Antiviral treatment might benefit patients with chronic CNS enteroviral infections in the setting of agammaglobulinemia or those who develop poliomyelitis as a complication of polio vaccine administration.

Vaccination is an effective method of preventing the development of meningitis and other neurologic complications associated with poliovirus, mumps, and measles infection. A live attenuated VZV vaccine (Varivax) is available in the United States. Clinical studies indicate an effectiveness rate of 70 to 90% for this vaccine. Reduction in primary VZV infection would be expected to reduce the frequency and/or severity both

of primary neurologic complications of varicella and of the consequences of later reactivation (e.g., shingles).

Prognosis In adults, the prognosis for full recovery from viral meningitis is excellent. Rare patients complain of persisting headache, mild mental impairment, incoordination, or generalized asthenia for weeks to months. The outcome in infants and neonates (<1 year) is less certain; intellectual impairment, learning disabilities, hearing loss, and other lasting sequelae have been reported in some studies.

VIRAL ENCEPHALITIS

Definition In distinction to meningitis, where the infectious process and associated inflammatory response is limited largely to the meninges, in encephalitis the brain parenchyma is also involved. Many patients with encephalitis also have evidence of associated meningitis (meningoencephalitis) and, in some cases, involvement of the spinal cord or nerve roots (encephalomyelitis, encephalomyeloradiculitis).

Clinical Manifestations In addition to the acute febrile illness with evidence of meningeal involvement characteristic of meningitis, the patient with encephalitis commonly has an altered level of consciousness, an abnormal mental state, and evidence of either focal or diffuse neurologic signs and symptoms. Any degree of altered consciousness may occur, ranging from mild lethargy to deep coma. Patients with encephalitis are frequently confused, delirious, and disoriented. Mental aberrations may include hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state. Focal or generalized seizures occur in >50% of patients with severe encephalitis. Virtually every possible type of focal neurologic disturbance has been reported in viral encephalitis; the signs and symptoms reflect the sites of infection and inflammation. The most commonly encountered focal findings are aphasia, ataxia, hemiparesis (with hyperactive tendon reflexes and extensor plantar responses), involuntary movements (e.g., myoclonic jerks), and cranial nerve deficits (e.g., ocular palsies, facial weakness). Involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or the development of SIADH. Despite the clear neuropathologic evidence that viruses differ in the regions of the CNS they injure, it is often impossible to distinguish reliably on clinical grounds alone one type of viral encephalitis (e.g., that caused by HSV) from others (see "Differential Diagnosis," below).

Etiology The number of viruses reported to cause encephalitis is legion. In the United States, there are approximately 20,000 reported cases per year. The same organisms responsible for aseptic meningitis are also responsible for encephalitis, although their relative frequencies differ (Table 373-5;Fig. 373-1). The most important viruses causing sporadic cases of encephalitis in immunocompetent adults are HSV-1,VZV, and, less commonly, enteroviruses. Epidemics of encephalitis are caused by arboviruses, which belong to several different viral taxonomic groups including *Alphavirus* of the family Togaviridae (e.g. Eastern equine encephalitis virus, Western equine encephalitis virus), *Flavivirus* of the family Flaviviridae (e.g., St. Louis encephalitis virus, Powassan virus), and *Bunyavirus* of the family Bunyaviridae (e.g., California encephalitis virus serogroup, LaCrosse virus). In most years, the largest number of cases of arbovirus encephalitis are generally due to St. Louis encephalitis virus and the California encephalitis virus serogroup. New causes of viral encephalitis are constantly appearing, as evidenced by

the recent outbreak of ~300 cases of encephalitis with a 40% mortality rate in Malaysia caused by Nipah virus, a new member of the Paramyxovirus family. Similarly, well-known viruses may suddenly appear in unexpected locations, as illustrated by a recent outbreak of encephalitis in New York City due to West Nile virus.

Laboratory Diagnosis

CSFexamination CSF examination should be performed in all patients with suspected viral encephalitis unless contraindicated by the presence of severely increased intracranial pressure (ICP). The characteristic CSF profile is indistinguishable from that of viral meningitis and consists of a lymphocytic pleocytosis, a mildly elevated protein level, and a normal glucose level. A CSF pleocytosis (>5 cells per microliter) occurs in>95% of patients with documented viral encephalitis, and its absence should prompt a careful search for other causes of an encephalopathy. In rare cases, a pleocytosis may be absent on the initial lumbar puncture but present subsequently. Patients who are severely immunocompromised by HIV infection, steroid or other immunosupressant drugs, chemotherapy, or certain lymphoreticular malignancies may fail to mount a CSF inflammatory response. CSF cell counts exceed 500/uL in only about 10% of patients with encephalitis. Infections with certain arboviruses (e.g., Eastern equine encephalitis or California encephalitis viruses), mumps, andLCMV may occasionally result in cell counts >1000/uL, but this degree of pleocytosis should suggest the possibility of nonviral infections or other inflammatory processes. Atypical lymphocytes in the CSF may be seen inEBVinfection and less commonly with other viruses, includingCMV,HSV, and enteroviruses. The presence of substantial numbers ofPMNsafter the first 48 h should prompt consideration of bacterial infection, leptospirosis, amebic infection, and noninfectious processes such as acute hemorrhagic leukoencephalitis. Large numbers of CSF PMNs may be present in patients with viral encephalitis due to Eastern equine encephalitis virus, echovirus 9, and, more rarely, other enteroviruses. About 20% of patients with encephalitis will have a significant number of red blood cells (>500/uL) in the CSF in a nontraumatic tap. The pathologic correlate of this may be the presence of a hemorrhagic encephalitis of the type seen with HSV, Colorado tick fever virus, and occasionally California encephalitis virus. A decreased CSF glucose level is distinctly unusual in viral encephalitis and should suggest the possibility of fungal, tuberculous, parasitic, leptospiral, syphilitic, sarcoid, or neoplastic meningitis. Rare patients with mumps, LCMV, or advanced HSV encephalitis may have low CSF glucose concentrations.

CSFPCR PCRamplification of viral nucleic acid has become the diagnostic procedure of choice for many types of viral encephalitis. Recent studies withHSVencephalitis indicate that the sensitivity (~98%) and specificity (~94%) of CSF PCR equal or exceed those of brain biopsy. Although less detailed specificity and sensitivity data are available for most other viruses, PCR has become the primary diagnostic test forCNSinfections caused byCMV,EBV,VZV, and enteroviruses (see "Viral Meningitis," above). Studies of HSV encephalitis indicate that the incidence of positive CSF PCR gradually declines after the second week of illness. PCR results are generally not affected by£1 week of antiviral therapy. In one study 98% of CSF specimens remained PCR-positive during the first week of initiation of antiviral therapy, but the numbers fell to ~50% 8 to 14 days, and to ~21% by³15 days after initiation of therapy.

Patients suspected of having HSV encephalitis should be started on acyclovir (see below), and their CSF should be assayed for the presence of HSV DNA by PCR. A positive CSF PCR in the appropriate clinical setting is diagnostic of HSV encephalitis. A negative PCR test effectively excludes the diagnosis, unless the test is performed late in the course of illness or following prolonged antiviral therapy (see above). Blood or blood breakdown products may inhibit PCR reactions and generate false-negative results. Nonetheless the negative predictive value of a negative CSF PCR is ~98% and provides sufficient basis to discontinue acyclovir therapy unless mitigating circumstances likely to generate a false-negative PCR are present.

CSF culture Attempts to culture viruses from the CSF in cases of encephalitis are often disappointing (Table 373-3). Cultures are invariably negative in cases of HSV-1 encephalitis.

Serologic Studies and Antigen Detection The basic approach to the serodiagnosis of viral encephalitis is identical to that discussed earlier for viral meningitis. In patients with HSV encephalitis, both antibodies to HSV-1 glycoproteins and glycoprotein antigens have been detected in the CSF. Optimal detection of both HSV antibodies and antigen typically occurs after the first week of illness, limiting the utility of these tests in acute diagnosis. Nonetheless, CSF HSV antibody testing may be of value in selected patients whose illness is >1 week's duration and who are CSF PCR-negative for HSV.

MRI, CT, EEG Patients with suspected encephalitis almost invariably undergo neuroimaging studies and often EEG. These tests help identify or exclude alternative diagnoses and assist in the differentiation between a focal, as opposed to diffuse, encephalitic process. Focal findings in a patient with encephalitis should always raise the possibility of HSV encephalitis. Examples of focal findings include: (1) areas of increased signal intensity in the frontotemporal, cingulate, or insular regions of the brain on T2-weighted spin-echo MRI images (Fig. 373-2); (2) temporoparietal areas of low absorption, mass effect, and contrast enhancement on CT; or (3) periodic focal temporal lobe spikes on a background of slow or low-amplitude ("flattened") activity on EEG. Approximately 10% of patients with PCR-documented HSV encephalitis will have a normal MRI, although nearly 90% will have abnormalities in the temporal lobe. CT is less sensitive than MRI and is normal in up to 33% of patients. EEG abnormalities occur in >90% of PCR-documented cases of HSV encephalitis; they typically involve the temporal lobes but are often nonspecific.

Brain Biopsy Brain biopsy is now generally reserved for patients in whom CSF PCR studies fail to lead to a specific diagnosis, who have focal abnormalities on MRI, and who continue to show progressive clinical deterioration despite treatment with acyclovir and supportive therapy. The isolation of HSV from brain tissue obtained at biopsy was once considered the "gold standard" for the diagnosis of HSV encephalitis, although with the advent of CSF PCR tests for HSV it is no longer necessary to perform brain biopsy for this purpose. The need for brain biopsy to diagnose other forms of viral encephalitis has also declined greatly with the widespread availability of CSF PCR diagnostic tests for EBV, CMV, VZV, and enteroviruses. When biopsy is performed, the tissue is cultured for virus and examined histopathologically and ultrastructurally. The biopsy is typically carried out under general anesthesia through a craniectomy. Tissue should be taken from a site that appears to be significantly involved on the basis of

clinical and laboratory criteria. Although brain biopsy is not an innocuous procedure, the mortality rate is low (<0.2%). Potential morbidity, in addition to that related to general anesthesia, includes local bleeding and edema, the development of a seizure focus, and wound dehiscence or infection. From a practical viewpoint, the incidence of serious morbidity appears to be between 0.5 and 2%.

Differential Diagnosis The differential diagnosis includes both infectious and noninfectious causes of encephalitis. Some of the most common illnesses masquerading as viral encephalitis, as identified in multicenter clinical trials using brain biopsy as a diagnostic standard, were vascular diseases; abscess and empyema; fungal, parasitic, rickettsial, and tuberculous infections; tumors; Reye's syndrome; toxic encephalopathy; subdural hematoma; and systemic lupus erythematosus. Of the nonviral infections, particular attention should be paid to *Listeria, Mycoplasma, Leptospira*, *Cryptococcus*, and *Mucor* infections, as well as to toxoplasmosis and tuberculosis.

Once nonviral causes of encephalitis have been excluded, the major diagnostic impetus is to distinguishHSV from other viruses that cause encephalitis. This distinction is particularly important because in virtually every other instance the therapy is supportive, whereas specific and effective antiviral therapy is available for HSV, and its efficacy is enhanced when it is instituted early in the course of infection. HSV encephalitis should be considered when clinical features suggesting involvement of the inferomedial frontotemporal regions of the brain are present, including prominent olfactory or gustatory hallucinations, anosmia, unusual or bizarre behavior or personality alterations, or memory disturbance. HSV encephalitis should always be suspected in patients with focal findings on clinical examination, neuroimaging studies, orEEG. The diagnostic procedure of choice in these patients isCSFPCRanalysis for HSV. A positive CSF PCR establishes the diagnosis, and a negative test dramatically reduces the likelihood of HSV encephalitis (see above).

Epidemiologic factors may provide important clues. Particular attention should be paid to the season of the year (Table 373-2), the age of the patient (Table 373-6), the geographic location and travel history (Fig. 373-1;Table 373-6), and possible exposure to animal bites, rodents, and ticks. *Morbidity and Mortality Weekly Reports* provides regular information about the prevalence of particular viruses causing encephalitis by season and region of the country. State public health authorities provide another valuable resource concerning isolation of particular agents in individual regions.

TREATMENT

Specific antiviral therapy should be initiated when appropriate. Vital functions, including respiration and blood pressure, should be monitored continuously and supported as required. In the initial stages of encephalitis, many patients will require care in an intensive care unit. Basic management and supportive therapy should include careful monitoring ofICP, fluid restriction and avoidance of hypotonic intravenous solutions, and suppression of fever. Seizures should be treated with standard anticonvulsant regimens, and prophylactic therapy should be considered in view of the high frequency of seizures in severe cases of encephalitis (>50%). As with all seriously ill, immobilized patients with altered levels of consciousness, encephalitis patients are at risk for aspiration

pneumonia, stasis ulcers and decubiti, contractures, deep venous thrombosis and its complications, and infections of indwelling lines and catheters.

Acyclovir is of benefit in the treatment of HSV and should be started empirically in all patients with suspected viral encephalitis. Treatment should be discontinued in patients found not to have HSV encephalitis, with the possible exception of patients with severe encephalitis due to VZV or EBV. HSV, VZV, and EBV all encode an enzyme, deoxypyrimidine (thymidine) kinase, that phosphorylates acyclovir to produce acyclovir-5¢-monophosphate. Host cell enzymes then phosphorylate this compound to form a triphosphate derivative. It is the triphosphate that acts as an antiviral agent by inhibiting viral DNA polymerase and by causing premature termination of nascent viral DNA chains. The specificity of action depends on the fact that uninfected cells do not phosphorylate significant amounts of acyclovir to acyclovir-5¢-monophosphate. A second level of specificity is provided by the fact that the acyclovir triphosphate is a more potent inhibitor of viral DNA polymerase than of the analogous host cell enzymes.

Adults should receive a dose of 10 mg/kg of acyclovir intravenously every 8 h (30 mg/kg per day total dose) for a minimum of 14 days. Although no studies directly addressing this issue are yet available, we suggest repeating the CSF PCR after completion of 14 days of acyclovir therapy, and discontinuing the acyclovir in PCR-negative patients. Patients with a persisting positive CSF PCR for HSV should be treated for an additional 7 days, and the PCR repeated. Neonatal HSV CNS infection is less responsive to acyclovir therapy than HSV encephalitis in adults; it is recommended that neonates with HSV encephalitis receive 20 mg/kg of acyclovir every 8 h (60 mg/kg per day total dose) for a minimum of 21 days.

Prior to intravenous administration, acyclovir should be diluted to a concentration £7 mg/mL. (A 70-kg person would receive a dose of 700 mg, which would be diluted in a volume of 100 mL.) Each dose should be infused slowly over 1 h rather than by rapid or bolus infusion, to minimize the risk of renal dysfunction. Care should be taken to avoid extravasation or intramuscular or subcutaneous administration. The alkaline pH of acyclovir can cause local inflammation and phlebitis (9%). Dose adjustment is required in patients with impaired renal glomerular filtration. Penetration into CSF is excellent, with average drug levels approximately 50% of serum levels. Complications of therapy include elevations in BUN and creatinine levels (5%), thrombocytopenia (6%), gastrointestinal toxicity (nausea, vomiting, diarrhea) (7%), and neurotoxicity (lethargy or obtundation, disorientation, confusion, agitation, hallucinations, tremors, seizures) (1%). Acyclovir resistance may be mediated by changes in either the viral deoxypyrimidine kinase or DNA polymerase. To date, acyclovir-resistant isolates have not been a significant clinical problem in immunocompetent individuals. However, there have been reports of clinically virulent acyclovir-resistant HSV isolates from sites outside the CNS in immunocompromised individuals, including those with AIDS.

Oral antiviral drugs with efficacy against HSV, VZV, and EBV, including acyclovir, famciclovir, and valacyclovir, have not been evaluated in the treatment of encephalitis either as primary therapy or as supplemental therapy following completion of a course of parenteral acyclovir. An NIAID/NINDS-sponsored phase III trial of supplemental oral valacyclovir therapy (2 g, tid for 3 months) following the initial 14- to 21-day course of therapy with parenteral acyclovir has recently been initiated in patients with HSV

encephalitis; it may help clarify the role of extended oral antiviral therapy.

Both ganciclovir and foscarnet have been shown to be effective in the treatment of CMV-related CNS infections. These drugs are often used in combination. Cidofovir (see below) may provide an alternative in patients who fail to respond to ganciclovir and foscarnet, although data concerning its use in CMV CNS infections are extremely limited.

Ganciclovir is a synthetic nucleoside analogue of 2¢-deoxyguanosine. The drug is preferentially phosphorylated by virus-induced cellular kinases. Ganciclovir triphosphate acts as a competitive inhibitor of the CMV DNA polymerase, and its incorporation into nascent viral DNA results in premature chain termination. Following intravenous administration, CSF concentrations of ganciclovir are 25 to 70% of coincident plasma levels. The usual dose for treatment of severe neurologic illnesses is 5 mg/kg every 12 h given intravenously at a constant rate over 1 h. Induction therapy is followed by maintenance therapy of 5 mg/kg every day for an indefinite period. Induction therapy should be continued until patients show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR testing (where available). Doses should be adjusted in patients with renal insufficiency. Treatment is often limited by the development of granulocytopenia and thrombocytopenia (20 to 25%), which may require reduction in or discontinuation of therapy. Gastrointestinal side effects including nausea, vomiting, diarrhea, and abdominal pain occur in ~20% of patients. Some patients treated with ganciclovir for CMV retinitis have developed retinal detachment, but the causal relationship to ganciclovir treatment is unclear.

Foscarnet is a pyrophosphate analogue that inhibits viral DNA polymerases by binding to the pyrophosphate-binding site. Following intravenous infusion, CSF concentrations range from 15 to 100% of coincident plasma levels. The usual dose for serious CMV-related neurologic illness is 60 mg/kg every 8 h administered by constant infusion over 1 h. Induction therapy for 14 to 21 days is followed by maintenance therapy (60 to 120 mg/kg per day). Induction therapy may need to be extended in patients who fail to show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR tests (where available). Approximately one-third of patients develop renal impairment during treatment, which is reversible following discontinuation of therapy in most, but not all, cases. This is often associated with elevations in serum creatinine and proteinuria and is less frequent in patients who are adequately hydrated. Many patients experience fatigue and nausea. Reduction in serum calcium, magnesium, and potassium occur in approximately 15% of patients and may be associated with tetany, cardiac rhythm disturbances, or seizures.

Cidofovir is a nucleotide analogue that is effective in treating CMV retinitis and equivalent or better than ganciclovir in some experimental models of murine CMV encephalitis, although data concerning its efficacy in human CMV CNS disease are limited. The usual dose is 5 mg/kg intravenously once weekly for 2 weeks, then biweekly for 2 or more additional doses, depending on clinical response. Patients must be prehydrated with normal saline (e.g., 1 L over 1 to 2 h) prior to each dose, and treated with probenecid (e.g., 1 g 3 h before cidofovir and 1 g 2 and 8 h after cidofovir). Nephrotoxicity is common; the dose should be reduced if renal function deteriorates.

Intravenous ribavarin (15 to 25 mg/kg per day in divided doses given every 8 h) has been reported to be of benefit in isolated cases of severe encephalitis due to California encephalitis (LaCrosse) virus. Ribavarin might be of benefit for the rare patients, typically infants or young children, with severe adenovirus or rotavirus encephalitis, and in patients with encephalitis due to LCMV or other arenaviruses. However, clinical trials are lacking. Hemolysis, with resulting anemia, has been the major side effect limiting therapy.

Sequelae There is considerable variation in the incidence and severity of sequelae in patients surviving viral encephalitis. In the case of Eastern equine encephalitis virus infection, nearly 80% of survivors have severe neurologic sequelae. At the other extreme are infections due to EBV, California encephalitis virus, and Venezuelan equine encephalitis virus, where severe sequelae are unusual. For example, approximately 5 to 15% of children infected with LaCrosse virus have a residual seizure disorder, and 1% have persistent hemiparesis. Detailed information about sequelae in patients with HSV encephalitis treated with acyclovir are available from the NIAID-CASG trials. Of 32 acyclovir-treated patients, 26 survived (81%). Of the 26 survivors, 12 (46%) had no or only minor sequelae, 3 (12%) were moderately impaired (gainfully employed but not functioning at their previous level), and 11 (42%) were severely impaired (requiring continuous supportive care). The incidence and severity of sequelae were directly related to the age of the patient and the level of consciousness at the time of initiation of therapy. Patients with severe neurologic impairment (Glasgow coma score 6) at initiation of therapy either died or survived with severe sequelae. Young patients (<30 years) with good neurologic function at initiation of therapy did substantially better (100% survival, 62% with no or mild sequelae) compared with their older counterparts (>30 years); (64% survival, 57% no or mild sequelae). Recent studies using quantitative CSF PCR tests for HSV indicate that clinical outcome following treatment also correlates with the amount of HSV DNA present in CSF at the time of presentation.

ACUTE MYELITIS AND RADICULITIS

Myelitis is a viral infection of the spinal cord, which may occur as an isolated syndrome or in association with encephalitis (encephalomyelitis) or infection involving the nerve roots (myeloradiculitis). Viral infection involving sensory ganglia and nerve roots may also occur as an isolated syndrome, most commonly in the form of shingles.

MYELITIS

Clinical Features and Epidemiology The prototypical viral myelitis is the syndrome of acute anterior poliomyelitis caused by polioviruses. Paralytic polio (Chap. 193) is a rarity in the United States (four to eight cases per year), although it remains a major problem in some regions of the world. Most cases of paralytic polio in the United States occur as a result of the exceedingly rare reversion of vaccine strains to virulence. The cases are divided among those recently vaccinated and unvaccinated nonimmune adults exposed to recently vaccinated children. Occasional outbreaks have occurred in nonimmunized populations such as the Amish in Pennsylvania. Illness typically begins with prodromal symptoms, including fever, headache, myalgia, pharyngitis, nausea and vomiting, and meningeal signs. These are associated with the typical CSF profile of aseptic meningitis. In some patients these symptoms are followed by the development of muscle weakness

resulting from viral injury to the motor neurons in the anterior horn of the spinal cord or in brainstem motor nuclei. The incidence, severity, and pattern of weakness are age-dependent, with more severe disease being seen with increasing age. Young children often develop weakness of one leg, older children weakness of both legs, and adults asymmetric quadriparesis, often with associated urinary retention. Weakness is associated with fasciculations, loss of deep and superficial reflexes, and the development of atrophy. Involvement of the brainstem (bulbar polio) can result in dysphagia, dysarthria, respiratory impairment, and vasomotor disturbances. Although some patients complain of paresthesia, objective sensory loss is not present.

A distinctive polio-like syndrome is produced by enterovirus 70. Patients develop acute hemorrhagic conjunctivitis, followed days to weeks later by a poliomyelitis-like weakness.

Viruses may also affect both the anterior and posterior portions of the spinal cord over a considerable longitudinal extent, producing "transverse" myelitis. The clinical syndrome is one of acute muscle weakness, which may be of the flaccid hyporeflexic type initially but usually develops into spastic paralysis with hyperreflexia and extensor plantar responses. Sensory loss is almost invariably present and typically involves both pain-temperature and position-vibration modalities, producing a sensory level. Urinary symptoms (retention, overflow incontinence, or, in milder cases, hesitancy or decreased voiding sensation) and constipation or even fecal incontinence are present in virtually all patients. Although this syndrome can be caused by a variety of viruses, most cases in immunocompetent patients are due to HSV-2, VZV, or EBV. CMV is an important cause of myelitis in immunocompromised patients, notably those with HIV infection.

A mild form of myelitis predominantly affecting the sacral spinal cord occurs in association with genital HSV-2 infection. At the time of the first episode of genital herpes, about 25% of women, and a smaller percentage of men, develop an aseptic meningitis syndrome. In some individuals this may be associated with urinary retention, dysesthesia, paresthesia, or neuralgia in the legs, buttocks, or genital area, and weakness in one or both legs.

Chronic viral myelitis is associated with advanced HIV infection (vacuolar myelopathy) and with infection due to HTLV-1 (tropical spastic paraparesis and HTLV-I-associated myelopathy). *For further discussion of these infections see Chap. 309.*

Diagnosis Almost all patients with viral myelitis will have inflammatory changes in the CSF including a lymphocytic pleocytosis and elevated protein; glucose is normal. An exception to this pattern occurs in HIV-associated CMV myeloradiculopathy in which a polymorphonuclear pleocytosis and low CSF glucose are characteristic. For myelitis caused by HSV, EBV, CMV, and VZV, CSF PCR studies may be diagnostic. Some patients show evidence of intrathecal synthesis of antibody or the presence of CSF IgM antibodies, and these studies may be helpful in PCR-negative patients. Viral cultures are frequently positive in patients with CMV myelitis and may be positive in some cases of myelitis due to HSV-2. Neuroimaging studies may be helpful in identifying the site and extent of the myelitis. The usual findings are areas of increased T2 signal within the spinal cord parenchyma. Patients with HIV-associated CMV radiculomyelopathy may show increased signal and enhancement of the nerve roots. Perhaps the most important

role of MRI is to exclude compressive lesions and other causes of acute myelopathy.

TREATMENT

Reports of treatment of viral myelitis are usually isolated case reports or small series. Patients with myelitis due to HSV, EBV, or VZV should be treated with intravenous acyclovir (10 mg/kg, tid) for 10 to 14 days. Patients with HIV-associated CMV radiculomyelopathy should receive ganciclovir plus foscarnet (see above under CMV encephalitis for dose), although the results of treatment are frequently disappointing.

GANGLIONITIS AND RADICULITIS

Herpes Zoster (See also Chap. 183)

Clinical Features Reactivation of VZV latent in neurons within the trigeminal or spinal sensory ganglia produces zoster (*shingles*). Zoster is a distinctive clinical syndrome consisting of paresthesia or dysesthesia in a dermatomal distribution followed by a localized cutaneous eruption. Zoster occurs in patients previously infected with chickenpox (varicella). During the initial varicella infection, virus in the skin travels up the sensory nerves to become latent within neurons in the trigeminal and spinal sensory ganglia. Reactivation results in active viral replication in sensory ganglia followed by spread of virus through nerves to the skin, where a dermatomal vesicular eruption occurs. The incidence of zoster increases with age and is higher in patients with compromised cellular immunity. The typical history is one of several days of itching, tingling, burning, or pain in a dermatomal distribution that is followed by a vesicular eruption consisting of clear vesicles on an erythematous base (Fig. 373-CD1). The vesicles become cloudy, dry, and crust over after 1 to 2 weeks. The lesions are most commonly found in the thoracic dermatomes, with T5-T10 accounting for approximately two-thirds of cases. Most patients will have hypalgesia and hypesthesia in the affected dermatome. About 5% of patients develop motor weakness and atrophy (zoster paresis) in the associated myotome. Rare patients can have zoster-like neuralgic pain in the absence of a cutaneous eruption (*zoster sine herpete*). Diagnosis in these patients depends on serologic studies in serum or CSF or the identification of VZV DNA in CSF by PCR.

Characteristic syndromes result from zoster eruptions involving the trigeminal and geniculate distribution. In 10 to 15% of cases, reactivation of virus in the trigeminal ganglia results in a rash in the distribution of the ophthalmic division of the trigeminal nerve (*ophthalmic zoster*). Vesicular eruption may be conjoined with conjunctivitis, keratitis, ocular muscle palsies, ptosis, and mydriasis. In rare cases, an attack is followed by the development of cerebral angiitis involving the ipsilateral carotid and/or middle cerebral arteries. Vascular compromise may lead to hemiplegia, aphasia, or other focal deficits contralateral to the side of the facial eruption. Reactivation of virus from the geniculate ganglion produces the *Ramsay Hunt syndrome*, consisting of facial palsy often associated with loss of taste in the anterior tongue, tinnitus, hearing loss, and vertigo. Zoster eruptions are found in the external auditory meatus.

Some 45% of patients over age 50 who develop shingles will experience pain persisting for >6 weeks after disappearance of the rash (*postherpetic neuralgia*). Postherpetic

neuralgia is almost never seen in children who develop zoster and is rare (6%) in adults younger than 50. (See "Treatment" below, and Chap. 183).

Diagnosis The diagnosis of shingles is generally made on clinical grounds. RecurrentHSVinfection may produce a similar syndrome of a cutaneous eruption in a dermatomal distribution associated with paresthesia. Unlike shingles, in which more than two or three recurrences in a lifetime would be virtually unknown, multiple recurrences are characteristic of HSV infection. The presence ofVZV can be confirmed by culture orPCR of material obtained from the vesicular lesions. Direct detection of varicella zoster virus antigens in vesicle scrapings by immunocytochemistry or fluorescent microscopy is more sensitive and specific than the traditional Tzanck preparation and more sensitive than culture. A Tzanck preparation is made by smearing material obtained from the base of a vesicle onto a slide, which is then stained with Wright or Giemsa stain. The presence of syncytial giant cells with intranuclear inclusions is typical of a herpesvirus infection but does not distinguish between VZV and HSV.

TREATMENT

Shingles in Immunocompetent Adults Three antiviral drugs, acyclovir, famciclovir, and valacyclovir, are available for treatment of herpes zoster (shingles). Famciclovir is the diacetyl prodrug form of the nucleoside penciclovir. Following oral administration famciclovir is enzymatically converted to penciclovir (which is not absorbed well orally). Penciclovir acts intracellularly like acyclovir, but its active triphosphate metabolite has an extended half-life compared to acyclovir triphosphate in infected cells. Valacyclovir is the 6-valine ester of acyclovir and is enzymatically converted to acyclovir in the liver. Valacyclovir is better absorbed than acyclovir and allows for significantly (~fourfold) higher serum andCSFacyclovir levels than can be achieved with equimolar doses of oral acyclovir.

Acyclovir, valacyclovir, and famciclovir all produce more rapid resolution of cutaneous lesions and decreased duration of viral shedding compared to placebo if therapy is started within 72 h of rash onset, and decrease the duration of pain. These effects are generally modest, and supportive therapy alone is probably sufficient in immunocompetent patients <50 years who do not have significant pain and whose lesions do not involve the trigeminal dermatome. Immunocompetent patients with trigeminal zoster should be treated with antiviral drugs to reduce the risk of developing keratitis or other ophthalmologic complications of zoster. Patients >50 years should be treated with antiviral drugs in an effort to reduce the risk or duration of postherpetic neuralgia (see below). Typical doses in immunocompetent adults are acyclovir, 800 mg five times per day for 7 to 10 days; famciclovir, 500 mg tid for 7 days; and valacyclovir 1000 mg tid for 7 days.

The role of adjunctive glucocorticoid therapy has not been definitively established. Its use is not recommended in patients <50 or in immunocompromised individuals. In immunocompetent individuals>50, glucocorticoids do not appear to increase complications when used in conjunction with antiviral agents and may reduce the incidence of postherpetic neuralgia. A typical regimen, which should only be used in patients also receiving antiviral therapy, is prednisone, 30 mg bid for 1 week, then 15 mg bid for a second week, and 7.5 mg bid for a final week.

Shingles in Immunocompromised Patients Immunocompromised patients, including those with HIV infection, who have evidence of disease involving more than one dermatome or in the trigeminal distribution should be treated with intravenous acyclovir (10 mg/kg tid for 10 to 14 days). Immunocompromised patients with mild disease limited to a single dermatome (other than the trigeminal) can be treated initially with oral agents. These patients should be closely monitored and switched to intravenous acyclovir if they show any signs of disease progression while receiving oral therapy. Adverse effects of famciclovir, valacyclovir, and acyclovir are generally minor, with headache and nausea being reported in about 8 to 20% of recipients. Patients with renal insufficiency require reduction in dosing.

Postherpetic Neuralgia Controlled trials of both amitriptyline and desipramine have shown these drugs to be of benefit in the treatment of postherpetic neuralgia. Amitriptyline should be started at low dose (12.5 to 25 mg/d) and gradually increased until pain is controlled or side effects prevent further dose increases; the optimal dose is usually in the range of 75 to 150 mg/d. Desipramine is probably equally efficacious; however, selective serotonin reuptake inhibitors appear to be of limited utility. In a controlled study, carbamazepine was shown to be effective in reducing neuropathic lancinating pain but not continuous aching or burning pain. Treatment should be started at 200 mg/d and gradually increased until pain is controlled or side effects limit further therapy. The usual effective dose is ~600 mg/d, but some patients may require up to 1200 mg/d. Gabapentin has also been shown to be effective in a randomized controlled trial. Patients should be started on 300 mg tid, with a gradual increase to a maximum of 1200 mg tid. Phenytoin and valproate sodium may also be effective for neuropathic zoster pain. Topical agents such as 2.5% lidocaine-2.5% prilocaine cream or 5% lidocaine gel may benefit some patients with milder symptoms.

VIRAL INFECTION OF THE PERIPHERAL NERVOUS SYSTEM

The distinction between ganglionitis, radiculitis, and neuritis are somewhat arbitrary and depend largely on the whether the brunt of injury involves the ganglia, nerve roots (radiculitis), or peripheral nerves (neuritis). Direct viral infection of peripheral nerves is unusual and should be distinguished from postviral immune-mediated injury to nerves. Many viruses, including CMV, HSV, EBV, VZV, mumps virus, and hepatitis B virus (HBV) have been associated, based predominantly on seroepidemiologic studies, with Guillain-Barre syndrome. It is presumed that the antecedent viral infection triggers an immunologic reaction that subsequently results in damage to peripheral nerve myelin (Chap. 378). A Guillain-Barre-like syndrome can also be seen in association with HIV infection, although these patients typically have a CSF pleocytosis rather than the classic albuminocytologic dissociation (elevated protein, zero or few cells).

Patients with HIV infection may develop CMV infection of peripheral nerves, either alone or in combination with involvement of nerve roots and spinal cord. Patients present with back and leg pain, flaccid paraparesis with areflexia, multimodal sensory loss, and impairment of bowel and bladder function. The CSF shows a polymorphonuclear pleocytosis with an elevated protein and, in some patients, a decreased glucose. As noted earlier, this CSF profile is extremely unusual in viral infections and should suggest the diagnosis of CMV polyradiculopathy in the appropriate clinical setting. CMV

inclusions and antigen can be detected in Schwann cells of affected nerves, and CSF cultures or PCR are frequently positive for CMV. Rare cases of CMV-associated multiple mononeuropathy have also been reported. Patients present with radial, peroneal, or sural neuropathies alone or in combination. CMV antigen can be detected in Schwann cells of involved nerves, indicating that the neuropathies are caused by direct viral infection. Evidence of demyelination may be present, and immune mechanisms may contribute to the pathogenesis of the nerve injury.

Viral spread from the site of initial inoculation to the CNS through nerves is integral to the pathogenesis of rabies virus infection (Chap. 197). Rabies virus particles have been detected by electron microscopy and rabies virus antigen by immunocytochemistry in nerves innervating the site of initial viral inoculation. Neural spread of virus is also a central feature of the pathogenesis of shingles (see above) and of recurrent herpes labialis and genitalis (Chap. 182).

Isolated cranial nerve palsies, especially of the facial nerve (Bell's palsy), have been attributed to HSV, VZV (Ramsay Hunt syndrome), HIV, EBV, enteroviruses, and mumps virus, although in many cases the etiologic relationship appears rather tenuous. Pathologic specimens are almost never available from acute cases of Bell's palsy because of the generally benign and self-limited nature of the illness. Virus has never been cultured from the facial nerve, nor have viral antigens or nucleic acid been detected. However, in a study of patients with peripheral facial palsy undergoing decompressive facial nerve surgery, HSV DNA was found by PCR in endoneurial fluid from the facial nerve in ~80% of 14 patients with Bell's palsy, and VZV DNA was found in ~90% of those with Ramsay Hunt syndrome. This represents the strongest evidence to date for the direct role of these viruses in facial palsy.

Auditory and/or vestibular syndromes may also result from viral injury to the eighth cranial nerve. Mumps, measles, and VZV have been associated with cases of unilateral or bilateral nerve deafness. Seroepidemiologic studies also suggest a possible role for parainfluenza viruses, adenoviruses, and HSV in acute hearing loss. HSV has also been suggested to have a role in the pathogenesis of some cases of vestibular neuritis, based on detection of HSV DNA by PCR in vestibular ganglia.

CHRONIC AND PERSISTENT VIRAL CNS DISEASE

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Clinical Features and Pathology Progressive multifocal leukoencephalopathy (PML) is a progressive disorder characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the CNS. In addition to demyelination, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes. Astrocytes are tremendously enlarged and contain hyperchromatic, deformed, and bizarre nuclei and frequent mitotic figures. Oligodendrocytes have enlarged, densely staining nuclei that contain viral inclusions formed by crystalline arrays of JC virus particles. Patients often present with visual deficits (45%), typically a homonymous hemianopia, and mental impairment (38%) (dementia, confusion, personality change). Motor weakness may not be present early but eventually occurs in 75% of cases.

Almost all patients (>95%) have an underlying immunosuppressive disorder. Prior to the HIV epidemic, common associated diseases included lymphoproliferative disorders, immune deficiency states, myeloproliferative disease, and chronic infectious or granulomatous diseases. Since 1984, the importance of these associated disorders in PML has been dwarfed by that of AIDS; >60% of currently diagnosed PML cases occur in patients with AIDS. Conversely, it has been estimated that nearly 1% of AIDS patients will develop PML. Early indications suggest that the basic features of AIDS-associated PML do not differ significantly from those of non-AIDS-associated PML.

Diagnostic Studies The diagnosis of PML is frequently suggested by MRI or less commonly CT. MRI is more sensitive than CT and reveals multifocal asymmetric, coalescing white matter lesions located periventricularly, in the centrum semiovale, in the parietal-occipital region, and in the cerebellum. These lesions have increased T2 and decreased T1 signal. The lesions of PML are generally nonenhancing or show only minimal peripheral enhancement and are not associated with edema or mass effect. CT shows hypodense nonenhancing white matter lesions without edema or mass effect.

The CSF is typically normal, although mild elevation in protein and/or IgG may be found. Pleocytosis occurs in <25% of cases, is predominantly mononuclear, and rarely exceeds 25 cells/uL. PCR amplification of JC virus DNA from CSF has become an important diagnostic tool. CSF PCR for JC virus DNA has high specificity, but sensitivity has varied among studies. Rare cases of positive CSF PCR for JC virus DNA in the absence of clinical or radiographic evidence of PML have been described in HIV-infected patients. It remains to be established whether these results are false positives or are indicative of preclinical PML.

The presence of a positive CSF PCR for JC virus DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML. Patients with negative CSF PCR studies may require brain biopsy for definitive diagnosis. In biopsy or necropsy specimens of brain, JC virus antigen and nucleic acid can be detected by immunocytochemistry, in situ hybridization, or PCR amplification. Detection of JC virus antigen or genomic material should only be considered diagnostic of PML if accompanied by characteristic pathologic changes, since both antigen and genomic material have been found in the brains of normal patients.

TREATMENT

No effective therapy for PML is available. Intravenous and/or intrathecal cytarabine were not shown to be of benefit in a recent randomized controlled trial. Based on isolated case reports of benefit in some patients, a randomized controlled trial of cidofovir is currently under way. Some patients with HIV-associated PML have shown dramatic clinical improvement associated with improvement in their immune status following institution of highly active antiretroviral therapy.

SUBACUTE SCLEROSING PANENCEPHALITIS

Clinical Features and Epidemiology SSPE is a rare chronic progressive demyelinating disease of the CNS associated with a chronic nonpermissive infection of

brain tissue with measles virus. Fewer than 10 cases per year are reported in the United States. The incidence has declined substantially since the introduction of a measles vaccine. Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6 to 8 years by the development of a progressive neurologic disorder. Some 85% of patients are between 5 and 15 years old at diagnosis. Initial manifestations include poor school performance and mood and personality changes. Typical signs of a CNS viral infection, including fever and headache, do not occur. As the disease progresses, patients develop progressive intellectual deterioration, focal and/or generalized seizures, myoclonus, ataxia, and visual disturbances. In the late stage of the illness, patients are unresponsive, quadriparetic, and spastic, with hyperactive tendon reflexes and extensor plantar responses.

Diagnostic Studies The EEG shows a characteristic periodic pattern with bursts every 3 to 8 s of high-voltage, sharp slow waves, followed by periods of attenuated ("flat") background. The CSF is acellular with a normal or mildly elevated protein level and a markedly elevated g-globulin level (>20% of total CSF protein). CSF antimeasles antibody levels are invariably elevated, and oligoclonal antimeasles antibodies are often present. CT and MRI show evidence of multifocal white matter lesions, cortical atrophy, and ex vacuo ventricular enlargement. Measles virus can be cultured from brain tissue using special cocultivation techniques. Viral antigen can be identified immunocytochemically, and viral genome can be detected by in situ hybridization or PCR amplification.

TREATMENT

No definitive therapy for SSPE is available. Treatment with Inosiplex (isoprinosine) (100 mg/kg per day), alone or in combination with intrathecal or intraventricular interferon, has been reported to prolong survival and produce clinical improvement in some patients but has never been subjected to a controlled clinical trial.

PROGRESSIVE RUBELLA PANENCEPHALITIS

Clinical Features and Epidemiology This is an extremely rare disorder that primarily affects children with congenital rubella syndrome, although isolated cases have been reported following childhood rubella. All the approximately 20 cases reported to date have been in male children. After a latent period of 8 to 19 years, patients develop progressive neurologic deterioration. The initial manifestations are similar to those seen in SSPE and include decline in school performance, behavioral alterations, and seizures, followed by severe progressive dementia, prominent ataxia, pyramidal signs (spasticity, hyperreflexia, extensor plantar responses), and visual deterioration. In the terminal stages of the illness, patients are globally demented, mute, and quadriparetic, often with associated ophthalmoplegia.

Diagnostic Studies CSF shows a mild lymphocytic pleocytosis, slightly elevated protein level, markedly increased g-globulin, and rubella virus-specific oligoclonal bands. CT scan may show enlarged ventricles, cortical and cerebellar atrophy, and hypodensity in the white matter. Rubella virus has been isolated from explant and cocultivation cultures of brain biopsy material in one reported case.

TREATMENT

No therapy is currently available. Isoprinosine and amantadine are of no benefit. Universal prevention of both congenital and childhood rubella through the use of the available live attenuated rubella vaccine would be expected to eliminate the disease.

(Bibliography omitted in Palm version)

374. CHRONIC AND RECURRENT MENINGITIS - *Walter J. Koroshetz, Morton N. Swartz*

Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not successfully treated. The condition is most commonly diagnosed when a characteristic neurologic syndrome exists for >4 weeks and is associated with a persistent inflammatory response in the cerebrospinal fluid (CSF) (white blood cell count >5/uL). The causes are varied, and appropriate treatment depends on identification of the etiology. Five categories of disease account for most cases of chronic meningitis: (1) meningeal infections, (2) malignancy, (3) noninfectious inflammatory disorders, (4) chemical meningitis, and (5) parameningeal infections.

CLINICAL PATHOPHYSIOLOGY

Neurologic manifestations of chronic meningitis (Table 374-1) are determined by the anatomic location of the inflammation and its consequences. Persistent headache with or without stiff neck and hydrocephalus, cranial neuropathies, radiculopathies, and cognitive or personality changes are the cardinal features. These can occur alone or in combination. When they appear in combination, widespread dissemination of the inflammatory process alongCSFpathways has occurred. In some cases, the presence of an underlying systemic illness points to a specific agent or class of agents as the probable cause. The diagnosis of chronic meningitis is usually made when the clinical presentation prompts the astute physician to examine the CSF for signs of inflammation.

CSFis produced by the choroid plexus of the cerebral ventricles, exits through narrow foramina into the subarachnoid space surrounding the brain and spinal cord, circulates around the base of the brain and over the cerebral hemispheres, and is resorbed by arachnoid villi projecting into the superior sagittal sinus. CSF flow provides a pathway for rapid spread of infectious and malignant processes over the brain, spinal cord, and cranial and spinal nerve roots. Spread from the subarachnoid space into brain parenchyma may occur via the arachnoid cuffs that surround blood vessels that penetrate brain tissue (Virchow-Robin spaces).

Intracranial Meningitis Nociceptive fibers of the meninges (Chap. 15) are stimulated by the inflammatory process, resulting in headache or neck or back pain. Obstruction ofCSFpathways at foramina or arachnoid villi may produce *hydrocephalus* and symptoms of raised intracranial pressure, including headache, vomiting, apathy or drowsiness, gait instability, papilledema, visual loss, impaired upgaze, or palsy of the seventh cranial nerve (CN) (Chap. 376). Cognitive and behavioral changes during the course of chronic meningitis may also result from vascular damage, which may similarly produce seizures, stroke, or myelopathy.

Inflammatory deposits seeded via the CSFcirculation are often prominent around the brainstem and cranial nerves and along the undersurface of the frontal and temporal lobes. Such cases, termed *basal meningitis*, often present as multiple cranial neuropathies, with visual loss (CN II), facial weakness (CN VII), hearing loss (CN VIII), diplopia (CNs III, IV, and VI), sensory or motor abnormalities of the oropharynx (CNs IX, X, and XII), decreased olfaction (CN I), or facial sensory loss and masseter weakness (CN V).

Spinal Meningitis Injury may occur to motor and sensory roots as they traverse the subarachnoid space and penetrate the meninges. These cases present as multiple radiculopathies with combinations of radicular pain, sensory loss, motor weakness, and sphincter dysfunction. Meningeal inflammation can encircle the cord, resulting in myelopathy. Patients with slowly progressive involvement of multiple cranial nerves and/or spinal nerve roots are likely to have chronic meningitis. Electrophysiologic testing (electromyography, nerve conduction studies, and evoked response testing) may be helpful in determining whether there is involvement of cranial and spinal nerve roots.

Systemic Manifestations In some patients, evidence of systemic disease provides clues to the underlying cause of chronic meningitis. A careful history and physical examination are essential before embarking on a diagnostic workup, which may be costly, prolonged, and associated with risk from invasive procedures. A complete history of travel, sexual practice, and exposure to infectious agents should be sought. Infectious causes are often associated with fever, malaise, anorexia, and signs of localized or disseminated infection outside the nervous system. Infectious causes are of major concern in the immunosuppressed patient, especially in patients with AIDS, in whom chronic meningitis may present without headache or fever. Noninfectious inflammatory disorders often produce systemic manifestations, but meningitis may be the initial manifestation. Carcinomatous meningitis may or may not be accompanied by clinical evidence of the primary neoplasm.

Approach to the Patient

The occurrence of chronic headache, hydrocephalus, cranial neuropathy, radiculopathy, and/or cognitive decline in a patient should prompt consideration of a lumbar puncture for evidence of meningeal inflammation. On occasion the diagnosis is made when an imaging study [computed tomography (CT) or magnetic resonance imaging (MRI)] shows contrast enhancement of the meninges, always an abnormal finding except after a recent neurosurgical procedure. Once chronic meningitis is confirmed byCSFexamination, effort is focused on identifying the cause (Tables 374-2 and374-3) by (1) further analysis of the CSF, (2) diagnosis of an underlying systemic infection or noninfectious inflammatory condition, or (3) pathologic examination of meningeal biopsy specimens.

Two clinical forms of chronic meningitis exist. In the first, the symptoms are chronic and persistent, whereas in the second there are recurrent, discrete episodes of illness. In the latter group, all symptoms, signs, andCSFparameters of meningeal inflammation resolve completely between episodes without specific therapy. In such patients, the likely etiologies include infection with herpes simplex virus (HSV) type 2; chemical meningitis due to leakage into CSF of contents from an epidermoid tumor, craniopharyngioma, or cholesteatoma; primary inflammatory conditions, including Vogt-Koyanagi-Harada syndrome, Behcet's syndrome (Chap. 316), Mollaret's meningitis, and systemic lupus erythematosus (SLE; Chap. 311); and drug hypersensitivity with repeated administration of the offending agent. The duration of chronic meningitis may also be of value in diagnosis; for example, an untreated patient with tuberculous meningitis is unlikely to survive beyond 4 to 6 weeks.

The epidemiologic history is of considerable importance and may provide direction for selection of laboratory studies. Pertinent features include a history of tuberculosis or exposure to a likely case; past travel to areas endemic for fungal infections (the San Joaquin Valley in California and southwestern states for coccidioidomycosis; midwestern states for histoplasmosis, southeastern states for blastomycosis); travel to the Mediterranean region or ingestion of imported unpasteurized dairy products (*Brucella*); time spent in areas endemic for Lyme disease (e.g., Connecticut, New York, Massachusetts); exposure to sexually transmitted disease (syphilis); exposure of an immunocompromised host to pigeons and their droppings (*Cryptococcus*); gardening (*Sporothrix schenkii*); ingestion of poorly cooked meat or contact with a household cat (*Toxoplasma gondii*); residence in Thailand or Japan (*Gnathostoma spinigerum*) or the South Pacific (*Angiostrongylus cantonensis*); rural residence and raccoon exposure (*Baylisascaris procyonis*); and residence in Latin America, the Philippines, or Southeast Asia when eosinophilic meningitis is present (*Taenia solium*).

The presence of focal cerebral signs in a patient with chronic meningitis suggests the possibility of a brain abscess or other parameningeal infection; identification of a potential source of infection (chronic draining ear, sinusitis, right-to-left cardiac or pulmonary shunt, chronic pleuropulmonary infection) supports this diagnosis. In some cases, diagnosis may be established by recognition and biopsy of unusual skin lesions (Behcet's syndrome, cryptococcosis, blastomycosis,SLE, Lyme disease, intravenous drug use, sporotrichosis, trypanosomiasis) or enlarged lymph nodes (lymphoma, tuberculosis, sarcoid, infection with HIV, secondary syphilis, or Whipple's disease). A careful ophthalmologic examination may reveal uveitis [Vogt-Koyanagi-Harada syndrome, sarcoid, or central nervous system (CNS) lymphoma], keratoconjunctivitis sicca (Sjogren's syndrome), or iridocyclitis (Behcet's syndrome) and is essential to assess visual loss from hydrocephalus. Aphthous oral lesions, genital ulcers, and hypopyon suggest Behcet's syndrome. Hepatosplenomegaly suggests lymphoma, sarcoid, tuberculosis, or brucellosis. Herpetic lesions in the genital area or on the thighs suggestsHSV-2 infection. A breast nodule, a suspicious pigmented skin lesion, or an abdominal mass directs attention to possible carcinomatous meningitis.

Imaging Once the clinical syndrome is recognized as a potential manifestation of chronic meningitis, proper analysis of theCSF is essential. However, if the possibility of raised intracranial pressure exists, a brain imaging study should be performed before lumbar puncture. In patients with communicating hydrocephalus caused by impaired resorption of CSF, lumbar puncture is safe and may lead to temporary improvement. However, if intracranial pressure is elevated because of a mass lesion, brain swelling, or a block in ventricular CSF outflow (obstructive hydrocephalus), then lumbar puncture carries the potential risk of brain herniation (Fig. 374-1). Obstructive hydrocephalus usually requires direct ventricular drainage of CSF.

Contrast-enhancedMRI orCTstudies of the brain and spinal cord can identify meningeal enhancement, parameningeal infections (including brain abscess), encasement of the spinal cord (malignancy or inflammation and infection), or nodular deposits on the meninges or nerve roots (malignancy or sarcoidosis). Imaging studies are also useful to localize areas of meningeal disease prior to meningeal biopsy.

Cerebral angiography may be indicated in patients with chronic meningitis and stroke to

identify cerebral arteritis (granulomatous angiitis, infectious arteritis).

Cerebrospinal Fluid Analysis The CSF pressure should be measured and samples sent for bacterial culture, cell count and differential, Gram's stain, and measurement of glucose and protein. In cases without a known cause, CSF should be sent for the Venereal Disease Research Laboratories (VDRL) test, acid-fast bacillus (AFB) stain and culture, fungal wet mount and India ink preparation and culture, culture for fastidious bacteria and fungi, assays for cryptococcal antigen and oligoclonal immunoglobulin bands, and cytology. Other specific CSF tests (Tables 374-2 and 374-3) or blood tests and cultures should be ordered as indicated on the basis of the history, physical examination, or preliminary CSF results (i.e., eosinophilic, mononuclear, or polymorphonuclear meningitis). Rapid diagnosis may be facilitated by polymerase chain reaction (PCR) testing to identify DNA sequences in the CSF that are specific for the suspected pathogenic organism.

In most categories of chronic (not recurrent) meningitis, mononuclear cells predominate in the CSF. When neutrophils predominate after 3 weeks of illness, the principal etiologic considerations are *Nocardia asteroides*, *Actinomyces israelii*, *Brucella*, *Mycobacterium tuberculosis* (5 to 10% of early cases only), various fungi (*Blastomyces dermatitidis*, *Candida albicans*, *Histoplasma capsulatum*, *Aspergillus* species, *Pseudallescheria boydii*, *Cladophialophora bantiana*) and noninfectious causes (SLE, exogenous chemical meningitis). When eosinophils predominate or are present in limited numbers in a primarily mononuclear cell response in the CSF, the differential diagnosis includes parasitic diseases (*A. cantonensis*, *G. spinigerum*, *B. procyonis*, or *Toxocara canis* infection, cysticercosis, schistosomiasis, echinococcal disease, *T. gondii* infection), fungal infections (6 to 20% eosinophils along with a predominantly lymphocyte pleocytosis, particularly with coccidioidal meningitis), neoplastic disease (lymphoma, leukemia, metastatic carcinoma), or other inflammatory processes (sarcoidosis, hypereosinophilic syndrome).

It is often necessary to broaden the number of diagnostic tests if the initial workup does not reveal the cause. In addition, repeated samples of large volumes of CSF may be required to diagnose certain infectious and malignant causes of chronic meningitis. For instance, lymphomatous or carcinomatous meningitis may be diagnosed by examination of sections cut from a cell block formed by spinning down the sediment from a large volume of CSF. The diagnosis of fungal meningitis may require large volumes of CSF for culture of sediment. If standard lumbar puncture is unrewarding, a cervical cisternal tap to sample CSF near to the basal meninges may be fruitful.

Laboratory Investigation In addition to the CSF examination, an attempt should be made to uncover pertinent underlying illnesses. Tuberculin skin test, chest radiograph, urine analysis and culture, blood count and differential, renal and liver function tests, and measurement of electrolytes (including calcium and phosphate), sedimentation rate, antinuclear antibody, and serum angiotensin-converting enzyme level are often indicated. Liver or bone marrow biopsy may be diagnostic in some cases of miliary tuberculosis, disseminated fungal infection, sarcoidosis, or metastatic malignancy. Abnormalities discovered on chest radiograph or chest CT can be pursued by bronchoscopy or transthoracic needle biopsy.

Meningeal Biopsy A diagnostic meningeal biopsy should be strongly considered in patients who are severely disabled, who need chronic ventricular decompression, or whose illness is progressing rapidly. The activities of the surgeon, pathologist, microbiologist, and cytologist should be coordinated so that a large enough sample is obtained and the appropriate cultures and histologic and molecular studies, including electron microscopic and PCR studies, are performed. The diagnostic yield of meningeal biopsy can be increased by targeting regions that enhance with contrast on MRI or CT. With current microsurgical techniques, most areas of the basal meninges can be accessed for biopsy via a limited craniotomy. In a series from the Mayo Clinic reported by Cheng et al., MRI demonstrated meningeal enhancement in 47% of patients undergoing meningeal biopsy. Biopsy of an enhancing region was diagnostic in 80% of cases; biopsy of nonenhancing regions was diagnostic in only 9%; sarcoid (31%) and metastatic adenocarcinoma (25%) were the most common conditions identified.

Approach to the Enigmatic Case In approximately one-third of cases, the diagnosis is not known despite careful evaluation of CSF and potential extraneural sites of disease. A number of the organisms that cause chronic meningitis may take weeks to be identified by cultures. In enigmatic cases several options are available, determined by the extent of the clinical deficits and rate of progression. It is prudent to wait until cultures are finalized if the patient is asymptomatic or symptoms are mild and not progressive. Unfortunately, in many cases progressive neurologic deterioration occurs, and rapid treatment is required. Ventricular-peritoneal shunts may be placed to relieve hydrocephalus, but the risk of disseminating the undiagnosed inflammatory process into the abdomen must be considered.

Empirical Treatment Diagnosis of the causative agent is essential because effective therapies exist for many etiologies of chronic meningitis, but if the condition is left untreated, progressive damage to the CNS and cranial nerves and roots is likely to occur. Occasionally, empirical therapy must be initiated when all attempts at diagnosis fail. In general, empirical therapy in the United States consists of antimycobacterial agents, amphotericin for fungal infection, or glucocorticoids for noninfectious inflammatory causes. It is important to direct empirical therapy of lymphocytic meningitis at tuberculosis, particularly if the condition is associated with hypoglycorrhachia and sixth and other CN palsies, since untreated disease is fatal in 4 to 8 weeks. In the Mayo Clinic series, the most useful empirical therapy was administration of glucocorticoids rather than antituberculous therapy. Carcinomatous or lymphomatous meningitis may be difficult to diagnose initially, but the diagnosis becomes evident with time.

THE IMMUNOSUPPRESSED PATIENT

Chronic meningitis is not uncommon in the course of HIV infection. Pleocytosis and mild meningeal signs often occur at the onset of HIV infection, and occasionally low-grade meningitis persists. Toxoplasmosis commonly presents as intracranial abscesses and may also be associated with meningitis. Other important causes of chronic meningitis in AIDS include infection with *Cryptococcus*, *Nocardia*, *Candida*, or other fungi; syphilis; and lymphoma. Toxoplasmosis, cryptococcosis, nocardiosis, and other fungal infections are important etiologic considerations in individuals with immunodeficiency states other than AIDS, including those due to immunosuppressive medications. Because of the increased risk of chronic meningitis and the attenuation of clinical signs of meningeal

irritation in immunosuppressed individuals,[CSF](#)examination should be performed for any persistent headache or unexplained change in mental state.

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375. PRION DISEASES - *Stanley B. Prusiner, Patrick Bosque*

Creutzfeldt-Jakob disease (CJD) is a degenerative disease of the central nervous system (CNS) that is caused by infectious proteins called *prions*. CJD typically presents with dementia and myoclonus, is relentlessly progressive, and usually results in death within a year of onset. Most patients with CJD are between 50 and 75 years of age; however, patients as young as 17 years and as old as 83 years have been recorded.

In mammals, prions reproduce by binding to the normal, *c*ellular isoform of the *pri*on *p*rotein (PrPc) and stimulating its conversion into the di*s*ease-*c*ausing isoform (PrPsc). PrPc is rich in a-helix and has littleb-sheet, while PrPschas less a-helix and a highb-sheet content (Fig. 375-1). This a tob transition in prion protein (PrP) structure is the fundamental event underlying prion diseases, which are disorders of protein conformation (Table 375-1).

Four new concepts have emerged from studies of prions. First, prions are the only known infectious pathogens that are devoid of nucleic acid. All other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny. Second, prion diseases may be manifest as infectious, genetic, and sporadic disorders. No other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations. Third, prion diseases result from the accumulation ofPrPsc, the conformation of which differs substantially from that of its precursorPrPc. Fourth, PrPsccan exist in a variety of different conformations, each of which seems to specify a specific disease phenotype. How a specific conformation of a PrPscmolecule is imparted to PrPcduring prion replication to produce nascent PrPscwith the same conformation is unknown. Additionally, it is unclear what factors determine where in theCNS a particular PrPscmolecule will be deposited.

SPECTRUM OF PRION DISEASES

The sporadic form ofCJD is the most common prion disorder in humans. Sporadic CJD (sCJD) accounts for ~85% of all cases of human prion disease, while inherited prion diseases account for 10 to 15% of all cases (Table 375-2). Familial CJD (fCJD), Gerstmann-Straussler-Scheinker disease (GSS), and fatal familial insomnia (FFI) are all dominantly inherited prion diseases that are caused by mutations in thePrPgene.

Although infectious prion diseases account for <1% of all cases and infection does not seem to play an important role in the natural history of these illnesses, the transmissibility of prions is an important biologic feature. Kuru of the Fore people of New Guinea is thought to have resulted from the consumption of brains from dead relatives during ritualistic cannibalism. With the cessation of ritualistic cannibalism in the late 1950s, kuru has nearly disappeared with the exception of a few recent patients exhibiting incubation periods of almost 40 years. Iatrogenic CJD (iCJD) seems to be the result of the accidental inoculation of patients with prions. New variant CJD (nvCJD) in teenagers and young adults in Europe is the result of exposure to tainted beef from cattle with bovine spongiform encepalopathy (BSE).

Six diseases of animals are caused by prions (Table 375-2). Scrapie of sheep and goats is the prototypic prion disease. Mink encephalopathy,BSE, feline spongiform

encephalopathy, and exotic ungulate encephalopathy are all thought to occur after the consumption of prion-infected foodstuffs. The origin of chronic wasting disease, a prion disease endemic in deer and elk in regions of North America, is uncertain.

EPIDEMIOLOGY

CJDis found throughout the world. The incidence ofsCJD is approximately one case per million population. Although many geographic clusters of CJD have been reported, each has been shown to segregate with aPrP gene mutation that results in a nonconservative substitution. Attempts to identify common exposure to some etiologic agent have been unsuccessful for both the sporadic and familial cases. Ingestion of scrapie-infected sheep or goat meat as a cause of CJD in humans has not been demonstrated by epidemiologic studies although speculation about this potential route of inoculation continues. Studies with Syrian hamsters demonstrate that oral infection with prions can occur, but the process is inefficient compared to intracerebral inoculation.

PATHOGENESIS

The human prion diseases were initially classified as neurodegenerative disorders of unknown etiology on the basis of pathologic changes being confined to theCNS. With the transmission of kuru andCJD to apes, investigators began to view these diseases as CNS infectious illnesses caused by slow viruses. Even though the familial nature of a subset of CJD cases was well described, the significance of this observation became more obscure with the transmission of CJD to animals. Eventually, the meaning of heritable CJD became clear with the discovery of mutations in the*PrP*gene of these patients. The prion concept explains how a disease can manifest as a heritable as well as an infectious illness. Moreover, the hallmark common to all of the prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant metabolism of the prion protein.

A major feature that distinguishes prions from viruses is the finding that both PrP isoforms are encoded by a chromosomal gene. In humans, the*PrP*gene is designated *PRNP* and is located on the short arm of chromosome 20. Limited proteolysis ofPrP_{Sc}produces a smaller, protease-resistant molecule of ~142 amino acids designated PrP 27-30; under the same conditions,$PrP_C$is completely hydrolyzed (Fig. 375-2). In the presence of detergent, PrP 27-30 polymerizes into amyloid. Prion amyloid formed by limited proteolysis and detergent extraction is indistinguishable from the filaments that aggregate to form PrP amyloid plaques in theCNS. Both the rods and the PrP amyloid filaments found in brain tissue exhibit similar ultrastructural morphology and green-gold birefringence after staining with Congo red dye.

Species Barrier Studies on the role of the primary and tertiary structures ofPrP in the transmission of prion disease have given new insights into the pathogenesis of these maladies. The amino acid sequence of PrP encodes the species of the prion, and the prion derives itsPrP_{Sc}sequence from the last mammal in which it was passaged. While the primary structure of PrP is likely to be the most important or even sole determinant of the tertiary structure ofPrP_C, PrP_{Sc}seems to function as a template in determining the tertiary structure of nascent PrP_{Sc}molecules as they are formed from PrP_C. In turn, prion diversity appears to be enciphered in the conformation of PrP_{Sc}, and thus, prion strains

seem to represent different conformers of PrP𝒔𝒄.

In general, transmission of prion disease from one species to another is inefficient, in that not all intracerebrally inoculated animals develop disease, and those that fall ill do so only after long incubation times that can approach the natural lifespan of the animal. This "species barrier" to transmission is correlated with the degree of homology between the amino acid sequence of PrPc in the inoculated host and of PrPsc in the prion inoculum. The importance of sequence homology between the host and donor PrP argues that PrPc directly interacts with PrPsc in the prion conversion process.

Prion Strains The existence of prion strains raised the question of how heritable biologic information can be enciphered in a molecule other than nucleic acid. Strains or varieties of prions have been defined by incubation times and the distribution of neuronal vacuolation. Subsequently, the patterns of PrPsc deposition were found to correlate with vacuolation profiles, and these patterns were also used to characterize strains of prions.

Persuasive evidence that strain-specific information is enciphered in the tertiary structure of PrPsc comes from transmission of two different inherited human prion diseases to mice expressing a chimeric human-mouse PrP transgene. In FFI, the protease-resistant fragment of PrPsc after deglycosylation has a molecular mass of 19 kDa, whereas in fCJD and most sporadic prion diseases, it is 21 kDa (Table 375-3). This difference in molecular mass was shown to be due to different sites of proteolytic cleavage at the NH₂ termini of the two human PrPsc molecules, reflecting different tertiary structures. These distinct conformations were not unexpected because the amino acid sequences of the PrPs differ.

Extracts from the brains of patients with FFI transmitted disease into mice expressing a chimeric human-mouse PrP transgene and induced formation of the 19-kDa PrPsc, whereas fCJD and sCJD produced the 21-kDa PrPsc in mice expressing the same transgene. On second passage, these differences were maintained, demonstrating that chimeric PrPsc can exist in two different conformations based on the sizes of the protease-resistant fragments even though the amino acid sequence of PrPsc is invariant.

This analysis was extended when patients with sporadic fatal insomnia (sFI) were identified. Although they did not carry a *PrP* gene mutation, the clinical and pathologic phenotype was indistinguishable from that of patients with FFI. Furthermore, 19-kDa PrPsc was found in their brains, and on passage of prion disease to mice expressing a chimeric human-mouse PrP transgene, PrPsc was also found. These findings indicate that the disease phenotype is dictated by the conformation of PrPsc and not the amino acid sequence. PrPsc acts as a template for the conversion of PrPc into nascent PrPsc.

SPORADIC AND INHERITED PRION DISEASES

Initiation of sporadic disease may hypothetically follow from a somatic mutation and thus follow a path similar to that for germline mutations in inherited disease. In this situation, the mutant PrPsc must be capable of targeting wild type PrPc, a process known to be

possible for some mutations but less likely for others. Alternatively, the activation barrier separating wild type PrP$_C$ from PrP$_{Sc}$ could be crossed on rare occasions when viewed in the context of a population. Most individuals would be spared, while presentations in the elderly with an incidence of ~1 per million would be seen.

Twenty different mutations resulting in nonconservative substitutions in the human *PrP* gene have, to date, been found to segregate with inherited human prion diseases. Missense mutations and expansions in the octapeptide repeat region of the gene are responsible for familial forms of prion disease. Five different mutations of the *PrP* gene have been linked genetically to heritable prion disease.

Although phenotypes may vary dramatically within families, specific phenotypes tend to associate with certain mutations. A clinical phenotype indistinguishable from typical sporadic CJD is usually seen with substitutions at codons 180, 183, 200, 208, 210, and 232. Substitutions at codons 102, 105, 117, 198, and 217 are associated with the GSS variant of prion disease. The normal human PrP sequence contains five repeats of an eight or nine peptide sequence. Insertions from two to nine extra octapeptide repeats are frequently associated with variable phenotypes ranging from a condition indistinguishable from sporadic CJD to a slowly progressive dementing illness of many years duration. A mutation at codon 178 resulting in substitution of asparagine for aspartate produces FFI if a methionine is encoded at the polymorphic 129 residue on the same allele. Typical CJD is seen if a valine is encoded at position 129 of the same allele.

Human *PrP* Gene Polymorphisms Polymorphisms influence the susceptibility to sporadic, inherited, and infectious forms of prion disease. The methionine/valine polymorphism at position 129 not only modulates the age of onset of some inherited prion diseases but also determines the clinical phenotype. The influence of the codon 129 polymorphism iatrogenic and sporadic forms of prion disease has also been documented. The finding that homozygosity at codon 129 predisposes to sCJD supports a model of prion production that favors PrP interactions between homologous proteins.

Substitution of the basic residue lysine at position 219 produced dominant negative inhibition of prion replication in neuroblastoma cells. A lysine at 219 has been found in 12% of the Japanese population, and this group seems to be resistant to prion disease. Dominant negative inhibition of prion replication was also found with substitution of the basic residue arginine at position 171; sheep with arginine are resistant to scrapie.

INFECTIOUS PRION DISEASES

IATROGENIC CJD

Accidental transmission of CJD to humans appears to have occurred with corneal transplantation, contaminated electroencephalogram (EEG) electrode implantation, and surgical procedures. Corneas from donors with inapparent CJD have been transplanted to apparently healthy recipients who developed CJD after prolonged incubation periods. The same improperly decontaminated EEG electrodes that caused CJD in two young patients with intractable epilepsy caused CJD in a chimpanzee 18 months after their experimental implantation.

Surgical procedures may have resulted in accidental inoculation of patients with prions during their operations, presumably because some instrument or apparatus in the operating theater became contaminated when a CJD patient underwent surgery. Although the epidemiology of these studies is highly suggestive, no proof for such episodes exists.

Dura Mater Grafts More than 70 cases of CJD after implantation of dura mater grafts have been recorded. All of the grafts were thought to have been acquired from a single manufacturer whose preparative procedures were inadequate to inactivate human prions. One case of CJD occurred after repair of an eardrum perforation with a pericardium graft.

Human Growth Hormone and Pituitary Gonadotropin Therapy The possibility of transmission of CJD from contaminated human growth hormone (hGH) preparations derived from human pituitaries has been raised by the occurrence of fatal cerebellar disorders with dementia in >100 patients ranging in age from 10 to 41 years. These patients received injections of hGH every 2 to 4 days for 4 to 12 years. If it is assumed that these patients developed CJD from injections of prion-contaminated hGH preparations, the possible incubation periods range from 4 to 30 years. Even though several investigations argue for the efficacy of inactivating prions in hGH fractions prepared from human pituitaries with 6 *M* urea, it seems doubtful that such protocols will be used for purifying hGH because recombinant hGH is available. Four cases of CJD have occurred in women receiving human pituitary gonadotropin.

NEW VARIANT CJD

The restricted geographic occurrence and chronology of nvCJD have raised the possibility that BSE prions have been transmitted to humans. Approximately 70 cases of nvCJD have been recorded, and the fact that the incidence has remained relatively constant has made establishing the origin of nvCJD difficult. No set of dietary habits distinguishes patients with nvCJD from apparently healthy individuals. Moreover, there is no explanation for the predilection of nvCJD for teenagers and young adults. Epidemiologic studies over the past three decades have failed to find evidence for transmission of sheep prions to humans. Attempts to predict the future number of cases of nvCJD on the basis of possible exposure to bovine prions before the offal ban in 1998 that prevented further feeding of meat and bone meal (MBM) to cattle have been uninformative because so few cases of nvCJD have occurred. Are we at the beginning of a human prion disease epidemic in Great Britain similar to those seen for BSE and kuru, or will the number of nvCJD cases remain small as seen with iCJD caused by cadaveric hGH?

It is possible that a particular conformation of bovine PrP^{Sc} was selected for heat resistance during the rendering process and was then reselected multiple times as cattle infected by ingesting prion-contaminated MBM were slaughtered and their offal rendered into more MBM. Recent studies of PrP^{Sc} from brains of patients who died of nvCJD show a pattern of PrP glycoforms different from those found for sCJD or iCJD. But the usefulness of measuring PrP glycoforms is questionable when trying to relate BSE to nvCJD because PrP^{Sc} is formed after the protein is glycosylated and enzymatic

deglycosylation of PrP$_{Sc}$requires denaturation.

The most compelling evidence thatnvCJDcomes fromBSEprions was obtained from experiments in mice expressing the bovine PrP transgene. Both BSE and nvCJD prions were efficiently transmitted to these transgenic mice. In contrast to sporadicCJDprions, nvCJD did not transmit disease efficiently to mice expressing a chimeric human-mousePrPtransgene. Earlier studies with nontransgenic mice suggested that nvCJD and BSE might be derived from the same source because both sources of inocula transmitted disease with similar but very long incubation periods.

NEUROPATHOLOGY

Frequently, the brains of patients withCJD have no recognizable abnormalities on gross examination. Patients who survive for several years have variable degrees of cerebral atrophy.

On light microscopy, the pathologic hallmarks ofCJD are spongiform degeneration and astrogliosis. The lack of an inflammatory response in CJD and other prion diseases is an important pathologic feature of these degenerative disorders. Spongiform degeneration is characterized by many 1- to 5-um vacuoles in the neuropil between nerve cell bodies. Generally, the spongiform changes occur in the cerebral cortex, putamen, caudate nucleus, thalamus, and molecular layer of the cerebellum. Astrocytic gliosis is a constant but nonspecific feature of prion diseases. Widespread proliferation of fibrous astrocytes is found throughout the gray matter of brains infected with CJD prions. Astrocytic processes filled with glial filaments form extensive networks.

Amyloid plaques have been found in ~10% ofCJDcases. Purified CJD prions from humans and animals exhibit the ultrastructural and histochemical characteristics of amyloid when treated with detergents during limited proteolysis. In first passage from some human Japanese CJD cases, amyloid plaques have been found in mouse brains. These plaques stain with antisera raised againstPrP.

The amyloid plaques ofGSS are morphologically distinct from those seen in kuru or scrapie. GSS plaques consist of a central dense core of amyloid surrounded by smaller globules of amyloid. Ultrastructurally, they consist of a radiating fibrillar network of amyloid fibrils with scant or no neuritic degeneration. The plaques can be distributed throughout the brain but are most frequently found in the cerebellum. They are often located adjacent to blood vessels. Congophilic angiopathy has been noted in some cases of GSS.

InnvCJD, a characteristic feature is the presence of "florid plaques." These are composed of a central core ofPrPamyloid surrounded by vacuoles in a pattern suggesting petals on a flower.

CLINICAL FEATURES

Nonspecific prodromal symptoms occur in about a third of patients withCJD and may include fatigue, sleep disturbance, weight loss, headache, malaise, and ill-defined pain. Most patients with CJD present with deficits in higher cortical function. These deficits

virtually always progress over weeks or months to a state of profound dementia characterized by memory loss, impaired judgment, and a decline in virtually all aspects of intellectual function. A few patients present with either visual impairment or cerebellar gait and coordination deficits. Frequently, the cerebellar deficits are rapidly followed by progressive dementia. Visual problems often begin with blurred vision and diminished acuity, rapidly followed by dementia.

Other symptoms and signs include extrapyramidal dysfunction manifested as rigidity, masklike facies, or choreoathetoid movements; pyramidal signs (usually mild); seizures (usually major motor) and, less commonly, hypesthesia; supranuclear gaze palsy; optic atrophy; and vegetative signs such as changes in weight, temperature, sweating, or menstruation.

Myoclonus Most patients (~90%) with CJD exhibit myoclonus that appears at various times throughout the illness. Unlike other involuntary movements, myoclonus persists during sleep. Startle myoclonus elicited by loud sounds or bright lights is frequent. It is important to stress that myoclonus is neither specific nor confined to CJD. Dementia with myoclonus can also be due to Alzheimer's disease (AD) (Chap. 362), to cryptococcal encephalitis (Chap. 204), or to the myoclonic epilepsy disorder Unverricht-Lundborg disease (Chap. 360).

Clinical Course In documented cases of accidental transmission of CJD to humans, an incubation period of 1.5 to 2.0 years preceded the development of clinical disease. In other cases, incubation periods of up to 30 years have been suggested. Most patients with CJD live 6 to 12 months after the onset of clinical signs and symptoms, whereas some live for up to 5 years.

DIAGNOSIS

The constellation of dementia, myoclonus, and periodic electrical bursts in an afebrile 60-year-old patient generally indicates CJD. Clinical abnormalities in CJD are confined to the CNS. Fever, elevated sedimentation rate, leukocytosis in blood, or a pleocytosis in cerebrospinal fluid (CSF) should alert the physician to another etiology to explain the patient's CNS dysfunction.

Important variations in the typical course of CJD appear in certain inherited and transmitted forms of the disease. fCJD has an earlier mean age of onset than sCJD. In GSS, ataxia is usually a prominent and presenting feature, with dementia occurring late in the disease course. GSS may present earlier than CJD (mean age, 43 years; range, 24 to 66 years) and is typically more slowly progressive than CJD; death usually occurs within 5 years of onset. FFI is characterized by insomnia and dysautonomia; dementia occurs only in the terminal phase of the illness. Rare sporadic cases have been identified. nvCJD has an unusual clinical course, with a prominent psychiatric prodrome that may include visual hallucinations and early ataxia, while frank dementia usually is a late sign of nvCJD (see below).

DIFFERENTIAL DIAGNOSIS

Many conditions may mimic CJD superficially. AD is occasionally accompanied by

myoclonus but is usually distinguished by its protracted course and lack of motor and visual dysfunction.

Intracranial vasculitides (Chap. 317) may produce nearly all of the symptoms and signs associated with CJD, sometimes without systemic abnormalities. Myoclonus is exceptional with cerebral vasculitis, but focal seizures may confuse the picture; furthermore, myoclonus is often absent in the early stages of CJD. Stepwise change in deficits, prominent headache, abnormal cerebrospinal fluid, and focal magnetic resonance imaging (MRI) or angiographic abnormalities all favor vasculitis.

Neurosyphilis (Chap. 172) may present with dementia and myoclonus that progresses in a relatively rapid fashion but is easily distinguished from CJD by CSF findings, as is cryptococcal meningoencephalitis. A diffuse intracranial tumor (gliomatosis cerebri; Chap. 370) may occasionally be confused with CJD. In rare cases of CNS neoplasia, neuroimaging studies are normal and there are no signs of increased intracranial pressure; however, CSF protein is usually elevated. Adult onset leukodystrophies (ceroid lipofuscinosis or Kuf's disease) and myoclonic epilepsy with Lafora bodies (Chap. 360) may be responsible for dementia, myoclonus, and ataxia; but the less acute courses and prominent seizures distinguish them from CJD. A number of diseases that may simulate CJD are easily distinguished by noting the clinical setting in which they occur. These diseases include anoxic encephalopathy, subacute sclerosing panencephalitis, progressive rubella panencephalitis, herpes simplex encephalitis (in immunoincompetent hosts), dialysis dementia, uremia, and portasystemic shunt encephalopathy.

When CJD begins atypically, it may for a short time resemble other disorders such as Parkinson's disease, progressive supranuclear palsy (Chap. 363), or progressive multifocal leukoencephalopathy (Chap. 373). However, this resemblance usually fades early in the course of CJD.

Certain drug intoxications, particularly lithium and bismuth, may produce a syndrome with encephalopathy and myoclonus. The rare condition known as Hashimoto's encephalopathy, which presents with a subacutely progressive encephalopathy and myoclonus with periodic triphasic complexes on the EEG should be excluded in every case of suspected CJD. It is diagnosed by the finding of high titers of antithyroglobulin or antithyroid perioxidase (antimicrosomal) antibodies in the blood, and improves with glucocorticoid therapy. Unlike CJD, fluctuations in severity typically occur in Hashimoto's encephalopathy.

The AIDS dementia complex (Chap. 309) may occasionally imitate CJD in onset, early course, physical signs, computed tomography (CT) findings, and lack of abnormalities on routine CSF studies. The few such patients without manifestations of systemic immunodeficiency (<10%) should be questioned about risk factors and should have serum antibodies to HIV determined. Additionally, more specific CSF tests are likely to be abnormal; in one study, CSF oligoclonal bands were present in six of nine patients, and intra-blood-brain barrier synthesis of IgG specific for HIV was elevated in eight of nine.

LABORATORY TESTS

With the exception of brain biopsy, there are no specific tests for CJD. If the constellation of pathologic changes frequently found in CJD is seen in a brain biopsy, then the diagnosis is reasonably secure (see Neuropathology, above). The rapid and reliable diagnosis of CJD postmortem can be accomplished with antisera to PrP. Numerous western blotting studies have consistently demonstrated PrP immunoreactive proteins that are proteinase K-resistant in the brains of patients with CJD. Because PrPSc is not uniformly distributed throughout the CNS, the apparent absence of PrPSc in a limited sample such as a biopsy does not rule out prion disease. A highly sensitive and quantitative immunoassay was developed based on epitopes that are exposed in PrPC but buried in PrPSc. Unlike all other immunoassays for PrPSc, this conformation-dependent immunoassay (CDI) does not require limited proteolysis to hydrolyze PrPC before measurement of the protease-resistant core of PrPSc (PrP 27-30).

If the patient has a family history suggestive of inherited CJD, sequencing the *PrP* gene may facilitate the diagnosis. Sometimes, the PrP sequence is helpful for even seemingly nonfamilial cases.

CT may be normal or show cortical atrophy. The MRI scan may show a subtle increased intensity in the basal ganglia with T2 or diffusion weighted imaging, but this finding is neither sensitive nor specific enough to make a diagnosis. CSF is nearly always normal but may show a minimal protein elevation. Although the stress protein 14-3-3 is elevated in the CSF of most patients with CJD, similar elevations of 14-3-3 are found in herpes simplex virus encephalitis, multi-infarct dementia, and stroke. In AD, 14-3-3 is generally not elevated. In the serum of some patients with CJD, the S-100 protein is elevated; but like 14-3-3, this elevation is not specific.

The EEG is often useful in the diagnosis of CJD. During the early phase of CJD, the EEG is usually normal or shows only scattered theta activity. In most advanced cases, repetitive, high voltage, triphasic, and polyphasic sharp discharges are seen, but in many cases their presence is transient. The presence of these stereotyped periodic bursts of <200 ms duration, occurring every 1 to 2 s, makes the diagnosis of CJD very likely. These discharges are frequently but not always symmetric; there may be a one-sided predominance in amplitude. As CJD progresses, normal background rhythms become fragmentary and slower.

CARE OF CJD PATIENTS

It is important to stress that CJD is neither a contagious nor a communicable disease, but it is transmissible. Although the risk of accidental inoculation by aerosols is very small, procedures producing aerosols should be performed in certified biosafety cabinets. Biosafety level 2 practices, containment equipment, and facilities are recommended by the Centers for Disease Control and Prevention and the National Institutes of Health. The primary problem in caring for patients with CJD is the inadvertent infection of healthcare workers by needle and stab wounds, whereas the possible transmission of a contagion through the air has never been documented. Electroencephalographic and electromyographic needles should not be reused after studies on patients with CJD have been performed.

There is no reason for pathologists or morgue dieners to resist performing autopsies on patients whose clinical diagnosis was CJD. Standard microbiologic practices outlined here, along with specific recommendations for decontamination, seem to be adequate precautions for the care of patients with CJD and the handling of infected specimens.

DECONTAMINATION OF CJD PRIONS

Prions are extremely resistant to common inactivation procedures, and there is some disagreement about the optimal conditions for sterilization. Some investigators recommend treating CJD-contaminated materials once with 1 *N* NaOH at room temperature, but we believe this procedure may be inadequate for sterilization. Autoclaving at 132°C for 5 h or treatment with 2 *N* NaOH for several hours is recommended for sterilization of prions. The term "sterilization" implies complete destruction of prions; any residual infectivity can be hazardous.

PREVENTION AND THERAPEUTICS

There is no known effective therapy for treating or preventing CJD. With one possible exception, there are no well-documented cases of patients with CJD showing recovery either spontaneously or after therapy.

Several compounds have been demonstrated to eliminate prions from prion-infected cultured cells. A class of compounds known as "dendrimers" seems particularly efficacious in this regard. Several drugs delay the onset of disease in animals inoculated with prions if the drugs are given around the time of the inoculation. The most common scenarios in which one would want to treat humans are either patients showing signs of disease or presymptomatic patients carrying mutations predisposing them to develop prion disease. No treatment has shown any efficacy in animal models of these two scenarios.

Structure-based drug design predicated on dominant negative inhibition of prion formation has produced several promising compounds. Whether this approach or that of enhanced clearance of misfolded proteins will provide general methods for developing novel therapeutics for Alzheimer's disease and Parkinson's disease, as well as amyotrophic lateral sclerosis (ALS), remains to be established.

(Bibliography omitted in Palm version)

376. CRITICAL CARE NEUROLOGY - *J. Claude Hemphill, M. Flint Beal, Daryl R. Gress*

Advances in the understanding of the pathophysiology of acute nervous system injury and the development of treatments that target these injury mechanisms have led to the growth of critical care neurology as a discipline. Life-threatening neurologic illness may be caused by a primary disorder affecting any region of the neuroaxis or may occur as a consequence of a systemic disorder such as hepatic failure, multisystem organ failure (MSOF), or cardiac arrest (Table 376-1). Critical care neurology focuses on preservation of neurologic tissue and prevention of secondary brain injury caused by ischemia, edema, and elevated intracranial pressure (ICP).

PATHOPHYSIOLOGY

Brain Edema Swelling, or edema, of brain tissue occurs with many types of brain injury. The two principal types of edema are vasogenic and cytotoxic. *Vasogenic edema* refers to the influx of fluid and solutes into the brain through an incompetent blood-brain barrier (BBB). In the normal cerebral vasculature, endothelial tight junctions associated with astrocytes create an impermeable barrier (the BBB), through which access into the brain interstitium is dependent upon specific transport mechanisms (Chap. 355). The BBB may be compromised in ischemia, trauma, infection, and metabolic derangements. Typically, vasogenic edema develops rapidly following injury. *Cytotoxic edema* refers to cellular swelling. Originally described as a response to exogenous toxins, cellular swelling occurs in a variety of settings including brain ischemia and trauma. Early astrocytic swelling is a hallmark of ischemia.

Brain edema that is clinically significant usually represents a combination of vasogenic and cellular components. Edema can lead to increasedICP as well as tissue shifts and brain displacement from focal processes. These tissue shifts can cause injury by mechanical distraction and compression in addition to the ischemia of impaired perfusion consequent to the elevated ICP.

Cerebral Perfusion and Autoregulation Brain tissue requires constant perfusion in order to ensure adequate delivery of substrate, principally oxygen and glucose. The hemodynamic response of the brain has the capacity to preserve perfusion across a wide range of systemic blood pressures. Cerebral perfusion pressure (CPP), defined as the mean systemic arterial pressure (MAP) minus theICP, provides the driving force for circulation across the capillary beds of the brain. *Autoregulation* refers to the physiologic response whereby cerebral blood flow (CBF) remains relatively constant over a wide range of blood pressures as a consequence of alterations of cerebrovascular resistance (Fig. 376-1). If systemic blood pressure drops, cerebral perfusion is preserved through vasodilatation of arterioles in the brain; likewise, arteriolar vasoconstriction occurs at high systemic pressures to prevent hyperperfusion. At the extreme limits of MAP or CPP (high or low), flow becomes directly related to perfusion pressure. These autoregulatory changes occur in the microcirculation and are mediated by vessels below the resolution of those seen on angiography. CBF is also strongly influenced by pH and P_{CO_2}. CBF increases with hypercapnia and acidosis and decreases with hypocapnia and alkalosis. This forms the basis for the use of hyperventilation to lower ICP, and this effect on ICP is mediated through a decrease in intracranial blood volume. Cerebral autoregulation is

critical to the normal homeostatic functioning of the brain, and this process may be disordered focally and unpredictably in disease states such as traumatic brain injury and severe focal cerebral ischemia.

Cerebrospinal Fluid and Intracranial Pressure The cranial contents consist essentially of brain, cerebrospinal fluid (CSF), and blood. CSF is produced principally in the choroid plexus of each lateral ventricle, exits the brain via the foramina of Luschka and Magendi, and flows over the cortex to be absorbed into the venous system along the superior sagittal sinus. Approximately 150 mL of CSF are contained within the ventricles and surrounding the brain and spinal cord; the cerebral blood volume is also ~150 mL. The bony skull offers excellent protection for the brain but allows little tolerance for additional volume. Significant increases in volume eventually result in increasedICP. Obstruction of CSF outflow, edema of cerebral tissue, or increases in volume from tumor or hematoma may increase ICP. Elevated ICP diminishes cerebral perfusion and can lead to tissue ischemia. Ischemia in turn may lead to vasodilatation via autoregulatory mechanisms designed to restore cerebral perfusion. However, vasodilatation also increases cerebral blood volume, which in turn then increases ICP, lowersCPP, and provokes further ischemia (Fig. 376-2). This vicious cycle is commonly seen in traumatic brain injury, massive intracerebral hemorrhage, and large hemispheric infarcts with significant tissue shift.*Excitotoxicity and mechanisms of cell death are discussed in Chap. 355.*

Approach to the Patient

Critically ill patients with severe central nervous system dysfunction require rapid evaluation and intervention in order to limit primary and secondary brain injury. Initial neurologic evaluation should be performed concurrent with stabilization of basic respiratory, cardiac, and hemodynamic parameters. Significant barriers may exist to neurologic assessment in the critical care unit. Endotracheal intubation and the use of sedative or paralytic agents to facilitate critical care procedures can make clinical assessment challenging.

An impaired level of consciousness is frequent in critically ill patients. The essential first task in assessment is to determine whether the cause of dysfunction is related to a diffuse, usually metabolic, process or whether a focal, usually structural, process is implicated. Examples of diffuse processes include metabolic encephalopathies related to organ failure, drug overdose, or hypoxia-ischemia. Focal processes include ischemic and hemorrhagic stroke and traumatic brain injury, especially with intracranial hematomas. Since these two categories of disorders have fundamentally different causes, treatments, and prognoses, the initial focus is on making this distinction rapidly and accurately.*The approach to the confused or comatose patient is discussed in Chap. 24; etiologies are listed in Table 24-1.*

Minor focal deficits may be present on the neurologic examination in patients with metabolic encephalopathies. However, the finding of prominent focal signs such as pupillary asymmetry, hemiparesis, gaze palsy, or paraplegia should alert the examiner to the possibility of a structural lesion. All patients with a decreased level of consciousness associated with focal findings should undergo an urgent neuroimaging procedure, as should all patients with coma of unknown etiology. Computed

tomographic (CT) scanning is usually the most appropriate initial study because it can be performed quickly in critically ill patients and demonstrates hemorrhage, hydrocephalus, and intracranial tissue shifts well. Magnetic resonance imaging (MRI) may provide more specific information in some situations, such as acute ischemic stroke (diffusion-weighted imaging, DWI) and cerebral venous sinus thrombosis (magnetic resonance venography, MRV). Any suggestion of trauma from the history or examination should alert the examiner to the possibility of cervical spine injury and prompt an imaging evaluation using plain x-rays, MRI, or CT.

Other diagnostic studies are best utilized in specific circumstances, usually when neuroimaging studies fail to reveal a structural lesion and the etiology of the altered mental state remains uncertain. Electroencephalography (EEG) can be important in the evaluation of critically ill patients with severe brain dysfunction. The EEG of encephalopathy typically reveals generalized slowing. One of the most important uses of EEG is to help exclude inapparent seizures, especially nonconvulsive status epilepticus. Untreated continuous or frequently recurrent seizures may cause neuronal injury, making the diagnosis and treatment of seizure crucial in this patient group. Lumbar puncture (LP) may be necessary to exclude infectious processes, and an elevated opening pressure may be an important clue to cerebral venous sinus thrombosis. In patients with coma or profound encephalopathy, it is preferable to perform a neuroimaging study prior to LP. If bacterial meningitis is suspected, an LP may be performed first or antibiotics may be empirically administered before the diagnostic studies are completed. Standard laboratory evaluation of critically ill patients should include assessment of serum electrolytes (especially sodium and calcium), glucose, renal and hepatic function, complete blood counts, and coagulation. Serum or urine toxicology screens should be performed in patients with encephalopathy of unknown cause. EEG, LP, and other specific laboratory tests are most useful when the mechanism of the altered level of consciousness is uncertain; they are not routinely performed in clear-cut cases of stroke or traumatic brain injury.

Monitoring of ICP can be an important tool in selected patients. Indications for ICP monitoring, as well as specific types of monitors, vary. In general, patients who should be considered for ICP monitoring are those with primary neurologic disorders, such as stroke or traumatic brain injury, who are not moribund and who are at significant risk for secondary brain injury due to elevated ICP and decreased CPP. Such patients include those with severe traumatic brain injury resulting in coma [Glasgow Coma Scale (GCS) score of £8 (Table 369-1)]; those with large tissue shifts from supratentorial ischemic or hemorrhagic stroke resulting in decreased consciousness; and those with (or at risk for) hydrocephalus from subarachnoid hemorrhage, intraventricular hemorrhage, or posterior fossa stroke. An additional disorder in which ICP monitoring can add important information is fulminant hepatic failure, in which elevated ICP may be treated with barbiturates or, eventually, liver transplantation. In general, ventriculostomy is preferable to ICP monitoring devices that are placed in brain parenchyma, because ventriculostomy allows CSF drainage as a method of treating elevated ICP. However, parenchymal ICP monitoring is most appropriate for patients with diffuse edema and small ventricles (which may make ventriculostomy placement more difficult) or any degree of coagulopathy (in which ventriculostomy carries a higher risk of hemorrhagic complications).

Treatment of Elevated ICP Elevated ICP may occur in a wide range of disorders including head trauma, intracerebral hemorrhage, subarachnoid hemorrhage with hydrocephalus, and fulminant hepatic failure. Because CSF and blood volume can be redistributed initially, by the time elevated ICP occurs intracranial compliance is severely impaired. At this point, small changes in the volume of CSF, intravascular blood, edema, or a mass lesion may result in significant changes in ICP. Elevated ICP then diminishes cerebral perfusion. This is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. Specific thresholds of ICP vary, but in general, ICP should be maintained at <20 mmHg and CPP should be maintained at ³70 mmHg.

A number of different interventions may lower ICP, and ideally the selection of treatment will be based on the underlying mechanism responsible for the elevated ICP (Table 376-2). For example, in hydrocephalus from subarachnoid hemorrhage, the principal cause of elevated ICP is impairment of CSF drainage. In this setting, ventricular drainage of CSF is likely to be sufficient and most appropriate. In head trauma and stroke, cytotoxic edema may be most responsible, and the use of osmotic diuretics such as mannitol becomes an appropriate early step. As described above, elevated ICP may cause tissue ischemia, and, if cerebral autoregulation is intact, the resulting vasodilatation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor agents to increase mean arterial pressure may actually lower ICP by improving perfusion, thereby allowing autoregulatory vasoconstriction as ischemia is relieved and ultimately decreasing intracranial blood volume.

Early signs of elevated ICP include drowsiness and a diminished level of consciousness. Neuroimaging studies may reveal evidence of edema and mass effect. Hypotonic intravenous fluids should be avoided, and elevation of the head of the bed is recommended. Patients must be carefully observed for risk of aspiration and compromise of the airway as the level of alertness declines. Coma and unilateral pupillary changes are late signs and require immediate intervention. Emergent treatment of elevated ICP is most quickly achieved by intubation and hyperventilation, which causes vasoconstriction and reduces cerebral blood volume. Because of the concern of provoking or worsening cerebral ischemia, hyperventilation is best used for short periods of time until a more definitive treatment can be instituted. Furthermore, the effects of continued hyperventilation on ICP are short-lived, often only for several hours because of the buffering capacity of the cerebral interstitium, and rebound elevated ICP may accompany abrupt discontinuation of hyperventilation. As the level of consciousness declines to coma, the ability to follow the neurologic status of the patient by examination deteriorates and measurement of ICP must be considered. If a ventriculostomy device is in place, direct drainage of CSF to reduce ICP is possible. Finally, high-dose barbiturates or hypothermia are sometimes used for refractory elevated ICP, although these have significant side effects and have not been shown to improve outcome.

CRITICAL CARE DISORDERS OF THE CENTRAL NERVOUS SYSTEM ASSOCIATED WITH SYSTEMIC DISEASE

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Hypoxic-ischemic encephalopathy occurs from lack of delivery of oxygen to the brain because of hypotension or respiratory failure. The most common causes are myocardial infarction, cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxia may predominate. Carbon monoxide and cyanide poisoning are termed *histotoxic hypoxia* since they cause a direct impairment of the respiratory chain.

Clinical Manifestations Mild degrees of pure hypoxia, such as occur at high altitudes, cause impaired judgment, inattentiveness, motor incoordination, and, at times, euphoria. However, with hypoxia-ischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3 to 5 min, full recovery may occur, but if hypoxia-ischemia lasts beyond 3 to 5 min, some degree of permanent cerebral damage is the rule. Except in extreme cases, it may be difficult to judge the precise degree of hypoxia-ischemia, and some patients make a relatively full recovery after even 8 to 10 min of global cerebral ischemia. The distinction between pure hypoxia and hypoxia-ischemia is important, since a Pa_{O_2} as low as 20 mmHg (2.7 kPa) can be well tolerated if it develops gradually and normal blood pressure is maintained, but short durations of very low or absent cerebral circulation may result in permanent impairment.

Clinical examination at different time points after a hypoxic-ischemic insult (especially cardiac arrest) is useful in assessing prognosis for long-term neurologic outcome (Fig. 376-3). The prognosis is better for patients with intact brainstem function, as indicated by normal pupillary light responses, intact oculocephalic (doll's-eyes), oculovestibular (caloric), and corneal reflexes. Absence of these reflexes and the presence of persistently dilated pupils that do not react to light are grave prognostic signs. A uniformly dismal prognosis from hypoxic-ischemic coma is conveyed by the clinical findings of absence of pupillary light reflex or absence of a motor response to pain on day 3 following the injury. Electrophysiologically, the finding of bilateral absence of the early cortical somatosensory evoked response (SSEPs) in the first week also conveys a poor prognosis. Long-term consequences of hypoxic-ischemic encephalopathy include persistent coma or vegetative state (Chap. 24), dementia, visual agnosia (Chap. 25), parkinsonism, choreoathetosis, cerebellar ataxia, myoclonus, seizures, and an amnestic state, which may be a consequence of selective damage to the hippocampus (Chap. 26).

Pathologic Findings Principal histologic findings are extensive multifocal or diffuse laminar cortical necrosis (Fig. 376-4), with almost invariable involvement of the hippocampus. The hippocampal CA1 neurons are vulnerable to even brief episodes of hypoxia-ischemia, perhaps explaining why selective persistent memory deficits may occur after brief cardiac arrest. Scattered small areas of infarction or neuronal loss may be present in the basal ganglia, hypothalamus, or brainstem. In some cases, extensive bilateral thalamic scarring may affect thalamic and extrathalamic pathways that mediate arousal, and this has been suggested as one pathologic explanation for the persistent vegetative state. A specific form of hypoxic-ischemic encephalopathy, so-called watershed infarcts, occurs at the distal territories between the major cerebral arteries and can cause cognitive deficits, including visual agnosia, and weakness that is greater in proximal than in distal muscle groups.

Diagnosis Diagnosis is based upon the history of a hypoxic-ischemic event such as

cardiac arrest. Blood pressure <70 mmHg systolic or Pa_{O_2}< 40 mmHg is usually necessary, although both absolute levels as well as duration of exposure are important determinants of cellular injury. Occasionally the clinical and radiographic features of a hypoxic-ischemic syndrome are seen without documented profound hypotension or hypoxia. Carbon monoxide intoxication can be confirmed by measurement of carboxyhemoglobin and is suggested by a cherry red color of the skin.

TREATMENT

Treatment should be directed at restoration of normal cardiorespiratory function. This includes securing a clear airway, ensuring adequate oxygenation and ventilation, and restoring cerebral perfusion, whether by cardiopulmonary resuscitation, fluid, pressors, or cardiac pacing. Hypothermia and neuroprotective agents that target different aspects of the cell injury cascade are experimental approaches that have not yet been shown to have clinical value.

Severe carbon monoxide intoxication may be treated with hyperbaric oxygen. Anticonvulsants may be needed to control seizures, although these are not usually given prophylactically. Posthypoxic myoclonus may respond to oral administration of clonazepam at doses of 1.5 to 10 mg daily or valproate at doses of 300 mg to 1200 mg daily in divided doses. Myoclonic status epilepticus after a severe hypoxic-ischemic insult portends a universally poor prognosis, even if seizures are controlled.

DELAYED POSTANOXIC ENCEPHALOPATHY

Delayed postanoxic encephalopathy is an uncommon phenomenon in which patients appear to make an initial recovery from hypoxic-ischemic insult but then develop a relapse characterized by apathy, confusion, and agitation. Progressive neurologic deficits may include shuffling gait, diffuse rigidity and spasticity, persistent parkinsonism or myoclonus, and, on occasion, coma and death after 1 to 2 weeks. Widespread cerebral demyelination may be present.

Carbon monoxide and cyanide intoxication can also cause a delayed encephalopathy. Little clinical impairment is evident when the patient first regains consciousness, but a parkinsonian syndrome characterized by akinesia and rigidity without tremor may develop. Symptoms can worsen over months, accompanied by increasing evidence of damage in the basal ganglia as seen on bothCT andMRI.

METABOLIC ENCEPHALOPATHIES

Altered mental states, variously described as confusion, delirium, disorientation, and encephalopathy, are present in many patients with severe illness in an intensive care unit (ICU). Older patients are particularly vulnerable to delirium, a confusional state characterized by disordered perception, frequent hallucinations, delusions, and sleep disturbance. This is often attributed to medication effects, sleep deprivation, pain, and anxiety. The term *ICU psychosis* has been used to describe a mental state with profound agitation occurring in this setting. The presence of family members in the ICU may help to calm and orient agitated patients, and in severe cases, low doses of neuroleptics (e.g., haloperidol 0.5 to 1 mg) can be useful. Ultimately, the psychosis

resolves with improvement in the underlying illness and a return to familiar surroundings.

In the ICU setting, several metabolic causes of an altered level of consciousness predominate. Hypercarbic encephalopathy can present with headache, confusion, stupor, or coma. Hypoventilation syndrome occurs most frequently in patients with a history of chronic CO_2 retention who are receiving oxygen therapy for emphysema or chronic pulmonary disease (Chap. 263). The elevated Pa_{CO_2} leading to CO_2 narcosis may have a direct anesthetic effect, and cerebral vasodilatation from increased Pa_{CO_2} can lead to increased ICP. Hepatic encephalopathy is suggested by asterixis and can occur in chronic liver failure or acute fulminant hepatic failure. Both hyperglycemia and hypoglycemia can cause encephalopathy, as can hypernatremia and hyponatremia. Confusion, impairment of eye movements, and gait ataxia are the hallmarks of acute Wernicke's disease (see below).

SEPTIC ENCEPHALOPATHY

Pathogenesis In patients with sepsis, the systemic response to infectious agents leads to the release of circulating inflammatory mediators that appear to contribute to encephalopathy. Critical illness, in association with the systemic inflammatory response syndrome (SIRS), can lead to MSOF. This syndrome can occur in the setting of apparent sepsis, severe burns, or trauma, even without clear identification of an infectious agent. Many patients with critical illness, sepsis, or SIRS develop encephalopathy without obvious explanation. This condition is broadly termed *septic encephalopathy*. While the specific mediators leading to neurologic dysfunction remain uncertain, it is clear that the encephalopathy is not simply the result of metabolic derangements of multiorgan failure. The cytokines tumor necrosis factora, interleukin (IL) 1, IL-2, and IL-6 are thought to play a role in this syndrome.

Diagnosis Septic encephalopathy presents clinically as a diffuse dysfunction of the brain without prominent focal findings. Confusion, disorientation, agitation, and fluctuations in level of alertness are typical. In more profound cases, especially with hemodynamic compromise, the decrease in level of alertness can be more prominent, at times resulting in coma. Hyperreflexia and frontal release signs such as a grasp or snout reflex (Chap. 356) can be seen. Abnormal movements such as myoclonus, tremor, or asterixis can occur. Septic encephalopathy is quite common, occurring in the majority of patients with sepsis and MSOF. Diagnosis is often difficult because of the multiple potential causes of neurologic dysfunction in critically ill patients, and requires exclusion of structural, metabolic, toxic, and infectious (e.g., meningitis or encephalitis) causes. Although the mortality of patients with septic encephalopathy severe enough to produce coma approaches 50%, this reflects the severity of the underlying critical illness and is not a direct result of the septic encephalopathy. Neurologically, successful treatment of the underlying critical illness almost always results in complete resolution of the encephalopathy, without significant residua.

CENTRAL PONTINE MYELINOLYSIS

This disorder typically presents in a devastating fashion as quadriplegia and pseudobulbar palsy. Predisposing factors include severe underlying medical illness or

nutritional deficiency; most cases are associated with rapid correction of hyponatremia or with hyperosmolar states. The pathology consists of demyelination without inflammation in the base of the pons, with relative sparing of axons and nerve cells.MRI is useful in establishing the diagnosis (Fig. 376-5) and may also identify partial forms that present as confusion, dysarthria, and/or disturbances of conjugate gaze without quadriplegia. Therapeutic guidelines for the restoration of severe hyponatremia should aim for gradual correction, i.e., by £10 mmol/L (10 meq/L) within 24 h and 20 mmol/L (20 meq/L) within 48 h.

WERNICKE'S DISEASE

Wernicke's disease is a common and preventable disorder due to a deficiency of thiamine (Chap. 75). In the United States, alcoholics account for most cases, but patients with malnutrition due to hyperemesis, starvation, renal dialysis, cancer, or AIDS are also at risk. The characteristic clinical triad is that of ophthalmoplegia, ataxia, and global confusion. However, only one-third of patients with acute Wernicke's disease present with the classic clinical triad. Most patients are profoundly disoriented, indifferent, and inattentive, although rarely they have an agitated delirium related to ethanol withdrawal. If the disease is not treated, stupor, coma, and death may ensue. Ocular motor abnormalities include horizontal nystagmus on lateral gaze, lateral rectus palsy (usually bilateral), conjugate gaze palsies, and rarely ptosis. Gait ataxia probably results from a combination of polyneuropathy, cerebellar involvement, and vestibular paresis. The pupils are usually spared, but they may become miotic with advanced disease.

Wernicke's disease is usually associated with other manifestations of nutritional disease, such as polyneuropathy. Rarely, amblyopia or spinal spastic ataxia occurs. Tachycardia and postural hypotension may be related to impaired function of the autonomic nervous system or to the coexistence of cardiovascular beriberi. Patients who recover show improvement in ocular palsies within hours after the administration of thiamine, but horizontal nystagmus may persist. Ataxia improves more slowly than the ocular motor abnormalities. Approximately half recover incompletely and are left with a slow, shuffling, wide-based gait and an inability to tandem walk. Apathy, drowsiness, and confusion improve more gradually. As these symptoms recede, an amnestic state with impairment in recent memory and learning may become more apparent (*Korsakoff's psychosis*). Korsakoff's psychosis is frequently persistent; the residual mental state is characterized by gaps in memory, confabulation, and disordered temporal sequencing.

Pathology Lesions in the periventricular regions of the diencephalon, midbrain, and brainstem as well as the superior vermis of the cerebellum consist of symmetric discoloration of structures surrounding the third ventricle, aqueduct, and fourth ventricle, with petechial hemorrhages in occasional acute cases and atrophy of the mamillary bodies in most chronic cases. There is frequently endothelial proliferation, demyelination, and some neuronal loss. These changes may be detected byMRIscanning (Fig. 376-6). The amnestic defect is related to lesions in the dorsal medial nuclei of the thalamus.

Pathogenesis Thiamine is a cofactor of several enzymes, including transketolase,

pyruvate dehydrogenase, and a-ketoglutarate dehydrogenase. Thiamine deficiency produces a diffuse decrease in cerebral glucose utilization and results in mitochondrial damage. Glutamate accumulates owing to impairment ofa-ketoglutarate dehydrogenase activity and, in combination with the energy deficiency, may result in excitotoxic cell damage.

TREATMENT

Wernicke's disease is a medical emergency and requires immediate administration of thiamine, in a dose of 50 mg either intravenously or intramuscularly. The dose should be given daily until the patient resumes a normal diet and should be begun prior to treatment with intravenous glucose solutions. Glucose infusions may precipitate Wernicke's disease in a previously unaffected patient or cause a rapid worsening of an early form of the disease. For this reason, thiamine should be administered to all alcoholic patients requiring parenteral glucose.

CRITICAL CARE DISORDERS OF THE PERIPHERAL NERVOUS SYSTEM ASSOCIATED WITH SYSTEMIC DISEASE

Critical illness with disorders of the peripheral nervous system (PNS) arises in two contexts: (1) primary neurologic diseases that require critical care interventions such as intubation and mechanical ventilation, and (2) secondary PNS manifestations of systemic critical illness, often involvingMSOF. The former include acute polyneuropathies such as Guillain-Barre syndrome (Chap. 378), neuromuscular junction disorders including myasthenia gravis (Chap. 380) and botulism (Chap. 144), and primary muscle disorders such as polymyositis (Chap. 382). The latter result either from the systemic disease itself or as a consequence of interventions.

General principles of respiratory evaluation in patients withPNSinvolvement, regardless of cause, include assessment of pulmonary mechanics, such as maximal inspiratory force (MIF) and vital capacity (VC), and evaluation of strength of bulbar muscles. Regardless of the cause of weakness, endotracheal intubation should be considered when the MIF falls to<-25 cmH$_2$O or the VC is <1 L. Also, patients with severe palatal weakness may require endotracheal intubation in order to prevent acute upper airway obstruction or recurrent aspiration. Arterial blood gases and percutaneous oxygen saturation are used to follow patients with potential respiratory compromise from PNS dysfunction; however, intubation and mechanical ventilation should be undertaken long before oxygen saturation drops or CO$_2$retention develops from hypoventilation.*Principles of mechanical ventilation are discussed in Chap. 266.*

NEUROPATHY

While encephalopathy may be the most obvious neurologic dysfunction in critically ill patients, dysfunction of thePNS is also quite common. It is typically present in patients with prolonged critical illnesses lasting several weeks and involving sepsis; clinical suspicion is aroused when there is failure to wean from mechanical ventilation despite improvement of the underlying sepsis and critical illness. *Critical illness polyneuropathy* refers to the most common PNS complication related to critical illness; it is seen in the setting of prolonged critical illness, sepsis, andMSOF. Neurologic findings include

diffuse weakness, decreased reflexes, and distal sensory loss. Electrophysiologic studies demonstrate a diffuse, symmetric, distal axonal sensorimotor neuropathy, and pathologic studies have confirmed axonal degeneration. The precise mechanism of critical illness polyneuropathy remains unclear, but circulating factors such as cytokines, which are associated with sepsis and SIRS, are thought to play a role. It has been reported that up to 70% of patients with the sepsis syndrome have some degree of neuropathy, although far fewer have a clinical syndrome profound enough to cause severe respiratory muscle weakness requiring prolonged mechanical ventilation or resulting in failure to wean. Treatment is supportive, with specific intervention directed at treating the underlying illness. While spontaneous recovery is usually seen, the time course may extend over weeks to months and necessitate long-term ventilatory support and care even after the underlying critical illness has resolved.

DISORDERS OF NEUROMUSCULAR TRANSMISSION

A defect in neuromuscular transmission may be a source of weakness in critically ill patients. Myasthenia gravis (Chap. 380) may be a consideration; however, persistent weakness secondary to impaired neuromuscular junction transmission is almost always due to administration of drugs. A number of medications impair neuromuscular transmission; these include antibiotics, especially aminoglycosides, and beta-blocking agents. In the ICU, the nondepolarizing neuromuscular blocking agents (nd-NMBAs), also known as muscle relaxants, are most commonly responsible. Included in this group of drugs are such agents as pancuronium, vecuronium, rocuronium, and atracurium. They are often used to facilitate mechanical ventilation or other critical care procedures, but with prolonged use persistent neuromuscular blockade may result in weakness even after discontinuation of these agents hours or days earlier. Risk factors for this prolonged action of neuromuscular blocking agents include female sex, metabolic acidosis, and renal failure.

Prolonged neuromuscular blockade does not appear to produce permanent damage to the PNS. Once the offending medications are discontinued, full strength is restored, although this may take days. In general, the lowest dose of neuromuscular blocking agent should be used to achieve the desired result, and, when these agents are used in the ICU, a peripheral nerve stimulator should be used to monitor neuromuscular junction function.

MYOPATHY

Critically ill patients, especially those with sepsis, frequently develop muscle wasting, often in the face of seemingly adequate nutritional support. The assumption has been that this represents a catabolic myopathy brought about as a result of multiple factors, including elevated cortisol and catecholamine release and other circulating factors induced by the SIRS. In this syndrome, known as *cachectic myopathy*, serum creatine kinase levels and electromyography (EMG) are normal. Muscle biopsy shows type II fiber atrophy. Panfascicular muscle fiber necrosis may also occur in the setting of profound sepsis. This so-called *septic myopathy* is characterized clinically by weakness progressing to a profound level over just a few days. There may be associated elevations in serum creatine kinase and urine myoglobin. Both EMG and muscle biopsy may be normal initially but eventually show abnormal spontaneous activity and

panfascicular necrosis with an accompanying inflammatory reaction.

Acute quadriplegic myopathy describes a clinical syndrome of severe weakness seen in the setting of glucocorticoid and nd-NMBA use. The most frequent scenario in which this is encountered is the asthmatic patient who requires high-dose glucocorticoids and nd-NMBA to facilitate mechanical ventilation. This muscle disorder is not due to prolonged action of nd-NMBAs at the neuromuscular junction but, rather, is an actual myopathy with muscle damage; it has occasionally been described with high-dose glucocorticoid use alone. Clinically this syndrome is most often recognized when a patient fails to wean from mechanical ventilation despite resolution of the primary pulmonary process. Pathologically, there may be vacuolar changes in both type I and type II muscle fibers with evidence of regeneration. Acute quadriplegic myopathy has a good prognosis. If patients survive their underlying critical illness, the myopathy invariably improves and patients usually return to normal. However, because this syndrome is a result of true muscle damage, not just prolonged blockade at the neuromuscular junction, this process may take weeks or months, and tracheostomy with prolonged ventilatory support may be necessary. At present, it is unclear how to prevent this myopathic complication, except by avoiding use of nd-NMBAs, a strategy not always possible. Monitoring with a peripheral nerve stimulator can help to avoid the overuse of these agents. However, this is more likely to prevent the complication of prolonged neuromuscular junction blockade than it is to prevent this myopathy.

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SECTION 3 - DISORDERS OF NERVE AND MUSCLE

377. APPROACH TO THE PATIENT WITH PERIPHERAL NEUROPATHY - *Arthur K. Asbury*

Peripheral neuropathy is a general term indicating peripheral nerve disorders of any cause; the manifestations of neuropathy may be so diverse that it is difficult for the physician to know where to begin and how to proceed.

The clinical and electrodiagnostic (EDX) approach to evaluation and management of a neuropathic disorder is summarized in Fig. 377-1. The EDX approach consists of electrophysiologic examination of nerve and muscle, including nerve conduction studies and electromyography. It is part of the evaluation of any neuropathy and is considered to be an extension of the neurologic examination. Using this scheme, the examiner determines for each patient the tempo, distribution, and severity of the neuropathy and makes a judgment as to whether the problem represents a mononeuropathy, a mononeuropathy multiplex, or a polyneuropathy. Often this distinction is obvious. With the sum of clinical and EDX information in hand, the differential diagnostic possibilities and treatment options are usually narrowed to a manageable number.

MONONEUROPATHY

Mononeuropathy refers to focal involvement of a single nerve trunk and therefore implies a local cause. Direct trauma, compression, and entrapment are the usual ones. Ulnar neuropathies, due to lesions either at the ulnar groove or in the cubital tunnel, and median neuropathy due to compression in the carpal tunnel constitute the great majority of mononeuropathies encountered in clinical practice. These are described below, and other common mononeuropathies are listed in Table 377-1. EDX examination is part of the evaluation of mononeuropathies, mainly to judge the nature of the focal lesion (demyelinating or axonal degeneration) and, in severe mononeuropathies, to determine whether any nerve fibers remain in continuity.

In the absence of a history of trauma to the nerve trunk, factors favoring conservative management of a mononeuropathy include sudden onset, no motor deficit, few or no sensory findings (even though pain and sensory symptoms may be present), and no evidence of axonal degeneration by EDX criteria. Factors favoring active measures including surgical intervention are chronicity and worsening neurologic deficit on examination, particularly if motor and EDX evidence suggests that the lesion has produced a degree of wallerian degeneration.

Ulnar Neuropathy Complete ulnar paralysis results in a characteristic claw-hand deformity owing to wasting and weakness of many of the small hand muscles and hyperextension of the fingers at the metacarpophalangeal joints and flexion at the interphalangeal joints. The flexion deformity is most pronounced in the fourth and fifth fingers. Sensory loss occurs over the fifth finger, the ulnar aspect of the fourth finger, and the ulnar border of the palm. The superficial location of the nerve at the elbow makes it a common site of pressure palsy. The ulnar nerve may also become entrapped just distal to the elbow in the cubital tunnel formed by the aponeurotic arch linking the two heads of the flexor carpi ulnaris. Also, prolonged pressure on the base of the palm,

as occurs with use of hand tools or bicycle riding, may result in damage to the deep palmar branch of the ulnar nerve, causing weakness of the small hand muscles but no sensory loss (Table 377-1).

Carpal Tunnel Syndrome The median nerve in the carpal tunnel lies in close quarters with nine tendons. Entrapment of the nerve at the wrist (*carpal tunnel syndrome*) may be secondary to excessive use of the wrist, tenosynovitis with arthritis, or local infiltration, e.g., by a thickening of connective tissue as in acromegaly or by deposit of amyloid or by one of the mucopolysaccharidoses. Other systemic diseases associated with an increased incidence of carpal tunnel syndrome are hypothyroidism, rheumatoid arthritis, and diabetes mellitus, but underlying diseases account for only a small fraction of all cases. The main symptoms of carpal tunnel syndrome are nocturnal paresthesias of thumb, index, and middle fingers. With worsening, numbness occurs in that distribution, and is demonstrable by pin examination. Eventually weakness and atrophy of the abductor pollicis brevis (thenar eminence) becomes evident. The principal treatment of carpal tunnel syndrome is surgical section of the carpal ligament to relieve entrapment. Incomplete lesions of the median nerve between the axilla and wrist may result in *causalgia* (a particularly severe type of burning pain;Chap. 12;Table 377-1).

Tarsal Tunnel Syndrome The distal tibial nerve, along with several tendons and the posterior tibial artery, lies in the tarsal tunnel just posterior to the medial malleolus. Because of its superficial site, the distal tibial nerve is subject to compression or to direct trauma. Causes include sprain or fracture of the ankle, ill-fitting footwear, posttraumatic fibrosis, cysts, or ganglia adjacent to the nerve, arthritis, and tenosynovitis. Characteristic symptoms are pain in the ankle and the sole of the foot with paresthesias, particularly upon walking. On examination, the tibial nerve trunk in the tarsal tunnel is usually tender to palpation, sensory deficit should be demonstrable on the sole of the foot, and weakness of the toe plantar-flexor muscles may be noted.EDXexamination and also nerve block using local anesthetic are useful in establishing the diagnosis. Definitive treatment is extensive surgical decompression of the tibial nerve in the tarsal tunnel. Tarsal tunnel syndrome, in terms of its pathophysiology and management, is similar to carpal tunnel syndrome but is much less common (Table 377-1).

POLYNEUROPATHY

The prototypical picture of polyneuropathy occurs with acquired toxic or metabolic neuropathic states. The first symptoms tend to be sensory and consist of tingling, prickling, burning, or bandlike dysesthesias in the balls of the feet or tips of the toes, or in a general distribution over the soles (Chap. 23). Symptoms and findings are usually symmetric and graded distally. If the polyneuropathy remains mild, objective motor or sensory signs may not be detectable.

With progression, dysesthesias spread up the lower legs. Pansensory loss is usually found over both feet, ankle jerks are lost, and weakness of dorsiflexion of the toes, best demonstrated in the great toe, is present. In some instances, the process begins with weakness in the feet, without preceding sensory symptoms. As worsening occurs, sensory loss moves centripetally in a graded "stocking" fashion, and the patient may complain that the feet have a numb or "wooden" feeling or may say "I feel as though I'm

walking on stumps." Patients have difficulty walking on their heels during examination, and their feet may slap while walking. Later, the knee jerk reflex disappears and foot drop becomes more apparent. By the time sensory disturbance has reached the upper shin, dysesthesias are usually noticed in the tips of the fingers. The degree of spontaneous pain varies but is often considerable. Light stimuli to hypesthetic areas, once perceived, may be experienced as extremely uncomfortable (*hyperpathia*). Unsteadiness of gait may be out of proportion to muscle weakness because of proprioceptive loss.

Worsening is more severe in the legs than in the arms and proceeds in a centripetal, symmetrically graded manner with pansensory loss, areflexia, and muscle atrophy; motor weakness is usually greater in the extensor muscles than in corresponding flexor groups. When the sensory disturbance reaches the elbows and mid-thighs, a tent-shaped area of hypesthesia may often be demonstrated on the lower abdomen. This area will grow broader, and its apex will extend rostrally toward the sternum as the neuropathy worsens. By this time, patients generally cannot stand or walk or hold objects in their hands.

Overall, nerve fibers are affected according to axon length, without regard to root or nerve trunk distribution -- hence the aptness of the term *stocking-glove* to describe the pattern of sensory deficit. In general, the motor deficit is also graded, distal, and symmetric.

Although *polyneuropathy* connotes a widespread symmetric process, usually distal and graded, polyneuropathies are quite diverse because of the variability of tempo, severity, mix of sensory and motor features, and presence or absence of positive symptoms. For instance, a patient with a subacute, severely dysesthetic sensory polyneuropathy and alopecia who is in the early phases of thallium intoxication bears little similarity to the patient with a 40-year history of insidiously progressive clumsiness of gait whose findings are foot drop, lower leg atrophy, pes cavus, and minimal asymptomatic distal sensory deficit due to a hereditary polyneuropathy (Chap. 379). These two patients fall at opposite ends of the spectrum of polyneuropathy.

The classification of peripheral neuropathies has become increasingly complex as the capacity to discriminate new subgroups and identify new associations with toxins and systemic disorders improves. Further, our grasp of the pathophysiologic basis of the clinical phenomena observed in neuropathy has increased rapidly. But these advances are primarily descriptive; little progress has been made in understanding the fundamental pathogenic events in nervous tissue that eventuate in any of the polyneuropathies.

The important features of each major grouping of polyneuropathies are summarized in Table 377-2, and key aspects of specific polyneuropathies are given in 377-3, 377-4, 377-5, and 377-6.

MONONEUROPATHY MULTIPLEX (MULTIFOCAL NEUROPATHY)

Mononeuropathy multiplex refers to simultaneous or sequential involvement of individual noncontiguous nerve trunks, either partially or completely, evolving over days to years.

Since the disease process underlying mononeuropathy multiplex involves peripheral nerves in a multifocal and random fashion, progression of the disease involves a tendency for the neurologic deficit to become less patchy and multifocal and more confluent and symmetric. As a result, some patients present with a distal symmetric neuropathy. Attention to the pattern of early symptoms is therefore important in making the judgment that a particular neuropathy is indeed a mononeuropathy multiplex.

ASSESSMENT AND DIAGNOSIS OF POLYNEUROPATHY AND MONONEUROPATHY MULTIPLEX

Clues to the diagnosis of these neuropathies often lie in unnoticed or forgotten events occurring weeks or months prior to the onset of symptoms. Inquiry should be made about recent viral illnesses; other systemic symptoms; institution of new medications; exposures to solvents, pesticides, or heavy metals; the occurrence of similar symptoms in family members or coworkers; habits concerning alcohol; and the presence of preexisting medical disorders. Patients should be asked if they would feel well if free of their neuropathic symptoms; answers will suggest the presence or absence of an underlying systemic illness.

How did symptoms first appear? Even with distal polyneuropathies, symptoms may appear in the sole of one foot a few days or a week before the other, but usually the patient will describe a distal graded disturbance that moves evenly and symmetrically in centripetal fashion. Symptoms that first appear in the distribution of individual digital nerves, involving only half of a digit at a time, and then gradually spread and coalesce suggest a multifocal process (mononeuropathy multiplex), as might occur with a systemic vasculitis or cryoglobulinemia.

The evolution of neuropathy ranges from rapid worsening over a few days to an indolent process lasting many years. Polyneuropathies that progress slowly, over more than 5 years, are most likely to be genetically determined, particularly if the major manifestations are distal atrophy and weakness with few or no positive sensory symptoms. Diabetic polyneuropathy and paraproteinemic neuropathies also progress insidiously over 5 to 10 years. Axonal degenerations of toxic or metabolic origin tend to evolve over several weeks to a year or more, and the rate of progression of demyelinating neuropathies is highly variable, ranging from a few days in Guillain-Barre syndrome (GBS;Chap. 378) to many years in others.

Major fluctuations in the course of neuropathy raise two possibilities: (1) relapsing forms of neuropathy and (2) repeated toxic exposures. Slow fluctuation in symptoms taking place over weeks or months (reflecting changes in the activity of neuropathy) should not be confused with day-to-day variation or diurnal undulation of symptoms. The latter are common to all neuropathic disorders. An example is carpal tunnel syndrome, in which dysesthesias may be prominent at night but absent during the day.

Palpation of the nerve trunk to detect enlargement is a frequently forgotten part of the neurologic examination. In mononeuropathy or mononeuropathy multiplex, the entire course of the nerve trunk in question should be explored manually for focal thickening, for the presence of neurofibroma, point tenderness, or Tinel's phenomenon (generation of a tingling sensation in the sensory territory of the nerve by tapping along the course

of the nerve trunk); and for pain elicited by stretching of the nerve trunk. In leprous neuritis, fusiform thickening of nerve trunks is frequent, and beading of nerve trunks may be encountered in amyloid polyneuropathy. In genetically determined hypertrophic neuropathies, uniform thickening of all nerve trunks may occur, often to the caliber of a clothesline or larger.

Most neuropathies involve nerve fibers of all sizes, but damage is sometimes restricted to either large or small fibers. In a polyneuropathy affecting mainly small fibers, diminished pinprick and temperature sensation, often with painful, burning dysesthesias, will predominate, along with autonomic dysfunction but with relative sparing of motor power, balance, and tendon jerks. Some cases of amyloid and distal diabetic polyneuropathies fall into this category. In contrast, large-fiber polyneuropathy is characterized by areflexia, sensory ataxia, relatively minor cutaneous sensory deficit, and variable degrees of motor dysfunction, sometimes severe.

For patients with polyneuropathy or mononeuropathy multiplex, standard tests should include a complete blood count and measurement of erythrocyte sedimentation rate, urinalysis, chest x-ray, postprandial blood glucose determination, and serum protein electrophoresis. Further tests are dictated by the combined results of the history and the physical and EDX examination (Fig. 377-1).

Electrodiagnosis EDX examination is a key procedure in all patients with suspected neuropathy. It is generally not possible to make the distinction between axonal and demyelinating disorders by clinical examination alone; here EDX analysis is particularly useful. EDX features of demyelination are slowing of nerve conduction velocity (NCV), dispersion of evoked compound action potentials, conduction block (major decrease in amplitude of muscle compound action potentials on proximal stimulation of the nerve, as compared to distal stimulation), and marked prolongation of distal latencies (Chap. 357). In contrast, axonal neuropathies are characterized by a reduction in amplitude of evoked compound action potentials with relative preservation of NCV. The distinction between a primarily demyelinating neuropathy and an axonal neuropathy is crucial because of the differing approaches to diagnosis and management.

EDX studies also help to determine the presence or absence of a sensory involvement when that is not clear by clinical examination alone. It provides information about the distribution of subclinical findings, thus sharpening the diagnostic focus. Other issues that may be clarified by the electrodiagnostician include:

1. The distinction between disorders primary to nerve and to muscle (neuropathy versus myopathy)

2. The distinction between root or plexus involvement and more distal nerve trunk involvement

3. The distinction between generalized polyneuropathic processes and widespread multifocal nerve trunk involvement

4. The distinction between upper and lower motor neuron weakness

5. The distinction, in a given generalized polyneuropathic process, between primary demyelinating neuropathy and axonal degeneration

6. The assessment, in both primary axonal and demyelinating neuropathies, of features bearing on the nature, activity, and likely prognosis of the neuropathy

7. The assessment, in mononeuropathies, of the site of the lesion and its major effect on nerve fibers, especially the distinction between demyelinating conduction block and wallerian degeneration

8. The characterization of disorders of the neuromuscular junction

9. The identification, often in muscle of normal bulk and strength, of important features such as chronic partial denervation, fasciculations, and myotonia

10. The analysis of cramp, and its distinction from physiologic contracture

If in a particular instance of progressive polyneuropathy of subacute or chronic evolution the EDX findings are those of an axonopathy, a long list of metabolic states and exogenous toxins comes under consideration (Tables 377-3 and 377-4). If the course is protracted over several years, it raises the likelihood of a hereditary neuropathy (Chap. 379); family members must be examined and additional attention given to the family history. If the EDX findings indicate primary demyelination of nerve, the approach is entirely different. The possibilities then include acquired demyelinating neuropathy, thought to be immunologically mediated (Chap. 378), and genetically determined neuropathies, some of which are marked by uniform and drastic slowing of nerve conduction velocities (Chap. 379).

If the clinical features indicate mononeuropathy multiplex, the EDX question is whether the process is primarily axonal or demyelinating. Almost one-third of all adults with the clinical syndrome of mononeuropathy multiplex have a clear-cut picture of a demyelinating disorder, often with foci of persistent conduction block on EDX examination. Multifocal demyelinating neuropathy may represent part of the spectrum of chronic inflammatory demyelinating neuropathy (CIDP), or, if multifocal and only motor, would fit into the related category of multifocal motor neuropathy. *For further discussion of the management of multifocal motor neuropathy, see Chap. 378.*

The remaining two-thirds of patients with mononeuropathy multiplex have a picture of patchy axonal involvement by EDX examination. Although ischemia should be suspected as the basis of neuropathy in these patients, only about one-half can be shown to have disease of the vasa nervorum, usually vasculitis. Management of those with proven vasculitis of vasa nervorum is often the same as treatment for systemic vasculitis (Chaps. 317 and 378). If the cause of mononeuropathy multiplex remains undiagnosed even on follow-up, management should be conservative. In many patients the disease will stabilize or reverse, at least partially.

Mononeuropathy multiplex syndrome may also be seen as a manifestation of leprosy, sarcoidosis, certain types of amyloidosis, hypereosinophilia syndrome, cryoglobulinemia, neuroAIDs, and multifocal types of diabetic neuropathy.

Nerve Biopsy The sural nerve at the ankle is the preferred site for cutaneous nerve biopsy. There are few indications to employ this invasive technique. The main one is in asymmetric and multifocal neuropathic disorders producing a clinical picture of mononeuropathy multiplex, the basis of which is still unclear after other laboratory investigations are complete. Diagnostic considerations include vasculitis, multifocal demyelinating neuropathies, amyloidosis, leprosy, and occasionally sarcoidosis. Nerve biopsy is also helpful when one or more cutaneous nerves are palpably enlarged. Another clinical application is in establishing the diagnosis in some genetically determined childhood disorders such as metachromatic leukodystrophy, Krabbe's disease, giant axonal neuropathy, and infantile neuroaxonal dystrophy. In all of these recessively inherited diseases, both the central nervous system and the peripheral nervous system are affected.

There is a tendency to carry out sural nerve biopsy in distal symmetric polyneuropathies of subacute or chronic evolution. This practice is discouraged because its yield is low. Nerve biopsy in this situation may be useful as part of an approved research protocol when the biopsy will provide crucial information not otherwise obtainable.

SPECIAL CATEGORIES OF NEUROPATHY

Some neuropathies require individual description because of their importance or distinctiveness.

Diabetic Neuropathies The neuropathies of diabetes mellitus are classified in Table 377-5. A limitation of this classification is that most patients do not fit neatly into any single category but instead have overlapping clinical features of several. For instance, many diabetic patients with distal, primarily sensory polyneuropathy can also be shown to have autonomic dysfunction, usually in the form of vasomotor disturbance in the limbs and abnormalities of sweating. Similarly, patients who develop a proximal motor syndrome often have dysautonomic features (including sexual impotence in males) and some degree of distal sensory polyneuropathy. To compound matters, such patients appear at risk of developing a cranial mononeuropathy. Pain is a frequent feature of diabetic neuropathies (Table 377-5) but is variable in incidence and degree.

Diabetic neuropathies occur in the setting of long-standing hyperglycemia (decades), whether the diabetes is insulin-dependent or not. By far the most common neuropathies related to diabetes mellitus are the diffuse sensory and autonomic types (categories 1 and 2 under "Symmetric" in Table 377-5). Sensory and autonomic polyneuropathy, chronic and indolent in evolution, may first be noticed in the third to fifth decades in patients with juvenile-onset diabetes but tends to occur after age 50 in patients with adult-onset diabetes. Focal and multifocal types of neuropathy are less common but quite dramatic (categories 1, 2, and 3 under "Asymmetric" in Table 377-5). They rarely occur before the age of 45 and are usually subacute or acute in onset. Cranial mononeuropathies are isolated sixth or third nerve palsies. The latter spares the pupil in three-fourths of cases, and some local pain or headache occurs in one-half. Truncal (thoracoabdominal) neuropathy is painful, involves one or more intercostal or lumbar nerves unilaterally, and frequently coexists with the asymmetric proximal motor neuropathy. In asymmetric proximal motor neuropathy, the most evident features are

weakened muscles innervated by the femoral and obturator nerves (quadriceps femoris, iliopsoas, adductor magnus) and ipsilateral loss of the knee jerk reflex. Sensory deficit is minor, but pain in the hip and anterior thigh may be prominent. In all these multifocal and focal neuropathies, the pain usually subsides within weeks to a year, and function is usually partly or completely recovered. The same is true for symmetric proximal motor neuropathy (category 3 under "Symmetric" in Table 377-5).

Focal and multifocal diabetic neuropathies are considered to be ischemic in origin, and ischemia may also underlie symmetric polyneuropathies, which are also thought to involve abnormality of nerve metabolism.

Management of diabetic neuropathies is directed toward optimal glycemic control and symptomatic pain suppression. In the long-term Diabetes Control and Complications Trial, patients who controlled their diabetes meticulously showed significantly less neuropathy. The role of aldose reductase inhibitors in preventing or reversing diabetic complications, including neuropathy, remains unclear. Entrapment neuropathies are frequently amenable to surgical decompression.

Neuropathies with HIV Infection Neuropathies are common in infection with HIV, but different types of neuropathy are seen according to the stage of the disease.GBS orCIDP(Chap. 378) are the neuropathies likely to occur following conversion to seropositivity and during the asymptomatic phase of HIV infection. Treatment is the same as for HIV-negative patients. In later, symptomatic stages, mononeuritis multiplex, axonal in nature, can occur; the course is typically subacute or chronic. In some cases, vasculitis of the vasa nervorum has been demonstrated.

The most common neuropathy is a distal, symmetric, mainly sensory polyneuropathy, which evolves slowly in the late symptomatic stages of HIV infection and frequently coexists with symptomatic encephalopathy and myelopathy (Table 377-3;Chap. 309). Improvement of this polyneuropathy with zidovudine treatment has been claimed. Sensory polyneuropathy of late-stage HIV infection must be distinguished from toxic polyneuropathy that may result from the use of nucleoside analogue treatment (Table 377-4). Also in the late stages, a severe, destructive, subacute, asymmetric polyradiculopathy involving the cauda equina may be seen; it is caused by an opportunistic infection of the nerve roots with cytomegalovirus. Ganciclovir, started early, can arrest the disorder.

Neuropathies with Lyme Disease A focal or multifocal radiculoneuropathy may occur weeks, months, or even years after primary infection by the tick-borne spirochete *Borrelia burgdorferi*. Although usually sensory and either dysesthetic or painful, the neuropathy is variable in distribution, affecting cranial nerves and spinal roots or nerves in a patchy, asymmetric fashion. Neuropathy is often chronic and persistent; cerebrospinal fluid pleocytosis is the rule. In many, improvement occurs spontaneously, but the course is shortened by treatment with antibiotics, usually intravenous ceftriaxone (Chap. 176).

Herpes Zoster This is a sensory neuritis due to infection with varicella-zoster virus and is characterized by acute inflammation of one or more dorsal root ganglia. Lancinating pain and hyperalgesia over the skin surface supplied by the affected roots occur for 3 to

4 days, followed by the appearance in the same segment of a herpetic eruption characterized by painful raised blisters on reddened bases. Pain usually subsides in a few weeks. If the inflammatory process spreads to involve related motor roots, segmental motor weakness and wasting appear. Paralysis of the oculomotor nerves may occur in conjunction with involvement of the ophthalmic division of the trigeminal ganglion (ophthalmoplegic zoster). Facial paralysis may occur with involvement of the geniculate ganglion and herpetic eruption on the ipsilateral tympanic membrane or external ear canal (Ramsay Hunt syndrome).

In fewer than 5% of patients, neuropathic pain persists in the dermatomal distribution of the affected ganglia. This pain, known as *postherpetic neuralgia*, is intense, burning, hyperpathic, and unrelenting; it often dominates the lives of those affected. Advancing age is a risk factor for this outcome. In some patients, blunting of the pain to tolerable levels is achieved by use of carbamazepine or a tricyclic antidepressant such as desipramine (Chap. 12).

Leprous Neuritis This is a major worldwide cause of neuropathy. *Mycobacterium leprae* organisms readily invade Schwann cells in cutaneous nerve twigs, particularly those associated with unmyelinated nerve fibers. *M. leprae* thrives best in the coolest tissues in the body. Two major forms of leprous neuritis are recognized, tuberculoid and lepromatous, which actually represent the ends of a spectrum of disease, the middle of which is called borderline (dimorphous) leprosy (patchy and multifocal involvement of skin and nerve). The treatment of a given case depends on where it falls in this spectrum (Chap. 170). Tuberculoid (high-resistance) leprosy consists of a single patch of hypesthetic or anesthetic skin in any location. The skin patch is frequently thickened, reddened, or hypopigmented. Few or no *M. leprae* bacilli may be demonstrated. If a superficially placed nerve trunk, typically a cutaneous nerve, courses just beneath the area of affected skin, it may be engulfed in the inflammatory reaction, resulting in an associated mononeuropathy. Such a nerve may be palpably enlarged and beaded. Lepromatous (low-resistance) leprosy is marked by immunologic tolerance, numerous bacilli, and widespread skin thickening, cutaneous anesthesia, and anhidrosis, which spare only the warmest parts of the body, notably the axilla, the groin, and beneath the scalp hair. Motor signs (focal weakness and atrophy) result from damage to mixed nerves lying close to the skin, particularly the median, ulnar, peroneal, and facial nerves.

Bell's Palsy This seventh nerve palsy is due to inflammation of the facial nerve in the facial canal, the basis for which remains obscure. Edema may play a part in causing compression of nerve fibers, with resulting acute unilateral paralysis of facial muscles (Chap. 367).

Sarcoidosis This may involve single or multiple peripheral nerves, producing asymmetric mononeuritis or polyneuritis. Unilateral or bilateral facial paralysis is described in association with parotitis and uveitis (Heerfordt's syndrome).

Polyneuritis Cranialis This is a relapsing and remitting mononeuropathy multiplex restricted to cranial nerves (Chap. 367). It is usually associated with indolent tuberculous cervical adenitis (scrofula) or sarcoidosis. Treatment of the underlying condition will halt the cranial nerve palsies.

SPECIAL NEUROPATHIC PRESENTATIONS

Some disorders selectively affect the peripheral nervous system, limiting dysfunction to specific systems or sites, such as motor nerves, brachial plexus, or the autonomic nervous system.

Autonomic Neuropathy The autonomic nervous system regulates the visceral organs and vegetative functions (Chap. 366). Many pharmacologic agents modify specific autonomic functions, but autonomic neuropathy (dysautonomia) with structural changes in pre- and postganglionic neurons can also occur. Usually autonomic neuropathy is a manifestation of a more generalized polyneuropathy also affecting somatic peripheral nervous function, as in diabetic neuropathy,GBS, and alcoholic polyneuropathy, but occasionally syndromes of pure pandysautonomia are encountered. Symptoms of dysautonomia are mainly negative (i.e., loss of function) and include postural hypotension with faintness or syncope, anhidrosis, hypothermia, bladder atony, obstipation, dry mouth and dry eyes from failure of salivary and lacrimal glands to secrete, blurring of vision from lack of pupillary and ciliary regulation, and sexual impotence in males. Positive phenomena (hyperfunction) may also occur and include episodic hypertension, diarrhea, hyperhidrosis, and either tachycardia or bradycardia. Management is symptomatic and also directed at the underlying cause, if it can be identified.

Pure Motor Neuropathy Disorder affecting any level of the motor unit -- anterior horn cell, motor axon, or neuromuscular junction -- can result in a purely lower motor syndrome without sensory disturbance. Distinguishing anterior horn cell disorders (motor neuronopathies) from motor axonopathies may be difficult clinically because they share manifestations (weakness, muscle denervation atrophy, hypo- or areflexia, fasciculations).EDXexamination may also fail to localize the primary site of the lesion (neuropathic versus neuronopathic) unless the lesion is demyelinating in nature, in which case it is by definition neuropathic.

Examples of motor neuronopathies include the lower-motor form of amyotrophic lateral sclerosis, poliomyelitis, hereditary spinal muscular atrophies, and adult variant of hexosaminidase A deficiency. Motor neuropathies may be seen with lead or dapsone intoxication, occasionally with porphyria, and also with multifocal motor neuropathy. The latter is a chronic asymmetric disorder of mid-life associated with persistent conduction block onEDXexamination, and often high titers of antiganglioside antibodies (particularly anti-GM$_1$). Neuromuscular junction disorders (e.g., Lambert-Eaton myasthenic syndrome, tick bite paralysis, other types of toxic neuromuscular blockade) are purely motor and can be recognized and localized electrodiagnostically. Some motor-sensory polyneuropathies have predominant motor symptoms and signs, such as hereditary motor-sensory neuropathies,GBS, andCIDP, but the subclinical sensory component is readily demonstrated electrodiagnostically or by quantitative sensory testing.

Pure Sensory Neuropathy Clinical presentations involving primary sensation only (Table 377-6;Chap. 23) are not uncommon. Manifestations may (1) reflect mainly large afferent fiber involvement with deficits of vibratory and proprioceptive sense, areflexia, and sensory ataxia with or without tingling dysesthesias; (2) reflect mainly small afferent fiber involvement with numbness and cutaneous hypesthesia to pin-prick and

temperature stimuli, often with painful, burning dysesthesias; or (3) be pansensory, with both large and small fiber manifestations. The pattern of distribution, although variable, is often distal and symmetric, particularly for large-fiber neuropathies.

The most severe and widespread of these pure sensory syndromes exhibit poor or no recovery, suggesting irreversible lesions of nerve cell bodies in dorsal root and trigeminal ganglia. These are referred to as *sensory neuronopathies*. With sensory neurotoxins, moderate doses lead to potentially reversible neuropathy, but high doses appear to cause irreversible neuronopathy (Table 377-6).

Plexopathy This term refers to disorders of either the brachial or the lumbosacral plexus. Lesions of the brachial plexus are characterized by motor and sensory signs different from those expected in either mononeuropathies of the upper limb or polyneuropathies. The usual causes are direct trauma to the plexus, idiopathic brachial neuritis (also called *neuralgic amyotrophy*), cervical rib or band, infiltration by malignant tumor, or prior radiation therapy. When the upper parts of the brachial plexus, arising from cervical roots 5 through 7, are affected, weakness and atrophy of shoulder girdle and upper arm muscles occur. Injuries to the lower brachial plexus, arising from the eighth cervical and first thoracic roots, produce distal arm weakness, atrophy, and focal sensory deficit in the forearm and hand. In general, idiopathic brachial neuritis, irradiation with >60 Gy (6000 rad), and particular types of trauma (arm jerked downward) result in damage to the upper portions of the brachial plexus. In contrast, infiltration by malignant tumor, cervical rib or band, and certain other types of trauma (arm jerked upward) cause damage to the lower brachial plexus. Lumbosacral plexopathies are less common; they may be due to idiopathic lumbosacral plexitis, retroperitoneal hemorrhage, or malignant tumor infiltration or may occur in association with long-standing diabetes mellitus.

Cold Effects Cold exerts direct deleterious effects on peripheral nerve, independent of ischemia. Cold injury to nerve occurs after prolonged exposure, usually of a limb, to moderately low temperatures, as with immersion of the feet in seawater; actual freezing of tissue is not required. Axonal degeneration of myelinated fibers is the pathologic expression of cold injury. Frequently, limbs affected by cold injury to nerve show sensory deficit and dysesthesias, cutaneous vasomotor instability, pain, and marked sensitivity to minimal cold exposure, which persist for many years. The pathophysiology of these phenomena is uncertain.

Trophic Changes The array of observable changes in completely denervated muscle, bone, and skin, including hair and nails, is well known, if incompletely understood. It is unclear what portion of the changes is due purely to denervation versus that caused by disuse, immobility, lack of weight bearing, and particularly recurrent, unnoticed, painless trauma. Considerable evidence favors the view that ulceration of skin, poor healing, tissue resorption, neurogenic arthropathy, and mutilation are the result of repeated unheeded injury to insensitive parts. This sequence of events is avoidable with proper attention to and care of the insensitive parts by both patient and physician.

RECOVERY FROM NEUROPATHY

In contrast to axons in the central nervous system, peripheral nerve fibers have an

excellent ability to regenerate under proper circumstances. The process of regeneration following axonal degeneration may take from 2 months to more than a year, depending on the severity of the neuropathy and the length of regeneration required. Regeneration can take place when the cause of the neuropathy has been eliminated, such as removal from contact with a neurotoxic substance or correction of an abnormal metabolic state. A deficit secondary to demyelination may recover rapidly, since intact axons may remyelinate in just a few weeks. For example, a patient with GBS, in whom demyelination but no secondary axonal degeneration has occurred, may recover to normal strength from bedfastness and paralysis of arms and legs in as little as 3 to 4 weeks.

PERIPHERAL NERVE TUMORS

These tumors are mostly benign and can arise on any nerve trunk or twig. Although peripheral nerve tumors can occur anywhere in the body, including the spinal roots and cauda equina, many are subcutaneous in location and present as a soft swelling, sometimes with a purplish discoloration of the skin. Two major categories of peripheral nerve tumors are recognized: neurilemmoma (schwannoma) and neurofibroma. Neurilemmomas are usually solitary and grow in the nerve sheath, rendering the tumor relatively easy to dissect free. In contrast, neurofibromas tend to be multiple, grow in the endoneurial substance, which renders them difficult to dissect, may undergo malignant changes, and are the hallmark of von Recklinghausen's neurofibromatosis (NF1) (Chap. 370).

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378. GUILLAIN-BARRE SYNDROME AND OTHER IMMUNE-MEDIATED NEUROPATHIES - *Arthur K. Asbury, Stephen L. Hauser*

GUILLAIN-BARRE SYNDROME

Guillain-Barre syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature. It occurs year-round at a rate of about one case per million per month, or approximately 3500 cases per year in the United States and Canada. Males and females are equally at risk, and in western countries adults are more frequently affected than children.

CLINICAL MANIFESTATIONS

GBS manifests as rapidly evolving areflexic motor paralysis with or without sensory disturbance. The usual pattern is an ascending paralysis that may be first noticed as rubbery legs. Weakness typically evolves over hours to a few days and is frequently accompanied by tingling dysesthesias in the extremities. The legs are usually more affected than the arms, and facial diparesis is present in 50% of affected individuals. The lower cranial nerves are also frequently involved, causing bulbar weakness and difficulty with handling secretions and maintaining an airway. Most patients require hospitalization, and almost 30% require ventilatory assistance at some time during the illness. Fever and constitutional symptoms are absent at the onset, and, if present, cast doubt on the diagnosis. Deep tendon reflexes usually disappear within the first few days of onset. Cutaneous sensory deficits, e.g., loss of pain and temperature sensation, are usually relatively mild; but functions subserved by large sensory fibers, such as deep tendon reflexes and proprioception, are more severely affected. Bladder dysfunction may occur in severe cases but is usually transient. If bladder dysfunction is a prominent feature and comes early in the course, possibilities other than GBS should be considered, particularly spinal cord disease. Once clinical worsening stops and the patient reaches a plateau, the crisis is usually past. Improvement may begin within days of the plateau.

Several subtypes of GBS are now recognized, as determined primarily by electrodiagnostic and pathologic distinctions (Table 378-1). In severe cases of GBS requiring critical care management, autonomic involvement is common. Usual features are loss of vasomotor control with wide fluctuation in blood pressure, postural hypotension, and cardiac dysrhythmias. These features require close monitoring and management and can be fatal. Pain is another common feature of GBS; several types are encountered. Most common is deep aching pain in weakened muscles, which patients liken to having over-exercised the previous day. Other pains in GBS include back pain involving the entire spine and sometimes dysesthetic pain in the extremities as a manifestation of sensory nerve fiber involvement. These pains are self-limited and should be treated with standard analgesics.

A range of limited or regional GBS syndromes may be encountered, although uncommonly. These include (1) the M. Fisher syndrome (Table 378-1 and see "Immunopathogenesis," below); (2) pure sensory forms; (3) ophthalmoplegia with anti-GQ1b antibodies (see "Immunopathogenesis," below), as part of severe motor-sensory GBS; (4) GBS with severe bulbar and facial paralysis, sometimes

associated with antecedent cytomegalovirus infection and anti-GM2 antibodies; and (5) acute pandysautonomia.

ANTECEDENT EVENTS

Seventy-five percent of cases of GBS are preceded 1 to 3 weeks by an acute infectious process, usually respiratory or gastrointestinal. Culture and seroepidemiologic techniques show that 20 to 30% of all cases occurring in North America, Europe, and Australia are preceded by infection or reinfection with *Campylobacter jejuni*. A similar proportion is preceded by a human herpes virus infection, often cytomegalovirus or Epstein-Barr virus. Other viruses and also Mycoplasma pneumoniae have been identified as agents involved in antecedent infections. Recent immunization has also been associated with GBS. The swine influenza vaccine, administered widely in the United States in 1976, is the most notable example; influenza vaccines in use from 1992 to 1994, however, resulted in only one additional case of GBS per million persons vaccinated. Older type rabies vaccine, prepared in nervous system tissue, is implicated as a trigger of GBS in developing countries where it is still used; the mechanism is presumably immunization against neural antigens. GBS also occurs more frequently than can be attributed to chance alone in patients with lymphoma, including Hodgkin's disease (Chap. 112), in HIV-seropositive individuals (Chap. 309), and in patients with systemic lupus erythematosus (Chap. 311).

IMMUNOPATHOGENESIS

Several lines of evidence support an autoimmune basis for acute inflammatory demyelinating polyneuropathy (AIDP), the most common and best studied type of GBS; by analogy the concept extends to all of the subtypes of GBS (Table 378-1).

It is likely that both cellular and humoral immune mechanisms contribute to tissue damage in AIDP. T cell activation is suggested by the finding that elevated levels of cytokines and cytokine receptors are present in serum [interleukin (IL)2, soluble IL-2 receptor] and in cerebrospinal fluid (CSF) [IL-6, tumor necrosis factora, interferon-g]. AIDP is also closely analogous to an experimental T cell-mediated immunopathy designated experimental allergic neuritis (EAN); EAN is induced in laboratory animals by immune sensitization against protein fragments derived from peripheral nerve proteins, and in particular against the P2 protein. Based on analogy to EAN, it was initially thought that AIDP was likely to be primarily a T cell-mediated disorder, however, abundant data now suggest that autoantibodies directed against nonprotein determinants may be central to many cases.

Circumstantial evidence suggests that all GBSresults from immune responses to nonself antigens (infectious agents, vaccines) that misdirect to host nerve tissue through a resemblance-of-epitope (molecular mimicry) mechanism (Fig. 378-1) (Chap. 307). The neural targets are likely to be glycoconjugates, specifically gangliosides (Fig. 378-2). Gangliosides are complex glycosphingolipids that contain one or more sialic acid residues; various gangliosides participate in cell-cell interactions (including those between axons and glia), modulation of receptors, and regulation of growth. They are typically exposed on the plasma membrane of cells, rendering them susceptible to an antibody-mediated attack. Gangliosides and other glycoconjugates are present in large

quantity in human nervous tissues and in key sites, such as nodes of Ranvier. Antiganglioside antibodies, most frequently to GM1, are common in GBS (20 to 50% of cases), particularly in those preceded by *C. jejuni* infection. Furthermore, isolates of *C. jejuni* from stool cultures of patients with GBS have surface glycolipid structures that antigenically cross react with gangliosides, including GM1, concentrated in human nerves. Another line of evidence is derived from experience in Europe with parenteral use of purified bovine brain gangliosides for treatment of various neuropathic disorders. Five to 15 days after injection some recipients developed acute motor axonal GBS with high titers of anti-GM1 antibodies that recognized epitopes at nodes of Ranvier and motor endplates.

Particularly noteworthy is the M. Fisher syndrome (MFS), which presents as rapidly evolving ataxia and areflexia of limbs without weakness, and ophthalmoplegia often with pupillary paralysis. The MFS variant accounts for ~5% of all GBS cases. Anti-GQ1b antibodies are found in >90% of patients with MFS (Table 378-1; Fig. 378-2), and titers of IgM and IgG are highest early in the course. Anti-GQ1b antibodies are not found in other forms of GBS unless there is extraocular motor nerve involvement. Of note, extraocular motor nerves are enriched in GQ1b gangliosides in comparison to limb nerves. Further, a monoclonal anti-GQ1b antibody raised against *C. jejuni* isolated from a patient with MFS blocked neuromuscular transmission experimentally.

Taken together, these observations provide strong but still inconclusive evidence that anti-ganglioside antibodies play an important pathogenic role in GBS. Definitive proof requires the passive transfer of GBS with specific antibodies; this procedure has not yet been accomplished, although a single case of apparent maternal-fetal transplacental transfer of GBS has been described.

PATHOPHYSIOLOGY

In the demyelinating forms of GBS, the basis for flaccid paralysis and sensory disturbance is conduction block. This finding, demonstrable electrophysiologically, implies that the axonal connections remain intact. Hence, recovery can take place rapidly as remyelination occurs. In severe cases of demyelinating GBS, secondary axonal degeneration usually occurs; its extent can be estimated electrophysiologically. More secondary axonal degeneration correlates with a slower rate of recovery and a greater degree of residual disability. When a primary axonal pattern is encountered electrophysiologically, the implication is that axons have degenerated and become disconnected from their targets, specifically the neuromuscular junctions, and must therefore regenerate for recovery to take place. In motor axonal cases in which recovery is rapid, the lesion is thought to be localized to preterminal motor branches, allowing regeneration and reinnervation to take place quickly.

LABORATORY FEATURES

CSF findings are distinctive, consisting of an elevated CSF protein level (100 to 1000 mg/dL) without accompanying pleocytosis. The CSF is often normal when symptoms have been present for £48 h; by the end of the first week the level of protein is usually elevated. An increased white cell count in the CSF (10 to 100/uL) in otherwise typical GBS raises the possibility of unrecognized HIV infection (Chap. 309). Electrodiagnostic

features are mild or absent in the early stages and lag behind the clinical evolution. In cases with demyelination (Table 378-1) prolonged distal latencies, conduction velocity slowing, evidence of conduction block, and temporal dispersion of compound action potential are the usual features. In cases with primary axonal pathology, the principal electrodiagnostic finding is reduced amplitude of compound action potentials without conduction slowing or prolongation of distal latencies.

DIAGNOSIS

GBSis a descriptive entity. The diagnosis is made by recognizing the pattern of rapidly evolving paralysis with areflexia, absence of fever or other systemic symptoms, and characteristic antecedent events (Table 378-2). In the early phases, laboratory tests are helpful only to exclude other disorders that can resemble GBS. Electrodiagnostic features may be minimal, and theCSFprotein level may not rise until the end of the first week. If the diagnosis is strongly suspected, treatment should be initiated without waiting for evolution of the characteristic electrodiagnostic and CSF findings to occur. GBS patients with risk factors for HIV or with CSF pleocytosis should have a serologic test for HIV.

TREATMENT

Treatment should be initiated as soon after diagnosis as possible. Each day counts; ~2 weeks after the first motor symptoms, immunotherapy is no longer effective. Either high-dose intravenous immune globulin (IVIg) or plasmapheresis can be initiated, as they are equally effective (Table 378-3). A combination of the two therapies is not significantly better than either alone. IVIg is usually administered as five daily infusions for a total dose of 2 g/kg body weight. A course of plasmapheresis, consisting of ~40 to 50 mL/kg plasma exchange (PE) daily for 4 to 5 days, is usually employed. In patients who are treated early in the course of GBSand improve, relapse may occur in the second or third week. Brief treatment with the original therapy is usually effective. Glucocorticoids have not been found to be effective in GBS.

In the worsening phase of GBS, most patients require monitoring in a critical care setting, with particular attention to vital capacity, cardiovascular status, and chest physiotherapy. As noted, ~30% of patients with GBS require ventilatory assistance, sometimes for prolonged periods of time (several weeks or longer). Frequent turning and assiduous skin care are important, as are daily range-of-motion exercises to avoid joint contractures.

PROGNOSIS AND RECOVERY

Approximately 85% of patients withGBSachieve a full functional recovery within several months to a year, although minor findings on examination (such as areflexia) may persist. The mortality rate is <5% in optimal settings; death usually results from secondary pulmonary complications. The outlook is worst in patients with severe proximal motor and sensory axonal damage. Such axonal damage may be either primary or secondary in nature (see "Pathophysiology," above), but in either case successful regeneration cannot occur. Other factors that worsen the outlook for recovery are advanced age, a fulminant or severe attack, and a delay in the onset of

treatment.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Chronic inflammatory demyelinating polyneuropathy (CIDP) is distinguished fromGBS by its chronic course. In other respects, this neuropathy shares many features with GBS, including elevatedCSFprotein levels and the electrodiagnostic findings of acquired demyelination. Most cases occur in adults, and males are affected slightly more often than females. The incidence of CIDP is lower than that of GBS, but due to the protracted course the prevalence is greater.

CLINICAL MANIFESTATIONS

Onset is usually gradual, sometimes subacute; and, in a few, the initial attack is indistinguishable from that ofGBS. Symptoms are both motor and sensory in most cases. Weakness of the limbs is usually symmetric but can be strikingly asymmetric. There is considerable variability from case to case. Some patients have a chronic progressive course, whereas others, usually younger patients, have a relapsing and remitting course. Some have only motor findings, and a small proportion present with a relatively pure syndrome of sensory ataxia. Tremor occurs in ~10% and may become more prominent during periods of subacute worsening or improvement. A small proportion have cranial nerve findings, including external ophthalmoplegia.CIDPtends to ameliorate over time with treatment; the result is that many years after onset nearly 75% of patients have a reasonable functional recovery with only modest degrees of disability. Death from CIDP is uncommon.

DIAGNOSIS

The diagnosis rests on characteristic clinical,CSF, and electrophysiologic findings. The CSF is usually acellular with an elevated protein level, sometimes several times normal. Electrodiagnostically, variable degrees of conduction slowing, prolonged distal latencies, temporal dispersion of compound action potentials, and conduction block are the principal features. In particular, the presence of conduction block is a certain sign of an acquired demyelinating process. Evidence of axonal loss, presumably secondary to demyelination, is present in >50% of patients. In all patients withCIDP, serum protein electrophoresis with immunofixation is indicated to screen for monoclonal gammopathy and associated conditions (see "Monoclonal Gammopathy of Undetermined Significance," below).

PATHOGENESIS

Although there is evidence of immune activation inCIDP, the precise mechanisms of pathogenesis are unknown. Biopsy typically reveals little inflammation and onion-bulb thickening of nerves resulting from recurrent demyelination and remyelination. The response to therapy suggests that CIDP is immune-mediated; interestingly, CIDP responds to glucocorticoids (see below), whereasGBS does not. Approximately 25% of patients with clinical features of CIDP also have a monoclonal gammopathy of undetermined significance (MGUS). Cases associated with monoclonal IgA or IgG usually respond to treatment as favorably as cases without a monoclonal gammopathy.

Patients with IgM monoclonal gammopathy tend to have more sensory findings, a more protracted course and may have a less satisfactory response to treatment, although this is an area of controversy.

TREATMENT

Most authorities initiate treatment for CIDP when progression is rapid or walking is compromised. If the disorder is mild, management can be expectant, awaiting spontaneous remission. Controlled studies have shown that high dose IVIg, PE, and glucocorticoids are all more effective than placebo. Initial therapy is usually either IVIg or PE, which appear to be equally effective. IVIg is administered as 0.4 g/kg body weight daily for 5 days; most patients require periodic retreatment at approximately 6-week intervals. PE is initiated at 2 to 3 treatments per week for 6 weeks; periodic retreatment may also be required. Treatment with oral glucocorticoids is another option (60 to 80 mg prednisone daily for 1 to 2 months, followed by a gradual dose reduction of 10 mg per month as tolerated), but long-term adverse effects including bone demineralization, gastrointestinal bleeding, and cushingoid changes are problematic. Approximately one-half of patients with CIDP fail to adequately respond to the initial therapy chosen; a different treatment should then be tried. Patients who fail therapy with IVIg, PE, and glucocorticoids may benefit from treatment with immunosuppressive agents such as azathiaprine, methotrexate, cyclosporine, and cyclophosphamide, either alone or as adjunctive therapy. Use of these therapies requires periodic reassessment of their risks and benefits.

MULTIFOCAL MOTOR NEUROPATHY

Multifocal motor neuropathy (MMN) is a distinctive but uncommon neuropathy that presents as a slowly progressive motor weakness and atrophy evolving over years in the distribution of selected nerve trunks, associated with sites of persistent focal motor conduction block in the same nerve trunks. Sensory fibers are relatively spared. The arms are affected more frequently than the legs, and>75% of all patients are male. Some cases have been confused with lower motor neuron forms of amyotrophic lateral sclerosis (Chap. 365). Approximately 50% of patients present with high titers of polyclonal IgM antibody to the ganglioside GM1. It is uncertain how this finding relates to the discrete foci of persistent motor conduction block, but high concentrations of GM1 gangliosides are normal constituents of nodes of Ranvier in peripheral nerve fibers. Pathology reveals demyelination and mild inflammatory changes at the sites of conduction block.

Most patients with MMN respond to high-dose IVIg (dosages as for CIDP, above) and some refractory patients have responded to cyclophosphamide. Glucocorticoids and PE are not effective.

NEUROPATHIES WITH MONOCLONAL GAMMOPATHY

MULTIPLE MYELOMA

Clinically overt polyneuropathy occurs in ~5% of patients with the commonly encountered type of multiple myeloma, which exhibits either lytic or diffuse osteoporotic

bone lesions. These neuropathies are sensorimotor, are usually mild but may be severe, and generally do not reverse with successful suppression of the myeloma. In most cases, electrodiagnostic and pathologic features are consistent with a process of axonal degeneration.

In contrast, myeloma with osteosclerotic features, although representing only 3% of all myelomas, is associated with polyneuropathy in one-half of cases. These neuropathies, which may also occur with solitary plasmacytoma, are distinct because they (1) are usually demyelinating in nature, (2) often respond to radiation therapy or removal of the primary lesion, (3) are associated with different monoclonal proteins and light chains (almost always lambda as opposed to primarily kappa in the lytic type of multiple myeloma), and (4) may occur in association with other systemic findings including thickening of the skin, hyperpigmentation, hypertrichosis, organomegaly, endocrinopathy, anasarca and clubbing of fingers. These are features of the POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, M protein, and *s*kin changes). The pathogenesis of this uncommon syndrome and the explanation for its association with lambda light chains are unknown.

Neuropathies are also encountered in other systemic conditions with gammopathy including Waldenstrom's macroglobulinemia, primary systemic amyloidosis, and cryoglobulinemic states (mixed essential cryoglobulinemia, some cases of hepatitis C).

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Chronic polyneuropathies occurring in association with MGUS are usually associated with the immunoglobulin isotypes IgG, IgA, and IgM. From a clinical standpoint, many of these patients are indistinguishable from patients with CIDP without monoclonal gammopathy (see Chronic Inflammatory Demyelinating Polyneuropathy, above), and their response to immunosuppressive agents is also similar. An exception is the syndrome of IgM kappa monoclonal gammopathy associated with an indolent, longstanding, sometimes static sensory neuropathy, frequently with tremor and sensory ataxia. Most patients are male and over age 50. In the majority, the monoclonal IgM immunoglobulin binds to a normal peripheral nerve constituent, myelin-associated glycoprotein (MAG), found in the paranodal regions of Schwann cells. Binding appears to be specific for a polysaccharide epitope that is also found in other normal peripheral nerve myelin glycoproteins, P0 and PMP22, and also in other normal nerve-related glycosphingolipids (Fig. 378-1). In the MAG-positive cases, IgM paraprotein is incorporated into the myelin sheaths of affected patients and widens the spacing of the myelin lamellae, thus producing a distinctive ultrastructural pattern. Demyelination and remyelination are the hallmarks of the lesions. The chronic demyelinating neuropathy appears to result from a destabilization of myelin metabolism rather than activation of an immune response. Therapy with chlorambucil or cyclophosphamide often results in improvement of the neuropathy associated with a prolonged reduction in the levels in the circulating paraprotein; chronic use of these alkylating agents is associated with significant risks (Chap. 84). In a small proportion of patients, MGUS will in time evolve into frankly malignant conditions, such as multiple myeloma (Chap. 113) or lymphoma (Chap. 112).

VASCULITIC NEUROPATHY

Peripheral nerve involvement is common in polyarteritis nodosa (PAN), appearing in half of all cases clinically and in 100% of cases at postmortem studies (Chap. 317). The most common pattern is multifocal (asymmetric) motor-sensory neuropathy (mononeuropathy multiplex) due to ischemic lesions of nerve trunks and roots; however, some cases of vasculitic neuropathy present as a distal, symmetric motor-sensory neuropathy. Symptoms of neuropathy are a common presenting complaint in patients with PAN. The electrodiagnostic findings are those of an axonal process. Small- to medium-sized arteries of the vasa nervorum, particularly the epineural vessels, are affected in PAN, resulting in a widespread ischemic neuropathy. A high frequency of neuropathy is also present in allergic angiitis and granulomatosis (Churg-Strauss syndrome).

Systemic vasculitis should always be considered when a subacute or chronically evolving mononeuropathy multiplex occurs in conjunction with constitutional symptoms (fever, anorexia, weight loss, loss of energy, malaise and nonspecific pains). Diagnosis of suspected vasculitic neuropathy is made by a combined nerve and muscle biopsy, with serial section or skip-serial techniques (Chap. 377).

Approximately one-third of biopsy-proven cases of vasculitic neuropathy are "nonsystemic" in that the vasculitis appears to affect only peripheral nerve. Constitutional symptoms are absent, and the course is more indolent than that of PAN. The erythrocyte sedimentation rate may be elevated, but other tests for systemic disease are negative. Nevertheless, clinically silent involvement of other organs is likely, and vasculitis is frequently found in muscle biopsied at the same time as nerve.

Vasculitic neuropathy may also be seen as part of the vasculitis syndrome occurring in the course of other connective tissue disorders. The most frequent is rheumatoid arthritis, but ischemic neuropathy due to involvement of vasa nervorum may also occur in mixed cryoglobulinemia, Sjogren's syndrome, Wegener's granulomatosis, hypersensitivity angiitis (Chap. 317), and progressive systemic sclerosis (Chap. 313). Management of these neuropathies including the "nonsystemic" vasculitic neuropathy consists of treatment of the underlying condition as well as the aggressive use of glucocorticoids and other immunosuppressant drugs, usually cyclophosphamide.

ANTI-HU PARANEOPLASTIC NEUROPATHY

This uncommon immune-mediated disorder manifests as a sensory neuronopathy, i.e., selective damage to dorsal root ganglia. The onset is often asymmetric with dysesthesias and sensory loss in the limbs that soon progress to affect all limbs, the torso, and face. Marked sensory ataxia, pseudoathetosis, and inability to walk, stand, or even sit unsupported are frequent features and are secondary to the extensive deafferentation. Subacute sensory neuronopathy is often idiopathic, but ~25% of cases are paraneoplastic, primarily related to lung cancer, and most of those are small cell lung cancer (SCLC) (Chap. 101). The gene *HuD*, ordinarily expressed only in neurons, is expressed in SCLC cells; the gene product functions as an RNA binding protein. Host anti-Hu antibodies to this tumor gene product cross-react with the same epitope expressed in dorsal root ganglion neurons, which results in immune-mediated neuronal destruction. An encephalomyelitis may accompany the sensory neuronopathy and

presumably has the same pathogenesis. Neurologic symptoms usually precede, by 1 year on average, the identification of SCLC. The sensory neuronopathy runs its course in a few weeks or months and stabilizes, leaving the patient disabled. Most cases are unresponsive to treatment with glucocorticoids,IVIg,PE, or immunosuppressant drugs.

(Bibliography omitted in Palm version)

379. CHARCOT-MARIE-TOOTH DISEASE AND OTHER INHERITED NEUROPATHIES - *Phillip F. Chance, Thomas D. Bird*

CHARCOT-MARIE-TOOTH DISEASE

GENERAL CLINICAL FEATURES

Charcot-Marie-Tooth (CMT) neuropathy comprises a heterogeneous group of inherited peripheral nerve diseases (Table 379-1). Transmission is most frequently autosomal dominant but may also be autosomal recessive or X-linked. An estimated 1 in 2500 persons has a form of CMT, making it one of the most frequently encountered inherited neurologic syndromes.

The neuropathy of CMT affects both motor and sensory nerves. Typical features consist of distal muscle weakness and atrophy, impaired sensation, and absent or hypoactive deep tendon reflexes. Common signs and symptoms are related to muscle loss and weakness, initially involving the feet and legs and later progressing to the hands and forearms. A history of an abnormal high-stepped (steppage) gait with frequent tripping and falling is frequently elicited. Complaints related to foot deformity (pes cavus, or high-arched feet) result from loss of intrinsic muscles of the feet. Despite the involvement of sensory nerves in CMT, complaints of limb pain or sensory disturbances are unusual.

Onset is most often during the first or second decade of life, although presentation in mid-adult life is not unusual. The variation in clinical presentation is exceptionally wide, ranging from individuals whose only clinical finding is pes cavus and minimal or no distal muscle weakness to those with severe distal atrophy and marked hand and foot deformity. However, it is unusual for patients with CMT to lose ambulation. There are no therapies that can prevent the onset or delay progression of disability associated with CMT. Patients frequently benefit from physical therapy, use of ankle-foot orthroses (AFOs) to alleviate foot drop, and, in some cases, surgical procedures to the foot. Surgery should be undertaken only when pain or difficulty walking due to severe foot deformity cannot be managed by more conservative means.

CLASSIFICATION BY PHENOTYPE

A widely accepted classification system distinguishes demyelinating forms of CMT (also designated as CMT type 1, or CMT1) from those due to axonal degeneration (CMT type 2, or CMT2). Individuals with CMT1 have electrophysiologic findings of reduced motor and sensory nerve conduction velocities (NCVs; typically<38 to 40 m/s) and pathologic findings of hypertrophic demyelinating neuropathy ("onion bulbs"). By contrast, in CMT2 there is relative preservation of the myelin sheath and these individuals have normal or near-normal NCVs. CMT3 refers to Dejerine-Sottas disease (DSD; see below), CMT4 to autosomal recessive forms of CMT, and CMTX to X-linked varieties.

An alternative classification system designates these disorders as hereditary motor and sensory neuropathies (HMSN); HMSNI refers to CMT1, HMSNII to CMT2, HMSNIII to DSD, and HMSNIV to Refsum disease (see below).

Approach to the Patient

A clinical diagnosis of an inherited peripheral neuropathy consistent with a form of CMT (CMT1 or CMT2) should be established prior to undertaking specific genetic tests. Other causes of peripheral neuropathy (e.g., diabetes mellitus, alcoholism, heavy metal poisoning, immune neuropathies) should also be considered and, if necessary, ruled out. An environmental exposure may affect multiple family members, thereby potentially mimicking a hereditary illness. CMT is usually a chronic, slowly progressive condition. One should be suspicious of cases that seem to have a rapid course of deterioration. As noted above, the neurologic findings show great variability in patients with CMT; mild pes cavus and depressed deep tendon reflexes may be the only signs of disease.

Although symptoms related to sensory disturbances are uncommon in CMT, a careful sensory examination is nonetheless essential. In patients who have no objective signs of sensory impairment and no evidence of sensory nerve dysfunction on electrophysiologic studies, alternative diagnoses including primary motor system disorders (e.g., distal spinal muscle atrophy, juvenile amyotrophic lateral sclerosis) should be considered.

The pedigree is of paramount importance in the diagnosis of CMT. Examination of multiple family members, particularly parents, for subtle signs of neuropathy may help to establish a diagnosis. If possible, it is also important to obtain NCVs and an electromyogram (EMG) from all at-risk family members.

GENETIC CONSIDERATIONS

CMT Neuropathy Type 1A (CMT1A) The overwhelming majority of autosomal dominant CMT1 pedigrees demonstrate linkage to chromosome 17p11.2-12 (CMT1A) and are most frequently associated with a tandem 1.5-megabase (Mb) DNA duplication in this chromosomal region. The DNA duplication is usually inherited as a stable Mendelian trait; however, it may also arise as a de novo event. The de novo duplication is responsible for most sporadic cases of CMT1 and may also account for some cases of CMT1 previously thought to occur on the basis of an autosomal recessive mode of inheritance. When present as a de novo event, the duplication results more commonly from an error in spermatogenesis; however, ~10% of de novo cases have been found to result from an error in oogenesis.

The critical gene for CMT1A is peripheral myelin protein-22 (PMP22), which is expressed in Schwann cells. The *PMP22* gene encodes a 160-amino-acid protein localized to the compact portion of peripheral nerve myelin; it contains four putative transmembrane domains and is highly conserved in evolution. The level of expression of PMP22 is crucial for proper myelination of peripheral nerves. The neuropathy in patients with the 17p11.2-12 duplication results from the presence of three copies of PMP22 leading to increased expression at this locus. In rare cases, patients homozygous for the CMT1A duplication have been identified, and in some cases these individuals exhibit a more severe phenotype than their heterozygous siblings or parents. As discussed below, monosomic underexpression of PMP22 results in hereditary neuropathy with liability to pressure palsies (HNPP).

Rare CMT1 pedigrees that are linked to chromosome 17p11.2-12 yet lack the DNA duplication may harbor missense mutations within the *PMP22* gene.

Approximately three-quarters of patients with a clinical diagnosis of CMT1 carry the 17p11.2-12 duplication. DNA testing for CMT1A (including the associated chromosome 17 duplication and sequencing to detect point mutations in PMP22) has become available and is now an accepted part of the evaluation of many patients with suspected hereditary neuropathies (see below).

CMT Neuropathy Type 1B (CMT1B) CMT1B is much less common than CMT1A; it results from mutations in the human myelin protein zero gene (*MPZ*, or P_0), which maps to chromosome 1q22-q23. P_0 is the major structural protein component of peripheral nervous system myelin (quantitatively 50% by weight) and represents ~10% of total Schwann cell mRNA. P_0 is a member of the immunoglobulin gene superfamily of cell adhesive molecules and localizes to the compact portion of peripheral nerve myelin. P_0 protein consists of 248 amino acids and contains an intracellular and a glycosylated extracellular domain with a single transmembrane segment. Many different point mutations in the P_0 gene have been found in patients with CMT1B, and these mutations predominately map to the extracellular domain of its gene product.

At the clinical level it is not possible to differentiate patients with CMT1A from those with CMT1B. Molecular genetic testing is available.

Dejerine-Sottas Disease DSD (also called *HMSN III*) is a severe, infantile or childhood onset, hypertrophic demyelinating polyneuropathy. NCVs are greatly prolonged (typically <10 m/s), and elevations in the cerebrospinal fluid (CSF) protein level are typically present. The clinical features of DSD overlap those of severe CMT1, and for this reason, the continued clinical separation of CMT1 and DSD is perhaps unwarranted. Many cases of DSD appear to be sporadic, occuring in the absence of a family history of neuropathy.

Molecular genetic studies indicate that DSD may be associated with point mutations in the P_0 or the *PMP22* genes, although pedigrees have been described that lack mutations in either the P_0, *PMP22*, or *Cx32* gene (see below). All DSD mutations identified to date appear to function as dominant genetic traits. Recently, a point mutation in the P_0 gene has been proposed as a mechanism for congenital hypomyelinating neuropathy (CHN), likely an even more severe form of DSD.

Hereditary Neuropathy with Liability to Pressure Palsies HNPP (also called *tomaculous neuropathy*) is an autosomal dominant disorder that produces an episodic, recurrent demyelinating neuropathy. HNPP typically develops during adolescence and may cause attacks of numbness, muscular weakness, and atrophy. Peroneal palsies, carpal tunnel syndrome, and other entrapment neuropathies are manifestations of HNPP. Motor and sensory NCVs are mildly reduced in affected patients as well as in asymptomatic gene carriers. Pathologic changes observed in HNPP include segmental demyelination and tomaculous, or sausage-like, formations in peripheral nerves. Because of mild overlap of clinical features with CMT1, HNPP patients may on occasion be misdiagnosed as having CMT1.

The HNPP locus maps to chromosome 17p11.2-12 and is associated with a 1.5-Mb deletion. The duplicated CMT1A chromosome (described earlier) and the deleted HNPP chromosome are the reciprocal products of unequal crossing-over during meiosis. In the case of HNPP, loss of a copy of the *PMP22* gene and underexpression of this critical myelin gene lead to demyelination. Most HNPP patients have the associated chromosome 17 deletion; however, rare patients with HNPP have been found to have point mutations in the *PMP22* gene. Molecular genetic testing is clinically available.

Treatment for HNPP is largely supportive. Surgical decompression of nerves has been proposed but is controversial. There is some evidence that surgical repair of carpal tunnel syndrome in HNPP is of little benefit and that transposition of the ulnar nerve at the elbow may produce poor results because the nerves are especially sensitive to manipulation and minor trauma.

CMT Neuropathy Type 2 CMT2 is less common than CMT1, and less progress has been made towards its molecular understanding. In general, CMT2 has a later age of onset, produces less involvement of the intrinsic muscles of the hands, and lacks palpably enlarged nerves. Extensive demyelination with "onion bulb" formation is not present in CMT2. Motor NCVs are normal or only slightly reduced in affected persons. A CMT2 locus was assigned by linkage studies to the short arm of chromosome 1 (1p35-36) and designated as CMT2A. One CMT2 pedigree was found to demonstrate linkage to markers from chromosome 3q13-q22 and has been designated CMT2B. Further genetic heterogeneity within CMT2 is likely as kindreds with the features of axonal neuropathy, weakness of the diaphragm, and vocal cord paralysis have been described and are designated as having CMT2C. Another form of CMT2, designated CMT2D, has been mapped to chromosome 7p14. More recently, in a large Russian pedigree a CMT2 gene was mapped to chromosome 8p21 (designated CMT2E) and a mutation was found in the neurofilament-light gene. Additionally, certain P_0 or connexin32 (Cx32, see below) mutations have been found to be the underlying genetic defect in a subset of patients with CMT1 or CMTX who were initially thought to have CMT2 because of only mild slowing of NCVs. DNA testing is not available for CMT2.

X-linked CMT Neuropathy The clinical features of X-linked CMT disease (CMTX) include demyelinating neuropathy, absence of male-to-male transmission, and an earlier age of onset and faster rate of progression in males. NCVs vary widely in CMTX from nearly normal to moderately slowed. CMTX accounts for ~10% of all patients thought to have a form of demyelinating CMT (i.e., CMT1). CMTX should be suspected when the commonly associated chromosome 17 duplication is not present and there is no history of father-to-son transmission of the neuropathy.

The gene for CMTX maps to chromosome Xq13-21 and results from point mutations in the connexin32 (*Cx32*) gene. Connexin32 encodes a major component of gap junctions and is expressed in peripheral nerves. Cx32 is structurally similar to PMP22, as both of these proteins contain four putative transmembrane domains in similar orientation. Over 200 different mutations in the *Cx32* gene have been described in patients with CMTX, and the distribution pattern of these mutations suggests that all parts of the connexin32 protein are functionally important. DNA testing is clinically available for Cx32 mutations causing CMTX.

Cx32 has a pattern of expression in peripheral nerve similar to that of other myelin protein genes; however, immunohistochemical studies show a different localization. Unlike PMP22 and P$_0$, which are present in compact myelin, Cx32 is located at uncompacted folds of Schwann cell cytoplasm around the nodes of Ranvier and at Schmidt-Lanterman incisures. This localization suggests a role for gap junctions composed of Cx32 in providing a pathway for the transfer of ions and nutrients around and across the myelin sheath. Mutations in the Cx32 protein have been suggested to alter its cellular localization and its trafficking and interfere with cell-to-cell communication.

CMT Variants Mutations in the putative zinc finger domain of the early growth response 2 gene (*EGR2*, or *Krox-20*) have been implicated as the underlying defect in CMT1 families that were found to be negative for the CMT1A duplication, as well as for mutations in either PMP22, P$_0$, or Cx32. Studies have shown that EGR2 acts as a direct transactivator of myelination genes in differentiating Schwann cells. EGR2 mutations have also been reported in a family with CHN.

Rare families with autosomal recessive motor and sensory neuropathy have been reported, particularly Tunisian families with parental consanguinity. Both demyelinating and axonal types of neuropathy have been described and given the designation CMT4. One form of autosomal recessive demyelinating neuropathy has been mapped to chromosome 8q13-q21 (CMT4A). Another form of CMT, characterized by focally folded myelin sheaths (CMT4B), has been mapped to chromosome 11q23 and recently shown to be caused by mutations in MTMR2, a gene encoding myotubularin-related protein-2, which is thought to be a transcriptional regulator. An additional pedigree with phenotypic features of CMT4B did not show linkage to chromosome 11 or to any other known CMT loci, implicating further genetic heterogeneity. Currently, DNA testing is not clinically available for any form of CMT4 or for mutations in EGR2.

Genetic Evaluation of CMT and HNPP An approach for evaluating an individual patient suspected of having an inherited peripheral neuropathy is presented in Fig. 379-1. If a proband has evidence for CMT1, determination of NCVs is a useful screening tool for parents and other at-risk family members. The *CMT1* gene is penetrant in early life, and correct disease status can probably be determined with nerve conduction screening by age 5. However, if a proband's nerve conduction is normal or only mildly prolonged, the diagnosis may be CMT2. In this case the screening examination will need to focus on determination of motor unit amplitudes and other electrical signs of denervation. Rare patients have been found to have point mutations in either P$_0$ or Cx32 resulting in very mild demyelination and misclassification as CMT2.

The overwhelming proportion of CMT1 and CMT2 pedigrees have autosomal dominant inheritance. In pedigrees lacking male-to-male inheritance and/or those in which males are more severely affected than females and have an earlier onset, CMTX should be suspected. Determination of autosomal dominant versus X-linked CMT is important as the genetic counseling for these two modes of inheritance is different. For any form of autosomal dominant CMT, the likelihood of an affected parent (of either sex) having an affected child is 50% for each pregnancy, regardless of the sex of the child. For CMTX, all daughters of an affected father will inherit the gene, and none of the sons will be

affected. For a woman with CMTX, there is a 50% likelihood that her children will be affected regardless of their sex.

Sporadic cases in males can be especially difficult to evaluate, as the neuropathy could be nongenetic or the pattern of inheritance could be autosomal dominant, X-linked, or even autosomal recessive. Sporadic cases may also represent de novo duplications (CMT1A) or de novo deletions (HNPP). False paternity is another explanation for apparent sporadic CMT or HNPP.

Molecular genetic testing is currently available for the DNA duplication (or deletion) associated withCMT1A orHNPP and for point mutations in the *PMP22*, *P0*or *Cx32* genes associated with other forms of CMT1 and CMTX.

CHEMOTHERAPY IN PATIENTS WITH CMT

Chemotherapeutic agents known to affect peripheral nerves should be used with great caution in patients with inherited neuropathies, and in the case of vincristine, total avoidance is strongly advised. A number of reports have documented the serious consequences of vincristine treatment administered in standard oncologic dosages in patients withCMT, including well-documented CMT1A and CMT2. The complications ranged from the precipitation of severe neuropathies in clinically asymptomatic at-risk individuals, through degrees of marked clinical worsening, and even death due to respiratory collapse.

OTHER INHERITED NEUROPATHIES

HEREDITARY SENSORY NEUROPATHIES

Hereditary sensory neuropathies (HSN) are a heterogeneous group of disorders affecting sensory neurons. The most common form of HSN, HSN type I, is an autosomal degenerative disorder of sensory and motor neurons. Phenotypically, distal sensory loss, distal muscle wasting and weakness, and variable neural deafness are observed. The disease involves progressive loss of dorsal root ganglion cells and axons in peripheral nerves. Age of onset is the second decade of life or later. The HSN-I locus maps to chromosome 9q22.1-q22.3. Because of the presence of muscular weakness in some patients with HSN, this disorder may be clinically confused withCMT.

FAMILIAL AMYLOID NEUROPATHY

Familial amyloid polyneuropathy (FAP) is an autosomal dominant disorder that classically presents as progressive sensory peripheral neuropathy, with early involvement of the autonomic nervous system and an associated cardiomyopathy. Postmortem studies have shown extensive amyloid deposition in multiple organs throughout the body. Transthyretin (TTR) is the most common constituent amyloid fibril protein deposited in FAP. Several different point mutations in the TTR gene have been described in TTR-related FAP, and DNA testing for these mutations is clinically available. *Amyloidosis is discussed in Chap. 319.*

REFSUM DISEASE

This autosomal recessive disorder is characterized by a progressive sensorimotor demyelinating polyneuropathy, associated with cerebellar ataxia and retinitis pigmentosa. Neural deafness, cardiomyopathy, cataracts, and icthyosis are additional features. Onset is in late childhood or early adulthood. Patients often complain of night blindness as the earliest symptom. The CSF protein is typically elevated. Diagnosis is made by demonstration of elevated levels of phytanic acid (a 20-carbon branched-chain fatty acid) in the serum and urine. The disorder appears to be due to a deficiency of a peroxysomal enzyme, phytanic acid oxidase, responsible for alpha oxidation of phytanic acid. Therapy, consisting of avoidance of dietary sources of phytanic acid, and plasmapheresis in some cases, is partially effective.

(Bibliography omitted in Palm version)

Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is a decrease in the number of available acetylcholine receptors (AChRs) at neuromuscular junctions due to an antibody-mediated autoimmune attack. Treatment now available for MG is highly effective, although a specific cure has remained elusive.

PATHOPHYSIOLOGY

In the neuromuscular junction (Fig. 380-1), acetylcholine (ACh) is synthesized in the motor nerve terminal and stored in vesicles (quanta). When an action potential travels down a motor nerve and reaches the nerve terminal, ACh from 150 to 200 vesicles is released and combines with AChRs that are densely packed at the peaks of postsynaptic folds. The structure of the AChR has been fully elucidated; it consists of five subunits (2a, b,d, and g ore) arranged around a central pore. When ACh combines with the binding sites on the AChR, the channels in the AChRs open, permitting the rapid entry of cations, chiefly sodium, which produces depolarization at the end-plate region of the muscle fiber. If the depolarization is sufficiently large, it initiates an action potential that is propagated along the muscle fiber, triggering muscle contraction. This process is rapidly terminated by hydrolysis of ACh by acetylcholinesterase (AChE) and by diffusion of ACh away from the receptor.

In MG, the fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane. In addition, the postsynaptic folds are flattened, or "simplified." These changes result in decreased efficiency of neuromuscular transmission. Therefore, although ACh is released normally, it produces small end-plate potentials that may fail to trigger muscle action potentials. Failure of transmission at many neuromuscular junctions results in weakness of muscle contraction.

The amount of ACh released per impulse *normally* declines on repeated activity (termed *presynaptic rundown*). In the myasthenic patient, the decreased efficiency of neuromuscular transmission combined with the normal rundown results in the activation of fewer and fewer muscle fibers by successive nerve impulses and hence increasing weakness, or *myasthenic fatigue*. This mechanism also accounts for the decremental response to repetitive nerve stimulation seen on electrodiagnostic testing.

The neuromuscular abnormalities in MG are brought about by an autoimmune response mediated by specific anti-AChR antibodies. The anti-AChR antibodies reduce the number of available AChRs at neuromuscular junctions by three distinct mechanisms: (1) accelerated turnover of AChRs by a mechanism involving cross-linking and rapid endocytosis of the receptors; (2) blockade of the active site of the AChR, i.e., the site that normally binds ACh; and (3) damage to the postsynaptic muscle membrane by the antibody in collaboration with complement. The pathogenic antibodies are IgG and are T cell dependent. Thus, immunotherapeutic strategies directed against T cells are effective in this antibody-mediated disease.

How the autoimmune response is initiated and maintained in MG is not completely

understood. However, the thymus appears to play a role in this process. The thymus is abnormal in ~75% of patients with MG; in about 65% the thymus is "hyperplastic," with the presence of active germinal centers, while 10% of patients have thymic tumors (thymomas). Muscle-like cells within the thymus (myoid cells), which bear AChRs on their surface, may serve as a source of autoantigen and trigger the autoimmune reaction within the thymus gland.

CLINICAL FEATURES

MG is not rare, having a prevalence of at least 1 in 7500. It affects individuals in all age groups, but peaks of incidence occur in women in their twenties and thirties and in men in their fifties and sixties. Overall, women are affected more frequently than men, in a ratio of approximately 3:2. The cardinal features are *weakness* and *fatigability* of muscles. The weakness increases during repeated use (fatigue) and may improve following rest or sleep. The course of MG is often variable. Exacerbations and remissions may occur, particularly during the first few years after the onset of the disease. Remissions are rarely complete or permanent. Unrelated infections or systemic disorders often lead to increased myasthenic weakness and may precipitate "crisis" (see below).

The distribution of muscle weakness has a characteristic pattern. The cranial muscles, particularly the lids and extraocular muscles, are often involved early, and diplopia and ptosis are common initial complaints. Facial weakness produces a "snarling" expression when the patient attempts to smile. Weakness in chewing is most noticeable after prolonged effort, as in chewing meat. Speech may have a nasal timbre caused by weakness of the palate or a dysarthric "mushy" quality due to tongue weakness. Difficulty in swallowing may occur as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or aspiration of liquids or food. In approximately 85% of patients, the weakness becomes generalized, affecting the limb muscles as well. The limb weakness in MG is often proximal and may be asymmetric. Despite the muscle weakness, deep tendon reflexes are preserved. If weakness of respiration becomes so severe as to require respiratory assistance, the patient is said to be in *crisis*.

DIAGNOSIS AND EVALUATION (Table 380-1)

The diagnosis is suspected on the basis of weakness and fatigability in the typical distribution described above, without loss of reflexes or impairment of sensation or other neurologic function. The suspected diagnosis should always be confirmed definitively before treatment is undertaken; this is essential because (1) other treatable conditions may closely resemble MG, and (2) the treatment of MG may involve surgery and the prolonged use of drugs with adverse side effects.

Anticholinesterase Test Drugs that inhibit the enzyme AChE allow ACh to interact repeatedly with the limited number of AChRs, producing improvement in the strength of myasthenic muscles. Edrophonium is used most commonly, because of the rapid onset (30 s) and short duration (about 5 min) of its effect. An objective end-point must be selected to evaluate the effect of edrophonium. The examiner should focus on one or more unequivocally weak muscle groups and evaluate their strength objectively. For

example, weakness of extraocular muscles, impairment of speech, or the length of time that the patient can maintain the arms in forward abduction may be useful measures. An initial dose of 2 mg of edrophonium is given intravenously. If definite improvement occurs, the test is considered positive and is terminated. If there is no change, the patient is given an additional 8 mg intravenously. The dose is administered in two parts because some patients react to edrophonium with unpleasant side effects such as nausea, diarrhea, salivation, fasciculations, and rarely syncope or bradycardia. Atropine (0.6 mg) should be drawn up in a syringe, ready for intravenous administration if these symptoms become troublesome.

False-positive tests occur in occasional patients with other neurologic disorders, such as amyotrophic lateral sclerosis, and in placebo-reactors. False-negative or equivocal tests also may occur. In some cases it is helpful to use a longer-acting drug such as neostigmine (15 mg given orally), since this permits more time for detailed evaluation of strength. In virtually all instances, it is desirable to carry out further testing to establish the diagnosis of MG definitively.

Electrodiagnostic Testing *Repetitive nerve stimulation* often provides helpful diagnostic evidence of MG. Anti-AChE medication is stopped 6 to 24 h before testing. It is best to test weak muscles or proximal muscle groups. Electric shocks are delivered at a rate of two or three per second to the appropriate nerves, and action potentials are recorded from the muscles. In normal individuals, the amplitude of the evoked muscle action potentials does not change at these rates of stimulation. However, in myasthenic patients there is a rapid reduction in the amplitude of the evoked responses of more than 10 to 15%. As a further test, a single dose of edrophonium may be given to prevent or diminish this decremental reaction.

Antiacetylcholine Receptor Antibody As noted above, anti-AChR antibodies are detectable in the serum of approximately 80% of all myasthenic patients, but in only about 50% of patients with weakness confined to the ocular muscles. The presence of anti-AChR antibodies is virtually diagnostic of MG, but a negative test does not exclude the disease. The measured level of anti-AChR antibody does not correspond well with the severity of MG in different patients. However, in an individual patient, a treatment-induced fall in the antibody level often correlates with clinical improvement.

Inherited Myasthenic Syndromes The *congenital myasthenic syndromes* (CMS) comprise a heterogeneous group of disorders of the neuromuscular junction that are not autoimmune, but rather are due to genetic mutations in which virtually any component of the neuromuscular junction may be affected. Alterations in function of the presynaptic nerve terminal, the various subunits of the AChR or AChE have been identified in the various forms of CMS. These disorders share many of the clinical features of autoimmune MG, including weakness and fatigability of skeletal muscles, in some cases involving extraocular muscles (EOMs), lids, and proximal muscles, similar to the distribution in autoimmune MG. CMS should be suspected when symptoms of myasthenia have begun in infancy or childhood, and AChR antibody tests are consistently negative. Features of four of the most common forms of CMS are summarized in Table 380-2. Although clinical electrodiagnostic and pharmacologic tests may suggest the correct diagnosis, sophisticated electrophysiologic and molecular analysis are required for precise elucidation of the defect; this may lead to helpful

treatment as well as genetic counseling. In the forms that involve the AChR, a wide variety of mutations have been identified in each of the subunits, but the e subunit is affected in about 75% of these cases. In most of the recessively inherited forms of CMS, the mutations are heteroallelic; that is, *different* mutations affecting each of the two alleles are present.

Differential Diagnosis Other conditions that cause weakness of the cranial and/or somatic musculature include the nonautoimmuneCMSdiscussed above, drug-induced myasthenia, Lambert-Eaton myasthenic syndrome (LEMS), neurasthenia, hyperthyroidism, botulism, intracranial mass lesions, and progressive external ophthalmoplegia. Treatment with *penicillamine* (used for scleroderma or rheumatoid arthritis) may result in trueMG, but the weakness is usually mild, and recovery occurs within weeks or months after discontinuing its use. *Aminoglycoside antibiotics* in very large doses and *procainamide* can cause neuromuscular weakness in normal individuals or exacerbation of weakness in myasthenic patients.

LEMSis a presynaptic disorder of the neuromuscular junction that can cause weakness similar to that ofMG. The proximal muscles of the lower limbs are most commonly affected, but other muscles may be involved as well. Cranial nerve findings, including ptosis of the eyelids and diplopia, occur in up to 70% of patients and resemble features of MG. However, the two conditions are readily distinguished, since patients with LEMS have depressed or absent reflexes, show autonomic changes such as dry mouth and impotence, and show incremental responses on repetitive nerve stimulation. It is now known that LEMS is caused by autoantibodies directed against P/Q type calcium channels at the motor nerve terminals, which can be detected in approximately 85%of LEMS patients. These autoantibodies result in impaired release ofACh from nerve terminals. A majority of patients with this syndrome have an associated malignancy, most commonly small cell carcinoma of the lung, which is thought to trigger the autoimmune response. The diagnosis of LEMS may signal the presence of the tumor long before it would otherwise be detected, permitting early removal. Treatment of the neuromuscular disorder involves plasmapheresis and immunosuppression, as for MG.

Neurasthenia may present with weakness and fatigue, but muscle testing usually reveals the "jerky release" or "give-away weakness" characteristic of nonorganic disorders, and the complaint of fatigue in these patients means tiredness or apathy rather than decreasing muscle power on repeated effort. *Hyperthyroidism* is readily diagnosed or excluded by tests of thyroid function, which should be carried out routinely in patients with suspectedMG. Abnormalities of thyroid function (hyper- or hypothyroidism) may increase myasthenic weakness. *Botulism* can cause myasthenic-like weakness, but the pupils are often dilated, and repetitive nerve stimulation gives an *incremental* rather than decremental response. Diplopia that mimics the symptoms of MG may occasionally be due to an *intracranial mass lesion* that compresses nerves to theEOMs(e.g., sphenoid ridge meningioma), but magnetic resonance imaging (MRI) of the head and orbits usually reveals the lesion.

Progressive external ophthalmoplegia is a rare condition resulting in weakness of theEOMs, which may be accompanied by weakness of the proximal muscles of the limbs and other systemic features. Most patients with this condition have mitochondrial disorders that can be detected on muscle biopsy (Chaps. 67 and383).

Search for Associated Conditions (Table 380-3) Myasthenic patients have an increased incidence of several associated disorders. *Thymic abnormalities* occur in ~75% of patients, as noted above. Neoplastic change (thymoma) may produce enlargement of the thymus, which is detected by computed tomography (CT) or MRI scanning of the anterior mediastinum. A thymic shadow on CT scan may normally be present through young adulthood, but enlargement of the thymus in a patient >40 years is highly suspicious of thymoma. *Hyperthyroidism* occurs in 3 to 8% of patients and may aggravate the myasthenic weakness. Tests of thyroid function should be obtained. Because of the *association of MG with other autoimmune disorders*, blood tests for rheumatoid factor and antinuclear antibodies should be carried out in all patients. Chronic infection of any kind can exacerbate MG and should be sought carefully. Finally, measurements of *ventilatory function* are valuable because of the frequency and seriousness of respiratory impairment in myasthenic patients.

Because of the side effects of glucocorticoids and other immunosuppressive agents used in the treatment of MG, a thorough medical investigation should be undertaken, searching specifically for evidence of chronic or latent infection (such as tuberculosis or hepatitis), hypertension, diabetes, renal impairment, and glaucoma.

TREATMENT

(Fig. 380-2) The prognosis has improved strikingly as a result of advances in treatment; virtually all myasthenic patients can be returned to full productive lives with proper therapy. The most useful treatments for MG include anticholinesterase medications, immunosuppressive agents, thymectomy, and plasmapheresis or intravenous immunoglobulin (IVIg).

Anticholinesterase Medications Anticholinesterase medication produces at least partial improvement in most myasthenic patients, although improvement is complete in only a few. There is no substantial difference in efficacy among the various anticholinesterase drugs; oral pyridostigmine is the one most widely used in the United States. As a rule, the beneficial action of oral pyridostigmine begins within 15 to 30 min and lasts for 3 to 4 h, but individual responses vary. Treatment is begun with a moderate dose, e.g., 60 mg three to five times daily. The frequency and amount of the dose should be tailored to the patient's individual requirements throughout the day. For example, patients with weakness in chewing and swallowing may benefit by taking the medication before meals so that peak strength coincides with mealtime. Long-acting pyridostigmine tablets may help to get the patient through the night but should never be used for daytime medication because of their variable absorption. The maximum useful dose of pyridostigmine rarely exceeds 120 mg every 3 h during daytime. Overdosage with anticholinesterase medication may cause increased weakness and other side effects. In some patients, muscarinic side effects of the anticholinesterase medication (diarrhea, abdominal cramps, salivation, nausea) may limit the dose tolerated. In these cases, propantheline bromide may be used to block the autonomic side effects without altering the beneficial effects on skeletal muscle. Loperamide is useful for the treatment of diarrhea.

Thymectomy Two separate issues should be distinguished: (1) surgical removal of

thymoma, and (2) thymectomy as a treatment for MG. Surgical removal of a thymoma is necessary because of the possibility of local tumor spread, although most thymomas are benign. In the absence of a tumor, the available evidence suggests that up to 85% of patients experience improvement after thymectomy; of these, ~35% achieve drug-free remission. However, the improvement is typically delayed for months to years. The advantage of thymectomy is that it offers the possibility of long-term benefit, in some cases diminishing or eliminating the need for continuing medical treatment. In view of these potential benefits and of the negligible risk in skilled hands, thymectomy has gained widespread acceptance in the treatment of MG. It is the consensus that thymectomy should be carried out in all patients with generalized MG who are between the ages of puberty and at least 55 years. Whether thymectomy should be recommended in children, in adults >55 years of age, and in patients with weakness limited to the ocular muscles is still a matter of debate. Thymectomy must be carried out in a hospital where it is performed regularly and where the staff is experienced in the pre- and postoperative management, anesthesia, and surgical techniques of total thymectomy.

Immunosuppression Immunosuppression using glucocorticoids, azathioprine, and other drugs is effective in nearly all patients with MG. The choice of drugs or other immunomodulatory treatments should be guided by the relative benefits and risks for the individual patient and the urgency of treatment. *It is helpful to develop a treatment plan based on short-term, intermediate-term, and long-term objectives. For example, if immediate improvement is essential either because of the severity of weakness or because of the patient's need to return to activity as soon as possible, plasmapheresis should be undertaken or intravenous immunoglobulin (IVIg) administered. For the intermediate term, glucocorticoids and cyclosporine generally produce clinical improvement within a period of 1 to 3 months. The beneficial effects of azathioprine and mycophenolate mofetil usually begin after many months (up to a year), but these drugs have advantages for the long-term treatment of patients with MG.* The side effects of each drug may preclude its use in some patients, as indicated below.

Assessment of Patient's Status In order to evaluate the effectiveness of treatment as well as drug-induced side effects, it is important to assess the patient's clinical status at baseline and on repeated interval examinations in a systematic manner. Because of the variability of symptoms of MG, the interval history as well as findings on examination must be taken into account. The most useful clinical tests include forward arm abduction time (up to a full 5 min), forced vital capacity, range of eye movements, and time to development of ptosis on upward gaze. Manual muscle testing or, preferably, quantitative dynamometry of limb muscles, especially proximal muscles, is also important. An interval form can provide a succinct summary of the patient's status and a guide to treatment results; an abbreviated form is shown in Fig. 380-3. A progressive reduction in the patient's AChR antibody level also provides clinically valuable confirmation of the effectiveness of treatment; conversely, a rise in AChR antibody levels warns that tapering of immunosuppressive medication may lead to clinical exacerbation. Reliable quantitative measurement of AChR antibody levels provides important information about the results of treatment. It is best to compare antibody levels from prior frozen serum samples with current serum in simultaneously run assays.

Glucocorticoid Therapy Glucocorticoids, when used properly, produce improvement in myasthenic weakness in the great majority of patients. The initial dose of prednisone should be relatively low (15 to 25 mg/d) to avoid the early weakening that occurs in about one-third of patients treated initially with a high-dose regimen. The dose is increased stepwise, as tolerated by the patient (usually by 5 mg/d at 2- to 3-day intervals), until there is marked clinical improvement or a dose of 50 mg/d is reached. This dose is maintained for 1 to 3 months and then is gradually modified to an alternate-day regimen over the course of an additional 1 to 3 months; the goal is to reduce the dose to zero or to a minimal level on the "off day." Generally, patients begin to improve within a few weeks after reaching the maximum dose, and improvement continues to progress for months or years. The prednisone dosage may gradually be reduced, but usually months or years may be needed to determine the minimum effective dose, and close monitoring is required by patient and doctor. *Few patients are able to do without prednisone entirely*. Patients on long-term glucocorticoid therapy must be followed carefully to prevent or treat adverse side effects. The most common errors in the steroid treatment of myasthenic patients include (1) insufficient persistence -- improvement may be delayed and gradual; (2) too early, too rapid, or excessive tapering of steroid dosage; and (3) lack of attention to prevention and treatment of side effects. *The management of patients treated with glucocorticoids is discussed in Chap. 331.*

Other Immunosuppressive Drugs Azathioprine, cyclosporine, mycophenolate mofetil, or occasionally cyclophosphamide is effective in many patients, either alone or in combination with glucocorticoid therapy. Azathioprine has been the most widely used of these drugs because of its relative safety in most patients and long track record. Its therapeutic effect may add to that of glucocorticoids and/or allow the steroid dose to be reduced. However, up to 10% of patients are unable to tolerate azathioprine because of idiosyncratic reactions consisting of flulike symptoms of fever and malaise, bone marrow depression, or abnormalities of liver function. An initial dose of 50 mg/d should be used to test for adverse side effects. If this dose is tolerated, it is increased gradually until the white blood count falls to approximately 3000 to 4000/uL. In patients who are receiving glucocorticoids concurrently, leukocytosis precludes the use of this measure. A reduction of the lymphocyte count to<1000/uL and/or an increase of the mean corpuscular volume of red blood cells may be used as indications of adequacy of azathioprine dosage. The typical dosage range is 2 to 3 mg/kg total body weight (including fat in obese patients). The beneficial effect of azathioprine takes at least 3 to 6 months to begin and even longer to peak.

Cyclosporine is approximately as effective as azathioprine and is being used increasingly in the management of MG. Its beneficial effect appears more rapidly than that of azathioprine. It may be used alone but is usually used as an adjunct to glucocorticoids to permit reduction of the steroid dose. The usual dose of cyclosporine is 4 to 5 mg/kg per day, given in two divided doses (to minimize side effects). Side effects of cyclosporine include hypertension and nephrotoxicity, which must be closely monitored. "Trough" blood levels of cyclosporine are measured 12 h after the evening dose. The therapeutic range, as measured by radioimmunoassay, is 150 to 200 ng/L.

Mycophenolate mofetil, which has been used for immunosuppression in transplant patients, is now proving useful in the treatment of MG. A dose of 1 g bid is

recommended. Its mechanism of action involves inhibition of purine synthesis by the "de novo" pathway. Since lymphocytes lack the alternative "salvage" pathway that is present in all other cells, mycophenolate inhibits proliferation of lymphocytes but not proliferation of other cells. It does not kill or eliminate preexisting autoreactive lymphocytes, and therefore clinical improvement in autoimmune diseases such as MG may be delayed for many months to a year, until the preexisting autoreactive lymphocytes die spontaneously. The advantage of mycophenolate lies in its relative lack of adverse side effects, with only occasional production of diarrhea and rare development of leukopenia. This drug may become the choice for long-term treatment of myasthenic patients. Unfortunately, the present cost of mycophenolate may be prohibitively high.

Cyclophosphamide is reserved for occasional patients refractory to the other drugs, because of its relatively high risk of adverse side effects, including late development of malignancies.

Plasmapheresis and Intravenous Immunoglobulin Plasmapheresis has been used therapeutically in MG. Plasma, which contains the pathogenic antibodies, is mechanically separated from the blood cells, which are returned to the patient. A course of five exchanges (3 to 4 L per exchange) is generally administered over a 2-week period. Plasmapheresis produces a short-term reduction in anti-AChR antibodies, with clinical improvement in many patients. It is useful as a temporary expedient in seriously affected patients or to improve the patient's condition prior to surgery (e.g., thymectomy).

The indications for the use of IVIg are the same as those for plasma exchange: to produce rapid improvement to help the patient through a difficult period of myasthenic weakness or prior to surgery. This treatment has the advantages of not requiring special equipment or large-bore venous access. The usual dose is 2 g/kg, which is typically administered over 5 days (400 mg/kg/per day). If tolerated, the course of IVIg can be shortened to administer the entire dose over a 3-day period. Improvement occurs in about 70% of patients, beginning during treatment, or within 4 to 5 days thereafter, and continuing for weeks to months. The mechanism of action of IVIg is not known; the treatment has no consistent effect on the measurable amount of circulating AChR antibody. Adverse reactions are uncommon, but include headache, fluid overload, and rarely renal shutdown.

The intermediate and long-term treatment of myasthenic patients requires other methods of therapy outlined earlier in this chapter.

Management of Myasthenic Crisis Myasthenic crisis is defined as an exacerbation of weakness sufficient to endanger life; it usually consists of respiratory failure caused by diaphragmatic and intercostal muscle weakness. Treatment should be carried out in an intensive care unit staffed with physicians experienced in the management of myasthenia gravis, respiratory insufficiency, infectious disease, and fluid and electrolyte therapy. The possibility that the deterioration could be due to excessive anticholinesterase medication ("cholinergic crisis") is best excluded by temporarily stopping anticholinesterase drugs. The most common cause of crisis is intercurrent infection. This should be treated *immediately*, because the mechanical and immunologic defenses of the patient can be assumed to be compromised. The myasthenic patient

with fever and early infection should be treated like other immunocompromised patients. Early and effective antibiotic therapy, respiratory assistance, and pulmonary physiotherapy are essentials of the treatment program. As discussed above, plasmapheresis or[IVIg](#) is frequently helpful in hastening recovery.

(Bibliography omitted in Palm version)

381. APPROACH TO THE PATIENT WITH MUSCLE DISEASE - *Jerry R. Mendell*

Skeletal muscle diseases, or myopathies, are defined as disorders with structural changes or functional impairment of muscle. These conditions can be differentiated from other diseases of the motor unit by characteristic clinical and laboratory findings. *Myasthenia gravis and related disorders are discussed in Chap. 380; inflammatory muscle diseases and inclusion body myositis in Chap. 382; muscular dystrophies and inherited, metabolic, and toxic myopathies in Chap. 383.*

CLINICAL FEATURES

Muscle Weakness Symptoms of muscle weakness can be either intermittent or persistent. Some patients complain of weakness that physicians more accurately classify as fatigue. Disorders causing intermittent weakness (Fig. 381-1) include myasthenia gravis, periodic paralyses (hypokalemic, hyperkalemic, and paramyotonia congenita), and metabolic energy deficiencies of glycolysis (especially myophosphorylase deficiency) and fatty acid utilization (carnitine palmitoyltransferase deficiency). The states of energy deficiency cause activity-related muscle breakdown accompanied by myoglobinuria, appearing as light-brown- to dark-brown-colored urine. Most muscle disorders cause persistent weakness (Fig. 381-2). In the majority of these, including most types of muscular dystrophy, polymyositis, and dermatomyositis, the proximal muscles are weaker than the distal, and the facial muscles are spared, a pattern referred to as *limb-girdle*. For other patterns of weakness the differential diagnosis is more restricted. Cranial innervated muscle weakness causing ptosis and extraocular muscle weakness without diplopia points to oculopharyngeal muscular dystrophy, mitochondrial myopathies, or myotubular myopathy. Facial weakness (difficulty with eye closure and impaired smile) and scapular winging (Fig. 381-3) are characteristic of facioscapulohumeral dystrophy. Facial and distal limb weakness associated with hand grip myotonia is virtually diagnostic of myotonic dystrophy. A pathognomonic pattern exclusive to inclusion body myositis includes loss of strength in both proximal and distal muscles, handgrip weakness, and wasting of quadriceps muscles. Less frequently, but important diagnostically, is the presence of a dropped head syndrome indicative of selective neck extensor muscle weakness. The most common neuromuscular diseases causing this pattern of weakness include myasthenia gravis, polymyositis, and amyotrophic lateral sclerosis. A final pattern, recognized because of preferential distal extremity weakness, is typical of a unique category of muscular dystrophy, the distal myopathies (Chap. 383).

It is important to examine functional capabilities to help disclose certain patterns of weakness (Table 381-1). The Gowers' sign (Fig. 381-4) is particularly useful. Observing the gait of an individual may disclose a lordotic posture caused by combined trunk and hip weakness, frequently exaggerated by toe walking (Fig. 381-5). A waddling gait is caused by the inability of weak hip muscles to prevent hip drop or hip dip. Hyperextension of the knee (genu recurvatum or backkneeing) is characteristic of quadriceps muscle weakness; and a steppage gait, due to footdrop, accompanies distal weakness.

Any disorder causing muscle weakness may be accompanied by fatigue, referring to an inability to maintain or sustain a force (pathologic fatigability). This condition must be

differentiated from asthenia, a type of fatigue caused by excess tiredness or lack of energy (Fig. 381-2). Associated symptoms may help differentiate asthenia and pathologic fatigability. Asthenia is often accompanied by a tendency to avoid physical activities, complaints of daytime sleepiness, necessity for frequent naps, and difficulty concentrating on activities, such as reading. There may be feelings of overwhelming stress and depression. Thus, asthenia is not a myopathy. In contrast, pathologic fatigability occurs in disorders of neuromuscular transmission and in disorders altering energy production, including defects in glycolysis, lipid metabolism, or mitochondrial energy production. Pathologic fatigability also occurs in chronic myopathies because of difficulty accomplishing a task with less muscle. Pathologic fatigability is accompanied by abnormal clinical or laboratory findings. Fatigue without those supportive features almost never indicates a primary muscle disease.

Muscle Pain, Cramps, and Stiffness Muscle pain can be associated with involuntary muscle activity producing cramps, contractures, and stiff or rigid muscles (Chap. 22). In distinction, true myalgia (muscle aching), which can be localized or generalized, has no involuntary activity but may be accompanied by weakness, tenderness to palpation, or swelling. Certain drugs cause true myalgia (Table 381-2).

There are two painful muscle conditions of particular importance, neither of which is associated with muscle weakness. Fibromyalgia is a common, yet poorly understood type of myofascial pain syndrome. Patients complain of severe muscle pain and tenderness and have specific painful trigger points, sleep disturbances, and easy fatigability (Chap. 325). Polymyalgia rheumatica occurs in patients older than 50 years and is characterized by stiffness (without involuntary activity) and pain in the shoulders, lower back, hips, and thighs (Chap. 317). The erythrocyte sedimentation rate is elevated, and temporal arteritis may be present. Polymyalgia rheumatica is important to recognize because treatment with glucocorticoids can relieve discomfort and prevent the associated ischemic arteritis, which threatens vision.

Muscle cramps are painful, involuntary, localized, muscle contractions with a visible or palpable hardening of the muscle. They are abrupt in onset and short in duration, and they may cause abnormal posturing of the joint. The electromyogram (EMG) shows firing of motor units, reflecting an origin from spontaneous neurogenic activity. Muscle cramps are not a feature of most primary muscle diseases, although they occur commonly in Duchenne and related forms of muscular dystrophy (Chap. 383). Muscle cramps more often accompany neurogenic disorders, especially motor neuron disease (Chap. 365), radiculopathies, and polyneuropathies (Chap. 377).

A muscle contracture is different from a muscle cramp. In both conditions, the muscle becomes hard, but a contracture is associated with energy failure in glycolytic disorders. The muscle is unable to relax after an active muscle contraction. The EMG shows electrical silence. Confusion is created because contracture also refers to a muscle that cannot be passively stretched to its proper length (fixed contracture) because of fibrosis. In some muscle disorders, especially Emery-Dreifuss muscular dystrophy and Bethlem myopathy (Chap. 383), fixed contractures occur early and represent distinctive features of the disease.

Muscle stiffness can refer to different phenomena. Some patients with inflammation of

joints and periarticular surfaces feel stiff. This condition is different from the disorders of hyperexcitable motor nerves causing stiff or rigid muscles (Chap. 22). In *stiff-man syndrome* spontaneous discharges of the motor neuron of the spinal cord cause involuntary muscle contractions mainly involving the axial and proximal lower extremity muscles. Neuromyotonia (Isaac's syndrome) is another cause of motor nerve hyperexcitability.

Myotonia is a condition of prolonged muscle contraction followed by slow muscle relaxation. It always follows muscle activation, usually voluntary, but may be elicited by mechanical stimulation (percussion myotonia) of the muscle. Myotonia causes difficulty in releasing objects after a firm grasp. Usually it is worsened by cold temperatures and eases with continued activity. The sodium channelopathies (paramyotonia congenita and hyperkalaemic periodic paralysis) are accompanied by a unique phenomenon, paradoxical myotonia, in which repeated muscle contraction exacerbates the myotonia (Chap. 383). In hypokalemic periodic paralysis, myotonia of the eyelids may be present but limb muscles are usually spared.

Muscle Enlargement and Atrophy In most myopathies muscle tissue is replaced by fat and connective tissue, but the size of the muscle is usually not affected. However, in Duchenne and Becker muscular dystrophies enlarged calf muscles are typical. In the patients with these forms of dystrophy, the enlargement represents true muscle hypertrophy. The calf muscles remain very strong even late in the course of the disease. The term "pseudohypertrophy" should be avoided when referring to these patients. Muscle enlargement can also result from infiltration by sarcoid granulomas, amyloid deposits, bacterial and parasitic infections, and focal myositis. A tendon rupture, especially a biceps brachii tendon, is a common cause of focal muscle enlargement.

LABORATORY EVALUATION

A limited battery of tests can be used to evaluate a suspected myopathy. Nearly all patients require serum enzyme level measurements and electrodiagnostic studies as screening tools to differentiate muscle disorders from other motor unit diseases. The other tests described -- DNA studies, the forearm exercise test, and muscle biopsy -- are used to diagnose specific types of myopathies.

Serum Enzymes Creatine kinase (CK) is the preferred muscle enzyme to measure in the evaluation of myopathies. Damage to muscle causes the CK to leak from the muscle fiber to the serum. The MM isoenzyme predominates in skeletal muscle, while CK-MB is the marker for cardiac muscle. Serum CK can be elevated in normal individuals without provocation, presumably on a genetic basis or after strenuous activity, minor trauma (including the EMG needle), a prolonged muscle cramp, or a generalized seizure. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase (LDH) are enzymes sharing an origin in both muscle and liver. Problems arise when the levels of these enzymes are found to be elevated in a routine screening battery, leading to the erroneous assumption that liver disease is present when in fact muscle could be the cause. An elevated gamma-glutamyl transferase (GGT) helps to establish a liver origin since this enzyme is not found in muscle. Aldolase is often thought to be a muscle-specific enzyme but is also present in liver.

Electrodiagnostic Studies EMG, repetitive nerve stimulation, and nerve conduction studies (Chap. 357) are essential methods for evaluation of the patient with suspected muscle disease. In combination they provide the information necessary to differentiate myopathies from neuropathies and neuromuscular junction diseases. Certain features of the EMG will point to an acquired, inflammatory muscle disorder (e.g., irritability on needle placement) versus a long-standing myopathic disorder that is more suggestive of a dystrophic process. The EMG can also be invaluable in helping to choose an appropriately affected muscle to sample for biopsy. The EMG can be used to fully characterize suspected involuntary activity seen during the examination, such as myokymia and myotonia.

DNA Analysis Advances in molecular diagnosis have evolved over the past decade and now serve as important tools for diagnosis. Certain muscle disorders can be definitively diagnosed by DNA analysis; these are fully discussed inChap. 383. Nevertheless, important limitations need to be mentioned in seeking a molecular diagnosis. For example, in some disorders, such as Duchenne and Becker dystrophies, two-thirds of patients have deletion- or duplication-mutations that are easy to detect, while the remainder have point mutations that are much more difficult to find. For patients without identifiable gene defects, the muscle biopsy remains the main diagnostic tool.

Forearm Exercise Test In myopathies with intermittent symptoms, and especially those associated with myoglobinuria, there may be a defect in glycolysis. Many variations of the forearm exercise test exist. For safety, the test should not be performed under ischemic conditions to avoid an unnecessary insult to the muscle causing rhabdomyolysis. The test is performed by placing a small indwelling catheter into an antecubital vein. A baseline blood sample is obtained for lactic acid and ammonia. The forearm muscles are exercised by asking the patient to vigorously squeeze a sphygmomanometer bulb for 1 min. Blood is then obtained at intervals of 1, 2, 4, 6, and 10 min for comparison with the baseline sample. Normal controls must be established for each laboratory. A three- to fourfold rise of lactic acid is typical. The simultaneous measurement of ammonia serves as a control, since it should also rise with exercise. In patients with myophosphorylase deficiency or other glycolytic defects (Chap. 383), the lactic acid rise will be absent or below normal, while the rise in ammonia will reach control values. If there is lack of effort, neither lactic acid nor ammonia will rise. Patients with selective failure to increase ammonia may have myoadenylate deaminase deficiency. This condition has been reported to be a cause of myoglobinuria, but deficiency of this enzyme in asymptomatic individuals makes interpretation controversial.

Muscle Biopsy Muscle biopsy analysis is an important step in establishing the final diagnosis of suspected myopathy. The microscopic evaluation uses a combination of techniques -- histochemistry, immunocytochemistry with a battery of antibodies, and electron microscopy. Not all techniques need to be used on every case. A specific diagnosis can be established in many disorders. A combination of stains to identify mononuclear cells (polymyositis), complement (dermatomyositis), and amyloid (inclusion body myositis) help to distinguish the inflammatory myopathies. Mitochondrial and metabolic (e.g., myophosphorylase and acid maltase deficiencies) myopathies demonstrate distinctive histochemical and electron microscopic profiles. A battery of

antibodies is available for the identification of missing components of the dystrophin-glycoprotein complex and related proteins to help diagnose specific types of muscular dystrophies. In addition, the congenital myopathies have distinctive histologic features essential for diagnosis.

(Bibliography omitted in Palm version)

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382. POLYMYOSITIS, DERMATOMYOSITIS, AND INCLUSION BODY MYOSITIS - *Marinos C. Dalakas, Jr.*

The inflammatory myopathies represent the largest group of acquired and potentially treatable causes of skeletal weakness. On the basis of well defined clinical, demographic, histologic and immunopathological criteria, the inflammatory myopathies can be classified into three major groups: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM).

GENERAL CLINICAL FEATURES

The incidence of PM, DM, and IBM is approximately 1 in 100,000. PM is predominantly a disease of adults. DM affects both children and adults, and women more often than men. IBM is three times more frequent in men than in women, more common in Caucasians than African Americans, and is most likely to affect persons>50.

These disorders present as progressive and often symmetric muscle weakness. Patients usually report increasing difficulty with everyday tasks requiring the use of proximal muscles, such as getting up from a chair, climbing steps, stepping onto a curb, lifting objects, or combing hair. Fine-motor movements that depend on the strength of distal muscles, such as buttoning a shirt, sewing, knitting, or writing, are affected only late in the course of PM and DM, but fairly early in IBM. Falling is common in IBM because of early involvement of the quadriceps muscle with buckling of the knees. Ocular muscles are spared, even in advanced, untreated cases; if these muscles are affected, the diagnosis of inflammatory myopathy should be in doubt. Facial muscles are unaffected in PM and DM, but mild facial muscle weakness occurs in up to 60% of patients with IBM. In all forms of inflammatory myopathy, pharyngeal and neck-flexor muscles are often involved, causing dysphagia or difficulty in holding up the head (*neck drop*). In advanced and rarely in acute cases, respiratory muscles may also be affected. Severe weakness, if untreated, is almost always associated with muscle wasting. Sensation remains normal. The tendon reflexes are preserved but may be absent in severely weakened or atrophied muscles, especially in IBM where atrophy of the quadriceps and the distal muscles is common. Myalgia and muscle tenderness may occur in a small number of patients, usually early in the diseaese and more often in DM than in PM. Weakness in PM and DM progresses subacutely over a period of weeks or months and rarely acutely; by contrast, IBM progresses very slowly, over years, and its course may simulate late-life muscular dystrophies (Chap. 383) or slowly progressive motor neuron disorders (Chap. 365).

SPECIFIC FEATURES (Table 382-1)

Polymyositis In most patients, the actual onset of PM is not easily determined, and patients typically delay seeking medical advice for several months. This is in contrast to DM, in which the rash facilitates early recognition (see below). PM is a subacute inflammatory myopathy affecting adults, and rarely children, who *do not have* any of the following: rash, involvement of the extraocular and facial muscles, family history of a neuromuscular disease, history of exposure to myotoxic drugs or toxins, endocrinopathy, neurogenic disease, muscular dystrophy, biochemical muscle disorder (deficiency of a muscle enzyme), or IBM as excluded by muscle biopsy analysis (see

below). PM may occur either in isolation, in association with a systemic autoimmune or connective tissue disease, or with known viral or bacterial infection. D-Penicillamine and, on occasion, zidovudine (AZT) may also produce an inflammatory myopathy similar to PM.

Dermatomyositis ([Figs. 382-CD1](#),[382-CD2](#)and[382-CD3](#))[DM](#) is a distinctive entity identified by a characteristic rash accompanying, or more often preceding, muscle weakness. The rash may consist of a heliotrope rash (blue-purple discoloration) on the upper eyelids with edema, a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (*Gottron rash*) that later results in scaling of the skin (see [Plates IIE-63](#) and[IIE-65](#)). The erythematous rash can also occur on other body surfaces, including the knees, elbows, malleoli, neck and anterior chest (often in a *V sign*), or back and shoulders (*shawl sign*), and may worsen after sun exposure. In some patients the rash is pruritic, especially on the scalp, chest, and back. Dilated capillary loops at the base of the fingernails are also characteristic. The cuticles may be irregular, thickened, and distorted, and the lateral and palmar areas of the fingers may become rough and cracked, with irregular, "dirty" horizontal lines, resembling *mechanic's hands*. The weakness can be mild, moderate, or severe enough to lead to quadraparesis. At times, the muscle strength appears normal, hence the term *dermatomyositis sine myositis*. When muscle biopsy is performed in such cases, however, significant perivascular and perimysial inflammation is seen. In children, DM resembles the adult disease, except for more frequent extramuscular manifestations, as discussed later. A common early abnormality in children is "misery," defined as an irritable child who appears uncomfortable, has a red flush on the face, is fatigued, does not wish to socialize, and has a varying degree of proximal muscle weakness. A tiptoe gait due to flexion contracture of the ankles is also common.

[DM](#)usually occurs alone but may overlap with scleroderma and mixed connective tissue disease. Fasciitis and thickening of the skin similar to that seen in chronic cases of DM have occurred in patients with the *eosinophilia-myalgia syndrome* associated with the ingestion of contaminated L-tryptophan.

Inclusion Body Myositis In patients ^{3}50,[IBM](#) is the most common of the inflammatory myopathies. It is often misdiagnosed as[PM](#) and suspected only retrospectively when a patient with presumed PM does not respond to therapy. Weakness and atrophy of distal muscles, especially foot extensors and deep finger flexors, occur in almost all cases of IBM and may be a clue to early diagnosis. Some patients present with falls because their knees collapse due to early quadriceps weakness. Others present with weakness in the small muscles of the hands, especially finger flexors, and complain of inability to hold certain objects, such as golf clubs, or perform certain tasks, such as turning keys or tying knots. On occasion, the weakness and accompanying atrophy can be asymmetric and selectively involve the quadriceps, iliopsoas, triceps, biceps, and finger flexors, resembling a lower motor neuron disease. Dysphagia is common, occurring in up to 60% of IBM patients, and may lead to episodes of choking. Sensory examination is generally normal; some patients have mildly diminished vibratory sensation at the ankles that presumably is age-related. The distal weakness does not represent motor neuron or peripheral nerve involvement but results from the myopathic process affecting distal muscles. The diagnosis is always made by the characteristic findings on the muscle biopsy, as discussed below. Disease progression is slow but steady, and most

patients require an assistive device such as cane, walker, or wheelchair within several years of onset.

In at least 20% of cases, IBM is associated with systemic autoimmune or connective tissue diseases. Familial aggregation has also been noted in coaffected siblings with typical IBM; such cases have been designated as *familial inflammatory IBM*. This disorder is distinct from *hereditary inclusion body myopathy* (h-IBM), which describes a heterogeneous group of recessive and less frequently dominant, inherited syndromes. The h-IBMs are noninflammatory myopathies with clinical profiles distinct from sporadic IBM. A subset of h-IBM that spares the quadriceps muscle has emerged as a distinct entity. This disorder, originally described in Iranian Jews and now seen in many ethnic groups, is linked to chromosome 9p1.

ASSOCIATED CLINICAL FINDINGS

Extramuscular Manifestations In addition to the primary myopathy, a number of extramuscular manifestations may be present to a varying degree in patients with PM or DM:

1. *Systemic symptoms*, such as fever, malaise, weight loss, arthralgia, and Raynaud's phenomenon especially when inflammatory myopathy is associated with a connective tissue disorder.

2. *Joint contractures*, mostly in DM and especially in children.

3. *Dysphagia and gastrointestinal symptoms* due to involvement of the oropharyngeal striated muscles and upper esophagus. Dysphagia may be prominent in the active stages of DM and is frequent in IBM. Gastrointestinal ulcerations due to vasculitis and infection were common in children with DM before the use of immunosuppressive drugs.

4. *Cardiac disturbances*, including atrioventricular conduction defects, tachyarrythmias, dilated cardiomyopathy, and low ejection fraction. Congestive heart failure and myocarditis may also occur, either from the disease itself or from hypertension associated with long-term use of glucocorticoids.

5. *Pulmonary dysfunction*, due to primary weakness of the thoracic muscles, drug-induced pneumonitis (e.g., from methotrexate), or interstitial lung disease may cause dyspnea, nonproductive cough, and aspiration pneumonia. Interstitial lung disease may precede myopathy or occur early in the disease, and develops in up to 10% of patients with PM or DM.

6. *Subcutaneous calcifications*, sometimes extruding on the skin and causing ulcerations and infections, are seen in DM, primarily in children.

Malignancies Although all the inflammatory myopathies can have a chance association with malignant lesions, especially in older age groups, the incidence of malignant conditions appears to be specifically increased only in patients with DM but not PM or IBM. The most common tumors associated with DM are ovarian cancer, breast cancer, melanoma, and colon cancer. The extent of the search that should be conducted for an

occult malignant neoplasm in adults with DM depends on the clinical circumstances. Tumors in these patients are usually uncovered by abnormal findings in the medical history and physical examination and not through an extensive radiologic blind search. Thus the weight of evidence argues against performing expensive, invasive, and nondirected tumor searches. When a suspected malignancy is not apparent, a complete annual physical examination with pelvic, breast, and rectal examinations; urinalysis; complete blood count; blood chemistry tests; and a chest film should suffice.

Overlap The term *overlap syndrome* has been used loosely to describe the frequent association of inflammatory myopathies with connective tissue diseases. A well-characterized overlap syndrome occurs in patients with DM who also have manifestations of systemic sclerosis or mixed connective tissue disease, such as sclerotic thickening of the dermis, contractures, esophageal hypomotility, microangiopathy, and calcium deposits (Table 382-1). By contrast, signs of rheumatoid arthritis, systemic lupus erythematosus, or Sjogren's syndrome are very rare in patients with DM. Patients with the overlap syndrome of DM and systemic sclerosis may have a specific antinuclear autoantibody, the anti-PM/Scl, directed against a nucleolar-protein complex.

PATHOGENESIS

An autoimmune origin of these disorders is supported by their association with other systemic autoimmune, viral, or connective tissue diseases; the presence of various autoantibodies; their association with histocompatibility genes; the evidence of T cell-mediated myocytotoxicity or complement-mediated microangiopathy; and their response to immunotherapies. However, the specific muscle or capillary target antigens have not been identified, and the agents initiating self-sensitization are still unknown.

Autoantibodies and Immunogenetics Various autoantibodies against nuclear antigens (antinuclear antibodies) and cytoplasmic antigens are found in up to 20% of patients with inflammatory myopathies. The antibodies to cytoplasmic antigens, present in<10% of PM and DM patients, are directed against cytoplasmic ribonucleoproteins, which are involved in translation and protein synthesis. They include antibodies against various synthetases, translation factors, and proteins of the signal-recognition particles. The antibody directed against the histidyl-transfer RNA synthetase, called *anti-Jo-1*, accounts for 75% of all the anti-synthetases and is clinically useful because up to 80% of patients with anti-Jo-1 antibodies have interstitial lung disease. Some patients with the anti-Jo-1 antibody may also have Raynaud's phenomenon, nonerosive arthritis, and the HLA antigens DR3 and DRw52. In both PM and IBM, there is an increased frequency (up to 75%) of haplotypes of DR3 (molecular designation DRB1*0301, DQB1*0201), suggesting that these alleles may be risk factors for the development of these disorders (Chap. 306).

Immunopathologic Mechanisms In DM, the endomysial infiltrates have a higher than normal percentage of B cells, a higher ratio of CD4+ cells (helper cells) to CD8+ cells (suppressor-cytotoxic T cells), proximity of CD4+ cells to B cells and macrophages, and a relative absence of lymphocytic invasion of nonnecrotic muscle fibers, all of which suggest a mechanism mediated primarily by humoral processes. The immune process is directed against microvascular antigens and is mediated by the complement C5b-9

membranolytic attack complex, resulting in necrosis of the endothelial cells, reduced numbers of endomysial capillaries, ischemia, muscle-fiber destruction often resembling microinfarcts, and inflammation. Larger intramuscular blood vessels may also be affected in the same pattern, leading to actual muscle infarction. Residual perifascicular atrophy reflects the endofascicular hypoperfusion that is prominent in the periphery of the fascicles. Complement activation is thought to trigger release of proinflammatory cytokines, induce expression of vascular cell adhesion molecule (VCAM)-1 and intracellular adhesion molecule (ICAM)-1 on endothelial cells, and facilitate migration of activated lymphoid cells to the perimysial and endomysial spaces.

In PM and IBM there is evidence not of microangiopathy and muscle ischemia, as in DM, but of an antigen-directed cytotoxicity mediated by CD8+cytotoxic T cells. This conclusion is supported by the presence of CD8+ cells, which, along with macrophages, initially surround and eventually invade and destroy healthy, nonnecrotic muscle fibers that aberrantly express class I MHC molecules. MHC-I expression, absent from the sarcolemma of normal muscle fibers, is probably induced by cytokines secreted by activated T cells and macrophages. The cytotoxic autoinvasive CD8+ T cells contain perforin and granzyme granules directed towards the surface of the muscle fibers and capable of inducing cell death. The infiltrating endomysial T cells appear to be clonally restricted, suggesting an antigen-driven T cell response. The putative antigens are more likely to be endogenous sarcolemmal or cytoplasmic self-proteins synthesized within the muscle, rather than endogenous viral peptides, because viruses have not been identified within the muscle fibers.

T cell-derived cytokines (interleukins 2, 4, and 5 and interferong), the macrophage-derived cytokines (interleukins 1 and 6 and tumor necrosis factor a), and adhesion molecules on leukocytes (L-selectin and integrins LFA-1, VLA-4) and their respective ligands on endothelial cells (GlyCAM-1, ICAM-1, VCAM-1) in patients with PM, DM, and IBM; these may facilitate the adhesion and transmigration of activated T cells through the endothelial cell wall. T cell metalloproteinases (MMP-2 and MMP-9) are also upregulated and may facilitate adhesion of T cells to muscle, enhancing cytotoxicity.

The Role of Nonimmune Factors in IBM In IBM, the presence of vacuoles, the amyloid-positive deposits within some vacuolated muscle fibers, the abnormal muscle mitochondria with mitochondrial DNA deletions, and the relative resistance of the disease to immunosuppressive therapies suggest that, in addition to the autoimmune component, there is also a degenerative process. Similar to Alzheimer's disease, the amyloid deposits in IBM are immunoreactive against amyloid precurser protein (APP), chymotrypsin, apolipoprotein E, and phosphorylated tau, but it is unclear whether these deposits directly contribute to disease pathogenesis or are secondary phenomena. The same can be said for the mitochondrial abnormalities, which may also be secondary caused by the effects of aging and upregulated cytokines.

Association with Viral Infections and the Role of Retroviruses Several viruses, including coxsackieviruses, influenza, paramyxoviruses, mumps, cytomegalovirus, and Epstein-Barr virus have been indirectly associated with chronic and acute myositis. For the coxsackieviruses, an autoimmune myositis triggered by molecular mimicry has been proposed because of structural homology between histidyl-transfer RNA synthetase that

is the target of the Jo-1 antibody (see above) and genomic RNA of an animal picornavirus, the encephalomyocarditis virus. Very sensitive polymerase chain reaction (PCR) studies, however, have repeatedly failed to confirm the presence of such viruses in muscle biopsies from these patients.

The best evidence of a viral connection in PM and IBM is with the retroviruses. Monkeys infected with the simian immunodeficiency virus and humans infected with HIV and human T cell lymphotropic virus (HTLV) develop PM or, rarely, IBM. In humans infected with HIV or HTLV-1, an isolated inflammatory myopathy may occur as the initial manifestation of the retroviral infection or myositis may develop later in the disease course. Retroviral antigens have been detected only in occasional endomysial macrophages and not within the muscle fibers themselves, suggesting that persistent infection and viral replication within the muscle do not occur. Histologic findings in PM and IBM associated with HIV-1 and HTLV-1 infection are identical to retroviral-negative myositis, specifically CD8+ T cells and macrophages that invade or surround MHC-I antigen-expressing nonnecrotic muscle fibers. The development of PM or IBM in HIV-positive patients should be distinguished from a toxic myopathy related to long-term therapy with zidovudine, which is characterized by fatigue, myalgia, mild muscle weakness, and mild elevation of creatine kinase (CK). Zidovudine-induced myopathy, which generally improves when the drug is discontinued, is a mitochondrial disorder characterized histologically by the presence of numerous "ragged-red" fibers. Abnormal muscle mitochondria and depletion of the muscle mitochondrial DNA by zidovudine results from inhibition of g-DNA polymerase, an enzyme found solely in the mitochondrial matrix.

DIFFERENTIAL DIAGNOSIS

The clinical picture of skin rash and proximal or diffuse muscle weakness has few causes other than DM. However, proximal muscle weakness without skin involvement can be due to many conditions other than PM.

Subacute or Chronic Progressive Muscle Weakness This may be due to denervating conditions such as the spinal muscular atrophies or amyotrophic lateral sclerosis (Chap. 365). In addition to the muscle weakness, upper motor neuron signs in the latter aid in the diagnosis. The muscular dystrophies, such as those of Duchenne and Becker and the limb-girdle and facioscapulohumeral types, may be additional considerations (Chap. 383). However, the muscular dystrophies usually develop more slowly (over years rather than weeks or months) and rarely present after the age of 30. In rare patients it may be difficult, even with a muscle biopsy, to distinguish chronic PM from a rapidly advancing muscular dystrophy. This is particularly true of facioscapulohumeral muscular dystrophy, where interstitial inflammatory cell infiltration is commonly found early in the disease. Such doubtful cases should always be given an adequate trial of glucocorticoid therapy. Some metabolic myopathies, including glycogen storage disease due to myophosphorylase or acid maltase deficiency, lipid storage myopathies due to carnitine deficiency, and mitochondrial diseases produce muscle weakness, which is often associated with other characteristic clinical signs (Chap. 383); diagnosis rests upon histochemical and biochemical studies of the muscle biopsy. The endocrine myopathies such as those due to hypercorticosteroidism, hyper- and hypothyroidism, and hyper- and hypoparathyroidism require the appropriate laboratory investigations for diagnosis.

Muscle wasting in patients with an underlying neoplasm may be due to disuse, cachexia, or rarely to a paraneoplastic neuromyopathy (Chap. 101).

Diseases of the neuromuscular junction, including myasthenia gravis or the Lambert-Eaton myasthenic syndrome, cause fatiguing weakness that also affects the eye and cranial muscles (Chap. 380). Repetitive nerve stimulation and single-fiber electromyography (EMG) studies aid in diagnosis.

Acute Muscle Weakness This may be caused by an acute neuropathy such as Guillain-Barre syndrome (Chap. 378) or a neurotoxin. When combined with painful muscle cramps, rhabdomyolysis, and myoglobinuria, it may be due to metabolic disorders including some of the glycogen storage diseases, such as myophosphorylase deficiency (McArdle's disease), carnitine palmityltransferase deficiency, and myoadenylate deaminase deficiency (Chap. 383). Acute viral infections may cause a similar syndrome. Several animal parasites, such as protozoa (*toxoplasma*, *trypanosoma*), cestodes (cysticerci), and nematodes (trichinae), may produce a focal or diffuse inflammatory myopathy known as *parasitic polymyositis*. *Staphylococcus aureus*, *Yersinia*, *Streptococcus*, or other anaerobic bacteria may produce a suppurative myositis, known as *tropical polymyositis*, or *pyomyositis*. Pyomyositis, previously rare in the west, is now seen in occasional AIDS patients. Other bacteria, such as *Borrelia burgdorferi* (Lyme disease) and *Legionella pneumophila* (Legionnaire's disease) may infrequently cause myositis.

Chronic alcoholics may develop a painful myopathy with myoglobinuria after a bout of heavy drinking; present with a painless acute hypokalemic myopathy, which is completely reversible; or show an asymptomatic elevation of serumCK and myoglobin. Acute muscle weakness with myoglobinuria may occur with prolonged severe hypokalemia or with hypophosphatemia and hypomagnesemia, often seen in chronic alcoholics and in patients on nasogastric suction receiving parenteral hyperalimentation.

Macrophagic Myofasciitis This distinctive inflammatory muscle disorder, recently described in France, presents as diffuse myalgias, fatigue, and mild muscle weakness. Muscle biopsy reveals pronounced infiltration of the connective tissue around the muscle (epimysium, perimysium, and perifascicular endomysium) by sheets of periodic acid-Schiff-positive macrophages and occasional CD8+ T cells. TheCK or erythrocyte sedimentation rate is variably elevated. Most patients respond to glucocorticoid therapy, and the overall prognosis is favorable. Histologic involvement is focal and limited to sites of previous vaccinations, which may have been administered months or years earlier. This disorder, which to date has not been observed outside of France, has been linked to an aluminum-containing substrate used in vaccine preparation.

Drug-Induced Myopathies Penicillamine and procainamide may produce a true myositis resemblingPM, and aDM-like illness has been associated with contaminated preparations of L-tryptophan. As noted above, zidovudine causes a mitochondrial myopathy. Other drugs may elicit a toxic noninflammatory myopathy that is histologically different from DM, PM, or IBM. The most common drugs are the cholesterol-lowering agents such as clofibrate, lovastatin, simvastatin, or provastatin, especially when combined with cyclosporine or gemfibrozil. Rhabdomyolysis and myoglobinuria have been associated with amphotericin B, e-aminocaproic acid, fenfluramine, heroin, and

phencyclidine. The use of amiodarone, chloroquine, colchicine, carbimazole, emetine, etretinate, ipecac syrup, chronic laxative use resulting in hypocalcemia, licorice, glucocorticoids, and growth hormone has also been associated with myopathy. Some neuromuscular blocking agents such as pancuronium, in combination with glucocorticoids, may cause the acute critical illness myopathy. A careful drug history is essential for diagnosis of these drug-induced myopathies, which do not require immunosuppressive therapy.

Pain on Movement and Muscle Tenderness A number of conditions including *polymyalgia rheumatica* and arthritic disorders of adjacent joints may enter into the differential diagnosis of inflammatory myopathy, even though they do not cause myositis (Chap. 317). The muscle biopsy is either normal or discloses type II fiber atrophy. Patients with *fibrositis* and *fibromyalgia* complain of focal or diffuse muscle tenderness, fatigue, and aching, which is sometimes poorly differentiated from joint pain. In other patients there may be minor signs of a collagen vascular disorder, such as an increased erythrocyte sedimentation rate, antinuclear antibody, or rheumatoid factor. Occasionally there is slight but transient elevation of the serum CK. The muscle biopsy is usually normal and the prognosis favorable. Many such patients show some response to nonsteroidal anti-inflammatory agents, though most continue to have indolent complaints. *Chronic fatigue syndrome*, which may follow a viral infection, can present with debilitating fatigue, fever, sore throat, painful lymphadenopathy, myalgia, arthralgia, sleep disorder, and headache (Chap. 384). These patients do not have muscle weakness, and the muscle biopsy is usually normal.

DIAGNOSIS

The clinically suspected diagnosis of PM, DM, or IBM is confirmed by examining the serum muscle enzymes, EMG findings, and muscle biopsy (Table 382-2).

The most sensitive enzyme is CK, which in active disease can be elevated as much as 50-fold. Although the CK level usually parallels disease activity, it can be normal in some patients with active DM and is frequently normal or only slightly above normal in IBM, even from disease onset. CK may also be normal in patients with untreated, even active, childhood DM and in some patients with DM associated with a connective tissue disease, reflecting the concentration of the pathologic process in the intramuscular vessels and the perimysium. Along with the CK, the serum glutamic-oxaloacetic and glutamate pyruvate transaminases, lactate dehydrogenase, and aldolase may be elevated.

Needle EMG shows myopathic potentials characterized by short-duration, low-amplitude polyphasic units on voluntary activation and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. Mixed potentials (polyphasic units of short and long duration) indicating a chronic process and muscle fiber regeneration are often present in IBM. These EMG findings are not diagnostic of an inflammatory myopathy but are useful to identify the presence of active or chronic myopathy and to exclude neurogenic disorders.

Magnetic resonance imaging is not routinely used for the diagnosis of PM, DM, or IBM. However, it may guide the location of the muscle biopsy in certain clinical settings.

Muscle biopsy is the definitive test for establishing the diagnosis of inflammatory myopathy and for excluding other neuromuscular diseases. Inflammation is the histologic hallmark for these diseases; however, additional features are characteristic of each subtype.

In PM there are T cell infiltrates located primarily within the muscle fascicles (endomysially) and surrounding individual, healthy muscle fibers resulting in phagocytosis and necrosis. When the disease is chronic, connective tissue is increased and often reacts positively with alkaline phosphatase.

In DM the endomysial inflammation is predominantly perivascular or in the interfascicular septae and around, rather than within, the muscle fascicles. The intramuscular blood vessels show endothelial hyperplasia with tuboreticular profiles, fibrin thrombi (especially in children), and obliteration of capillaries. The muscle fibers undergo necrosis, degeneration, and phagocytosis, often in groups involving a portion of a muscle fasiculus in a wedgelike shape or at the periphery of the fascicle, due to microinfarcts within the muscle. This results in perifascicular atrophy, characterized by 2 to 10 layers of atrophic fibers at the periphery of the fascicles. The presence of perifascicular atrophy is diagnostic of DM, *even in the absence of inflammation*.

In IBM, the following occur: (1) intense endomysial inflammation with T cells invading muscle fibers in a pattern identical to (but often more severe) from that seen in PM; (2) basophilic granular deposits distributed around the edge of slitlike vacuoles (rimmed vacuoles); (3) loss of fibers, replaced by fat and connective tissue, and angulated or round fibers, scattered or in small groups; (4) eosinophilic cytoplasmic inclusions; (5) abnormal mitochondria characterized by the presence of ragged-red fibers and cytochrome-oxidase (COX)-negative fibers and supported by the presence of mitochondrial DNA deletions in up to 75% of patients; (6) tiny congophilic amyloid deposits within or next to the vacuoles, best visualized by Texas-red fluorescent optics; and (7) characteristic filamentous inclusions seen by electron microscopy in the vicinity of the rimmed vacuoles. Such filaments can be seen in other vacuolar myopathies; thus they are not unique to IBM. Although demonstration of the filaments by electron microscopy was previously essential for the diagnosis of IBM, currently this is not absolutely necessary if all the other characteristic light-microscopic features, including amyloid deposits, are present.

In some patients with an acquired myopathy that fulfills the clinical criteria for PM or IBM, the muscle biopsy specimen may fail to confirm the suspected diagnosis; in such cases, a diagnosis of probable PM or probable IBM is assigned. An intramuscular inflammatory response around nonnecrotic muscle fibers is an invariable feature of both PM and IBM, and the absence of inflammation raises a critical question about the diagnosis. It is not unreasonable in such cases to obtain another muscle biopsy specimen from a different site. When the patient has the typical clinical phenotype of IBM but the muscle biopsy shows only features of chronic inflammatory myopathy without the typical vacuoles, the diagnosis of probable IBM is also appropriate.

Diagnostic criteria are summarized in Table 382-2. The diagnosis of PM is *definite* if a patient has an acquired, subacute myopathy fulfilling the exclusion criteria noted above,

elevatedCKlevels, and a confirmatory muscle biopsy. The diagnosis ofDM is *definite* if the characteristic rash is present, even if there is no inflammation in the muscle biopsy specimen. The diagnosis ofIBM is *definite* when the characteristic histologic features are present in the muscle biopsy specimen from a patient with the appropriate clinical characteristics.

TREATMENT

The goal of therapy is to improve muscle strength, thereby improving function in activities of daily living. When strength improves the serumCK falls concurrently; however, the reverse is not always true. Unfortunately, there is a common tendency to "chase" or treat the CK level instead of the muscle weakness, a practice that has led to prolonged and unnecessary use of immunosuppressive drugs and erroneous assessment of their efficacy. It is prudent to discontinue these drugs if, after an adequate trial, there is no objective improvement in muscle strength whether or not CK levels are reduced. Agents used in the treatment ofPM andDMinclude:

1. *Glucocorticoids*. Oral prednisone is the initial treatment of choice; the effectiveness and side effects of this therapy determine the future need for stronger immunosuppressive drugs. High-dose prednisone, at least 1 mg/kg per day, is initiated as early in the disease as possible. After an initial period of 3 to 4 weeks, prednisone is tapered slowly over a period of 10 weeks to 1 mg/kg every other day. Then, if there is evidence of efficacy and no serious side effects, the dosage is further reduced by 5 or 10 mg every 3 to 4 weeks until the lowest possible dose that controls the disease is reached. The efficacy of prednisone is determined by an objective increase in muscle strength and activities of daily living, which almost always occurs by the third month of therapy. A feeling of increased energy or a reduction of theCK level without a concomitant increase in muscle strength is not a reliable sign of improvement. If prednisone provides no objective benefit after ~3 months of high-dose therapy, the disease is probably unresponsive to the drug and tapering should be accelerated while the next-in-line immunosuppressive drug is started. Although controlled trials have not been performed, almost all patients with true PMor DMrespond to glucocorticoids to *some degree and for some period of time*; in general, DM responds better than PM.

The long-term use of prednisone may cause increased weakness associated with a normal or unchangedCKlevel; this effect is referred to as *steroid myopathy*. In a patient who previously responded to high doses of prednisone, the development of increased weakness may be related to steroid myopathy or to disease activity that either will respond to a higher dose of glucocorticoids or has become glucocorticoid-resistant. In these circumstances, the decision to raise or lower the prednisone dosage may be influenced by reviewing the patient's history of muscle strength (especially with respect to mobility), serum CK levels, and changes in medications during the preceding 2 months. In uncertain cases, the prednisone dosage can be adjusted arbitrarily; judged by the changes in the patient's strength, the cause of the weakness is usually evident in 2 to 8 weeks.

2. *Immunosuppressive drugs*. Approximately 75% of patients ultimately require treatment with immunosuppressive drugs. Treatment is generally initiated when a patient fails to respond adequately to glucocorticoids after a 3-month trial, the patient

becomes glucocorticoid-resistant, glucocorticoid-related side effects appear, attempts to lower the prednisone dose repeatedly result in a new relapse, or rapidly progressive disease with evolving severe weakness and respiratory failure develops.

Drug selection is largely empirical, with choices based on personal experience, relative efficacy, and safety. The following agents are commonly used: (1) *Azathioprine* is well tolerated, has few side effects, and appears to be as effective for long-term therapy as other drugs. The dose is up to 3 mg/kg daily. (2) *Methotrexate* has a faster onset of action than azathioprine. It is given orally starting at 7.5 mg weekly for the first 3 weeks (2.5 mg every 12 h for 3 doses), with gradual dose escalation by 2.5 mg per week to a total of 25 mg weekly. An important side effect is methotrexate pneumonitis, which can be difficult to distinguish from the interstitial lung disease of the primary myopathy associated with Jo-1 antibodies (described above). (3) *Cyclophosphamide* (0.5 to 1 g/m$_2$intravenously monthly for 6 months) has limited success and significant toxicity. (4) *Chlorambucil* has variable results. (5) *Cyclosporine* has inconsistent and mild benefit. (6) *Mycophenolate mofetil* has recently shown some effectiveness.

3. *Immunomodulating procedures.* In a double-blind study of patients with refractoryDM, intravenous immunoglobulin (IVIg) improved not only the strength and rash but also the underlying immunopathology. The benefit can be impressive but is short-lived (£8 weeks); repeated infusions every 6 to 8 weeks are required to maintain improvement. A dose of 2 g/kg divided over 2 to 5 days per course is recommended. A controlled double-blind study inPM is not yet completed, but uncontrolled observations suggest that IVIg is beneficial for some patients. Neither plasmapheresis or leukapheresis appears to be effective in PM and DM.

The following sequential empirical approach to the treatment ofPM andDM is suggested: *Step 1*: High-dose prednisone; *step 2*: azathioprine or methotrexate; *step 3*:IVIg; *step 4*: a trial, with guarded optimism, of one of the following agents, chosen according to the patient's age, degree of disability, tolerance, experience with the drug, and the patient's general health: cyclosporine, chlorambucil, cyclophosphamide, mycophenolate. Patients with interstitial lung disease may benefit from aggressive treatment with cyclophosphamide.

Common pitfalls leading to failure of steroid or immunosuppressive treatment are inadequate initial dose of prednisone or cytotoxic drugs, short duration of therapy or quick tapering, early development of preventable side effects necessitating early discontinuation of prednisone, and wrong diagnosis. A patient with presumedPM who has not responded to any form of immunotherapy most likely hasIBM or another disease. In these cases, a repeat muscle biopsy and a more vigorous search for the putative "other disease" are recommended. In addition to IBM, the most often misdiagnosed disorders are metabolic myopathy such as phosphorylase deficiency, a dystrophic process with endomysial inflammation resembling polymyositis, drug-induced myopathy, or an endocrinopathy.

Calcinosis, a manifestation ofDM, is difficult to treat; however, new calcium deposits may be prevented if the primary disease responds to the available therapies. Diphosphonates, aluminum hydroxide, probenecid, colchicine, low doses of warfarin, calcium blockers, and surgical excision have all been tried without success.

IBMis resistant to immunosuppressive therapies. Prednisone together with azathioprine or methotrexate have been disappointing, but most experts try these agents for a few months in newly diagnosed patients. Because occasional patients may feel subjectively weaker after these drugs are discontinued, some clinicians prefer to maintain some patients on low-dose, every-other-day prednisone or weekly methotrexate in an effort to halt disease progression, even though there is no objective evidence or controlled study to support this practice. In one double-blind study ofIVIg in IBM, minimal benefit in up to 30% of the patients was found; the strength gains, however, were not of sufficient magnitude to justify the routine use of this drug. A second controlled trial combining IVIg with prednisone was ineffective in 36 IBM patients. Despite these disappointing results, many experts believe that a 2- to 3-month trial with IVIg may be reasonable for selected patients with IBM who experience rapid progression of muscle weakness or choking episodes due to worsening dysphagia.

PROGNOSIS

Although accurate data from large series is not available, it is believed that the 5-year survival rate for treated patients withPM andDM is approximately 80%; death is usually due to pulmonary, cardiac, or other systemic complications. Patients severely affected at presentation or treated after long delays, those with severe dysphagia or respiratory difficulties, older patients, and those with associated cancer have a worse prognosis. DM responds more favorably to therapy than PM and thus has a better prognosis. Most patients improve with therapy, and many make a full functional recovery, which is often sustained with maintenance therapy. Up to 30% may be left with some residual muscle weakness. Relapses may occur at any time.

IBMhas the least favorable prognosis of the inflammatory myopathies. Most patients will require the use of an assistive device such as a cane, walker, or wheelchair within 5 to 10 years of onset. In general, the older the age of onset in IBM, the more rapidly progressive is the course.

(Bibliography omitted in Palm version)

383. MUSCULAR DYSTROPHIES AND OTHER MUSCLE DISEASES- *Robert H. Brown, Jr., Jerry R. Mendell*

The muscle disorders discussed in this chapter include diseases that cause acute, subacute, and chronic muscle weakness. Some cause pain in addition to or instead of weakness. **Dermatomyositis and polymyositis are discussed in Chap. 382.*

HEREDITARY MYOPATHIES

Muscular dystrophy refers to a group of hereditary progressive diseases. Each type of muscular dystrophy has unique phenotypic and genetic features (Table 383-1).

DUCHENNE MUSCULAR DYSTROPHY

This X-linked recessive disorder, sometimes also called *pseudohypertrophic muscular dystrophy*, has an incidence of ~30 per 100,000 live-born males.

Clinical Features Duchenne dystrophy is present at birth, but the disorder usually becomes apparent between ages 3 and 5. The boys fall frequently and have difficulty keeping up with their friends when playing. Running, jumping, and hopping are invariably abnormal. By age 5, muscle weakness is obvious by muscle testing. On getting up from the floor, the patient uses his hands to climb up himself (Gowers' maneuver). Contractures of the heel cords and iliotibial bands become apparent by age 6, when toe walking is associated with a lordotic posture. Loss of muscle strength is progressive, with predilection for proximal limb muscles and the neck flexors; leg involvement is more severe than arm involvement. Between ages 8 and 10 walking may require the use of braces; joint contractures and limitations of hip flexion, knee, elbow, and wrist extension are made worse by prolonged sitting. By age 12, most patients are wheelchair dependent. Contractures become fixed, and a progressive scoliosis often develops that may be associated with pain. The chest deformity with scoliosis impairs pulmonary function, which is already diminished by muscle weakness. By age 16 to 18, patients are predisposed to serious, sometimes fatal pulmonary infections. Other causes of death include aspiration of food and acute gastric dilation.

A cardiac cause of death is uncommon despite the presence of a cardiomyopathy in almost all patients. Congestive heart failure seldom occurs except with severe stress such as pneumonia. Cardiac arrhythmias are rare. The typical electrocardiogram (ECG) shows an increase net RS in lead V_1; deep, narrow Q waves in the precordial leads; and tall right precordial R waves in V_1. Intellectual impairment in Duchenne dystrophy is common; the average intelligence quotient (IQ) is approximately one standard deviation below the mean. Impairment of intellectual function appears to be nonprogressive and affects verbal ability more than performance.

Laboratory Features Serum creatine kinase (CK) levels are invariably elevated to between 20 and 100 times normal. The levels are abnormal at birth but decline late in the disease because of inactivity and loss of muscle mass. Electromyography (EMG) demonstrates features typical of myopathy. The muscle biopsy shows muscle fibers of varying size as well as small groups of necrotic and regenerating fibers. Connective tissue and fat replace lost muscle fibers. A definitive diagnosis of Duchenne dystrophy

can be established on the basis of dystrophin deficiency in a biopsy of muscle tissue or mutation analysis on peripheral blood leukocytes as discussed below.

GENETIC CONSIDERATIONS

Duchenne dystrophy is caused by a mutation of the gene that encodes dystrophin, a 427-kDa protein localized to the inner surface of the sarcolemma of the muscle fiber. The dystrophin gene is more than 2000 kb in size and thus is one of the largest identified human genes. It is localized to the short arm of the X chromosome at Xp21. At present, mutations of the gene can be identified (in approximately two-thirds of Duchenne patients) with a battery of cDNA probes. Deletions are not uniformly distributed over the gene, but rather are most common near the beginning (5¢ end) and middle of the gene. Deletion size does not correlate with severity of disease. Less often, Duchenne dystrophy is caused by a gene duplication or point mutation. Identification of a specific mutation allows for an unequivocal diagnosis, makes possible accurate testing of potential carriers, and is useful for prenatal diagnosis.

A diagnosis of Duchenne dystrophy can also be made by western blot analysis of muscle biopsy specimens, revealing abnormalities on the quantity and molecular weight of dystrophin protein. In addition, immunocytochemical staining of muscle with dystrophin antibodies can be used to demonstrate absence or deficiency of dystrophin localizing to the sarcolemmal membrane. Carriers of the disease may demonstrate a mosaic pattern, but dystrophin analysis of muscle biopsy specimens for carrier detection is not reliable.

Pathogenesis Dystrophin is part of a large complex of sarcolemmal proteins and glycoproteins (Fig. 383-1). Dystrophin binds to F-actin at its amino terminus and to b-dystroglycan at the carboxyl terminus. b-Dystroglycan complexes toa-dystroglycan, which binds to laminin in the extracellular matrix (ECM). Laminin has a heterotrimeric molecular structure arranged in the shape of a cross with one heavy chain and two light chains,b1 and g1. The laminin heavy chain of skeletal muscle is designated laminin a2. Peripheral to laminin in the ECM are collagen proteins IV and VI. Likeb-dystroglycan, the transmembrane sarcoglycan proteins also bind to dystrophin; these five proteins (designateda- through e-sarcoglycan) complex tightly with each other. More recently, other membrane proteins implicated in muscular dystrophy have been found to be loosely affiliated with constituents of the dystrophin complex. These include caveolin-3 anda7 integrin (Fig. 383-1).

The dystrophin-glycoprotein complex appears to confer stability to the sarcolemma, although the function of each individual component of the complex is incompletely understood. Deficiency of one member of the complex may cause abnormalities in other components. For example, a primary deficiency of dystrophin (Duchenne dystrophy) may lead to secondary loss of the sarcoglycans and dystroglycan. The primary loss of a single sarcoglycan (see "Limb-Girdle Muscular Dystrophy," below) results in a secondary loss of other sarcoglycans in the membrane without uniformly affecting dystrophin. In either instance, disruption of the dystrophin-glycoprotein complexes weakens the sarcolemma, causing membrane tears and a cascade of events leading to muscle fiber necrosis. This sequence of events occurs repeatedly during the life of a patient with muscular dystrophy.

TREATMENT

Glucocorticoids, administered as prednisone in a dose of 0.75 mg/kg per day, significantly slow progression of Duchenne dystrophy for up to 3 years. Some patients cannot tolerate glucocorticoid therapy; weight gain in particular represents a significant deterrent for some boys.

BECKER MUSCULAR DYSTROPHY

This less severe form of X-linked recessive muscular dystrophy results from allelic defects of the same gene responsible for Duchenne dystrophy. Becker muscular dystrophy is approximately 10 times less frequent than Duchenne, with an incidence of about 3 per 100,000 live-born males.

Clinical Features The pattern of muscle wasting in Becker muscular dystrophy closely resembles that seen in Duchenne. Proximal muscles, especially of the lower extremities, are prominently involved. As the disease progresses, weakness becomes more generalized. Significant facial muscle weakness is not a feature. Hypertrophy of muscles, particularly in the calves, is an early and prominent finding.

Most patients with Becker dystrophy first experience difficulties between ages 5 and 15 years, although onset in the third or fourth decade or even later can occur. By definition, patients with Becker dystrophy walk beyond age 15, while patients with Duchenne dystrophy are typically in a wheelchair by the age of 12. Patients with Becker dystrophy have a reduced life expectancy, but most survive into the fourth or fifth decade.

Mental retardation may occur in Becker dystrophy, but it is not as common as in Duchenne. Cardiac involvement occurs in Becker dystrophy and may result in heart failure.

Laboratory Features Serum CK levels, results of EMG, and muscle biopsy findings closely resemble those in Duchenne dystrophy. The diagnosis of Becker muscular dystrophy requires western blot analysis of muscle biopsy samples demonstrating dystrophin of reduced amount or abnormal size. Mutation analysis of DNA from peripheral blood leukocytes recognizes deletions and duplications of the dystrophin gene in 65% of patients with Becker dystrophy, approximately the same percentage as in Duchenne dystrophy. In both Becker and Duchenne dystrophies, the size of the DNA deletion does not predict clinical severity; however, in ~95% of patients with Becker dystrophy, the DNA deletion does not alter the translational reading frame of messenger RNA. These "in-frame" mutations allow for production of some dystrophin, which accounts for the presence of altered rather than absent dystrophin on western blot analysis.

TREATMENT

The use of glucocorticoids has not been adequately studied in Becker dystrophy.

LIMB-GIRDLE MUSCULAR DYSTROPHY

The syndrome of limb-girdle muscular dystrophy (LGMD) represents more than one disorder.

Clinical Features Muscle weakness affects both males and females, with onset ranging from late in the first decade to the fourth decade. MostLGMDs are progressive and affect primarily the pelvic and shoulder girdle muscles. Respiratory insufficiency from weakness of the diaphragm may occur. The distribution of weakness and rate of progression vary from family to family. Similar to the dystrophinopathies, cardiac involvement may result in congestive heart failure or arrhythmias; occasional patients present with a cardiomyopathy. Intellectual function remains normal.

Laboratory Features An elevated serum CKlevel, myopathicEMGfindings, and muscle biopsy features indicative of myopathy are characteristic. Careful attention is required to exclude phenotypically similar disorders, such as spinal muscular atrophy (Chap. 365), inflammatory myopathies (Chap. 382), and metabolic myopathies (see below). The availability of western blot analysis for dystrophin allowsLGMD to be distinguished unequivocally from Becker and Duchenne muscular dystrophies.

GENETIC CONSIDERATIONS

LGMDmay be transmitted by autosomal dominant or autosomal recessive inheritance. In a new genetic classification, *LGMD1* refers to the dominantly inherited form and *LGMD2* to the recessively inherited form. Genetic linkage has identified three dominantly inherited disorders, LGMD1A-C. The recessively inherited forms of LGMD now number eight. In each case genetic linkage has been established; the specific protein deficiency is known for most forms (Table 383-2 andFig. 383-1). In LGMD2A the defect lies in a muscle-specific, calcium-activated neutral protease, calpain 3. LGMD2B arises from defects in dysferlin, a novel, membrane-associated muscle protein. Four sarcoglycans (a-d) are deficient in LGMD2C-F.

TREATMENT

At present, only supportive care can be offered. Long leg braces are useful for affected children but seldom helpful for adults. Wheelchairs may be essential or may be used to help preserve energy for work or recreational activities. Cardiac or respiratory muscle involvement may require individualized treatment. Studies of primary genetic therapy inLGMD are currently in progress.

EMERY-DREIFUSS MUSCULAR DYSTROPHY

This disorder is characterized by childhood onset of contractures at the elbows, weakness in the humeral and peroneal muscles, and cardiomyopathy. The contractures may precede the weakness. As the disease progresses, the weakness may spread to involve the proximal limb-girdle muscles. Perhaps the most critical clinical aspect of Emery-Dreifuss muscular dystrophy (EDMD) is the cardiomyopathy, which may appear as conduction defects of abrupt onset. Sudden death is not uncommon in EDMD, even in otherwise unaffected female carriers; early use of pacemakers may be lifesaving.

Most cases of EDMD are X-linked, arising because of defects in a gene encoding emerin, a nuclear membrane protein. Another group is inherited as autosomal dominant traits. In these instances the molecular defects are in the gene located on chromosome 1, encoding the proteins lamin A and lamin C. These proteins are splice variants that localize to the nuclear envelope where, in some cells, they co-localize with emerin.

CONGENITAL MUSCULAR DYSTROPHY

This rare autosomal recessive disorder includes at least six subgroups with overlapping clinical features. Variable involvement of the brain and eyes can help differentiate these conditions; three have been mapped to specific chromosomes, with a specific defect identified in each (Table 383-3). All the forms of congenital muscular dystrophy present at birth or in the first few months of life with hypotonia and proximal limb weakness. Varying degrees of joint contractures at the elbows, hips, knees, and ankles are seen in most patients. Contractures present at birth are referred to as *arthrogryposis*. Weakness of facial muscles may occur, but other cranial nerve musculature is spared. Severity varies greatly, but about half of affected individuals never achieve the ability to stand independently. Death may ensue because of respiratory insufficiency early in life. Some patients learn to walk, although difficulty in motor activities (e.g., running) persists.

In patients with a deficiency of laminin a2 (formerly called merosin), diffuse white matter changes typical of hypomyelination are seen by magnetic resonance imaging. The clinical manifestations of the cerebral hypomyelination are mild, with learning disability as the most severe problem. In *Fukuyama congenital muscular dystrophy*, found mainly in Japan, patients are severely disabled and mentally retarded; most have seizures and die by age 20. Microcephaly and enlarged ventricles occur. Micropolygyria is common. The primary defect in this dystrophy is in the gene encoding fukutin, a secreted protein whose function remains ill-defined. In some patients, the fukutin gene is disrupted by insertion of a transposon, a novel pathogenetic mechanism. Recently, it has been reported that a form of congenital muscular dystrophy arises from the absence of a7 integrin, a muscle membrane protein.

MYOTONIC DYSTROPHY

This disorder, the most common adult muscular dystrophy, has an incidence of 13.5 per 100,000 live births and affects males and females equally.

Clinical Features The clinical expression of myotonic dystrophy varies widely and involves many systems other than muscle. Affected patients have a typical "hatchet-faced" appearance due to temporalis, masseter, and facial muscle atrophy and weakness. Neck muscles, including flexors and sternocleidomastoids, and distal limb muscles are involved early. Weakness of wrist extensors, finger extensors, and intrinsic hand muscles impairs function. Ankle dorsiflexor weakness may cause footdrop. Proximal muscles remain stronger throughout the course, although preferential atrophy and weakness of quadriceps muscles occur in many patients. Palatal, pharyngeal, and tongue involvement produce a dysarthric speech, nasal voice, and swallowing problems. Some patients have diaphragm and intercostal muscle weakness, resulting in respiratory insufficiency.

Myotonia, which usually appears by age 5, is demonstrable by percussion of the thenar eminence, the tongue, and wrist extensor muscles. Myotonia causes a slow relaxation of hand grip after a forced voluntary closure. Advanced muscle wasting makes myotonia more difficult to detect.

Congenital myotonic dystrophy is a more severe form of the disease and occurs in ~25% of infants of affected mothers. It is characterized by severe facial and bulbar weakness and transient neonatal respiratory insufficiency.

Cardiac disturbances occur in most patients with myotonic dystrophy.ECGabnormalities are common, including first-degree heart block and more extensive conduction system involvement. Complete heart block and sudden death can occur. Congestive heart failure occurs infrequently but may result from cor pulmonale secondary to respiratory failure. Mitral valve prolapse also occurs commonly.

Other features associated with myotonic dystrophy include intellectual impairment, hypersomnia, posterior subcapsular cataracts, frontal baldness, gonadal atrophy, insulin resistance, and decreased esophageal and colonic motility.

Laboratory Features The diagnosis of myotonic dystrophy can usually be made on the basis of clinical findings. SerumCKlevels may be normal or mildly elevated.EMGevidence of myotonia is present in most cases. Muscle biopsy shows muscle atrophy, which selectively involves type 1 fibers in 50% of cases. Typically, increased numbers of central nuclei can be seen. Necrosis of muscle fibers and increased connective tissue, common in other muscular dystrophies, do not usually occur in myotonic dystrophy.

GENETIC CONSIDERATIONS

Myotonic dystrophy is an autosomal dominant disorder. New mutations do not appear to contribute to the pool of affected individuals. The disorder is transmitted by an intronic mutation consisting of an unstable expansion of a CTG trinucleotide repeat sequence at 19q13.3. An increase in the severity of the disease phenotype in successive generations (genetic anticipation) is accompanied by an increase in the number of trinucleotide repeats. A similar type of mutation has been identified in fragile X syndrome (Chap. 359). The unstable triplet repeat in myotonic dystrophy can be used for prenatal diagnosis. Congenital disease occurs almost exclusively in infants born to affected mothers; it is possible that sperm with greatly expanded triplet repeats do not function well.

How the CTG expansions impair function of muscle and other cells is not understood. They may alter expression of an adjacent protein kinase gene or of other neighboring genes. Alternatively, the expanded CTG might act as a sink that binds and inactivates important RNA binding proteins.

A subset of patients with multisystemic disease features similar to myotonic dystrophy do not have the diagnostic CTG expansion. Their weakness tends to be proximal rather than distal. This condition, termed proximal myotonic myopathy (PROMM), is genetically distinct from myotonic dystrophy.

TREATMENT

The myotonia in myotonic dystrophy rarely warrants treatment. Phenytoin is the preferred agent for the occasional patient who requires an antimyotonia drug; other agents, particularly quinine and procainamide, may worsen cardiac conduction. Cardiac pacemaker insertion should be considered for patients with unexplained syncope or advanced conduction system abnormalities with evidence of second-degree heart block, or trifascicular conduction disturbances with marked prolongation of the PR interval. Molded ankle-foot orthoses help prevent footdrop in patients with distal lower extremity weakness.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

This form of muscular dystrophy has an incidence of approximately 1 in 20,000. It is distinct from a similar disorder known as scapuloperoneal dystrophy.

Clinical Features The condition typically has an onset in childhood and young adulthood. In most cases, facial weakness is the initial manifestation, appearing as an inability to smile, whistle, or fully close the eyes. Weakness of the shoulder girdles, rather than the facial muscles, usually brings the patient to medical attention. Loss of scapular stabilizer muscles makes arm elevation difficult. Scapular winging becomes apparent with attempts at abduction and forward movement of the arms. Biceps and triceps muscles may be severely affected, with relative sparing of the deltoid muscles. Weakness is invariably worse for wrist extension than for wrist flexion, and weakness of the anterior compartment muscles of the legs may lead to footdrop.

In most patients, the weakness remains restricted to facial, upper extremity, and distal lower extremity muscles. In 20% of patients, weakness progresses to involve the pelvic girdle muscles, and severe functional impairment and possible wheelchair dependency result.

Characteristically, patients with facioscapulohumeral (FSH) dystrophy do not have involvement of other organ systems, although labile hypertension is common, and there is an increased incidence of nerve deafness. Coats' disease, a disorder consisting of telangiectasia, exudation, and retinal detachment, also occurs.

Laboratory Features The serum CK level may be normal or mildly elevated. EMG usually indicates a myopathic pattern. The muscle biopsy shows nonspecific features of a myopathy. A prominent inflammatory infiltrate, which is often multifocal in distribution, is present in some biopsy samples. The cause or significance of this finding is unknown.

GENETIC CONSIDERATIONS

An autosomal dominant inheritance pattern with almost complete penetrance has been established, but each family member should be examined for the presence of the disease, since ~30% of those affected are unaware of involvement. FSH dystrophy is caused by deletions of telomeric heterochromatin at chromosome 4q35. There is a

significant correlation between disease severity and the size of the 4q35-associated deletion. Although a specific FSH gene and protein have not been identified, carrier detection and prenatal diagnosis are possible. Most sporadic cases represent new mutations. Genetic heterogeneity has been documented for FSH dystrophy; in occasional families, the disease is linked to chromosome 10.

TREATMENT

No specific treatment is available; ankle-foot orthoses are helpful for patients with footdrop. Scapular stabilization procedures improve scapular winging but may not improve function.

OCULOPHARYNGEAL DYSTROPHY

This form of muscular dystrophy represents one of several disorders characterized by *progressive external ophthalmoplegia*, which consists of slowly progressive ptosis and limitation of eye movements with sparing of pupillary reactions for light and accommodation. Patients usually do not complain of diplopia, in contrast to patients having conditions with a more acute onset of ocular muscle weakness (e.g., myasthenia gravis).

Clinical Features Oculopharyngeal muscular dystrophy has a late onset; it usually presents with ptosis and/or dysphagia in the fourth to sixth decade. The extraocular muscle impairment is less prominent in the early phase but may be severe later. The swallowing problem may become debilitating and result in pooling of secretions and repeated episodes of aspiration. Mild weakness of the neck and extremities also occurs.

Laboratory Features The serum CK level may be two to three times normal. Myopathic EMG findings are typical. On biopsy, muscle fibers are found to contain vacuoles, which by electron microscopy are shown to contain membranous whorls, accumulation of glycogen, and other nonspecific debris related to lysosomes. A distinct feature of oculopharyngeal dystrophy is the presence of tubular filaments, 8.5 nm in diameter, in muscle cell nuclei.

GENETIC CONSIDERATIONS

Oculopharyngeal dystrophy has an autosomal dominant inheritance pattern with complete penetrance. The incidence is high in French-Canadians and in Spanish-American families of the southwestern United States. Large kindreds of Italian and of eastern European Jewish descent have been reported. The molecular defect in oculopharyngeal muscular dystrophy is a subtle expansion of a modest polyanine repeat tract in a poly-RNA binding protein (PABP2) in muscle; this disorder maps to chromosome 14q.

TREATMENT

Dysphagia can cause inanition, making oculopharyngeal muscular dystrophy a potentially life-threatening disease. Cricopharyngeal myotomy may improve swallowing, although it does not prevent aspiration. Eyelid crutches can improve vision in patients in

whom ptosis obstructs vision; candidates for ptosis surgery must be carefully selected -- those with severe facial weakness are not suitable.

DISTAL MYOPATHIES

Patients with predominantly distal weakness usually have a disease of peripheral nerve or anterior horn cells rather than of muscle. There is, however, a heterogeneous group of uncommon disorders of this type with histopathologic and electrophysiologic evidence of myopathy. These distal myopathies can be separated into two types with onset in late adulthood and two types with onset in early adulthood.

The most common late adult-onset form, described by Welander, is inherited as an autosomal dominant condition with onset in the fifth decade. Weakness begins in the hands, and distal anterior-compartment leg muscle involvement occurs later in the course. The serum CKlevel is either normal or mildly increased. Muscle biopsy shows vacuolated muscle fibers. This disorder genetically maps to chromosome 2p13.

Another late adult-onset form of distal myopathy, also inherited as an autosomal dominant trait, was first recognized in non-Scandinavian patients and also occurs in Finland. Weakness begins in the anterior compartment of the distal lower extremities. The serumCK level is normal or mildly elevated. Muscle fibers often have vacuoles. This disease, sometimes designated "Udd myopathy," maps to the locus for the skeletal muscle protein titin on chromosome 2q31-33.

Both of the distal myopathies with onset in early adulthood have autosomal recessive inheritance. In one type, the weakness usually begins in the anterior compartment of the distal lower extremities, although in some cases it begins in the hands. The serumCK level is moderately elevated (<10 times normal), and muscle biopsies reveal a myopathy with many fibers showing vacuoles. Many of these cases are genetically linked to the centromere on chromosome 9. The other form of early adult-onset distal myopathy (Miyoshi myopathy) is distinguished by weakness beginning in the posterior compartment, i.e., the gastrocnemius muscle. The serum CK level is markedly elevated (>10-fold), and biopsy shows a myopathy without vacuolated fibers. Like LGMB2B, Miyoshi myopathy is caused by defects in the gene encoding the protein dysferlin on chromosome 2p13.

CONGENITAL MYOPATHIES

These rare disorders are distinguished from muscular dystrophies by the presence of specific histochemical and structural abnormalities in muscle. Three major types are described: *central core disease*, *nemaline (rod) myopathy*, and *centronuclear (myotubular) myopathy*. Other rare types, such as multicore disease, fingerprint body myopathy, and sarcotubular myopathy, are not discussed here.

CENTRAL CORE DISEASE

Patients with central core disease may have decreased fetal movements and breech presentation. Hypotonia and delay in motor milestones, particularly in walking, are common. Later in childhood, patients develop problems with stair climbing, running, and

getting up from the floor. On examination, there is mild facial, neck-flexor, and proximal-extremity muscle weakness. Legs are more affected than arms. Skeletal abnormalities include congenital hip dislocation, scoliosis, and pes cavus; clubbed feet also occur. Most cases are nonprogressive, but exceptions are well documented.

The serum CK level is usually normal. Needle EMG demonstrates a myopathic pattern. Muscle biopsy shows fibers with single or multiple central or eccentric discrete zones (cores) devoid of oxidative enzymes. Cores occur preferentially in type 1 fibers and represent poorly aligned sarcomeres associated with Z disk streaming.

GENETIC CONSIDERATIONS

Autosomal dominant inheritance is characteristic; sporadic cases also occur. The disease is caused by point mutations of the ryanodine receptor gene on chromosome 19q, encoding the calcium-release channel of the sarcoplasmic reticulum of skeletal muscle; mutations of this gene also account for some cases of inherited malignant hyperthermia (Chap. 17).

Specific treatment is not required, but establishing a diagnosis of central core disease is extremely important, because these patients have a known predisposition to malignant hyperthermia during anesthesia.

NEMALINE MYOPATHY

The term *nemaline* refers to the distinctive presence in muscle fibers of rods or threadlike structures (Greek *nema*, "thread"). Nemaline myopathy is clinically heterogeneous. A severe neonatal form presents with hypotonia and feeding difficulties leading to early death. Most commonly, nemaline myopathy presents in infancy or childhood with delayed motor milestones. The course is nonprogressive or slowly progressive. The physical appearance may be striking because of the long, narrow facies, high-arched palate, and open-mouthed appearance due to a prognathous jaw. Other skeletal abnormalities include pectus excavatum, kyphoscoliosis, pes cavus, and clubfoot deformities. Facial and generalized muscle weakness are common. These two early childhood forms of nemaline myopathy are referred to as *congenital nemaline myopathy*, in contrast to an adult-onset disorder with progressive proximal weakness. Myocardial involvement is occasionally present in both the congenital and adult-onset forms of the disease.

The serum CK level is usually normal or slightly elevated. The EMG in weak muscles demonstrates a myopathic pattern with occasional fibrillation potentials. Muscle biopsy demonstrates clusters of small rods (nemaline bodies), which occur preferentially, but not exclusively, in type 1 muscle fibers. The muscle often shows type 1 muscle fiber predominance. Rods originate from the Z disk material of the muscle fiber. In the severe neonatal variant, rods are commonly observed in the nucleus of muscle fibers.

GENETIC CONSIDERATIONS

Nemaline myopathy shows at least two patterns of inheritance: autosomal recessive and autosomal dominant with incomplete penetrance. Sporadic cases also occur.

Nemaline myopathy is associated with mutations of three genes: TPM3 (a-tropomyosin slow) in both dominant and recessive forms, NEB (encoding nebulin) in the slowly progressive autosomal dominant variant, and ACTA1 (a-actin) in the severe neonatal form.

CENTRONUCLEAR MYOPATHY

Three distinct variants of centronuclear myopathy occur. A *neonatal form*, also known as myotubular myopathy, presents with severe hypotonia and weakness at birth. The *late infancy-early childhood form* presents with delayed motor milestones. Later, difficulty with running and stair climbing becomes apparent. A marfanoid, slender body habitus, long narrow face, and high-arched palate are typical. Scoliosis and clubbed feet may be present. Most patients exhibit progressive weakness, some requiring wheelchairs. Progressive external ophthalmoplegia with ptosis and varying degrees of extraocular muscle impairment are characteristic of both the neonatal and the late-infantile forms. A third variant, the *late childhood-adult form*, has an onset in the second or third decade. Patients have full extraocular muscle movements and rarely exhibit ptosis. There is mild, nonprogressive limb weakness and no associated skeletal abnormalities.

Normal or slightly elevated CK levels occur in each of the forms. EMG studies often give distinctive results, showing positive sharp waves and fibrillation potentials, complex and repetitive discharges, and rarely myotonic discharges. Muscle biopsy specimens in longitudinal section demonstrate rows of central nuclei, often surrounded by a halo. In transverse sections, central nuclei are found in 25 to 80% of muscle fibers.

GENETIC CONSIDERATIONS

A gene for the neonatal form of centronuclear myopathy has been localized to Xq28; this gene encodes myotubularin, a protein tyrosine phosphatase. Missense, frameshift and splice-site mutations predict loss of myotubularin function in affected individuals. Carrier identification and prenatal diagnosis are possible. The inheritance pattern for the late infancy-early childhood disorder is probably autosomal recessive, and for the late childhood-adult form is probably autosomal dominant.

DISORDERS OF MUSCLE ENERGY METABOLISM

There are two principal sources of energy for skeletal muscle -- fatty acids and glucose. Abnormalities in either glucose or lipid utilization can be associated with distinct clinical presentations that can range from an acute, painful syndrome with rhabdomyolysis and myoglobinuria to a chronic, progressive muscle weakness simulating muscular dystrophy.

GLYCOGEN STORAGE AND GYCOLYTIC DEFECTS

These disorders can be divided into those that can cause exercise intolerance, particularly intermittent muscle pain and myoglobinuria, and those in which fixed muscle weakness is the predominant clinical feature. The latter can mimic LGMD or inflammatory myopathies.

Disorders of Glycogen Storage Causing Fixed Muscle Weakness Three clinical forms of acid maltase deficiency (*type II glycogenosis*) can be distinguished, all of which have autosomal recessive inheritance. The gene for acid maltase is found on the long arm of chromosome 17. The *infantile form* is the most common, with onset of symptoms in the first 3 months of life. Infants develop severe muscle weakness, cardiomegaly, hepatomegaly, and respiratory insufficiency. Glycogen accumulation in motor neurons of the spinal cord and brainstem contributes to muscle weakness. Death usually occurs by 1 year of age. In the *childhood form*, the picture resembles muscular dystrophy. Delayed motor milestones result from proximal limb muscle weakness and involvement of respiratory muscles. The heart may be involved, but the liver and brain are unaffected. The *adult form* begins in the third or fourth decade. Respiratory failure and diaphragmatic weakness are often initial manifestations heralding progressive proximal muscle weakness. The heart and liver are not involved.

In all forms of acid maltase deficiency, the serum CK level is 2 to 10 times normal. EMG examination demonstrates a myopathic pattern, but other features are especially distinctive, including myotonic discharges, trains of fibrillation and positive waves, and complex repetitive discharges. EMG discharges are very prominent in the lumbosacral paraspinal muscles. The muscle biopsy shows vacuoles containing glycogen and the lysosomal enzyme acid phosphatase. Electron microscopy reveals membrane-bound and free tissue glycogen. Definitive diagnosis is established by enzyme determination in muscle.

No satisfactory treatment exists for acid maltase deficiency. A high-protein diet has been advocated, but efficacy has not been documented. Intravenous enzyme replacement has not shown benefit.

In *debranching enzyme deficiency (type III glycogenosis)*, a slowly progressive form of muscle weakness can develop after puberty. Rarely, myoglobinuria may be seen. Patients are usually diagnosed in infancy, however, because of hypotonia and delayed motor milestones, hepatomegaly, growth retardation, and hypoglycemia. *Branching enzyme deficiency (type IV glycogenosis)* is a rare and fatal glycogen storage disease characterized by failure to thrive and hepatomegaly. Hypotonia and muscle wasting may be present, but the skeletal muscle manifestations are minor compared to liver failure.

Disorders of Glycolysis Causing Exercise Intolerance Five glycolytic defects are associated with recurrent myoglobinuria: *myophosphorylase deficiency (type V glycogenosis)*, *phosphofructokinase deficiency (type VII glycogenosis)*, *phosphoglycerate kinase deficiency (type IX glycogenosis)*, *phosphoglycerate mutase deficiency (type X glycogenosis)*, and *lactate dehydrogenase deficiency (glycogensosis type XI)*. Myophosphorylase deficiency, also known as McArdle's disease, is by far the most common of the glycolytic defects associated with exercise intolerance. All are inherited as autosomal recessive traits, except for phosphoglycerate kinase deficiency, which is X-linked recessive. These five glycolytic defects result in a common failure to support energy production at the initiation of exercise, although the exact site of energy failure remains controversial.

Clinical muscle manifestations in these five conditions usually begin in adolescence.

Symptoms are precipitated by brief bursts of high-intensity exercise, such as running or lifting heavy objects. A history of myalgia and muscle stiffness usually precedes the intensely painful muscle contractures, which may be followed by myoglobinuria. Acute renal failure accompanies significant pigmenturia. Exercise tolerance can be enhanced by a slow induction phase (warm-up) or brief periods of rest, allowing for the start of the "second-wind" phenomenon (switching to utilization of fatty acids).

Certain features help distinguish some enzyme defects. Varying degrees of hemolytic anemia accompany deficiencies of both phosphofructokinase (mild) and phosphoglycerate kinase (severe). In phosphoglycerate kinase deficiency, the usual clinical presentation is a seizure disorder associated with mental retardation; exercise intolerance is an infrequent manifestation.

In all of these conditions, the serum CK levels fluctuate widely and may be elevated even during symptom-free periods. CK levels >100 times normal are expected, accompanying myoglobinuria. All patients with suspected glycolytic defects leading to exercise intolerance should undergo a forearm exercise test (Chap. 381). An impaired rise in venous lactate is highly indicative of a glycolytic defect. In lactate dehydrogenase deficiency, venous levels of lactate do not increase, but pyruvate rises to normal, after forearm exercise. In all glycolytic defects, a definitive diagnosis is made by muscle biopsy.

Training may enhance the second-wind phenomenon, but attempts to raise blood glucose or to modify these disorders through diet have not proved beneficial.

DISORDERS OF LIPID METABOLISM

Lipid is an important muscle energy source during rest and during prolonged, submaximal exercise. Fatty acids are derived from circulating very low-density lipoprotein (VLDL) in the blood or from triglycerides stored in muscle fibers. Oxidation of fatty acids occurs in the mitochondria. To enter the mitochondria, a fatty acid must first be converted to an "activated fatty acid," acyl-CoA. The acyl-CoA must be linked with carnitine by the enzyme carnitine palmitoyltransferase (CPT) I for transport into the mitochondria. CPT I is present on the inner side of the outer mitochondrial membrane. Carnitine is removed by CPT II, an enzyme attached to the inside of the inner mitochondrial membrane, allowing transport of acyl-CoA into the mitochondrial matrix for b-oxidation.

CARNITINE DEFICIENCY

Deficiency of this important substrate results in a myopathic and a systemic disorder.

Myopathic carnitine deficiency is associated with generalized muscle weakness, usually beginning in childhood. The clinical features overlap with those of muscular dystrophy and polymyositis. Patients develop progressive, painless proximal weakness. A severe cardiomyopathy may be present. Serum CK levels may be mildly to markedly (>10-fold) elevated. The muscle biopsy shows striking lipid accumulation. The serum carnitine level is normal. The cause for decreased muscle carnitine is not understood. Most cases are sporadic, but the inheritance pattern is thought to be autosomal recessive.

Some patients respond to oral carnitine supplementation; this treatment should be tried in all cases. Other patients have responded to prednisone, riboflavin, or propranolol. A diet substituting medium-chain for long-chain triglycerides has been helpful for some patients.

Systemic carnitine deficiency usually presents in infancy and early childhood and is characterized by progressive weakness and episodes of hepatic encephalopathy with nausea, vomiting, confusion, coma, and early death. Carnitine levels are reduced in muscle, liver, kidney, and heart; but the low serum carnitine levels are especially useful in distinguishing this condition from the myopathic form. No single cause has been identified to explain the low serum carnitine levels. Decreased hepatic synthesis explains some cases, while increased urinary excretion occurs in others. Serum CK levels may be slightly elevated. The muscle biopsy may show lipid storage. In some cases, the liver, heart, and kidney show increased lipid. Treatment with oral carnitine supplementation or glucocorticoids has helped some, but not all, patients.

Secondary carnitine deficiency accompanies a variety of disorders in which carnitine deficiency is caused by decreased synthesis (cirrhosis), insufficient intake (parenteral nutrition), or excessive loss (renal dialysis, Fanconi's syndrome, or organic acidemia). Carnitine deficiency may also be seen in the muscular dystrophies, where it is thought to be a nonspecific result of loss of muscle tissue. Oral carnitine supplementation has not been shown to clearly benefit patients with these secondary syndromes.

CARNITINE PALMITOYLTRANSFERASE DEFICIENCY

CPT II deficiency is the most common recognizable cause of recurrent myoglobinuria, more common than the glycolytic defects.

Clinical Features Onset is usually in the teenage years or early twenties. Muscle pain and myoglobinuria occur after prolonged exercise. Fasting predisposes to the development of symptoms. In contrast to disorders caused by defects in glycolysis, in which muscle cramps follow short, intense bursts of exercise, the muscle pain in CPT II deficiency does not occur until the limits of utilization have been exceeded and muscle breakdown has already begun. Episodes of rhabdomyolysis may produce severe weakness. In contrast to carnitine deficiency, strength is normal between attacks.

Laboratory Findings Serum CK levels and EMG findings are both usually normal between episodes. A normal rise of venous lactate during forearm exercise distinguishes this condition from glycolytic defects, especially myophosphorylase deficiency. Muscle biopsy does not show lipid accumulation and is usually normal between attacks. The diagnosis requires direct measurement of muscle CPT.

GENETIC CONSIDERATIONS

CPT II deficiency is much more common in men than women (5:1); nevertheless, all evidence indicates autosomal recessive inheritance. A mutation in the gene for CPT II causes the disease in some individuals.

TREATMENT

It has been suggested that frequent meals and a low-fat, high-carbohydrate diet can prolong exercise tolerance. Others suggest substituting medium-chain triglycerides in the diet. Neither approach has proven beneficial.

MYOADENYLATE DEAMINASE DEFICIENCY

The muscle enzyme myoadenylate deaminase converts adenosine 5¢-monophosphate (5¢-AMP) to inosine monophosphate (IMP) with liberation of ammonia. Myoadenylate deaminase may play a role in regulating adenosine triphosphate (ATP) levels in muscles. Most individuals with myoadenylate deaminase deficiency have no symptoms. Many questions have been raised about the clinical effects of myoadenylate deaminase deficiency, and, specifically, its relationship to exertional myalgia and fatigability; but there is no consensus. There have been a few reports of patients with this disorder who have exercise-exacerbated myalgia and myoglobinuria. The full clinical significance of myoadenylate deaminase deficiency has not been established.

MITOCHONDRIAL MYOPATHIES

In 1972, Olson and colleagues recognized that muscle fibers with significant numbers of abnormal mitochondria could be highlighted with the modified trichrome stain; the term "ragged red fibers" was coined. By electron microscopy, the mitochondria in ragged red fibers are enlarged and often bizarrely shaped and have crystalline inclusions. Since that seminal observation, the understanding of these disorders of muscle and other tissues has expanded (Chap. 67).

Mitochondria play a key role in energy production. Oxidation of the major nutrients derived from carbohydrate, fat, and protein leads to the generation of reducing equivalents. The latter are transported through the respiratory chain in the process known as oxidative phosphorylation. The energy generated by the oxidation-reduction reactions of the respiratory chain is stored in an electrochemical gradient coupled to ATP synthesis.

A novel feature of mitochondria is their genetic composition. Each mitochondrion possesses a DNA genome that is distinct from that of the nuclear DNA. Human mitochondrial DNA (mtDNA) consists of a double-stranded, circular molecule comprising 16,569 base pairs. It codes for 22 transfer RNAs, 2 ribosomal RNAs, and 13 polypeptides of the respiratory chain enzymes. The genetics of mitochondrial diseases differ from the genetics of chromosomal disorders. The DNA of mitochondria is directly inherited from the cytoplasm of the gametes, mainly from the oocyte. The sperm contributes very little of its mitochondria to the offspring at the time of fertilization. Thus, mitochondrial genes are derived almost exclusively from the mother, accounting for maternal inheritance of some mitochondrial disorders.

MTDNA DISORDERS OF MUSCLE

Many different classifications of mitochondrial myopathies are possible. A convenient scheme allows for disorders to be grouped by the type of mtDNA mutation: deletions or point mutations.

Disorders Associated with mtDNA Deletions The *Kearns-Sayre syndrome* (KSS) is a sporadic, noninherited disorder with onset before age 20. The characteristic findings include a triad of clinical features: progressive external ophthalmoplegia, pigmentary degeneration of the retina, and heart block. Some patients have only extraocular manifestations. Patients with KSS may also have short stature, ataxia, dementia, sensorineural hearing loss, diabetes, and hypothyroidism. Cerebrospinal fluid (CSF) lactate and pyruvate levels are elevated. The course is progressively downhill, and most patients die in their third or fourth decade. In KSS, two populations of mtDNA, wild type and mutant, are present in the same cell; the mutations in the latter consist of single mtDNA deletions. Heteroplasmy can be recognized on Southern blot analysis. The highest percentage of deleted mtDNA can be detected in postmitotic tissues, especially skeletal muscle. Other tissues can harbor the mutation (e.g., peripheral blood leukocytes, brain, liver, and fibroblasts). The absence of mutant mtDNA reflects both mitotic segregation early in embryogenesis and selection against a mutant cell line in a rapidly dividing tissue. KSS is not inherited, since mutations leading to an affected individual take place in the fertilized ovum.

An *autosomal dominant disorder with progressive external ophthalmoplegia and proximal weakness* shares clinical features with KSS: hearing loss, ataxia, peripheral neuropathy, mental retardation, and hypoparathyroidism. Some of these patients also have weakness of respiratory muscles, exercise intolerance, cataracts, and early death. The patients have ragged red fibers on muscle biopsy and multiple mtDNA deletions, rather than single deletions as in KSS. The mutation accounting for the autosomal dominant inheritance occurs in a nuclear gene that encodes a protein involved in the control of mtDNA replication. A failure or disruption of binding of this nuclear-encoded protein during mtDNA replication results in multiple deletions.

Disorders Associated with mtDNA Point Mutations *Myoclonic epilepsy and ragged red fibers*, called the *MERRF syndrome*, consists of mitochondrial myopathy, myoclonus, generalized seizures, intellectual deterioration, ataxia, and hearing loss. Extraocular movements are normal in MERRF. Onset is often in childhood or early adult life. As with other mitochondrial disorders, individuals display varying manifestations of the disease. Serum and CSF lactate and pyruvate levels are increased. The course is progressively downhill, and most patients die with severe encephalopathy. MERRF syndrome is maternally inherited. Most often, point mutations in the lysine transfer RNA gene of mtDNA can be found. This abnormality can be detected in mtDNA isolated from peripheral blood leukocytes or skeletal muscle and is useful for clinical diagnosis and genetic counseling. These mutations alter the normal conformation of the transfer RNA, impairing translation probably at the ribosomal level.

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes are referred to by the acronym *MELAS*. This disorder is a multisystem mitochondrial encephalomyopathy that begins in childhood after normal birth and early development. Patients have stunted growth and recurrent stroke-like episodes manifesting as hemiparesis, hemianopia, or cortical blindness. Episodic vomiting may occur, and some patients have hearing loss. Focal or generalized seizures and myoclonic epilepsy may be present. Full expression of the disease leads to dementia, a bedridden state, and death often before age 20. Lactic acidosis may be present. MELAS can be maternally

inherited, but sporadic cases are common. No large pedigrees have been reported. In 80 to 90% of patients, a point mutation of the leucine transfer RNA gene of mtDNA has been identified at nucleotide 3243. Some patients with this same mutation have only diabetes mellitus and hearing loss. Rarely, a mtDNA mutation of subunit 4 of complex I (ND4) of the respiratory chain causes MELAS. Mutation analysis provides a specific diagnostic test that can be performed on peripheral blood leukocytes or skeletal muscle.

A clinical syndrome with combined features of *skeletal and cardiac myopathies associated with lactic acidosis* that is distinct from MELAS has been described with a point mutation at nucleotide 3260 of the leucine transfer RNA gene of mtDNA.

ENDOCRINE AND METABOLIC MYOPATHIES

Many endocrine disorders cause weakness. Muscle fatigue is more common than true weakness. The cause of weakness in these disorders is not well defined. It is not even clear that weakness results from disease of muscle as opposed to another part of the motor unit since the serum CK level is often normal (except in hypothyroidism), and the muscle histology is characterized by atrophy rather than destruction of muscle fibers. Nearly all endocrine myopathies respond to treatment.

THYROID DISORDERS (See also Chap. 330)

Abnormalities of thyroid function can cause a wide array of muscle disorders. These conditions relate to the important role of thyroid hormones in regulating the metabolism of carbohydrates and lipids as well as the rate of protein synthesis and enzyme production. Thyroid hormones also stimulate calorigenesis in muscle, increase muscle demand for vitamins, and enhance muscle sensitivity to circulating catecholamines.

Hypothyroidism Patients with hypothyroidism have frequent muscle complaints, and proximal muscle weakness occurs in about one-third of them. Muscle cramps, pain, and stiffness are common. Features of slow muscle contraction and relaxation occur in 25% of patients, and the relaxation phase of muscle stretch reflexes is characteristically prolonged. The serum CK level is often elevated (up to 10 times normal), even when there is minimal clinical evidence of muscle disease. In both children and adults, a distinct syndrome has been described. Severely hypothyroid children, especially boys, may have the Debre-Kocher-Semelaigne syndrome, characterized by weakness, slowness of movement, and striking muscle hypertrophy, causing an "infant Hercules appearance." In adult hypothyroidism, Hoffman's syndrome results in prominent muscle enlargement and weakness with muscle stiffness. The cause of muscle enlargement in these two syndromes has not been determined. The muscle biopsy shows no distinctive morphologic abnormalities.

Hyperthyroidism Patients who are thyrotoxic commonly have proximal muscle weakness and atrophy on examination, but they rarely complain of the deficit. Muscle stretch reflexes are preserved and often brisk. Bulbar, respiratory, and even esophageal muscles may occasionally be affected, causing dysphagia, dysphonia, and aspiration. When bulbar involvement occurs, it is usually accompanied by chronic proximal limb weakness, but occasionally it presents in the absence of generalized thyrotoxic myopathy. Other neuromuscular disorders occur in association with hyperthyroidism,

including periodic paralysis, myasthenia gravis, and a progressive ocular myopathy associated with proptosis (Graves' ophthalmopathy). Serum CK levels are not elevated in thyrotoxic myopathy. The muscle histology usually shows only atrophy of muscle fibers.

PARATHYROID DISORDERS (See also Chap. 341)

Hyperparathyroidism Muscle weakness is an integral part of primary and secondary hyperparathyroidism. Proximal muscle weakness, muscle wasting, and brisk muscle stretch reflexes are the main features of this endocrinopathy. Serum CK levels are usually normal or slightly elevated. Serum calcium and phosphorus levels show no correlation with the clinical neuromuscular manifestations. Muscle biopsies show only varying degrees of atrophy without muscle fiber degeneration.

Hypoparathyroidism An overt myopathy due to hypocalcemia rarely occurs. Neuromuscular symptoms are usually related to localized or generalized tetany. Serum CK levels may be increased secondary to muscle damage after tetany. Hyporeflexia or areflexia is usually present and contrasts with the hyperreflexia in hyperparathyroidism.

ADRENAL DISORDERS (See also Chap. 331)

Conditions associated with glucocorticoid excess cause a myopathy; in fact, steroid myopathy is the most commonly diagnosed endocrine muscle disease. Steroid excess, either endogenous or exogenous (see "Toxic Myopathies," below), produces various degrees of proximal limb weakness. Muscle wasting may be striking. A cushingoid appearance invariably precedes or accompanies clinical signs of myopathy. Histologic sections demonstrate muscle fiber atrophy rather than degeneration or necrosis of muscle fibers. Adrenal insufficiency commonly causes muscle fatigue. Objective weakness occurs less often and is typically mild.

In primary hyperaldosteronism, or Conn's syndrome, neuromuscular complications are due to potassium depletion. The clinical picture is one of persistent muscle weakness. Long-standing hyperaldosteronism may lead to proximal limb weakness and wasting. Serum CK levels may be elevated, and a muscle biopsy may demonstrate degenerating fibers, some with vacuoles. These changes relate to hypokalemia and are not a direct effect of aldosterone on skeletal muscle.

PITUITARY DISORDERS (See also Chap. 328)

Patients with acromegaly usually have mild proximal weakness without muscle atrophy. Muscles often appear enlarged, but they have decreased force generation. The duration of acromegaly, rather than the serum growth hormone levels, correlates with the degree of myopathy.

DIABETES MELLITUS (See also Chap. 333)

Neuromuscular complications of diabetes mellitus are most often related to neuropathy with cranial and peripheral nerve palsies or distal sensorimotor polyneuropathy.

"Diabetic amyotrophy" is now known to be a neuropathy affecting the proximal major nerve trunks and lumbosacral plexus. More appropriate terms for this disorder include *diabetic proximal neuropathy* and *lumbosacral radiculoplexopathy*.

The only notable myopathy of diabetes mellitus is ischemic infarction of thigh muscles. This condition occurs in patients with poorly controlled diabetes and presents with acute onset of pain, tenderness, and edema of one thigh with a palpable mass. The muscles most often affected include the vastus lateralis, thigh adductors, and biceps femoris. Computed tomography or magnetic resonance imaging can demonstrate focal abnormalities in the affected muscle. Imaging of the muscle renders muscle biopsy unnecessary.

VITAMIN DEFICIENCY

Vitamin D deficiency is the most important cause of myopathy occurring as an integral part of a vitamin deficiency. Vitamin D deficiency (Chaps. 75 and 340) due to either decreased intake, decreased absorption, or impaired vitamin D metabolism (as occurs in renal disease) may lead to chronic muscle weakness. Pain reflects the underlying bone disease (osteomalacia). Vitamin E deficiency has been associated with a vacuolar myopathy. It has not been established that deficiency of other vitamins causes a myopathy.

MYOPATHIES OF SYSTEMIC ILLNESS

Systemic illnesses such as chronic respiratory, cardiac, or hepatic failure are frequently associated with severe muscle wasting and complaints of weakness. Strength testing often demonstrates mild weakness in such patients. Fatigue is a more significant problem.

Myopathy may be a manifestation of chronic renal failure, independent of the better known uremic polyneuropathy. Abnormalities of calcium and phosphorus homeostasis and bone metabolism in chronic renal failure result from a reduction in 1,25-dihydroxyvitamin D, leading to decreased intestinal absorption of calcium. Hypocalcemia, further accentuated by hyperphosphatemia due to decreased renal phosphate clearance, leads to secondary hyperparathyroidism. Renal osteodystrophy results from the compensatory hyperparathyroidism, which leads to osteomalacia from reduced calcium availability and to osteitis fibrosa from the parathyroid hormone excess. The clinical picture of the myopathy of chronic renal failure is identical to that of primary hyperparathyroidism and osteomalacia. There is proximal limb weakness with bone pain.

Gangrenous calcification represents a separate, rare, and sometimes fatal complication of chronic renal failure. In this condition, widespread arterial calcification occurs and results in ischemia. Extensive skin necrosis may occur along with painful myopathy and even myoglobinuria.

TOXIC MYOPATHIES

The classification of toxic myopathies is shown in Table 383-4. Drugs and chemicals

may produce focal or generalized damage to skeletal muscle.

The most common cause of focal damage is the injection of narcotic analgesics. Three agents in particular -- pentazocine, meperidine, and heroin -- may cause a severe fibrotic reaction in muscle. Common injection sites include deltoid, triceps, gluteus maximus, and quadriceps muscles. The muscles become indurated and may have local abscess formation. Cutaneous ulcerations and depressions may occur. Severe joint contractures may develop.

Other drugs may induce generalized muscle weakness, particularly affecting the proximal muscles. In most cases the exact mechanism of drug toxicity is poorly understood. D-Penicillamine induces a condition simulating the clinical and pathologic picture of polymyositis. A similar condition has been reported with cimetidine. Procainamide may cause myositis as part of a systemic lupus erythematosus-like reaction. Chloroquine administration may cause a vacuolar myopathy.

Zidovudine, used in the treatment of AIDS, produces proximal weakness and pain. On muscle biopsy, zidovudine myopathy demonstrates a distinctive pathologic alteration of skeletal muscle, affecting mitochondria and resembling ragged red fibers. Some patients may tolerate the reintroduction of zidovudine in lower doses.

The cholesterol-lowering agents, including fibric acid derivatives (clofibrate, gemfibrozil), 3-hydroxy-methyl-glutaryl-coenzyme A reductase inhibitors (lovastatin, simivastatin, pravastatin), and niacin have all been implicated in myopathies, occasionally causing myoglobinuria. Emetine hydrochloride (used for treatment of amebiasis), e-aminocaproic acid (an antifibrinolytic agent), and perhexiline (used for angina pectoris) have all been observed to cause muscle weakness and muscle fiber necrosis after several weeks of therapy.

Drug-induced myopathy accompanied by proximal weakness occurs with glucocorticoid therapy. Glucocorticoid drugs fluorinated in the 9a-position, such as triamcinolone, dexamethasone, and betamethasone, are most likely to cause weakness, but chronic administration of any glucocorticoid, including prednisone, causes weakness. Divided-dose, as opposed to single-morning-dose, regimens produce more severe weakness. A single-dose, alternate-day regimen is yet less toxic. The clinical diagnosis of steroid-induced muscle weakness can be difficult if the medication is being used to treat an underlying inflammatory myopathy. The presence of a normal serumCKlevel, minimal or no changes of myopathy onEMG, and type 2 muscle fiber atrophy on biopsy are helpful in suggesting steroid-induced weakness.

Excess alcohol intake causes acute muscle weakness with rhabdomyolysis and myoglobinuria by several different mechanisms, including prolonged obtundation, seizures, hypokalemia, and hypophosphatemia. The existence of a chronic myopathy causing slowly progressive weakness in this setting is controversial. Alcoholics often have chronic weakness resulting from neuropathy and poor nutrition.

A very serious drug-induced condition, *malignant hyperthermia*, occurs in susceptible individuals after exposure to certain general anesthetic and depolarizing muscle relaxants (Table 383-4). The local anesthetic amides, including lidocaine and

mepivacaine, have also been implicated as precipitating agents.

DISORDERS OF MUSCLE MEMBRANE EXCITABILITY

Elucidation of the molecular defects in the primary periodic paralyses provides insight into their pathogenesis and forms the basis for their classification (Table 383-5). These diseases are all characterized by muscle stiffness due to electrical irritability of the muscle membrane (myotonia), usually without significant permanent muscle weakness until late in the course. These clinical features (myotonia without dystrophy) distinguish these disorders from myotonic dystrophy in which there is significant distal weakness. In the nondystrophic myotonias, onset is usually in childhood or at adolescence; episodic weakness beginning after age 25 is almost never due to periodic paralysis. Attacks typically occur after rest or sleep and almost never in the midst of vigorous activity, although antecedent exercise often provokes weakness. Patients remain alert during the attacks. Early in the course of these disorders, interattack strength is normal. After many years of attacks, interictal weakness develops and may be progressive. These disorders are amenable to treatment, and progressive weakness can be prevented and even reversed. Diagnosis is based on the clinical history and confirmed by appropriate evaluation of serum electrolytes during attacks, by evaluation of the response of strength to provocative testing with glucose, insulin, potassium, and cold, or by DNA analysis of the appropriate gene.

CALCIUM CHANNEL DISORDERS OF MUSCLE

Hypokalemic Periodic Paralysis Hypokalemic periodic paralysis (hypoKPP) causes episodic weakness, which usually affects proximal limb muscles more than distal ones; rarely, ocular, bulbar, or respiratory muscles are affected. Respiratory muscle weakness may prove fatal. Meals high in carbohydrate or sodium can provoke attacks. Reflexes become hypoactive, and cardiac arrhythmias may occur during attacks owing to low serum potassium. Onset is at adolescence. Men are more often affected because of decreased penetrance in women. Some women have only infrequent attacks.

Diagnosis is established by demonstrating a low serum potassium level during a paralytic attack and by excluding secondary causes of hypokalemia. The molecular defect in the calcium channel can be defined in many patients. Muscle biopsy often shows the presence of single or multiple centrally placed vacuoles. Patients whose attacks are too infrequent for study of a spontaneous attack to be feasible require provocative testing with glucose and insulin administration. Provocative tests are potentially hazardous and require careful monitoring.

HypoKPPis caused by mutations in a voltage-sensitive, skeletal muscular calcium channel, although details of the pathogenesis are incompletely understood (Fig. 383-2).

The acute paralysis improves after the administration of potassium salts. Oral KCl (0.2 to 0.4 mmol/kg) should be given to patients with severe weakness and repeated at 15- to 30-min intervals depending on the response of theECG, serum potassium level, and muscle strength. Milder attacks usually resolve spontaneously. When patients are unable to swallow or are vomiting, intravenous therapy may be necessary. Small, repeated boluses of KCl (0.1 mmol/kg) may be administered over 5 to 10 min with

careful monitoring of the ECG and serum potassium level. If potassium is administered as a dilute solution (20 to 40 mmol/L) in 5% glucose or in physiologic saline solution, the serum potassium level may decline, and weakness may worsen. Mannitol is the preferred vehicle for administered intravenous potassium in such situations, since it facilitates rapid return of the serum potassium level to normal and does not cause the lowering of the serum potassium level that may be caused by glucose or saline solutions.

The goal of therapy is to eliminate attacks, which also prevents interattack weakness. Before effective means of attack prevention became available, chronic progressive interattack weakness frequently caused serious disability. Prophylactic administration of potassium salts, even in large doses, does not prevent attacks, but acetazolamide (125 to 1000 mg/d in divided doses) or dichlorphenamide (50 to 200 mg/d) abolishes attacks in most cases. The metabolic acidosis induced by acetazolamide may underlie the beneficial effect. Paradoxically, acetazolamide lowers the serum potassium level; to achieve an adequate response in some patients, it may be necessary to give supplementary potassium along with acetazolamide and to avoid high-carbohydrate meals. Chronic acetazolamide treatment may be associated with renal calculi, and patients should be monitored for this complication. In occasional patients, attacks may not respond to or may even be worsened by acetazolamide. In such patients, triamterene (25 to 100 mg/d) or spironolactone (25 to 100 mg/d) may prevent attacks.

SODIUM CHANNEL DISORDERS OF MUSCLE

Hyperkalemic Periodic Paralysis Hyperkalemic periodic paralysis (hyperKPP) causes episodic weakness of limb muscles; cranial and respiratory muscles are rarely involved. The term "hyperkalemic" is misleading, since patients are often normokalemic during attacks. It is the fact that attacks are precipitated by potassium administration that best defines the disorder. Paresthesias and muscle pain are present during many attacks.

Diagnosis is suggested by a modest elevation of the serum potassium level during attacks in nearly half of patients; at times, however, the serum potassium level is normal or even low. The so-called hyperkalemic and normokalemic forms of this disorder are not separate entities. Intravenous glucose-insulin loading does not precipitate weakness, but potassium-loading tests (0.05 to 0.15 g/kg) do induce weakness in such patients. Potassium-loading tests are potentially hazardous and are contraindicated in patients with renal disease and diabetes. Random serum potassium measurements may suggest the diagnosis, since potassium level elevations are frequent during attack-free intervals. EMGevidence of myotonia and the finding of vacuoles on muscle biopsy provide supporting data.

LikehypoKPP,hyperKPPmay also respond to chronic administration of acetazolamide or dichlorphenamide.

Paramyotonia Congenita Paramyotonia congenita (PC) causes attacks of paralysis either spontaneously or with cold provocation. PC with periodic paralysis is similar tohyperKPP, except that paradoxical myotonia (i.e., myotonia worsening with activity) and objective cold sensitivity are more prominent in PC.

In PC, attacks of weakness are seldom severe enough to require emergency treatment and are never fatal. Oral administration of glucose or other carbohydrate hastens recovery. Since interattack weakness may develop after repeated attacks, prophylactic treatment is usually indicated in PC. Thiazide diuretics (e.g., chlorothiazide, 250 to 1000 mg/d) are reported to be effective.

Potassium-Aggravated Myotonia Some patients with muscle sodium channel defects have severe muscle stiffness but no paralytic episodes. The stiffness is accentuated by elevations in serum potassium levels. Mutations in the skeletal muscle voltage-gated sodium channel SCN4A cause hyperKPP, PC and potassium-aggravated myotonia (PAM) (Fig. 383-2). In vitro study of these mutations demonstrates increased conductance through the sodium channels, often because of subnormal, slowed inactivation of the channel after action potential firing.

CHLORIDE CHANNEL DISORDERS OF MUSCLE

Myotonia Congenita In some families, severe, cold-aggravated muscle stiffness with muscle hypertrophy is transmitted as an inherited trait (dominant or recessive). This problem is usually evident in childhood; symptoms may become less severe in the adult years. This problem is caused by mutations in a skeletal muscle chloride channel resulting in impaired membrane repolarization. Myotonia congenita due to chloride channel defects can be distinguished from sodium channel myotonia by the rather striking muscle hypertrophy and by DNA mutational screening.

DISORDERS OF UNKNOWN PATHOGENETIC MECHANISM

Thyrotoxic Periodic Paralysis This disorder is clinically indistinguishable from hypoKPP. It is common in young Latin American and Asian men, among whom up to 10% of thyrotoxic patients may have this condition. The thyrotoxicosis may be overlooked for many months. Occasionally, the only indication of thyrotoxicosis is a depressed level of thyroid-stimulating hormone. Acute attacks respond to potassium administration. Treatment of the underlying thyrotoxicosis abolishes attacks. b-Adrenergic blocking agents are useful for reducing the frequency and severity of attacks while measures to control thyrotoxicosis are instituted. Acetazolamide is not helpful in preventing attacks. The pathogenesis of thyrotoxic periodic paralysis is uncertain, but there is evidence for a decrease in the activity of the calcium pump.

Andersen's Syndrome In this rare disorder patients manifest periodic paralysis (hyperkalemic or hypokalemic), cardiac dysrhythmias (even when normokalemic), and dysmorphic features (hypertelorism, low set ears, broad nose). Treatment of the episodic weakness is the same as for the other periodic paralyses, although cardiac status must be considered as well.

(Bibliography omitted in Palm version)

SECTION 4 - CHRONIC FATIGUE SYNDROME

384. CHRONIC FATIGUE SYNDROME - *Stephen E. Straus*

DEFINITION

Chronic fatigue syndrome (CFS) is the current name for a disorder characterized by debilitating fatigue and several associated physical, constitutional, and neuropsychological complaints (Table 384-1). This syndrome is not new; in the past, patients diagnosed with conditions such as the vapors, neurasthenia, effort syndrome, hyperventilation syndrome, chronic brucellosis, epidemic neuromyasthenia, myalgic encephalomyelitis, hypoglycemia, multiple chemical sensitivity syndrome, chronic candidiasis, chronic mononucleosis, chronic Epstein-Barr virus infection, and postviral fatigue syndrome may have had what is now called chronic fatigue syndrome. The U.S. Centers for Disease Control and Prevention (CDC) has developed diagnostic criteria for CFS based upon symptoms and the exclusion of other illnesses (Table 384-2).

EPIDEMIOLOGY

Patients with CFS are twice as likely to be women as men and are generally 25 to 45 years old, although cases in childhood and in later life have been described.

Cases are recognized in many developed countries. Most arise sporadically, but many clusters have also been reported. The most famous outbreaks of CFS occurred in Los Angeles County Hospital in 1934; in Akureyri, Iceland, in 1948; in the Royal Free Hospital, London, in 1955; in Punta Gorda, Florida, in 1956; and in Incline Village, Nevada, in 1985. While these clustered cases suggest a common environmental or infectious cause, none has been identified.

Estimates of the prevalence of CFS have depended on the case definition used and the method of study. Chronic fatigue itself is a common symptom, occurring in as many as 20% of patients attending general medical clinics; CFS is far less common. Community-based studies find that 100 to 300 individuals per 100,000 population in the United States meet the current CDC case definition.

PATHOGENESIS

The diverse names for the syndrome reflect the equally numerous and controversial hypotheses about its etiology. Several common themes underlie attempts to understand the disorder: It is often postinfectious, it is associated with immunologic disturbances, and it is commonly accompanied by neuropsychological complaints and depression.

Many studies in the 1980s and 1990s attempted to link CFS to infection with a persistent virus such as a lymphotropic herpesvirus, retrovirus, or enterovirus. In many patients with chronic fatigue, titers of antibodies to herpesviruses, measles virus, rubella virus, and coxsackievirus B are elevated. Reports that viral antigens and nucleic acids could be specifically identified in patients with CFS have not been confirmed. One study from the United Kingdom failed to detect any association between acute infections and subsequent prolonged fatigue. Another study found that chronic fatigue did not develop

after typical upper respiratory infections but did in some individuals after infectious mononucleosis. Thus, while cumulative experience suggests that antecedent viral infections are associated with CFS, a direct viral pathogenesis is unproven.

Changes in immune parameters of uncertain functional significance have been reported in CFS. Modest and nonspecific elevations in titers of antinuclear antibodies, reductions in immunoglobulin subclasses, deficiencies in mitogen-driven lymphocyte proliferation, reductions in natural killer cell activity, disturbances in cytokine production, and shifts in lymphocyte subsets with increases in cells expressing activation markers have been described. None of the immune findings appears in all patients, nor do any correlate with the severity of CFS. None are specific; thus they remain nondiagnostic. In theory, symptoms of CFS could result from excessive production of a cytokine, such as interleukin 1, that induces asthenia and other flulike symptoms; however, conclusive data in support of this long-held hypothesis are lacking.

Disturbances in endocrine function, consistent with reduced production of corticotropin-releasing hormone in the hypothalamus, have been reported in controlled studies of CFS. Mean serum cortisol concentrations were lower in patients than in controls; levels of adrenocorticotropic hormone were correspondingly high. Hypothetically, these neuroendocrine abnormalities could contribute to the impaired energy and depressed mood of patients.

Mild to moderate depression is present in half to two-thirds of patients. Much of this depression may be reactive, but its prevalence exceeds that seen in other chronic medical illnesses. Some propose that CFS is fundamentally a psychiatric disorder and that the various neuroendocrine and immune disturbances arise secondarily.

MANIFESTATIONS

Typically, CFS arises suddenly in a previously active individual. An otherwise unremarkable flulike illness or some other acute stress leaves unbearable exhaustion in its wake. Other symptoms, such as headache, sore throat, tender lymph nodes, muscle and joint aches, and frequent feverishness, lead to the belief that an infection persists, and medical attention is sought. Over several weeks, despite reassurances that nothing serious is wrong, the symptoms persist and other features of the syndrome become evident -- disturbed sleep, difficulty in concentration, and depression (Table 384-1).

Depending on the dominant symptoms and the beliefs of the patient, additional consultations may be sought from allergists, rheumatologists, infectious disease specialists, psychiatrists, ecologic therapists, homeopaths, or other professionals, frequently with unsatisfactory results. Once the pattern of illness is established, the symptoms may fluctuate somewhat. Many patients report that diverse complaints are linked -- that during periods of greatest fatigue they perceive the most pain and difficulty with concentration. Patients also commonly assert that excessive physical or emotional stress may exacerbate their symptoms.

Most patients remain capable of continuing to meet the obligations of family, work, or community despite their symptoms. The discretionary activities are abandoned first. Some feel unable to engage in any gainful employment. A minority of individuals require

help with the activities of daily living.

Ultimately, isolation, frustration, and pathetic resignation can mark the protracted course of illness. Patients may become angry at physicians for failing to acknowledge or resolve their plight. Fortunately, CFS does not appear to progress. On the contrary, many patients experience gradual improvement, and a minority recover fully.

DIAGNOSIS

Physical examination and routine laboratory tests are required to rule out other causes of the patient's symptoms. Prominent abnormalities argue strongly in favor of alternative diagnoses. No laboratory test, however, can diagnose this condition or measure its severity. In most cases, elaborate, expensive workups are not helpful. Magnetic resonance imaging of the brain may identify small T2 hyperintense signals in a minority of patients, but these findings do not aid diagnosis nor are they prognostic. The dilemma for patient and clinician alike is that CFS has no pathognomonic features and remains a constellation of symptoms and a diagnosis of exclusion. Often the patient presents with features that also meet criteria for other subjective disorders such as fibromyalgia and irritable bowel syndrome.

TREATMENT

The primary responsibility of a physician confronted with a chronically fatigued patient is to address the cause by taking a thorough history, conducting a complete physical examination, judiciously using the laboratory, and, throughout this process, considering the differential diagnosis. After other illnesses have been excluded, there are several points to address in the long-term care of a patient with chronic fatigue.

The patient should be informed about the illness and what is known of its pathogenesis; its potential impact on the physical, psychological, and social dimensions of life; and its prognosis. Patients are relieved when their complaints are taken seriously. Periodic reassessment is appropriate to identify a possible underlying process that is late in declaring itself and to address intercurrent symptoms that should not be simply dismissed as yet another subjective complaint.

Many symptoms of CFS respond to treatment. Nonsteroidal anti-inflammatory drugs alleviate headache, diffuse pain, and feverishness. Allergic rhinitis and sinusitis are common; antihistamines or decongestants may be helpful. Although the patient may be averse to psychiatric diagnoses, depression is often a prominent symptom and, when present, should be treated. Expert psychiatric assessment is sometimes advisable. Nonsedating antidepressants improve mood and disordered sleep and thereby attenuate the fatigue somewhat. Even modest improvements in symptoms can make an important difference in the patient's degree of self-sufficiency and ability to appreciate life's pleasures.

Practical advice should be given regarding lifestyle. Sleep disturbances are common; consumption of heavy meals with alcohol and caffeine at night can make sleep even more elusive, compounding fatigue. Total rest leads to further deconditioning and the self-image of being an invalid, whereas overexertion may worsen exhaustion and lead

to total avoidance of exercise. A moderate, carefully graded regimen should be encouraged and has been proven to relieve symptoms and enhance exercise tolerance.

Controlled therapeutic trials have established that acyclovir, intramuscular liver extract-folic acid-cyanocobalamin injections, and intravenous immunoglobulin, among others, are of no value. Two studies showed that low doses of hydrocortisone provide modest benefit, but they may lead to adrenal suppression. Countless anecdotes circulate regarding other traditional and nontraditional therapies. It is important to guide patients away from those therapeutic modalities that are toxic, expensive, or unreasonable.

The physician should promote the patient's efforts toward improvement. Three clinical trials in England showed behavioral therapy to be helpful. This approach aims to dispel misguided beliefs and fears about the illness that can contribute to inactivity and despair. For CFS, as for many other conditions, a comprehensive approach to physical, psychological, and social aspects of well-being is in order.

(Bibliography omitted in Palm version)

SECTION 5 - PSYCHIATRIC DISORDERS

385. MENTAL DISORDERS - *Victor I. Reus*

The term "mental disorders," as defined in the 4th edition of the standard psychiatric *Diagnostic and Statistical Manual* (DSM-IV), encompasses a broad range of conditions characterized by patterns of abnormal behavioral and psychological signs and symptoms that result in dysfunction. The implication that mental disorders lack a physical cause is unfortunate and incorrect, and the term survives only for want of a better substitute. Mental disorders are highly prevalent in medical practice and may present either as a primary disorder or as a comorbid condition. The total direct and indirect costs of all mental disorders in the United States has been estimated to be $148 billion dollars, only slightly less than costs incurred by cardiovascular diseases.

The DSM-IV-PC (Primary Care) manual provides a useful synopsis of mental disorders most likely to be seen in primary care practice. The current system of classification is multiaxial and includes the presence or absence of a major mental disorder (axis I), any underlying personality disorder (axis II), general medical condition (axis III), psychosocial and environmental problems (axis IV), and overall rating of general psychosocial functioning (axis V).

Changes in health care delivery underscore the need for primary care physicians to assume responsibility for the initial diagnosis and treatment of the most common mental disorders. Prompt diagnosis is essential to ensure that patients have access to appropriate medical services and to maximize the clinical outcome. Validated patient-based questionnaires have been developed that systematically probe for signs and symptoms associated with the most prevalent psychiatric diagnoses and guide the clinician into a more targeted historic assessment. Prime MD and the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC) are inventories that require only 10 min to complete and link patient responses to the formal diagnostic criteria of anxiety, mood, somatoform, and eating disorders and to alcohol abuse or dependence.

A physician who refers patients to a psychiatrist should know not only when doing so is appropriate but also how to do it, since societal misconceptions and the stigma of mental illness impede the process. Primary care physicians should base referrals to a psychiatrist on the presence of the signs and symptoms of a mental disorder and not simply on the absence of a physical explanation for a patient's complaint. The physician should discuss with the patient the reasons for requesting the referral or consultation and provide reassurance that he or she will continue to provide medical care and work collaboratively with the mental health professional. Consultation with a psychiatrist or transfer of care is appropriate when physicians encounter evidence of psychotic symptoms, mania, severe depression, or anxiety; symptoms of posttraumatic stress disorder (PTSD); suicidal or homicidal preoccupation; or a failure to respond to first-order treatment. *Eating disorders are discussed in Chap. 78.*

ANXIETY DISORDERS

Anxiety disorders, the most prevalent psychiatric illnesses in the general community, are present in 15 to 20% of medical clinic patients. Anxiety, defined as a subjective sense of

unease, dread, or foreboding, can indicate a primary psychiatric condition or can be a component of, or reaction to, a primary medical disease. The primary anxiety disorders are classified according to their duration and course and the existence and nature of precipitants.

When evaluating the anxious patient, the clinician must first determine whether the anxiety antedates or postdates a medical illness or is due to a medication side effect. Approximately one-third of patients presenting with anxiety have a medical etiology for their psychiatric symptoms, but an anxiety disorder can also present with somatic symptoms in the absence of a diagnosable medical condition.

PANIC DISORDER

Clinical Manifestations Panic disorder is defined by the presence of recurrent and unpredictable panic attacks, which are distinct episodes of intense fear and discomfort associated with a variety of physical symptoms, including palpitations, sweating, trembling, shortness of breath, chest pain, dizziness, and a fear of impending doom or death (Table 385-1). Paresthesias, gastrointestinal distress, and feelings of unreality are also common. Panic attacks have a sudden onset, developing within 10 min and usually resolving over the course of an hour, and they occur in an unexpected fashion. The frequency and severity of panic attacks varies, ranging from once a week to clusters of attacks separated by months of well-being. The first attack is usually outside the home. Onset is usually in late adolescence to early adulthood. In some individuals, anticipatory anxiety develops over time and results in a generalized fear and a progressive avoidance of places or situations in which a panic attack might recur. *Agoraphobia*, which occurs commonly in patients with panic disorder, is an acquired irrational fear of being in places where one might feel trapped or unable to escape (Table 385-2). Typically, it leads the patient into a progressive restriction in life-style and, in a literal sense, in geography. Frequently, patients are embarrassed that they are housebound and dependent on the company of others to go out into the world and do not volunteer this information; thus physicians will fail to recognize the syndrome if direct questioning is not pursued.

Differential Diagnosis A diagnosis of panic disorder is made after a medical etiology for the panic attacks has been ruled out. A variety of cardiovascular, respiratory, endocrine, and neurologic conditions can present with anxiety as the chief complaint. Patients with true panic disorder will often focus on one specific feature to the exclusion of others. For example, 20% of patients who present with syncope as a primary medical complaint have a primary diagnosis of a mood, anxiety, or substance-abuse disorder, the most common being panic disorder. The differential diagnosis of panic disorder is complicated by a high rate of comorbidity with other psychiatric conditions, especially alcohol and benzodiazepine abuse, which patients initially use in an attempt at self-medication. Some 75% of panic disorder patients will also satisfy criteria for major depression at some point in their illness.

When the history is nonspecific, physical examination and focused laboratory testing must be used to rule out medical anxiety states, such as those resulting from pheochromocytoma, thyrotoxicosis, or hypoglycemia. Electrocardiogram (ECG) and echocardiogram may detect some cardiovascular conditions associated with panic, such

as paroxysmal atrial tachycardia and mitral valve prolapse. In two studies, panic disorder was the primary diagnosis in 43% of patients with chest pain who had normal coronary angiograms and was present in 9% of all outpatients referred for cardiac evaluation. Panic disorder has also been diagnosed in many patients referred for pulmonary function testing or with symptoms of irritable bowel syndrome.

Etiology and Pathophysiology The etiology of panic disorder is unknown but appears to involve a genetic predisposition, altered autonomic responsivity, and social learning. Panic disorder shows familial aggregation, although concordance in monozygotic twins is only 30%. Acute panic attacks appear to be associated with increased noradrenergic discharge in the locus coeruleus. Intravenous infusion of sodium lactate evokes an attack in two-thirds of panic disorder patients, as do the a_2-adrenergic antagonist yohimbine and carbon dioxide inhalation. It is hypothesized that each of these stimuli activates a neural circuit involving noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe. Agents that block serotonin reuptake are therapeutic in preventing attacks. It is theorized that panic-disorder patients have a heightened sensitivity to somatic symptoms, which triggers increasing arousal, setting off the "panic attack" mechanism. Accordingly, successful therapeutic intervention involves altering the patient's cognitive interpretation of anxiety-producing experiences as well as preventing the attack itself.

TREATMENT

Achievable goals of treatment are to decrease the frequency of panic attacks and to reduce their intensity. The cornerstone of drug therapy is antidepressant medications (Tables 385-3,385-4, and385-5). The tricyclic antidepressant (TCA) agents imipramine and clomipramine can benefit 75 to 90% of panic disorder patients. Low doses (e.g., 10 to 25 mg/d) are given initially to avoid any increased anxiety associated with heightened monoamine levels in the initial stages of treatment. Selective serotonin reuptake inhibitors (SSRIs) are equally effective and do not have the adverse effects of TCAs. SSRIs should be started at one-third to one-half of their usual antidepressant dose (e.g., 5 to 10 mg fluoxetine, 25 to 50 mg sertraline, 10 mg paroxetine). Monoamine oxidase inhibitors (MAOIs) are at least as effective as TCAs and may specifically benefit patients who have comorbid features of atypical depression (i.e., hypersomnia and weight gain). Insomnia, orthostatic hypotension, and the need to maintain a low-tyramine diet (avoidance of cheese and wine) have limited their use, however. Antidepressants typically take 2 to 6 weeks to become effective, and doses may need to be adjusted according to clinical response.

Because of anticipatory anxiety and the need for immediate relief of panic symptoms, benzodiazepines are useful early in the course of treatment and sporadically thereafter (Table 385-6). For example, alprazolam, starting at 0.5 mg qid and increasing to 4 mg/d in divided doses, is effective, but patients must be monitored closely, as some develop dependence and begin to escalate the dose of this medication. Clonazepam, at a final maintenance dose of 2 to 4 mg/d, is also helpful; its longer half-life permits twice-daily scheduling, and patients appear less likely to develop dependence on this agent.

Early psychotherapeutic intervention and psychoeducation aimed at symptom control enhances the effectiveness of drug treatment. Patients can be taught breathing

techniques, can be educated about physiologic changes that occur with panic, and can learn to expose themselves voluntarily to precipitating events. Homework assignments and monitored compliance are important components of successful treatment. Once patients have achieved a satisfactory response, drug treatment should be maintained for 1 to 2 years to prevent relapse.

GENERALIZED ANXIETY DISORDER

Clinical Manifestations Patients with generalized anxiety disorder (GAD) have persistent, excessive, and/or unrealistic worry associated with other signs and symptoms, which commonly include muscle tension, impaired concentration, autonomic arousal, feeling "on edge" or restless, and insomnia (Table 385-7). Onset is usually before age 20, and a history of childhood fears and social inhibition may be present. The incidence of GAD is increased in first-degree relatives of patients with the diagnosis; family studies also indicate that GAD and panic disorder segregate independently. Over 80% of patients with GAD also suffer from major depression, dysthymia, or social phobia. Comorbid substance abuse is common in these patients, particularly alcohol and/or sedative/hypnotic abuse. Patients with GAD readily admit to worrying excessively over minor matters, with life-disrupting effects; unlike in panic disorder, complaints of symptoms such as shortness of breath, palpitations, and tachycardia are relatively rare.

Etiology and Pathophysiology In experimental models of anxiety, anxiogenic agents share in common the property of altering the binding of benzodiazepines to theg-aminobutyric acid (GABA) A receptor/chloride ion channel complex. Benzodiazepines are thought to bind two separate GABA$_A$receptor sites: type I, which has a broad neuroanatomic distribution, and type II, which is concentrated in the hippocampus, striatum, and neocortex. The antianxiety effects of the various benzodiazepines and side effects such as sedation and memory impairment are influenced by their relative binding to type I and type II receptor sites. Serotonin [5-hydroxytriptamine (5HT)] also appears to have a role in anxiety. Buspirone, a partial 5HT$_{1A}$receptor agonist, and certain 5HT$_{2A}$and 5HT$_{2C}$receptor antagonists (e.g., nefazodone) may also have beneficial effects.

TREATMENT

A combination of pharmacologic and psychotherapeutic interventions is most effective inGAD, but complete symptomatic relief is rare. A short course of a benzodiazepine is usually indicated, preferably lorazepam, oxazepam, or temazepam. (The first two of these agents are metabolized via conjugation rather than oxidation and thus do not accumulate if hepatic function is altered.) Administration should be initiated at the lowest dose possible and prescribed on an as-needed basis as symptoms warrant. Benzodiazepines differ in their milligram per kilogram potency, half-life, lipid solubility, metabolic pathways, and presence of active metabolites. Agents that are absorbed rapidly and are lipid soluble, such as diazepam, have a rapid onset of action and a higher abuse potential. Benzodiazepines should generally not be prescribed for>4 to 6 weeks because of the development of tolerance and the risk of abuse and dependence. It is important to warn patients that concomitant usage of alcohol or other sedating drugs may result in neurotoxicity and impair their ability to function. An optimistic

approach that encourages the patient to clarify environmental precipitants, anticipate his or her reactions, and plan effective response strategies are essential elements of therapy.

Adverse effects of benzodiazepines generally parallel their relative half-lives. Longer-acting agents, such as diazepam, chlordiazepoxide, flurazepam, and clonazepam, tend to accumulate active metabolites, with resultant sedation, impairment of cognition, and poor psychomotor performance. Shorter-acting compounds, such as alprazolam and oxazepam, can result in daytime anxiety, early morning insomnia, and with discontinuation, rebound anxiety and insomnia. Although patients develop tolerance to the sedative effects of benzodiazepines, they are less likely to habituate to the adverse psychomotor effects. Withdrawal from the longer half-life benzodiazepines can be accomplished through gradual, stepwise dose reduction (by ~10% every 1 to 2 weeks) over 6 to 12 weeks. It is usually more difficult to taper patients off shorter-acting benzodiazepines. Physicians may need to switch the patient to a benzodiazepine with a longer half-life or use an adjunctive medication, such as a beta blocker or carbamazepine, before attempting to discontinue the benzodiazepine. Withdrawal reactions vary in severity and duration; they can include depression, anxiety, delirium, lethargy, diaphoresis, tinnitus, autonomic arousal, unusual neuromuscular movements, and, rarely, seizures.

Buspirone, an azaspirone, is a nonbenzodiazepine anxiolytic agent. It is nonsedating, does not lead to tolerance or dependence, does not interact with benzodiazepine receptors or alcohol, and has no abuse or disinhibition potential. However, it requires several weeks to take effect and requires thrice-daily dosing. Patients who were previously responsive to a benzodiazepine are unlikely to rate buspirone as equally effective, but patients with head injury or dementia who have symptoms of anxiety and/or agitation may do well with this agent.

Administration of benzodiazepines to geriatric patients requires special care. Such patients have increased drug absorption; decreased hepatic metabolism, protein binding, and renal excretion; and an increased volume of distribution. These factors, together with the likely presence of comorbid medical illnesses and medication, dramatically increase the likelihood of toxicity. Iatrogenic psychomotor impairment can result in falls and fractures, confusional states, or motor vehicle accidents. If used, agents in this class should be started at the lowest possible dose, and results should be monitored closely. Benzodiazepines are contraindicated during pregnancy and breast-feeding.

PHOBIC DISORDERS

Clinical Manifestations The cardinal feature of phobic disorders is a marked and persistent fear of objects or situations, exposure to which results in an immediate anxiety reaction. The patient avoids the phobic stimulus, and this avoidance usually impairs occupational or social functioning. Panic attacks may be triggered by the phobic stimulus or may emerge spontaneously during the course of the illness. Unlike patients with other anxiety disorders, individuals with phobias experience anxiety only in specific situations. Common phobias include fear of closed spaces (claustrophobia), fear of blood, and fear of flying. Social phobia is distinguished by a specific fear of social or

performance situations in which the individual is exposed to unfamiliar individuals or to possible examination and evaluation by others. Examples include having to converse at a party, use public restrooms, and meet strangers. In each case, the affected individual is aware that the experienced fear is excessive and unreasonable given the circumstance. The specific content of a phobia may vary across gender, ethnic, and cultural boundaries.

Phobic disorders are common, with a 1-year prevalence rate of 9% and a lifetime rate of 10 to 11%. Onset is typically in childhood to early adulthood. Familial aggregation may occur. In one study of female twins, concordance rates for agoraphobia, social phobia, and animal phobia was found to be 23% for monozygotic twins and 15% for dizygotic twins. Full criteria for diagnosis are usually satisfied first in adulthood, but behavioral avoidance of unfamiliar people, situations, or objects dating from early childhood is common.

TREATMENT

Recent controlled trials have documented the efficacy of several pharmacologic agents in the treatment of phobic disorders. Beta blockers (e.g., propranolol, 20 to 40 mg orally 2 h before the event) are particularly effective in the treatment of "performance anxiety" (but not general social phobia) and appear to achieve their benefit by preventing the occurrence of peripheral manifestations of anxiety, such as perspiration, tachycardia, palpitations, and tremor.MAOIsalleviate social phobia independently of their antidepressant activity, andSSRIsappear to be effective also. Benzodiazepines can be helpful in reducing fearful avoidance, but the chronic nature of phobic disorders limits their usefulness.

Behaviorally focused psychotherapy is an important component of treatment, as relapse rates are high when medication is used as the sole treatment. Cognitive-behavioral strategies are the cornerstone of treatment; these are based upon the finding that distorted perceptions and interpretations of fear-producing stimuli play a major role in perpetuation of phobias. Individual and group therapy sessions teach the patient to identify specific negative thoughts associated with the anxiety-producing situation and help to reduce the patient's fear of loss of control. In desensitization therapy, hierarchies of feared situations are constructed and the patient is encouraged to pursue and master gradual exposure to the anxiety-producing stimuli.

Patients with social phobia, in particular, have a high rate of comorbid alcohol abuse, as well as of other psychiatric conditions (e.g., eating disorders), necessitating the need for parallel management of each disorder if anxiety reduction is to be achieved.

STRESS DISORDERS

Clinical Manifestations Patients may develop anxiety after exposure to extreme traumatic events such as the threat of personal death or injury or the death of a loved one. The reaction may occur shortly after the trauma (*acute stress disorder*) or be delayed and subject to recurrence (PTSD) (Table 385-8). In both syndromes, individuals experience associated symptoms of detachment and loss of emotional responsivity. The patient may feel depersonalized and unable to recall specific aspects of the trauma,

though typically it is reexperienced through intrusions in thought, dreams, or flashbacks, particularly when cues of the original event are present. Patients often actively avoid stimuli that precipitate recollections of the trauma and demonstrate a resulting increase in vigilance, arousal, and startle response. Patients with stress disorders are at risk for the development of other anxiety, mood, and substance-related disorders. Between 5 and 10% of Americans will at some time in their life satisfy criteria for PTSD, with women more likely to be affected than men.

Risk factors for the development of PTSD include a past psychiatric history and personality characteristics of high neuroticism and extroversion. Studies of monozygotic and dizygotic twins showed a substantial influence of genetics on all symptoms associated with PTSD, with no evidence for an environment effect.

Etiology and Pathophysiology It is hypothesized that in PTSD there is excessive release of norepinephrine from the locus coeruleus in response to stress. Increased noradrenergic activity at locus coeruleus projection sites in hippocampus and amygdala theoretically facilitates encoding of fear-based memories. Greater sympathetic responses to cues associated with the traumatic event occurs in PTSD.

TREATMENT

Acute stress reactions are usually self-limited, and treatment typically involves the short-term use of benzodiazepines and supportive/expressive psychotherapy. The chronic and recurrent nature of PTSD, however, requires a more complex approach employing drug and behavioral treatments. TCAs such as imipramine and amitriptyline, the MAOI phenelzine, and the SSRIs (fluoxetine, sertraline, citalopram, paroxetine) can all reduce anxiety, symptoms of intrusion, and avoidance behaviors. Trazodone, a sedating antidepressant, is frequently used at night to help with insomnia (50 to 150 mg qhs). Carbamazepine, valproic acid, or alprazolam have also independently produced improvement in uncontrolled trials. There is frequent comorbidity with substance abuse, especially alcohol.

Psychotherapeutic strategies are used in treatment of PTSD to help the patient overcome avoidance behaviors and demoralization and master fear of recurrence of the trauma; therapies that encourage the patient to dismantle avoidance behaviors through stepwise focusing on the experience of the traumatic event are the most effective.

OBSESSIVE-COMPULSIVE DISORDER

Clinical Manifestations Obsessive-compulsive disorder (OCD) was previously considered a relatively rare condition, but recent epidemiologic data indicate a lifetime prevalence of 2 to 3% worldwide. OCD is characterized by obsessive thoughts and compulsive behaviors that impair everyday functioning. Fears of contamination and germs are common, as are handwashing, counting behaviors, and having to check and recheck such actions as whether a door is locked. The degree to which the disorder is disruptive for the individual varies, but in all cases obsessive-compulsive activities take up >1 h per day and are undertaken to relieve the anxiety triggered by the core fear. Patients often conceal their symptoms, usually because they are embarrassed by the content of their thoughts or the nature of their actions. Physicians must ask specific

questions regarding recurrent thoughts and behaviors, particularly if physical clues such as chafed and reddened hands or patchy hair loss (from repetitive hair pulling, or trichotillomania) are present. Tics are sometimes associated with OCD. OCD usually has a gradual onset, beginning in early adulthood, but childhood onset is not rare. The disorder usually has a waxing and waning course, but some cases may show a steady deterioration in psychosocial functioning.

Etiology and Pathophysiology A genetic contribution to OCD is suggested by a higher monozygotic than dizygotic concordance rate and the fact that familial studies show an aggregation with Tourette's disorder. OCD is more common in males and in first-born children.

The anatomy of obsessive-compulsive behavior is thought to involve a frontal-subcortical neural circuit involving the orbital frontal cortex, caudate nucleus, and globus pallidus. Neuroimaging studies have demonstrated a decrease in caudate nucleus volume, abnormalities in frontal lobe white matter, and increases in glucose metabolism in the orbital cortex of the frontal lobes and the head of the caudate nucleus. The caudate nucleus seems particularly involved in the acquisition and maintenance of habit and skill learning, and interventions that are successful in reducing obsessive-compulsive behaviors are paralleled by a comparable decrease in caudate glucose metabolic rate.

TREATMENT

Clomipramine, fluoxetine, and fluvoxamine are approved for the treatment of OCD. Clomipramine is a TCA that is often tolerated poorly owing to significant anticholinergic and sedative side effects at the doses required to treat the illness (150 to 250 mg/d). Its efficacy in OCD is unrelated to its antidepressant activity. Fluoxetine (40 to 60 mg/d) and fluvoxamine (100 to 300 mg/d) are as effective as clomipramine and show a more benign side-effect profile. Fluvoxamine, a structurally unique SSRI, is metabolized through the hepatic P450 microsomal system (as is fluoxetine); it appears to inhibit the III A4 isoenzyme specifically and should not be given with other drugs that act on III A4, such as terfenadine and astemizole, because life-threatening cardiac arrhythmias may result. Only 50 to 60% of patients with OCD show an acceptable degree of improvement with pharmacotherapy alone. In treatment-resistant cases, augmentation with other serotonergic agents, such as buspirone, or with a neuroleptic or benzodiazepine may be beneficial. When a therapeutic response is achieved, long-duration maintenance therapy is usually indicated.

For many individuals, particularly those with time-consuming compulsions, behavior therapy will result in as much improvement as that afforded by medication. Effective techniques include the gradual increase in exposure to stressful situations, maintenance of a diary to clarify stressors, and homework assignments that substitute new activities for their compulsive behavior.

MOOD DISORDERS

Mood disorders are characterized by a disturbance in the regulation of mood, behavior, and affect. Mood disorders are subdivided into (1) depressive disorders, (2) bipolar

disorders, and (3) depression in association with medical illness or alcohol and substance abuse ([Chaps. 387](#) through 389). Depressive disorders are differentiated from bipolar disorders by the absence of a manic or hypomanic episode. The relationship between pure depressive syndromes and bipolar disorders is not well understood; depression occurs at increased frequency in families of bipolar individuals, but the reverse is not true. Depression in general is associated with high disability and societal cost; in the Global Burden of Disease Study conducted by the World Health Organization, unipolar major depression ranked fourth in percentage of disability-adjusted life years and was projected to rank second in the year 2020.

DEPRESSION IN ASSOCIATION WITH MEDICAL ILLNESS

Depression occurring in the context of medical illness is difficult to evaluate. Depressive symptomatology may reflect the psychological stress of coping with the disease, may be caused by the disease process itself or by the medications used to treat it, or may simply coexist in time with the medical diagnosis.

Virtually every class of *medication* includes some agent that can induce depression. Antihypertensive drugs, anticholesterolemic agents, and antiarrhythmic agents are commonly used classes of medications that can trigger depressive symptoms. Among the antihypertensive agents, b-adrenergic blockers and, to a lesser extent, calcium channel blockers are the most likely to cause depressed mood. Iatrogenic depression should also be considered in patients receiving glucocorticoids, antimicrobials, systemic analgesics, antiparkinsonian medications, and anticonvulsants. To decide whether a causal relationship exists between pharmacologic therapy and a patient's change in mood, it is necessary to chart the chronology of symptoms and sometimes to undertake an empirical trial of an alternative medication.

Between 20 and 30% of cardiac patients manifest a depressive disorder; an even higher percentage experience depressive symptomatology when self-reporting scales are used. Depressive symptoms following myocardial infarction impair rehabilitation and are associated with higher rates of mortality and medical morbidity. Depressed patients often show decreased variability in heart rate (an index of reduced parasympathetic nervous system activity), and this has been proposed as one mechanism by which depression may predispose individuals to ventricular arrhythmia and increased morbidity. Although TCAs have been used to treat depression in individuals with cardiac disease for a number of years, and although the quinidine-like effect of tricyclics may be useful in patients with preexisting arrhythmias, TCAs are contraindicated in patients with preexisting bundle branch block. They may also paradoxically precipitate arrhythmias. Tricyclic-induced tachycardia is an additional concern in patients with congestive heart failure. Experience with the SSRIs is more limited, but thus far they appear not to induce ECG changes or adverse cardiac events. SSRIs may interfere with hepatic metabolism of anticoagulants, however, causing increased anticoagulation.

Epidemiologic surveys of depression in patients with cancer show a wide variability in prevalence, as might be predicted by differences in tumor site, severity of illness, and type of medical or surgical intervention. There is an overall mean prevalence of 25%, but depression occurs in 40 to 50% of patients with cancers of the pancreas or oropharynx. Assessment of the validity of prevalence rates is complicated by the fact

that extreme cachexia may be misinterpreted as part of the symptom complex of depression. The higher prevalence of depression in patients with pancreatic cancer nevertheless persists when patients are compared to those with advanced gastric cancer. Initiation of antidepressant medication in cancer patients has been shown to improve quality of life as well as mood. Psychotherapeutic approaches, particularly group therapy, may have some effect on short-term depression, anxiety, and pain symptoms and on recurrence rates and long-term survival. In a study of female patients with metastatic breast cancer, patients in group therapy had longer survival than control patients.

Depression occurs frequently in patients with *neurologic disorders*, particularly cerebrovascular disorders, Parkinson's disease, multiple sclerosis, and traumatic brain injury. Left-hemisphere strokes, particularly those involving the dorsal lateral frontal cortex, are most likely to cause depression. Both tricyclic and SSRI antidepressants are effective in the treatment of depression secondary to stroke, as are stimulant compounds and, in some patients, MAOIs.

The reported prevalence of depression in patients with *diabetes mellitus* varies from 8 to 27%, with the severity of the mood state correlating with the physical symptoms of illness and the degree of hyperglycemia. Pharmacologic treatment of depression is complicated by antidepressant effects on the blood glucose level. MAOIs can induce hypoglycemia and weight gain. TCAs can lead to hyperglycemia and carbohydrate craving. SSRIs, like MAOIs, may cause a reduction in fasting plasma glucose, but they are easier to use and may also improve dietary and medication compliance.

Hypothyroidism is frequently associated with features of depression, most commonly depressed mood and memory impairment. Hyperthyroid states may also present in a similar fashion, usually in geriatric populations. Improvement in mood usually follows normalization of thyroid function, but adjunctive antidepressant medication is sometimes required. Patients with subclinical hypothyroidism can also experience symptoms of depression and cognitive difficulty that respond to thyroid replacement.

DEPRESSIVE DISORDERS

Clinical Manifestations *Major depression* is defined as depressed mood on a daily basis for a minimum duration of 2 weeks (Table 385-9). An episode may be characterized by sadness, indifference or apathy, or irritability and is usually associated with change in neurovegetative functions, including sleep patterns, appetite and weight, motor agitation or retardation, fatigue, impairment in concentration and decision making, feelings of shame or guilt, and thoughts of death or dying. Patients with depression have a profound loss of pleasure in all enjoyable activities, exhibit early morning awakening, feel that the dysphoric mood state is qualitatively different from sadness, and often notice a diurnal variation in mood (worse in morning hours). Paradoxically, these more severe features predict a good response to antidepressant treatment.

Approximately 15% of the population experiences a major depressive episode at some point in life, and 6 to 8% of all outpatients in primary care settings satisfy diagnostic criteria for the disorder. Depression is often undiagnosed, and, even more frequently, it is treated inadequately. If a physician suspects the presence of a major depressive

episode, the initial task is to determine whether it represents unipolar or bipolar depression or is one of the 10 to 15% of cases that are secondary to general medical illness or substance abuse. Physicians should also assess the risk of suicide by direct questioning, as patients are often reluctant to verbalize such thoughts without prompting. If specific plans are uncovered or if significant risk factors exist (e.g., a past history of suicide attempts, profound hopelessness, concurrent medical illness, substance abuse, or social isolation), the patient must be referred to a mental health specialist for immediate care. In evaluating suicidal risk the physician should specifically probe each of these areas in an empathic and hopeful manner, being sensitive to denial and possible minimization of distress. The presence of anxiety, panic, or agitation significantly increases near-term suicidal risk. Nearly 15% of patients whose depressive illness goes untreated will commit suicide; most will have sought help from a physician within 1 month of their death.

In some depressed patients, the mood disorder does not appear to be episodic and is not clearly associated with either psychosocial dysfunction or change from the individual's usual experience in life. *Dysthymic disorder* consists of a pattern of chronic (at least 2 years), ongoing, mild depressive symptoms that are less severe and less disabling than those found in major depression; the two conditions are sometimes difficult to separate, however, and can occur together ("double depression"). Many patients who exhibit a profile of pessimism, disinterest, and low self-esteem respond to antidepressant treatment. Dysthymic disorder exists in ~5% of primary care patients.

Studies of various cultures have shown that external manifestations of depression differ but the core symptoms remain the same. The incidence of depression increases with age; the disorder is approximately twice as prevalent in women as in men, regardless of age. These gender differences were previously believed to reflect sociocultural factors, but recent longitudinal twin studies indicate that the liability to major depression in adult women is largely genetic in origin, and that the effect of environmental factors is transitory and does not affect lifetime prevalence. The relationship between psychological stress, negative life events, and the onset of depressive episodes is complex. Negative life events can precipitate and contribute to depression, but recent data indicate that genetic factors influence the sensitivity of individuals to these stressful events. In most cases, both biologic and psychosocial factors are involved in the precipitation and unfolding of depressive episodes. The most potent stressors appear to involve death of a relative, assault, or severe marital or relationship problems.

Unipolar depressive disorders usually have their onset in early adulthood, and recurrences over the course of a lifetime are likely. The best predictor of future risk is the number of past episodes; 50 to 60% of patients who have a first episode have at least one or two more episodes. Some patients experience multiple episodes that become more severe and frequent over time. The duration of an untreated episode varies greatly, ranging from a few months to ³1 year. The pattern of recurrence and clinical progression in a developing episode is also variable. Within an individual, there is often long-term stability in phenotype (presenting symptoms, frequency and duration of episodes). In a minority of patients, the severity of the depressive episode may progress to psychotic symptomatology; in elderly patients, depressive symptoms may be associated with confusion and mistaken for dementia (i.e., "pseudodementia"). A seasonal pattern of depression, called *seasonal affective disorder*, may manifest with

onset and remission of episodes at predictable times of the year. This disorder is more common in women, whose symptoms are anergy, fatigue, weight gain, hypersomnia, and episodic carbohydrate craving. The prevalence increases with distance from the equator, and mood improvement may occur by altering light exposure.

Etiology and Pathophysiology The neurobiology of unipolar depression is poorly understood. Although evidence for genetic transmission is not as strong as in bipolar disorder, monozygotic twins have a higher concordance rate (46%) than dizygotic siblings (20%), with little evidence for any effect of a shared family environment. Parallels between the affective, motor, and cognitive dysfunctions seen in unipolar depression and those observed in diseases of the basal ganglia have suggested that neural networks involving prefrontal cortex and the basal ganglia may be involved. This hypothesis is supported by positron emission tomography (PET) studies of brain glucose metabolism that show a decrease in metabolic rate in the caudate nuclei and frontal lobes in depressed patients that returns to normal with recovery. Single-photon emission computed tomography (SPECT) studies show comparable changes in blood flow. Magnetic resonance imaging (MRI) findings in some patients include an increased frequency of subcortical white matter lesions. However, because these findings are more prevalent in patients with late onset of depressive illness, their significance remains unproven. A number of studies document increased ventricle-to-brain ratios in some patients with recurrent depression, but whether this finding is state-dependent or represents true cerebral atrophy is controversial.

Postmortem examination of brains of suicide victims suggest altered noradrenergic activity, including increased binding to a_1-, a_2-, and b-adrenergic receptors in the cerebral cortex and a decreased total number and density of noradrenergic neurons in the locus coeruleus. Involvement of the serotonin system is suggested by findings of reduced plasma tryptophan levels, a decreased cerebrospinal fluid level of 5-hydroxyindolacetic acid (the principal metabolite of serotonin in brain), and decreased platelet serotonergic transporter binding. An increase in brain serotonin receptors in suicide victims is also reported. Depletion of blood tryptophan, the amino acid precursor of serotonin, rapidly reverses the antidepressant benefit in depressed patients who have been successfully treated. However, a decrement in mood after tryptophan reduction is considerably less robust in untreated patients, indicating that, if presynaptic serotonergic dysfunction occurs in depression, it likely plays a contributing rather than a causal role.

Neuroendocrine abnormalities that reflect the neurovegetative signs and symptoms of depression include (1) increased cortisol and corticotropin-releasing hormone (CRH) secretion, (2) an increase in adrenal size, (3) a decreased inhibitory response of glucocorticoids to dexamethasone, and (4) a blunted response of thyroid-stimulating hormone (TSH) level to infusion of thyroid-releasing hormone (TRH). Antidepressant treatment leads to normalization of these pituitary-adrenal abnormalities.

Diurnal variations in symptom severity and alterations in circadian rhythmicity of a number of neurochemical and neurohumoral factors suggest that biologic differences may be secondary to a primary defect in regulation of biologic rhythms. Patients with major depression show consistent findings of a decrease in rapid eye movement (REM) sleep onset (REM latency), an increase in REM density, and, in some subjects, a decrease in stage IV delta slow-wave sleep.

Although antidepressant drugs result in a blockade of neurotransmitter uptake within hours, their therapeutic effects typically emerge over several weeks, implicating neuroadaptive changes in second messenger systems and transcription factors as possible mechanisms of action.

TREATMENT

Treatment planning requires coordination of short-term symptom remission with longer term maintenance strategies designed to prevent recurrence. The most effective intervention for achieving remission and preventing relapse is medication, but combined treatment, incorporating psychotherapy to help the patient cope with decreased self-esteem and demoralization, improves outcome (Fig. 385-1). About 40% of primary care patients with depression drop out of treatment and discontinue medication if symptomatic improvement is not noted within a month, unless additional support is provided. Outcome improves with (1) increased intensity and frequency of visits during the first 4 to 6 weeks of treatment, (2) supplemental educational materials, and (3) psychiatric consultation as indicated. Despite the widespread use of SSRIs, there is no convincing evidence that this class of antidepressant is more efficacious than TCAs. Between 60 and 70% of all depressed patients respond to any drug chosen, if it is given in a sufficient dose for 6 to 8 weeks. There is no ideal antidepressant; no current compound combines rapid onset of action, moderate half-life, a meaningful relationship between dose and blood level, a low side effect profile, minimal interaction with other drugs, and safety in overdose. A rational approach to selecting which antidepressant to use involves matching the patient's preference and medical history with the metabolic and side effect profile of the drug (Tables 385-4 and 385-5). A previous response, or a family history of a positive response, to a specific antidepressant would suggest that that drug be tried first. Before initiating antidepressant therapy, the physician should evaluate the possible contribution of comorbid illnesses and consider their specific treatment. In individuals with suicidal ideation, particular attention should be paid to choosing a drug with a low toxicity if taken in overdose. The SSRIs and other newer antidepressant drugs are distinctly safer in this regard; nevertheless, the advantages of TCAs have not been completely superseded. The existence of generic equivalents make TCAs relatively cheap, and for several tricyclics, particularly nortriptyline, imipramine, and desipramine, well-defined relationships between dose, plasma level, and therapeutic response exist. The steady-state plasma level achieved for a given drug dose can vary more than tenfold between individuals. Plasma levels may help in understanding resistance to treatment and/or unexpected drug toxicity. The principal disadvantages of TCAs are antihistamine side effects (sedation) and anticholinergic side effects (constipation, dry mouth, urinary hesitancy, and blurred vision). Severe cardiac toxicity due to conduction block or arrhythmias can also occur but is uncommon at therapeutic levels. TCAs are probably contraindicated in patients with cardiovascular risk factors. Tricyclic agents are lethal in overdose, with desipramine carrying the greatest risk. Prescribing only a 10-day supply may be judicious. Most patients require a daily dose of 150 to 200 mg of imipramine or amitriptyline or its equivalent to achieve a therapeutic blood level of 150 to 300 ng/mL and a satisfactory remission; some patients show a partial effect at lower doses. Geriatric patients in particular may require a low starting dose and slow escalation. Ethnic differences in drug metabolism are significant; Hispanic, Asian, and African American patients generally require lower doses than

Caucasians to achieve a comparable blood level.

Second-generation antidepressants include amoxapine, maprotiline, trazodone, and bupropion. Amoxapine is a dibenzoxazepine derivative that blocks norepinephrine and serotonin reuptake and has a metabolite that shows a degree of dopamine blockade. Long-term use of this drug carries a risk of tardive dyskinesia. Maprotiline is a potent noradrenergic reuptake blocker that has little anticholinergic effect but may produce seizures. Bupropion is a novel antidepressant whose mechanism of action is thought to involve enhancement of noradrenergic function. It has no anticholinergic, sedating, or orthostatic side effects and has a low incidence of sexual side effects. It may, however, be associated with aversive stimulant-like side effects, may lower seizure threshold, and has an exceptionally short half-life, requiring multiple dosing. An extended-release preparation is available.

SSRIssuch as fluoxetine, sertraline, paroxetine, and citalopram cause a lower frequency of anticholinergic, sedating, and cardiovascular side effects but a possibly greater incidence of gastrointestinal complaints, sleep impairment, and sexual dysfunction than doTCAs. Akathisia, involving an inner sense of restlessness and anxiety, may also be more common, particularly during the first week of treatment. A serious concern, aside from drug interaction, is the risk of "serotonin syndrome," thought to result from hyperstimulation of brainstem $5HT_{1A}$receptors and characterized by myoclonus, agitation, abdominal cramping, hyperpyrexia, hypertension, and potentially death. Combinations of serotonergic agonists should be monitored closely for this reason. Considerations such as half-life, compliance, toxicity, and drug-drug interactions may guide the choice of a particular SSRI. Fluoxetine and its principal active metabolite, norfluoxetine, for example, have a combined half-life of almost 7 days, resulting in a delay of 5 weeks before steady-state levels are achieved and a similar delay for complete drug excretion once its use is discontinued. All the SSRIs may impair sexual function, resulting in diminished libido, impotence, or difficulty in achieving orgasm. Sexual dysfunction frequently results in noncompliance and should be asked about specifically in patients using SSRIs. Sexual dysfunction can sometimes be ameliorated by lowering the dose, by instituting drug holidays over the weekend (two or three times a month), or by treatment with amantadine (100 mg tid), bethanechol (25 mg tid), or buspirone (10 mg tid). Paroxetine appears to be more anticholinergic than either fluoxetine or sertraline, and sertraline carries a lower risk of producing an adverse drug interaction than the other two. Rare side effects of SSRIs include vasospastic angina and alterations of prothrombin time. Citalopram is the most specific of currently available SSRIs and appears to have no specific inhibitory effects on the P450 system.

Venlafaxine, like imipramine, blocks the reuptake of both norepinephrine and serotonin, but it produces relatively little in the way of traditional tricyclic side effects. Unlike theSSRIs, it has a relatively linear dose-response curve. Patients should be monitored for a possible increase in diastolic blood pressure, and multiple daily dosing is required because of the drug's short half-life. An extended-release form is available and has a somewhat lower incidence of gastrointestinal side effects. Nefazadone is a selective $5HT_2$receptor antagonist that also inhibits the presynaptic reuptake of serotonin and norepinephrine. Its side effects are similar to those of the SSRIs, and twice-daily dosing produces a steady state within 4 to 5 days. The drug is related structurally to trazodone, which is currently used more for its sedative than its antidepressant properties.

Nefazadone appears to produce a lower incidence of sexual side effects than do the SSRIs. Mirtazapine is a tetracyclic antidepressant that has a comparatively unique spectrum of activity. It increases noradrenergic and serotonergic neurotransmission through a blockade of central a_2-adrenergic auto- and heteroreceptors and postsynaptic $5HT_2$ and $5HT_3$ receptors. It is also strongly antihistaminic and, as such, may produce sedation at lower doses.

With the exception of citalopram, each of the SSRIs, as well as nefazadone, may inhibit one or more cytochrome P450 enzymes (Table 385-5). Depending on the specific isoenzyme involved, the metabolism of a number of concomitantly administered medications can be dramatically affected. Fluoxetine and paroxetine, for example, by inhibiting 2D6, can cause dramatic increases in the blood level of type 1C antiarrhythmics, while sertraline and nefazadone, by acting on 3A4, may alter blood levels of terfenadine, carbamazepine, and astemizole. Because many of these compounds have a narrow therapeutic window and can cause iatrogenic ventricular arrhythmias at toxic levels, the possibility of an adverse drug interaction should be considered.

Other treatment options include the MAOIs and electroconvulsive therapy. The MAOIs are highly effective, particularly in atypical depression, but the risk of hypertensive crisis following intake of tyramine-containing food or sympathomimetic drugs makes them inappropriate as first-line agents. Common side effects include orthostatic hypotension, weight gain, insomnia, and sexual dysfunction. MAOIs should not be used concomitantly with SSRIs, because of the risk of serotonin syndrome, or with TCAs, because of possible hyperadrenergic effects. Electroconvulsive therapy is at least as effective as medication, but its use is reserved for treatment-resistant cases and delusional depressions.

Regardless of the medication chosen, the treatment response should be evaluated after approximately 2 months of therapy. Three-quarters of patients show an adequate response by this time, but if remission is inadequate, the patient should be questioned about medication compliance, and an increase in dose should be considered if side effects are not troublesome. If there is no improvement, consultation with or referral to a mental health specialist is advised. Strategies for treatment then include selection of an alternative drug, combinations of antidepressants, and/or adjunctive treatment with other classes of drugs, including lithium, thyroid hormone, and dopamine agonists. Patients whose response to an SSRI disappears over time may benefit from the addition of buspirone (10 mg tid) or pindolol (2.5 mg tid) or small amounts of a tricyclic antidepressant such as desipramine (25 mg bid or tid). Once significant remission is achieved, drug treatment should be continued for at least 6 to 9 months to prevent relapse. In patients who have had two or more episodes of depression, indefinite maintenance treatment should be considered.

It is essential to counsel patients about depression and the medications they are receiving. An educational approach is best, describing what is known about the depressive syndrome and how the medications may help. Advice about stress reduction, side effects, and expected length of treatment and cautions that alcohol may exacerbate depressive symptoms and impede drug response are helpful. Patients should be given time to describe their experience and the impact it has had on them,

their family, and their outlook. Occasional empathic silence may be as helpful for the treatment alliance as verbal reassurance.

BIPOLAR DISORDER

Clinical Manifestations Bipolar disorder is common, affecting approximately 3 million persons in the United States, but often difficult to diagnose. It is characterized by unpredictable swings in mood from mania (or hypomania) to depression. Some patients suffer only from recurrent attacks of *mania*, which in its pure form is associated with increased psychomotor activity; excessive social extroversion; decreased need for sleep; impulsivity and impairment in judgment; and expansive, grandiose, and sometimes irritable mood (Table 385-10). In severe mania, patients may experience delusions and paranoid thinking indistinguishable from schizophrenia. Half of patients with bipolar disorder present with a mixture of psychomotor agitation and activation with dysphoria, anxiety, and irritability. It may be difficult to distinguish *mixed mania* from *agitated depression*. In some bipolar patients (*bipolar II disorder*), the full criteria for mania are lacking, and the requisite recurrent depressions are separated by periods of mild activation and increased energy (hypomania). In *cyclothymic disorder*, there are numerous hypomanic periods, usually of relatively short duration, alternating with clusters of depressive symptoms that fail, either in severity or duration, to meet the criteria of major depression. The mood fluctuations are chronic and should be present for at least 2 years before the diagnosis is made.

Manic episodes typically emerge over a period of days to weeks, but onset within hours is possible, usually in the early morning hours. An untreated episode of either depression or mania can be as short as several weeks or last as long as 8 to 12 months, and rare patients have an unremitting chronic course. The term *rapid cycling* is used for patients who have four or more episodes of either depression or mania in a given year. This pattern occurs in 15% of all patients, almost all of whom are women. In some cases, rapid cycling is linked to an underlying thyroid dysfunction and, in others, is iatrogenically triggered by prolonged antidepressant treatment.

Although bipolar illness is associated with frequent episodic recurrence, it was once thought to have a favorable prognosis and outcome. More recent data, however, show that approximately half of patients with the disorder have sustained difficulties in work performance and psychosocial functioning. The most frequent age of onset for bipolar disorder is between 20 and 30 years of age, but many individuals report premorbid symptoms in late childhood or early adolescence. The prevalence is similar for men and women; women are likely to have more depressive and men more manic episodes over a lifetime.

Differential Diagnosis The differential diagnosis of mania includes toxic effects of stimulant or sympathomimetic drugs as well as secondary mania induced by hyperthyroidism, AIDS, or neurologic disorders, such as Huntington's or Wilson's disease, or cerebrovascular accidents. Comorbidity with alcohol and substance abuse is common, either because of poor judgment and increased impulsivity or because of an attempt at self-medication.

Etiology and Pathophysiology Evidence for a genetic predisposition to bipolar

disorder is significant. The concordance rate for monozygotic twin pairs approaches 80%, and segregation analyses are consistent with autosomal dominant transmission. Several chromosomal locations for the gene have been proposed in the past decade on the basis of linkage analysis in affected families. None, however, has yet received convincing confirmation.

The pathophysiologic mechanisms underlying the profound and recurrent mood swings of bipolar disorder remain unknown. Cellular models of changes in membrane Na_+- and K_+-activated ATPase and proposals of disordered signal transduction mechanisms involving the phosphoinositol system and GTP-binding proteins have received the most attention. Alterations in glutamate regulation and in neuroprotective transcription factors are also being investigated as possible explanations for the therapeutic effects of lithium.

Neurophysiologic studies suggest that patients with bipolar disorder have altered circadian rhythmicity. Lithium may exert its therapeutic benefit through a resynchronization of intrinsic rhythms keyed to the light/dark cycle (Chap. 27). Neuroimaging techniques have also identified a higher rate of subcortical white matter abnormalities in patients than in age-matched controls.

TREATMENT

(Table 385-11) Lithium carbonate is the mainstay of treatment in bipolar disorder, although sodium valproate is equally effective in acute mania. Carbamazepine is also efficacious. The response rate to lithium carbonate is 70 to 80% in acute mania, with beneficial effects appearing in 1 to 2 weeks. Lithium also has a prophylactic effect in prevention of recurrent mania, and, to a lesser extent, in the prevention of recurrent depression. A simple cation, lithium is rapidly absorbed from the gastrointestinal tract and remains unbound to plasma or tissue proteins. Some 95% of a given dose is excreted unchanged through the kidneys within 24 h.

Serious side effects from lithium administration are rare, but minor complaints such as gastrointestinal discomfort, nausea, diarrhea, polyuria, weight gain, skin eruptions, alopecia, and edema are common. Over time, urine-concentrating ability may be decreased, but significant nephrotoxicity does not occur. In a small subset of patients in whom excessive polyuria occurs (>3000 mL/24 h), dose or schedule adjustments or the adjunctive use of diuretics should be considered. Lithium exerts an antithyroid effect by interfering with the synthesis and release of thyroid hormones. Approximately 5% of patients taking lithium for ³18 months develop hypothyroidism, with women more likely to be affected than men. Iatrogenic hypothyroidism should be ruled out in any patient who experiences a recurrence of depressive symptomatology during lithium treatment. More serious side effects include tremor, interference with concentration and memory, ataxia, dysarthria, and incoordination.ECGchanges of T wave flattening and conduction delays may occur. There is suggestive, but not conclusive, evidence that lithium is teratogenic, inducing cardiac malformations in the first trimester.

In the treatment of acute mania, lithium is initiated at 300 mg bid or tid, and the dose is then increased by 300 mg every 2 to 3 days to achieve blood levels of 0.8 to 1.2 meq/L. Before initiating treatment the physician should obtain baseline measures of

electrolytes, creatinine, thyroid function, and a complete blood count (CBC). Because the therapeutic effect of lithium may not appear until 7 to 10 days of treatment, adjunctive usage of lorazepam (1 to 2 mg every 4 h) or clonazepam (0.5 to 1 mg every 4 h) may be beneficial to control agitation. Antipsychotics are indicated in patients with severe agitation who respond only partially to benzodiazepines. These agents should be discontinued in the transition to maintenance lithium therapy. Patients using lithium should be monitored closely, since the blood levels required to achieve a therapeutic benefit are close to those associated with neurotoxicity. Risk factors for neurotoxicity include concomitant medical illness, decrease in salt intake, or concurrent use of medications that may increase the serum level of lithium (neuroleptics, diuretics, and calcium channel blockers). Once stabilization is achieved, the lithium level can be monitored on a bimonthly basis, and thyroid and renal functions on a biannual basis, or more frequently if clinical change occurs.

Valproic acid is an alternative in patients who cannot tolerate lithium or respond poorly to it. Valproic acid may be better than lithium for patients who have a rapid-cycling course (i.e., more than four episodes a year) or who present with a mixed or dysphoric mania. Valproic acid is usually started at 500 to 750 mg/d in divided doses. The dose is increased every several days to achieve blood levels in the range of 50 to 100 ug/mL, which typically are achieved at a dose of 1000 to 2500 mg/d. The most serious adverse effects of valproic acid are hepatoxicity, which may be fatal, and hyponatremia. Such cases are fortunately rare, but periodic monitoring of liver enzymes, particularly during the first 90 days of treatment, is indicated.

Carbamazepine, although not formally approved by the U.S. Food and Drug Administration (FDA) for bipolar disorder, has clinical efficacy in the treatment of acute mania. Carbamazepine is initiated at 400 to 600 mg/d in divided doses, and the dose is increased to achieve a blood level of 4 to 12 mg/L. Carbamazepine may induce a benign leukopenia, but the risk of aplastic anemia is minimal. Nevertheless, it is wise to obtain a CBC periodically.

Preliminary evidence also suggests that other anticonvulsant agents such as gabapentin, lamotrigine, and topiramate may possess some therapeutic benefit.

The recurrent nature of bipolar mood disorder necessitates maintenance treatment. Maintenance of blood lithium levels of at least 0.8 mg/L is important to achieve optimal prophylaxis. Compliance is frequently an issue and often requires enlistment and education of concerned family members to avoid relapse. Efforts to identify and limit psychosocial factors that may trigger episodes are important, as is an emphasis on life-style regularity. Antidepressant medications are sometimes required for the treatment of severe breakthrough depressions, but their use should generally be avoided during maintenance treatment because of the risk of precipitating mania or accelerating the cycle frequency. Loss of efficacy over time may be observed with any of the mood-stabilizing agents. In such situations, an alternative agent or combination therapy is usually helpful.

Consensus guidelines for the treatment of acute mania and bipolar depression are described in Table 385-12.

SOMATOFORM DISORDERS

CLINICAL MANIFESTATIONS

Patients with multiple somatic complaints that cannot be explained by a known medical condition or by the effects of alcohol or of recreational or prescription drugs are seen commonly in primary care practice; one survey indicates a prevalence of 5%. The somatoform disorders include a variety of conditions that differ in terms of the specific symptoms that are present and in whether or not the symptoms are intentionally produced. In *somatization disorder*, the patient presents with multiple physical complaints referable to different organ systems (Table 385-13). Onset is usually before age 30, and the disorder is persistent. Formal diagnostic criteria require the recording of at least four pain, two gastrointestinal, one sexual, and one pseudoneurologic symptom. Patients with somatization disorder often present with dramatic complaints, but the complaints are inconsistent. Symptoms of comorbid anxiety and mood disorder are common and may be the result of drug interactions due to regimens initiated independently by different physicians. Patients with somatization disorder may be impulsive and demanding and frequently qualify for a formal comorbid psychiatric diagnosis. In *conversion disorder*, the symptoms focus on deficits that involve voluntary motor or sensory function and on psychological factors that initiate or exacerbate the medical presentation. Like somatization disorder, the deficit is not intentionally produced or simulated, as is the case in factitious disorder (malingering). In *hypochondriasis*, the essential feature is a belief of serious medical illness that persists despite reassurance and appropriate medical evaluation. As with somatization disorder, patients with hypochondriasis have a history of poor relationships with physicians stemming from their sense that they have been evaluated and treated inappropriately or inadequately. Hypochondriasis can be disabling in intensity and is persistent, with waxing and waning symptomatology.

In *factitious illnesses*, the patient consciously and voluntarily produces physical symptoms of illness. The term *Munchausen's syndrome* is reserved for individuals with particularly dramatic, chronic, or severe factitious illness. In true factitious illness, the sick role itself is gratifying. A variety of signs, symptoms, and diseases have been either simulated or caused by factitious behavior, the most common including chronic diarrhea, fever of unknown origin, intestinal bleeding or hematuria, seizures, and hypoglycemia. Factitious disorder is usually not diagnosed until 5 to 10 years after its onset, and it can produce significant social and medical costs. In *malingering*, the fabrication derives from a desire for some external reward, such as a narcotic medication or disability reimbursement.

TREATMENT

Patients with somatization disorders are frequently subjected to multiple diagnostic testing and exploratory surgeries in an attempt to find their "real" illness. Such an approach is doomed to failure and does not address the core issue. Successful treatment is best achieved through behavior modification, in which access to the physician is tightly regulated and adjusted to provide a sustained and predictable level of support that is less clearly contingent on the patient's level of presenting distress. Visits can be brief and should not be associated with a need for a diagnostic or

treatment action. Although the literature is limited, some patients with somatization disorder may benefit from antidepressant treatment. Fluoxetine and MAOIs have both been found to be useful in reducing obsessive ruminations, dysphoria, and anxious preoccupation in patients with multiple somatic complaints.

The treatment of factitious disorder is complicated in that any attempt to confront the patient usually only creates a sense of humiliation and causes the patient to abandon treatment from that caregiver. A better strategy is to introduce psychological causation as one of a number of possible explanations and to include factitious illness as an option in the differential diagnoses that are discussed. Without directly linking psychotherapeutic intervention to the diagnosis, the patient can be offered a face-saving means by which the pathologic relationship with the health care system can be examined and alternative approaches to life stressors developed.

PERSONALITY DISORDERS

CLINICAL MANIFESTATIONS

Personality disorders are characteristic patterns of thinking, feeling, and interpersonal behavior that are relatively inflexible and cause significant functional impairment or subjective distress for the individual. The observed behaviors are not secondary to another mental disorder, nor are they precipitated by substance abuse or a general medical condition. This distinction is often difficult to make in clinical practice, as personality change may be the first sign of serious neurologic, endocrine, or other medical illness. Patients with frontal lobe tumors, for example, can present with changes in motivation and personality while the results of the neurologic examination remain within normal limits. Personality traits are stable over time and environmental situation and are recognizable in adolescence or early adult life. Although DSM-IV portrays personality disorders as qualitatively distinct categories, there is an alternative perspective that personality characteristics vary as a continuum between normal functioning and formal mental disorder.

Personality disorders have been grouped into three clusters that share similar attributes. *Cluster A* includes paranoid, schizoid, and schizotypal personality disorders. It includes individuals who are odd and eccentric and who maintain an emotional distance from others. Individuals have a restricted emotional range and remain socially isolated. Patients with schizotypal personality disorder frequently have unusual perceptual experiences and express magical beliefs about the external world. The essential feature of paranoid personality disorder is a pervasive mistrust and suspiciousness of others to an extent that is unjustified by available evidence. *Cluster B* disorders include antisocial, borderline, histrionic, and narcissistic types and describe individuals whose behavior is impulsive, excessively emotional, and erratic. *Cluster C* incorporates avoidant, dependent, and obsessive-compulsive personality types; enduring traits are anxiety and fear. The boundaries between cluster types are to some extent artificial, and many patients who meet criteria for one personality disorder also meet criteria for aspects of another. The risk of a comorbid major mental disorder is increased in patients who qualify for a diagnosis of personality disorder.

TREATMENT

Historically, recommended treatment for personality disorders was long-term psychotherapy, in which the pathologic patterns of interaction with the world at large could be relived and examined through the corrective emotional experience of the controlled therapeutic relationship. More recently, the recognition that personality derives in part from biologically determined components of temperament has given rise to the empirical use of drugs to treat specific symptom clusters as well as any coexisting major mental disorder. Antidepressant medications and low-dose antipsychotic drugs have some efficacy in cluster A personality disorders, while anticonvulsant mood-stabilizing agents and MAOIs may be considered for patients with cluster B diagnoses who show marked mood reactivity, behavioral dyscontrol, and/or rejection hypersensitivity. Anxious or fearful cluster C patients often have a response to medication that parallels that for patients with axis I anxiety disorders. In all cases, it is important for both the physician and the patient to have reasonable expectations as to the possible effect of the medication and any associated side effects. Beneficial responses may be subtle and observable only over time.

SCHIZOPHRENIA

CLINICAL MANIFESTATIONS

Schizophrenia is a heterogeneous syndrome characterized by perturbations of language, perception, thinking, social activity, affect, and volition. There are no pathognomonic features. The syndrome commonly begins in late adolescence, has an insidious onset, and, classically, a poor outcome, progressing from social withdrawal and perceptual distortions to a state of chronic delusions and hallucinations. Patients may present with positive symptoms (such as conceptual disorganization, delusions, or hallucinations) or negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement) and must have at least two of these for a 1-month period and continuous signs for at least 6 months to meet formal diagnostic criteria. "Negative" symptoms predominate in one-third of the schizophrenic population and are associated with a poor long-term outcome and a poor response to drug treatment. However, marked variability in the course and individual character of symptoms is typical.

Schizophrenia can be classified according to the specific symptomatology present, although such distinctions do not correlate well with either course of illness or response to treatment, and many individuals have symptoms of more than one type. The four main symptom subtypes are catatonic, paranoid, disorganized, and residual. *Catatonic-type* describes patients whose clinical presentation is dominated by profound changes in motor activity, negativism, and echolalia or echopraxia. *Paranoid-type* describes patients who have a prominent preoccupation with a specific delusional system and who otherwise do not qualify as having *disorganized-type* disease, in which disorganized speech and behavior are accompanied by a superficial or silly affect. In *residual-type* disease, negative symptomatology exists in the absence of delusions, hallucinations, or motor disturbance. The diagnosis of *schizophreniform disorder* is reserved for patients who meet the symptom requirements but not the duration requirements for schizophrenia, and that of *schizoaffective disorder* is used for those whose symptoms of schizophrenia are independent of associated periods of mood

disturbance. Prognosis depends not on symptom severity but on the response to antipsychotic medication. Patients may present with acute rather than insidious onset of symptoms, and remission without recurrence does occur. About 10% of schizophrenic patients commit suicide. As currently defined, schizophrenia is present in 0.85% of individuals worldwide. Overall, lifetime prevalence is approximately 1 to 1.5%.

The societal costs of schizophrenia are substantial. An estimated 300,000 episodes of acute schizophrenia occur annually, resulting in direct and indirect costs that have been estimated at >$33 billion.

DIFFERENTIAL DIAGNOSIS

For a diagnosis of schizophrenia to be made, the symptom complex must cause significant dysfunction in social or occupational domains and last for at least 6 months. The diagnosis is principally one of exclusion, requiring the absence of significant associated mood symptoms, any relevant medical condition, and substance abuse. Drug reactions that cause hallucinations, paranoia, confusion, or bizarre behavior may be dose-related or idiosyncratic; b-adrenergic blockers, clonidine, cycloserine, quinacrine, and procaine derivatives are most commonly associated with these symptoms. Drug causes should be ruled out in any case of newly emergent psychosis. The general neurologic examination in patients with schizophrenia is usually normal, but motor rigidity, tremor, and dyskinesias are noted in one-quarter of untreated patients.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Epidemiologic surveys identify three principal risk factors for schizophrenia: (1) genetic susceptibility, (2) early developmental insults, and (3) winter birth. Family, twin, and adoption studies show that genetic factors are involved in at least a subset of individuals who develop schizophrenia. Using conservative diagnostic definitions, schizophrenia is observed in approximately 6.6% of all first-degree relatives of an affected proband. If both parents are affected, the risk for offspring is 40%. The concordance rate for monozygotic twins is 50%, compared to 10% for dizygotic twins. Examination of families in which aggregation of schizophrenia occurs has revealed an increased incidence of other psychotic and nonpsychotic psychiatric disorders as well, including schizoaffective disorder and *schizotypal* and *schizoid personality disorders*, the latter terms designating individuals who show a lifetime pattern of social and interpersonal deficits characterized by an inability to form close interpersonal relationships, eccentric behavior, and mild perceptual distortions. Some relatives and individuals with schizophrenia have been found to have distinctive patterns in expressing emotion, most often involving increased criticism, hostility, and emotional overinvolvement.

There is evidence that environmental influences modulate genetic factors in the expression of schizophrenia, and, in sporadic cases, may serve as a sufficient cause. Gestational and birth complications, including Rh factor incompatibility, prenatal exposure to influenza during the second trimester, and prenatal nutritional deficiency have been implicated. Studies of monozygotic twins discordant for schizophrenia have reported neuroanatomic differences between affected and unaffected siblings, supporting a "two-strike" etiology involving both genetic susceptibility and an environmental insult. The latter might involve localized hypoxia during critical stages of

brain development.

Neuroimaging and postmortem studies have identified a number of structural and functional abnormalities, including (1) enlargement of the lateral and third ventricles with associated cortical atrophy and sulcal enlargement; (2) volumetric reductions in the amygdala, hippocampus, right prefrontal cortex, and thalamus; (3) altered asymmetry of the planum temporale; and (4) decreases in neuronal metabolism in the thalamus and prefrontal cortex. Some, but not all, prospective studies record progressive reduction in hemispheric volume over years. Neuropathologic studies have reported changes in the size, orientation, and density of cells in the hippocampus and, in the prefrontal cerebral cortex, decreases in neuronal number and the density of interneurons in layer II as well as an increased density of pyramidal cells in layer V. These observations suggest that schizophrenia results from a disturbance in a cortical striatal-thalamic circuit resulting in deficits in sensory filtering and attentional behavior. Although the formal diagnostic requirements for schizophrenia are not usually met until early adult life, children who eventually develop the disorder may exhibit subtle deficits in motor function, cognition, and emotional expression from an early age.

The hypothesized alterations in cortical neuronal circuitry are paralleled clinically by impairments in attention and cortical information processing, autonomic nervous system activation, and habituation. Schizophrenic individuals are highly distractible and demonstrate deficits in perceptual-motor speed, ability to shift attention, and filtering out of background stimuli. Event-related evoked potential studies of schizophrenia have defined a specific reduction in P300 amplitude to a novel stimulus, which implicates an impairment in cognitive processing. Impaired information processing is found in unaffected family members.

Despite evidence for a genetic causation, the results of molecular genetic linkage studies in schizophrenia are inconclusive. Reports of linkage of schizophrenia to loci on chromosomes 1, 5, 6, 8, 11, and 22 and other regions have not been formally replicated and have led to larger scale association studies currently underway.

The *dopamine hypothesis* of schizophrenia is based on the serendipitous discovery that agents that diminish dopaminergic activity have beneficial effects in reducing the acute symptoms and signs of psychosis, specifically agitation, anxiety, and hallucinations. Amelioration of delusions and social withdrawal is less dramatic. Thus far, however, evidence for increased dopaminergic activity is indirect. An increase in the activity of nigrostriatal and mesolimbic systems and a decrease in mesocortical tracts innervating the prefrontal cortex is hypothesized, although it is likely that other neurotransmitters, including serotonin, acetylcholine, glutamate, and GABA also contribute to the pathophysiology of the illness. Involvement of excitatory amino acids is postulated, based on the finding that NMDA receptor antagonists and channel blockers, such as phencyclidine (PCP) and ketamine, produce characteristic signs of schizophrenia in normal individuals.

TREATMENT

Antipsychotic agents (Table 385-14) remain the cornerstone of acute and maintenance treatment of schizophrenia and are effective in the treatment of hallucinations,

delusions, and thought disorders, regardless of etiology. The exact mechanism of action remains incompletely understood, but dopaminergic receptor blockade in the limbic system and basal ganglia appears to be an essential element, since the clinical potencies of traditional antipsychotic drugs parallel their affinities for the D_2receptor, and even the newer "atypical" agents exert some degree of D_2receptor blockade. All neuroleptics induce expression of the immediate-early gene c-*fos* in the nucleus accumbens, a dopaminergic site connecting prefrontal and limbic cortices. The clinical efficacy of newer atypical neuroleptics, however, may involve D_1, D_3, and D_4receptor blockade,a_1- anda_2-noradrenergic activity, and/or altering the relationship between $5HT_2$ and D_2receptor activity.

Conventional neuroleptics differ in their potency and side-effect profile. Older agents, such as chlorpromazine and thioridazine, are more sedating and anticholinergic and more likely to cause orthostatic hypotension, while higher potency antipsychotics, such as haloperidol, perphenazine, and thiothixene, carry a higher risk of inducing extrapyramidal side effects. The model atypical antipsychotic agent is clozapine, a dibenzodiazepine that has a greater potency in blocking the $5HT_2$than the D_2receptor and a much higher affinity for the D_4 than the D_2receptor. Its principal disadvantage is risk of blood dyscrasia, requiring regular monitoring of theCBC. Unlike other antipsychotics, clozapine does not cause a rise in prolactin level. Approximately 30% of patients have a better antipsychotic response to these agents than to traditional neuroleptics, suggesting that they will increasingly displace the older-generation drugs. Clozapine appears to be the most effective member of this class; however, its side-effect profile makes it most appropriate for treatment-resistant cases. *Clozapine* increases the activity of the immediate-early gene c-*fos* in the prefrontal cortex, the neuroanatomic region having the highest concentration of D_4receptors and an area thought to mediate the specific executive functions that are prominently impaired in schizophrenia. *Risperidone*, a benzisoxazole derivative, is more potent at $5HT_2$than D_2receptor sites, like clozapine, but it also exerts significant$a_2$antagonism, a property that may contribute to its perceived ability to improve mood and increase motor activity. Risperidone is not as effective as clozapine in treatment-resistant cases but does not carry a risk of blood dyscrasia. *Olanzapine* is more similar neurochemically to clozapine but has a significant risk of inducing weight gain. *Quetiapine* is distinct in having a weak D_2effect but potenta_1 and histamine blockade.

Conventional antipsychotic agents are effective in ~70% of patients presenting with a first episode. Improvement may be observed within hours or days, but full remission usually requires 6 to 8 weeks. The choice of agent depends principally on the side-effect profile and cost of treatment or on a past personal or family history of a favorable response to the drug in question. Atypical agents appear to be more effective in treating negative symptoms and improving cognitive function. Equivalent treatment response can usually be achieved with relatively low doses of any drug selected, i.e., 4 to 6 mg/d of haloperidol, 10 to 15 mg of olanzapine, or 4 to 6 mg/d of risperidone. Doses in this range result in>80% D_2receptor blockade, and there is little evidence that higher doses increase either the rapidity or degree of response. Maintenance treatment requires careful attention to the possibility of relapse and monitoring for the development of a movement disorder. Intermittent drug treatment is less effective than regular dosing, but gradual dose reduction is likely to improve social functioning in many schizophrenic patients who have been maintained at high doses. If medications are completely

discontinued, however, the relapse rate is ~60% within 6 months. Long-acting injectable preparations (haloperidol decanoate and fluphenazine decanoate) are considered when noncompliance with oral therapy leads to relapses. In treatment-resistant patients, a transition to clozapine usually results in rapid improvement, but a prolonged delay in response in some cases necessitates a 6- to 9-month trial for maximal benefit to occur.

Antipsychotic medications can cause a broad range of side effects, including lethargy, weight gain, postural hypotension, constipation, and dry mouth. Extrapyramidal symptoms such as dystonia, akathisia, and akinesia are also frequent with traditional agents and may contribute to poor compliance if not specifically addressed. Anticholinergic and parkinsonian symptoms respond well to trihexyphenidyl, 2 mg bid, or benztropine mesylate, 1 to 2 mg bid. Akathisia may respond to beta blockers. In rare cases, more serious and occasionally life-threatening side effects may emerge, including ventricular arrhythmias, gastrointestinal obstruction, retinal pigmentation, obstructive jaundice, and neuroleptic malignant syndrome (characterized by hyperthermia, autonomic dysfunction, muscular rigidity, and elevated creatine phosphokinase levels). The most serious adverse effects of clozapine are agranulocytosis, which has an incidence of 1%, and induction of seizures, which has an incidence of 10%. Weekly white blood cell counts are required, particularly during the first 3 months of treatment.

A serious side effect of long-term use of the classic antipsychotic agents is *tardive dyskinesia*, characterized by repetitive, involuntary, and potentially irreversible movements of the tongue and lips (bucco-linguo-masticatory triad), and, in approximately half of cases, choreoathetoid movements of the limbs (Chap. 22). Tardive dyskinesia has an incidence of ~4% per year of exposure, and a maximal prevalence of ~20% in chronic patients treated with high-dose neuroleptics. The risk associated with the newer atypical agents is unknown but expected to be much less. The prevalence increases with age and with total dose and duration of drug administration, but unknown individual factors play the greatest part in determining risk. The cause of tardive dyskinesia is unknown, but evidence suggests that chronic neuroleptic treatment increases the formation of free radicals and perhaps damages mitochondrial energy metabolism. Vitamin E may reduce abnormal involuntary movements if given early in the syndrome.

Drug treatment of schizophrenia is by itself insufficient. Psychoeducational efforts directed towards families and relevant community resources have proven to be necessary to maintain stability and optimize prognosis. A treatment model involving a multidisciplinary case-management team that seeks out and closely follows the patient in the community has proven particularly effective, not only in maintaining pharmacologic adherence but also in facilitating occupational achievement and interactions with welfare, legal, and primary medical care systems.

ASSESSMENT AND EVALUATION OF VIOLENCE

Primary care physicians may encounter situations in which familial, domestic, or societal violence is discovered or suspected. Such an awareness can carry legal and moral obligations; many state laws mandate reporting of child, spousal, and elder abuse. Physicians are frequently the first point of contact for both victim and abuser. Between 1

and 2 million older Americans and 1.5 million U.S. children are thought to experience some form of physical maltreatment each year. Spousal abuse is thought to be even more prevalent. A recent survey of internal medicine practices found that 5.5% of all female patients had experienced domestic violence in the previous year, and that these individuals were more likely to suffer from depression, anxiety, somatization disorder, and substance abuse and to have attempted suicide. When domestic violence is suspected, direct but nonjudgmental questioning should be pursued with each party separately -- "Do you feel safe at home?" and "If there's a disagreement or a conflict between the two of you, how is it worked out?" In addition to obvious and suggestive physical injury, individuals who are abused frequently express low self-esteem, vague somatic symptomatology, social isolation, and a passive feeling of loss of control. Although it is essential to treat these elements in the victim, the first obligation is to ensure that the perpetrator has taken responsibility for preventing any further violence. Substance abuse and/or dependence and serious mental illness in the abuser may contribute to the risk of harm and require direct intervention. Depending on the situation, law enforcement agencies, community resources such as support groups and shelters, and individual and family counseling can be appropriate components of a treatment plan. A safety plan should be formulated with the victim, in addition to the provision of information about abuse, its likelihood of recurrence, and its tendency to increase in severity and frequency. Antianxiety and antidepressant medications may sometimes be useful in treating the acute symptoms, but only if independent evidence for an appropriate psychiatric diagnosis exists. Antidepressants are generally not indicated when the diagnosis is linked to the social situation, such as an adjustment disorder with depressed mood. The most important element in treatment is the development of a supportive doctor-patient relationship that avoids further blame of the victim.

In certain circumstances, a significant potential for societal violence may be discovered. Sympathetic, but direct, questioning about potential violent impulses, access to weapons, recreational drug use, and specific homicidal ideation is necessary and is sometimes therapeutic in its own right. The existence and possible contribution of such medical conditions as delirium and/or intoxication should be evaluated. Available disposition options for potentially violent patients include police custody, psychiatric hospitalization, and referral to home care, with involvement of family, friends, and caregivers. In deciding which treatment option is most appropriate, clinicians should endeavor to establish an empathic interaction with the patient, while avoiding interventions or stimuli that might precipitate or increase the risk of violent behavior. Formal verbal limit setting may be necessary if the patient reveals the existence of a weapon or becomes increasingly agitated or verbally abusive. Use of the least restrictive intervention is generally the best approach during the initial evaluation.

MENTAL HEALTH PROBLEMS IN THE HOMELESS

There is a high prevalence of mental disorders and substance abuse among homeless and impoverished people. The total number of homeless individuals in the United States is estimated at 2 to 3 million, one-third of whom qualify as having a serious mental disorder. Poor hygiene and nutrition, substance abuse, psychiatric illness, physical trauma, and exposure to the elements combine to make the provision of medical care a challenging enterprise. Only a minority of individuals receive formal mental health care; the main points of contact are outpatient medical clinics and emergency departments.

Primary care settings represent a critical site in which housing needs, treatment of substance dependence, and evaluation and treatment of psychiatric illness can most efficiently take place. Successful intervention is dependent on breaking down traditional administrative barriers to health care and recognizing the physical constraints and emotional costs imposed by homelessness. Simplifying health care instructions and follow-up, allowing frequent visits, and dispensing medications in limited amounts that require ongoing contact are possible techniques for establishing a successful therapeutic relationship. Child neglect, resulting in developmental delay and emotional difficulty in addition to other health problems, is unfortunately common and necessitates an effort to evaluate the well being of any offspring independently.

(Bibliography omitted in Palm version)

SECTION 6 - ALCOHOLISM AND DRUG DEPENDENCY

386. BIOLOGY OF ADDICTION - *Robert O. Messing*

Drug addiction is a chronic, relapsing disorder characterized by compulsion to take a drug and loss of self-control in limiting drug intake. The American Psychiatric Association (*DSM-IV*) uses the term *substance dependence* instead of drug addiction and requires at least three of the following symptoms to be present for diagnosis: (1) tolerance; (2) withdrawal; (3) persistent desire or unsuccessful attempts to reduce use; (4) use in larger amounts than intended; (5) reduction in important social, occupational, or recreational activities because of drug use; (6) considerable time spent obtaining the substance; and (7) continued use despite health, social, or economic problems resulting from substance use. *Substance abuse* is a milder disorder characterized by repetitive drug use that results in social or economic distress. Experimental studies in humans and in animal models (rodents and also simpler organisms such as flies and worms) have begun to elucidate the cellular and molecular mechanisms that mediate the loss of control in drug taking that is the hallmark of addiction. This chapter will review current understanding of the neurobiology of drug abuse relevant to the specific substances discussed in subsequent chapters, namely alcohol (Chap. 387), opioids (Chap. 388), cocaine and marijuana (Chap. 389), and nicotine (Chap. 390).

BEHAVIORAL RESPONSES TO DRUGS OF ABUSE

Drugs of abuse produce *euphoria*, which is an emotional state characterized by intensely pleasant feelings. A major reason why users are motivated to seek and take more of a drug is because they perceive the experience as *rewarding*. *Reinforcement* refers to the ability of a drug to produce a pleasurable response that motivates the user to take the drug repeatedly. The powerful reinforcing and rewarding properties of abusable drugs can be measured by the tremendous effort experimental animals will expend, e.g., by pressing a lever multiple times, to obtain an oral or intravenous dose of a drug.

Tolerance is a reduction in response to a drug after repeated use and is a normal, adaptive, physiologic response. *Pharmacokinetic tolerance* may arise through an increase in the rate of metabolism. For example, barbiturates induce hepatic microsomal enzymes resulting in more rapid metabolism. *Pharmacodynamic tolerance* results from drug-induced changes in cell signaling and gene expression. Behavioral *sensitization* is a process whereby repeated administration of a drug leads to a progressively stronger behavioral response. Sometimes called "reverse tolerance," it is often measured by examining drug-induced locomotor activation. It generally requires longer intervals between doses to develop than does tolerance. Both tolerance and sensitization can promote repeated drug use. Tolerance develops to the rewarding properties of most abusable drugs, requiring the user to employ higher doses to achieve a euphoric effect. Sensitization also promotes drug self-administration, since rodents will expend greater effort in lever-pressing for drugs to which they are sensitized.

Physical dependence is an adaptive state that develops through resetting of homeostatic mechanisms to permit normal function despite the continued presence of a drug. When drug intake is abruptly terminated in a physically dependent individual, a

withdrawal syndrome emerges. The symptoms of withdrawal tend to be opposite to those seen during acute drug exposure. Thus, abstinence from alcohol and other sedative-hypnotics causes nervous system hyperactivity, whereas withdrawal from cocaine and other stimulants is characterized by fatigue, sedation, and depression. Withdrawal symptoms are the principal evidence for physical dependence. Like tolerance, physical dependence is a normal physiologic response to repeated drug exposure and does not necessarily indicate drug abuse or addiction. However, withdrawal can cause intensely negative, unpleasant emotions such as dysphoria, anxiety, and irritability. In animal studies employing intracranial self-stimulation, withdrawal is also associated with reduced brain reward function. Thus, it appears that drug withdrawal can act as a negative reinforcer that contributes to repeated drug use.

Human patients prescribed opioids for treatment of pain may develop tolerance and physical dependence but rarely become addicted. Likewise, in experimental animals, establishing physical dependence is not sufficient to induce voluntary drug self-administration. Instead, it appears that animals and humans seek abusable drugs mainly for their positive reinforcing properties. In susceptible persons, repeated use of abusable drugs induces drug *craving*, a powerful motivational state in which the addict seeks the drug to the exclusion of other activities. Craving is a manifestation of *psychological dependence* on a drug and is most severe during acute abstinence. It is a long-lasting, conditioned response that may be evoked by environmental cues such as sights, smells, or situations associated with previous drug use, even after long periods of drug abstinence. Understanding the mechanisms that underlie susceptibility to drug craving is a critical task in addiction research.

GENETIC FACTORS IN ADDICTION

Genetic factors have been studied most extensively in alcoholism (Chap. 387). Patterns of inheritance in humans are most consistent with alcoholism being a polygenic disorder. Some genes confer a reduced risk for alcoholism. Approximately half of all individuals in Asian populations carry an allele of aldehyde dehydrogenase that encodes an isozyme with reduced enzymatic activity. After ingesting alcohol, they have increased blood levels of acetaldehyde and experience vasodilatation, tachycardia, hot sensations, and hypotension. They also report feeling intoxicated at very low doses of alcohol. Individuals expressing this isoenzyme rarely abuse alcohol. Other genetic factors predispose individuals to increased risk for alcoholism. A recent multicenter study of 105 families of alcoholics revealed evidence for susceptibility loci for alcohol dependence on chromosomes 1, 7, and possibly 2. An additional study of a Southwestern Native American population found evidence for genetic linkage to alcohol dependence on chromosomes 4 and 11. The identity of the genes associated with increased risk is not yet known.

NEUROANATOMY OF DRUG REWARD

Early studies of intracranial electrical self-stimulation in rodents identified key structures involved in drug reward and motivational aspects of drug dependence (Fig. 386-1). These include the midbrain ventral tegmental area (VTA), median forebrain bundle (MFB), nucleus accumbens, medial frontal cortex, amygdala, and lateral hypothalamus. Many of these structures are key components of a *mesocorticolimbic dopamine system*

that is now a principal focus of addiction research. Dopaminergic neurons in the VTA project axons via the MFB to the nucleus accumbens, amygdala, and frontal cortex. Reciprocal projections from g-aminobutyric acid (GABA)-containing neurons in the nucleus accumbens project back through the MFB onto VTA neurons. Other brain regions modulate this system through opioid peptide, GABA, serotonin, and glutamate inputs that interact with the VTA, nucleus accumbens, and other structures within the system.

Certain nuclei within the mesocorticolimbic dopamine system share similarities in architecture, receptor expression, and connectivity with other brain regions. These related structures reside in the basal forebrain and include the central medial amygdala, bed nucleus of the stria terminalis, and shell of the nucleus accumbens. They appear to constitute a functional entity that has been called the "extended amygdala." The extended amygdala receives inputs from the hippocampus, basolateral amygdala, midbrain, and lateral hypothalamus and sends efferents to the ventral pallidum, VTA, and lateral hypothalamus.

MOLECULAR TARGETS OF ABUSED DRUGS

Dopamine released from presynaptic terminals of VTA neurons in the nucleus accumbens is a major mediator of drug reward and reinforcement (Fig. 386-2A). Acute administration of all abusable drugs increases extracellular levels of dopamine in the shell of the nucleus accumbens. In addition, dopamine receptor antagonists injected into this region reduce drug self-administration in animals. Dopamine binds to a family of five G protein-coupled, seven-transmembrane receptors that can be grouped into two major classes, D_1-like (D_1 and D_5 receptors) and D_2-like (D_2, D_3, and D_4 receptors). D_1-like receptors activate adenylyl cyclase by coupling to the stimulatory G protein G_s, whereas D_2-like receptors inhibit adenylyl cyclase by coupling to inhibitory G_i proteins. Despite opposing actions on adenylyl cyclase, both classes of dopamine receptors appear to mediate drug reinforcement. Experimental animals will self-administer D_1-like and D_2-like receptor agonists, and antagonists of D_1, D_2, and D_3 receptors decrease the reinforcing properties of cocaine. These receptor-specific responses most likely result from dopamine actions on different subpopulations of cells in the nucleus accumbens.

Opioids, nicotine, psychostimulants, barbiturates, benzodiazepines, and cannabinoids elicit their acute behavioral effects by binding to specific seven-transmembrane neurotransmitter receptors (opioids and cannabinoids), neurotransmitter receptor-gated ion channels (nicotine, barbiturates, and benzodiazepines), or transporters (cocaine and amphetamines) on the plasma membrane of neuronal cells (Fig. 386-2). Ethanol interacts with several signaling proteins including serotonin 5HT-3 receptors, nicotinic receptors, voltage-gated calcium channels, and sodium-independent purine transporters, but GABA$_A$ receptors and the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors appear to be most sensitive to intoxicating concentrations of ethanol. As discussed below, drug actions at these targets lead to elevation of extracellular dopamine levels in the nucleus accumbens. This appears to be extremely important for the reinforcing properties of psychostimulants. For several other drugs of abuse, dopamine-independent pathways also contribute.

Dopamine Transporter Much evidence indicates that the rewarding properties of

cocaine and amphetamine are due primarily to their ability to elevate extracellular dopamine levels in the nucleus accumbens. Specific populations of neurons within the nucleus accumbens are activated during cocaine self-administration in rodents. In addition, selective destruction of dopaminergic terminals within the nucleus accumbens or administration of dopamine receptor antagonists into that region eliminates cocaine self-administration. Cocaine and amphetamines act by altering transport of dopamine through plasma membrane dopamine transporters (DATs) in presynaptic nerve terminals (Fig. 386-2*A*). Reuptake of dopamine through DATs is the major mechanism for termination of dopaminergic neurotransmission. DAT is a 12-transmembrane glycoprotein and a member of the large sodium- and chloride-dependent transporter family, which also includes carriers for GABA, glycine, serotonin, norepinephrine, and other organic molecules. Cocaine binds to DATs and inhibits dopamine reuptake. Amphetamine causes intracellular release of dopamine from vesicles and reverse transport of dopamine through DATs. These actions serve to elevate levels of extracellular dopamine at dopaminergic synapses.

Recent studies of mice lacking the DAT gene have revealed redundancy in systems mediating cocaine reinforcement. Psychostimulants fail to alter extracellular dopamine levels or induce locomotor activity in these mice. However, DAT-null mice can still be trained to press a lever to receive intravenous cocaine, suggesting that other genes can also mediate the reinforcing properties of cocaine. In addition to inhibiting DAT function, cocaine blocks reuptake of serotonin and norepinephrine. In DAT-null mice, residual binding of a cocaine analogue can be displaced by serotonin reuptake inhibitors, and cocaine stimulates neurons in brain regions with a high density of serotonergic fibers. Therefore, inhibition of serotonin uptake through plasma membrane serotonin transporters may also contribute to psychostimulant reward.

GABA$_A$Receptors The major inhibitory neurotransmitter in the nervous system is GABA. Binding of GABA to GABA$_A$receptors activates a Cl- current that is enhanced by benzodiazepines, barbiturates, and ethanol (Fig. 386-2*B*). Activation of this current maintains the neuronal plasma membrane close to its resting potential and thereby inhibits the generation of action potentials. GABA$_A$receptors appear to be pentameric membrane glycoproteins composed of a, b,g, and possibly d peptide subunits. Fifteen subunits are known to be expressed in the mammalian central nervous system (six a, three b, three g, one d, one e, one q) and RNA splice variants have been identified. In rodents, the GABA$_A$receptor agonist muscimol substitutes for ethanol in tests of drug discrimination; when injected into the nucleus accumbens, muscimol terminates ethanol self-administration. These results suggest that the reinforcing properties of ethanol are mediated in part by ethanol's actions at GABA$_A$receptors in the nucleus accumbens.

NMDA Receptors In the nervous system, excitatory synaptic activity evoked by glutamate and aspartate is mediated by neurotransmitter receptor-gated ion channels (ionotropic receptors) that regulate cation conductances and by G protein-coupled receptors (metabotropic receptors) that stimulate phosphoinositide hydrolysis. Ionotropic glutamate receptors have been subclassified based on activation by selective agonists into three groups: NMDA receptors, high-affinity kainate receptors, and a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. There is a rich glutamatergic projection from neurons in the frontal cortex to the nucleus accumbens where fibers terminate mainly on medium spiny GABA-ergic neurons.

NMDA receptors in the nucleus accumbens appear to play a role in the rewarding properties of several drugs. Thus, phencyclidine and other NMDA antagonists have rewarding actions when administered in the nucleus accumbens. The rewarding properties of ethanol may also be partly due to inhibition of NMDA-activated calcium currents. In addition, NMDA receptors modulate responses to psychostimulants since administration of the NMDA receptor antagonist MK-801 prior to cocaine or amphetamine prevents sensitization to these drugs.

Nicotinic Receptors Like other drugs of abuse, nicotine elicits dopamine release in the nucleus accumbens, and intravenous self-administration of nicotine is blocked by dopamine antagonists and by neurochemical lesions that destroy dopaminergic fibers in the nucleus accumbens. Nicotine increases dopamine release by activating nicotinic acetylcholine receptors (nAChRs) on cell bodies and nerve terminals of dopaminergic VTA neurons. Neuronal nAChRs are receptor-gated ion channels that allow entry of sodium into cells when acetylcholine is present. They appear to be pentameric complexes composed of different combinations of at least 10 different subunits. Targeted disruption of the b_2 subunit gene eliminates most high-affinity nicotine binding in the brain and prevents nicotine-induced dopamine release in the nucleus accumbens. In addition, mice that lack the b_2 subunit show attenuated nicotine self-administration, indicating that b_2-containing nAChRs mediate the reinforcing properties of nicotine.

Opioid Receptors Morphine and other opioids activate opioid receptors, which are a family of seven-transmembrane, G protein-coupled receptors (Figs. 386-2*C* and 386-3). Three classes, u, d, and k, have been identified. The rewarding action of opioids appears to be mediated by activation of u receptors since opioid reinforcement is blocked by selective u receptor antagonists and by targeted disruption of the u receptor gene. Binding of opioid agonists to u receptors activates the G proteins G_i and G_o. This results in inhibition of adenylyl cyclase, thereby decreasing levels of the intracellular second messenger cyclic AMP and reducing activity of cyclic AMP-dependent protein kinase A (PKA). In addition, these G proteins activate voltage-gated potassium channels and inhibit voltage-gated calcium channels. The net result is suppression of electrical excitability in neurons expressing u receptors.

GABA-containing interneurons in the VTA suppress firing of dopaminergic VTA neurons that project to the nucleus accumbens. Opioids disinhibit these dopaminergic neurons by binding to u receptors expressed by the GABA-containing interneurons. This increases the firing rate of dopaminergic VTA neurons and promotes dopamine release in the nucleus accumbens. Rodents will self-administer opioids into both the VTA and the nucleus accumbens. Opioid self-administration into the nucleus accumbens occurs even after dopaminergic projections to that region are destroyed. Thus, dopamine-dependent mechanisms involving the VTA and dopamine-independent mechanisms in the nucleus accumbens both contribute to opioid reward.

Opioid receptors also regulate ethanol consumption. Ethanol acutely inhibits opioid binding to d-opioid receptors, and chronic ethanol exposure increases the density of u- and d-opioid receptors. Nonselective opioid antagonists reduce ethanol self-administration in animals. Several regions of the extended amygdala appear to mediate this response, although the central nucleus of the amygdala appears most important. In two independent clinical trials, the opioid receptor antagonist naltrexone, in

combination with counseling, reduced craving and relapse in abstinent alcoholics. Thus, opioid systems appear to modulate ethanol craving in addicted individuals.

Cannabinoid Receptors The active ingredient of cannabis, D_9-tetrahydrocannabinol (D-9-THC), and the endogenous cannabinoid anandamide bind two subtypes of G protein-coupled cannabinoid receptors. Studies with mutant mice lacking the CB_1 receptor gene have revealed that the CB_1 receptor is responsible for the reinforcing properties of cannabinoids. When administered intravenously, D-9-THC increases dopamine levels in the nucleus accumbens. This is blocked by cannabinoid receptor antagonists and by u-opioid receptor antagonists administered into the VTA. Conversely, morphine reinforcement and the severity of opioid withdrawal are reduced in mice that lack CB_1 receptors. These results suggest that opioids and cannabinoids share common signaling pathways in the brain and can interact to promote each other's reinforcing properties.

ADAPTATION TO CHRONIC DRUG USE

Repeated drug exposure elicits changes in neural function that lead to drug dependence and craving. Several mechanisms are being elucidated, including drug-induced alterations in receptor and ion channel function, intracellular signal transduction, gene expression, and synaptic connectivity.

Chronic exposure to drugs of abuse can change the function of receptors and ion channels by altering their density, subunit composition, or coupling to signal transduction cascades. For example, chronic exposure to ethanol increases the density of NMDA receptors and L-type voltage-gated calcium channels in the brain. These changes contribute to neuronal hyperactivity observed during alcohol withdrawal since NMDA and L-type channel antagonists reduce signs of withdrawal in alcohol-dependent rodents deprived of ethanol. In addition, chronic exposure to ethanol decreases $GABA_A$ receptor function and abolishes potentiation by ethanol. Downregulation of $GABA_A$ receptor function contributes to manifestations of alcohol withdrawal since benzodiazepines and barbiturates, which activate $GABA_A$ receptors, are very helpful in reducing alcohol withdrawal symptoms.

Chronic exposure to many drugs of abuse induces adaptive changes in neuronal signal transduction pathways. This has been most clearly demonstrated for opioids, which increase cyclic AMP signaling in the locus coeruleus after chronic administration (Fig. 386-3). The locus coeruleus is the principal adrenergic nucleus in the brain and regulates attention states and the autonomic nervous system. Hyperactivity of this nucleus has been implicated in opioid withdrawal. Chronic opioid exposure increases expression of adenylyl cyclase, PKA, and the cyclic AMP response element binding protein, CREB, which mediates cyclic AMP-dependent gene expression. These changes increase the intrinsic firing rate of neurons in the locus coeruleus, in part through activation of an inward sodium current. Thus, upregulation of cyclic AMP signaling opposes the acute inhibitory action of opioids on this pathway.

Chronic exposure to cocaine, opioids, or ethanol upregulates cyclic AMP-mediated signaling in other brain regions, including the VTA and the nucleus accumbens. Upregulation of cyclic AMP signaling in the nucleus accumbens contributes to

psychostimulant tolerance since pharmacologic inhibition of[PKA] or overexpression of[CREB] in the nucleus accumbens decreases the rewarding properties of cocaine. Upregulation of cyclic AMP signaling may also account for supersensitivity of neurons in the nucleus accumbens to D_1receptor agonists following chronic cocaine administration. Additional neuroadaptive changes in dopamine signaling can modify drug-seeking behavior in rodents. Rats can be readily trained to voluntarily self-administer intravenous cocaine for several hours. If during a course of self-administration, saline is substituted for cocaine, the rate of self-administration declines dramatically. However, exposure to a single intraperitoneal priming injection of cocaine or a D_2-like receptor agonist causes the animal to resume lever pressing. In contrast, treatment with a D_1-like receptor agonist blocks the ability of cocaine to reinstate drug-seeking behavior. It appears that D_1-like agonists inhibit relapse in drug seeking. Therefore, they may prove to be useful in treatment of cocaine addiction.

A current hypothesis views addiction as a form of learning mediated by maladaptive recruitment of memory systems involving limbic structures. Mechanisms that could contribute to such learned, long-term adaptation include drug-induced gene expression and synaptic reorganization. For example, the transcription factor[CREB], which is activated by chronic drug use, has been implicated in models of learning. Repeated exposure to many drugs of abuse also causes prolonged activation of another transcription factor, *Fos*-related antigen, in the nucleus accumbens. Ethanol increases the number of dendritic spines on hippocampal pyramidal cells and somatosensory cortical neurons, whereas amphetamine increases dendritic length and the density of dendritic spines on neurons in the nucleus accumbens and prefrontal cortex. Such drug-induced changes in gene expression and neuronal connectivity could lead to long-term alterations in brain reward pathways that may underlie drug addiction in humans.

(Bibliography omitted in Palm version)

387. ALCOHOL AND ALCOHOLISM - *Marc A. Schuckit*

The yearly cost of alcohol-related problems in the United States is as much as $300 billion, including accidents, health problems, lost productivity, crime, and treatment. There are more than 22,000 deaths from alcohol-related auto accidents per year, as well as almost 2 million nonfatal injuries and damage to almost 5 million vehicles. In addition, alcohol is responsible for almost 5% of missed work time, with a 25% decrease in work performance among heavy drinkers. Men and women who fulfill criteria for alcohol use disorders decrease their life span by approximately 15 years, with abuse and dependence responsible for almost 25% of premature deaths in men and 15% in women, figures that represent a three- to sixfold odds ratio of early death even among people with higher levels of education and socioeconomic functioning.

PHARMACOLOGY AND NUTRITIONAL IMPACT OF ETHANOL

Ethanol is a weakly charged molecule that moves easily through cell membranes, rapidly equilibrating between blood and tissues. The effects of drinking depend in part on the amount of ethanol consumed per unit of body weight; the level of alcohol in the blood is expressed as milligrams or grams of ethanol per deciliter (e.g., 100 mg/dL or 0.10 g/dL). A level of 0.02 to 0.03 results from the ingestion of one to two typical drinks. In round figures, 340 mL (12 oz) of beer, 115 mL (4 oz) of nonfortified wine, and 43 mL (1.5 oz) (a shot) of 80-proof beverage each contain approximately 10 g of ethanol; 0.5 L (1 pint) of 86-proof beverage contains approximately 160 g, and 1 L of wine contains approximately 80 g of ethanol. Congeners found in alcoholic beverages may contribute to body damage with heavy drinking; these include low-molecular-weight alcohols (e.g., methanol and butanol), aldehydes, esters, histamine, phenols, tannins, iron, lead, and cobalt.

Ethanol is a central nervous system (CNS) depressant that decreases activity of neurons, although some behavioral stimulation is observed at low blood levels. This drug has cross-tolerance and shares a similar pattern of behavioral problems with other brain depressants, including the benzodiazepines and barbiturates. Alcohol is absorbed from mucous membranes of the mouth and esophagus (in small amounts), from the stomach and large bowel (in modest amounts), and from the proximal portion of the small intestine (the major site). The rate of absorption is *increased* by rapid gastric emptying; by the absence of proteins, fats, or carbohydrates (which interfere with absorption); by the absence of congeners; by dilution to a modest percentage of ethanol (maximum at about 20% by volume); and by carbonation (e.g., champagne).

Between 2% (at low blood alcohol concentrations) and about 10% (at high blood alcohol concentrations) of ethanol is excreted directly through the lungs, urine, or sweat, but the greater part is metabolized to acetaldehyde, primarily in the liver. At least two metabolic routes, each with different optimal concentrations of ethanol (K_m), result in the metabolism of approximately one drink per hour. The most important pathway occurs in the cell cytosol where alcohol dehydrogenase (ADH) produces acetaldehyde, which is then rapidly destroyed by aldehyde dehydrogenase (ALDH) in the cytosol and mitochondria. Each of these steps requires nicotinamide adenine dinucleotide (NAD) as a cofactor, and it is the increased ratio of the reduced cofactor (NADH) to NAD (NADH:NAD) that is responsible for many of the metabolic derangements observed

after drinking. A second pathway occurs in the microsomes of the smooth endoplasmic reticulum (the microsomal ethanol-oxidizing system, or MEOS), which is responsible for 10% or more of ethanol oxidation at high blood alcohol concentrations.

One gram of ethanol has approximately 29.7 kJ (7.1 kcal) of energy, and a drink contains between 293.0 and 418.6 kJ (70 and 100 kcal) from ethanol and other carbohydrates. However, these are "empty" of nutrients such as minerals, proteins, and vitamins. In addition, alcohol interferes with absorption of vitamins in the small intestine and decreases their storage in the liver. These actions affect folate (folacin or folic acid), pyridoxine (B$_6$), thiamine (B$_1$), nicotinic acid (niacin, B$_3$), and vitamin A. Heavy drinking can also produce low blood levels of potassium, magnesium, calcium, zinc, and phosphorus as a consequence of dietary deficiency and acid-base imbalances during excess alcohol ingestion or withdrawal.

An ethanol load in a fasting, healthy individual is likely to produce transient hypoglycemia within 6 to 36 h, secondary to the acute actions of ethanol on gluconeogenesis. This can result in glucose intolerance until the alcoholic has abstained for 2 to 4 weeks. Alcohol ketoacidosis, probably reflecting a decrease in fatty acid oxidation coupled with poor diet or recurrent vomiting, should not be misdiagnosed as diabetic ketosis. With the former, patients show an increase in serum ketones along with a mild increase in glucose but a large anion gap, a mild to moderate increase in serum lactate, and a b-hydroxybutyrate/lactate ratio of between 2:1 and 9:1 (with normal being 1:1).

BEHAVIORAL EFFECTS, TOLERANCE, AND DEPENDENCE

The effects of any drug depend on the dose, the rate of increase in plasma, the concomitant presence of other drugs, and the past experience with the agent. With alcohol, an additional factor is whether blood alcohol levels are rising or falling; the effects are more intense during the former period.

Even though "legal intoxication" requires a blood alcohol concentration of at least 80 to 100 mg/dL, behavioral, psychomotor, and cognitive changes are seen at levels as low as 20 to 30 mg/dL (i.e., after one to two drinks). Deep but disturbed sleep can be seen at twice the legal intoxication level, and death can occur with levels between 300 and 400 mg/dL. Beverage alcohol is probably responsible for more overdose deaths than any other drug.

The intoxicating effects of alcohol appear to be due to actions at specific neurotransmitter receptors and transporters. Alcohol enhances g-aminobutyric acid A (GABA$_A$) receptors, and inhibits *N*-methyl-D-asparate (NMDA) receptors (Chap. 386). In vitro studies suggest that additional effects involve inhibition of adenosine uptake and a translocation of the cyclic AMP-dependent protein kinase catalytic subunit from the cytoplasm to the nucleus. Neurons adapt quickly to these actions, and thus different effects may be present during chronic administration and withdrawal.

At least three types of compensation develop after repeated exposure to the drug, producing tolerance of higher ethanol levels. First, after 1 to 2 weeks of daily drinking, *metabolic or pharmacokinetic tolerance* develops, with a 30% increase in the rate of

hepatic ethanol metabolism. This alteration disappears almost as rapidly as it develops. Second, *cellular or pharmacodynamic tolerance* develops through neurochemical changes that may also contribute to physical dependence. Third, individuals can learn to adapt their behavior so that they can function better than expected under drug influence (*behavioral tolerance*).

The cellular changes caused by chronic ethanol exposure may not resolve for several weeks or longer following cessation of drinking. In the interim, the neurons require ethanol to function optimally, and the individual can be said to be physically dependent. This physical condition is distinct from psychological dependence, a concept indicating that the person is psychologically uncomfortable without the drug.

THE EFFECTS OF ETHANOL ON BODY SYSTEMS

While one to two drinks per day in an otherwise healthy and nonpregnant individual can have some beneficial effects, at higher doses alcohol is toxic to most body systems. Knowledge about the deleterious effects of alcohol helps the practicing physician to identify alcoholic patients. Signs and symptoms of ethanol abuse can be used to help motivate the patient to abstain. It is important to remember that the typical white- or blue-collar alcoholic functions at a fairly high level for years, and that not everyone develops each problem.

CENTRAL NERVOUS SYSTEM

Approximately 35% of drinkers may experience a *blackout*, an episode of temporary anterograde amnesia, in which the person forgets all or part of what occurred during a drinking evening. Another common problem, one seen after as few as one or two drinks, is that while alcohol can help someone to fall asleep, it also "fragments" the sleep pattern causing alterations between sleep stages and a deficiency in deep sleep. At the same time, alcohol diminishes rapid eye movement (REM) or dream sleep early in the evening, with resulting prominent and sometimes disturbing dreams later in the night. Finally, alcohol relaxes muscles in the pharynx, which can cause snoring and exacerbate sleep apnea, with symptoms of the latter in 75% of alcoholic men over age 60.

An additional problem related to the acute effects of alcohol on most drinkers is the impairment in judgment, balance, and motor coordination that contributes to the high incidence and severity of accidents. At least half of individuals who experience severe physical trauma in an accident have evidence of substance-related impairment, a finding that is consistent with the fact that 40% of drinkers in the United States have at some time driven while intoxicated with alcohol and that 15% of flight crews have evidence of repeated heavy drinking. Regarding the latter, at least one study noted that pilot performance is still impaired 14 h after a blood alcohol concentration of 100 mg/dL, despite subsequent abstinence.

The effect of alcohol on the nervous system is even more pronounced among alcohol-dependent individuals. Chronic intake of high doses of ethanol causes *peripheral neuropathy* in 5 to 15% of alcoholics, which is possibly related to thiamine deficiency. Patients complain of bilateral limb numbness, tingling, and paresthesias;

symptoms are more pronounced distally than proximally. The treatment is abstinence and thiamine supplementation.

Wernicke's syndrome (ophthalmoparesis, ataxia, and encephalopathy) and *Korsakoff's syndrome* (alcohol-induced persisting amnestic disorder), are seen in the United States at a rate of approximately 50 per million people per year. These disorders are the result of thiamine deficiency in vulnerable individuals, possibly owing to interaction with a genetic transketolase deficiency. Korsakoff's syndrome presents as profound and persistent anterograde amnesia (inability to learn new material) and a milder retrograde amnesia. Additional symptoms can include impairment in visuospatial, abstract, and conceptual reasoning but with a normal intelligence quotient (IQ). Some patients demonstrate an acute onset of Korsakoff's syndrome in association with the neurologic stigmata seen with Wernicke's syndrome (e.g., sixth nerve palsy and ataxia), whereas others have a more gradual onset. With oral thiamine replacement (50 to 100 mg/d), only one-quarter of Korsakoff's patients achieve full recovery, one-half experience partial improvement, and one-quarter show no improvement, even after many months of supplementation.*Wernicke's syndrome is discussed in detail in Chap. 376.*

About 1% of alcoholics develop *cerebellar degeneration*, a syndrome of progressive unsteady stance and gait often accompanied by mild nystagmus. Atrophy of the cerebellar vermis is seen on brain computed tomography and magnetic resonance imaging scans, but the cerebrospinal fluid is usually normal. Treatment consists of abstinence and multiple vitamin supplementation, although improvement is often minimal.

Alcoholics can show severe *cognitive* problems and impairment in recent and remote memory for weeks to months after an alcoholic binge. Increased size of the brain ventricles and cerebral sulci are seen in 50% or more of chronic alcoholics, but these changes are often reversible, returning toward normal after a year or more of abstinence. PermanentCNSimpairment (alcohol-induced persisting dementia) can develop and accounts for up to 20% of chronically demented patients. There is no single alcoholic dementia syndrome; rather, this label is used to describe patients who have apparently irreversible cognitive changes (possibly from diverse causes) in the midst of chronic alcoholism.

Finally, almost every psychiatric syndrome can be seen temporarily during heavy drinking or subsequent withdrawal. These include intense *sadness* lasting for days to weeks in the midst of heavy drinking in 40% of alcoholics, which is classified as an alcohol-induced mood disorder in the *Fourth Diagnostic and Statistical Manual* of the American Psychiatric Association (DSM-IV); severe *anxiety* in 10 to 30% of alcoholics, often beginning during alcohol withdrawal and which can persist for many months after cessation of drinking (alcohol-induced anxiety disorder); and auditory *hallucinations* and/or *paranoid delusions* in the absence of any obvious signs of withdrawal -- a state now called *alcohol-induced psychotic disorder* -- and reported at sometime in 1 to 10% of alcoholics. Treatment of all forms of alcohol-induced psychopathology includes abstinence and supportive care, with the likelihood of full recovery within several days to 6 weeks. A history of alcohol intake is an important consideration in *any* patient with one of these psychiatric symptoms.

THE GASTROINTESTINAL SYSTEM

Esophagus and Stomach Acute alcohol intake can result in inflammation of the esophagus (possibly secondary to reflux of gastric contents) and stomach (resulting from both an increase in acid production and damage to the gastric mucosal barrier). Esophagitis can cause epigastric distress, and gastritis, the most frequent cause of gastrointestinal bleeding in heavy drinkers, can present as anorexia and/or abdominal pain. Chronic heavy drinking, if associated with violent vomiting, can produce a longitudinal tear in the mucosa at the gastroesophageal junction -- a Mallory-Weiss lesion. Although many gastrointestinal problems are reversible, two complications of chronic alcoholism, esophageal varices secondary to cirrhosis-induced portal hypertension and atrophy of the gastric mucosa, may be irreversible.

Pancreas The incidence of acute pancreatitis in alcoholics (about 25 per 1000 per year) is almost threefold higher than in the general population, accounting for an estimated 10% or more of the cases of this disorder (Chap. 304).

Liver Ethanol absorbed from the small bowel is carried directly to the liver, where it becomes the preferred fuel; NADH accumulates and oxygen utilization escalates; gluconeogenesis is impaired (with a resulting fall in the amount of glucose produced from glycogen); lactate production increases; and there is a decreased oxidation of fatty acids in the citric acid cycle with an increase in fat accumulation within liver cells. In the healthy individual taking no medications, these changes are reversible, but with repeated exposure to ethanol, more severe changes in liver functioning are likely to occur. These include, in overlapping stages, fatty accumulation, alcohol-induced hepatitis, perivenular sclerosis, and cirrhosis, with the latter observed in an estimated 15 to 20% of alcoholics (Chap. 298).

CANCER

As discussed briefly below, the leading cause of death in alcoholics is cardiovascular disease, but cancer occupies a solid second place. Women drinking as few as 1.5 drinks per day increase their risk of breast cancer 1.4-fold. For both genders, four drinks per day increases the risk for oral and esophageal cancers by approximately threefold and rectal cancers by a factor of 1.5, whereas seven to eight or more drinks per day enhances the risks for many of these cancers by a factor of five. Overall, it has been estimated that alcoholics have a rate of carcinoma 10 times higher than the general population.

HEMATOPOIETIC SYSTEM

Ethanol exerts multiple reversible acute and chronic effects on all blood cells. The impact on red blood cells (RBC) is an increase in size (mean corpuscular volume, MCV), usually without anemia. This change appears to reflect the effect of alcohol on stem cells. If heavy drinking is accompanied by folic acid deficiency, there can also be hypersegmented neutrophils, reticulocytopenia, and hyperplastic bone marrow; if malnutrition is present, sideroblastic changes can also be observed. Chronic heavy drinking can also decrease production of most white blood cells (WBCs), decrease granulocyte mobility and adherence, and impair the delayed-hypersensitivity response

to new antigens (with a possible false-negative tuberculin skin test). Finally, many alcoholics present with mild thrombocytopenia. When due to repeated intoxication, the low platelet count usually resolves within a week of abstinence. Thrombocytopenia can also occur secondary to hepatic cirrhosis and congestive splenomegaly (increased destruction) or to folic acid deficiency (decreased production). Ethanol itself might not have a major effect on platelet function, but polyphenols and other constituents of some alcoholic beverages, particularly wine, may interfere with platelet aggregation.

CARDIOVASCULAR SYSTEM

Acutely, ethanol decreases myocardial contractility and causes peripheral vasodilation, with a resulting mild decrease in blood pressure and a compensatory increase in cardiac output. Exercise-induced increases in cardiac oxygen consumption are higher after alcohol intake. These acute effects have little clinical importance for the average healthy drinker but can produce problems in men and women with cardiac disease.

Chronic intake of even modest doses of alcohol can have both deleterious and beneficial effects. Regarding the latter, a maximum of one to two drinks per day over long periods may decrease the risk for cardiovascular death, perhaps through an increase in high-density lipoprotein (HDL) cholesterol or changes in clotting mechanisms. In one large national study, cardiovascular mortality was reduced by 30 to 40% among individuals reporting one or more drinks daily compared to nondrinkers, with overall mortality lowest among those consuming approximately one drink per day. Recent data have also corroborated the decreased risk for ischemic, but not hemorrhagic, stroke associated with regular light drinking.

The consumption of three or more drinks per day results in a dose-dependent increase in blood pressure, which returns to normal within weeks of abstinence. As a result, heavy drinking is an important contributor to mild to moderate hypertension. Chronic heavy drinking can cause cardiomyopathy, with symptoms ranging from unexplained arrhythmias in the presence of left ventricular impairment to heart failure with dilation of all four heart chambers and hypocontractility of heart muscle. Perhaps one-third of cases of cardiomyopathy are alcohol-induced. Mural thrombi can form in the left atrium or ventricle, while heart enlargement exceeding 25% can cause mitral regurgitation. Atrial or ventricular arrhythmias, especially paroxysmal tachycardia, can also occur after a drinking binge in individuals showing no other evidence of heart disease -- a syndrome known as the "holiday heart."

GENITOURINARY SYSTEM CHANGES, SEXUAL FUNCTIONING, AND FETAL DEVELOPMENT

Acutely, modest ethanol doses (e.g., blood alcohol concentrations of 100 mg/dL or even less) can both increase sexual drive and decrease erectile capacity in men. Even in the absence of liver impairment, a significant minority of chronic alcoholic men may show irreversible testicular atrophy with concomitant shrinkage of the seminiferous tubules, decreases in ejaculate volume, and a lower sperm count (Chap. 335).

The repeated ingestion of high doses of ethanol by women can result in amenorrhea, a decrease in ovarian size, absence of corpora lutea with associated infertility, and

spontaneous abortions. Heavy drinking during pregnancy results in the rapid placental transfer of both ethanol and acetaldehyde, which may have serious consequences for fetal development. The *fetal alcohol syndrome* can include any of the following: facial changes with epicanthal eye folds, poorly formed concha, and small teeth with faulty enamel; cardiac atrial or ventricular septal defects; an aberrant palmar crease and limitation in joint movement; and microcephaly with mental retardation. The specific amount of ethanol and/or specific time of vulnerability during pregnancy have not been defined, making it advisable for pregnant women to abstain completely.

OTHER EFFECTS OF ETHANOL

Between one-half and two-thirds of alcoholics have evidence of decreased skeletal muscle strength caused by acute *alcoholic myopathy*, a condition that improves but which might not disappear with abstinence. Effects of repeated heavy drinking on the *skeletal system* include alterations in calcium metabolism, lower bone density, and less growth in the epiphyses, with an increased risk for fractures and osteonecrosis of the femoral head. *Hormonal changes* include an increase in cortisol levels, which can remain elevated during heavy drinking; inhibition of vasopressin secretion at rising blood alcohol concentrations and the opposite effect at falling blood alcohol concentrations (with the final result that most alcoholics are likely to be slightly overhydrated); a modest and reversible decrease in serum thyroxine (T_4); and a more marked decrease in serum triiodothyronine (T_3).

ALCOHOLISM (ALCOHOL ABUSE OR DEPENDENCE)

Because many drinkers occasionally imbibe to excess, temporary alcohol-related pathology is common in nonalcoholics. The period of heaviest drinking is usually the late teens to the late twenties. This is also a time of high risk for temporary alcohol-related social, occupational, or driving difficulties. These phenomena are often isolated events or self-limited, but when repeated problems in multiple life areas develop, the person is likely to meet criteria for alcohol abuse or dependence.

DEFINITIONS AND EPIDEMIOLOGY

DSM-IV defines alcohol dependence as repeated alcohol-related difficulties in at least three of seven areas of functioning that cluster together over any 12-month period. These problems include any combination of tolerance, withdrawal, taking larger amounts of alcohol over longer periods than intended, an inability to control use, spending a great deal of time associated with alcohol use, giving up important activities to drink, and continued use of alcohol despite physical or psychological consequences. In this diagnosis a special emphasis is placed on evidence of tolerance and/or withdrawal, a condition referred to as "dependence with a physiological component" and which is associated wtih a more severe clinical course. Dependence occurs in both men and women, in individuals from all socioeconomic strata, and in people of all racial backgrounds. The diagnosis predicts a course of recurrent problems with the use of alcohol and the consequent shortening of the life span by a decade or more. In the absence of alcohol dependence, an individual can be given a diagnosis of *alcohol abuse* if he or she demonstrates *repetitive* problems with alcohol in any one of four life areas: an inability to fulfill major obligations, use in hazardous situations such as driving,

legal problems, or use despite social or interpersonal difficulties.

The clinical diagnosis of alcohol abuse or dependence rests on the documentation of a pattern of *difficulties associated with alcohol use*; the definition is *not* based on the quantity and frequency of alcohol consumption. Thus, in screening for alcohol abuse or dependence, it is important to probe for life problems and then attempt to tie in use of alcohol or another substance. Information regarding marital or job problems, legal difficulties, histories of accidents, medical problems, evidence of tolerance, etc., is an important component of all evaluations and yields data that are of use even for nonalcoholic individuals.

The lifetime risk for alcohol dependence in most western countries is about 10 to 15% for men and 5% for women. When alcohol abuse is also considered, the rates are even higher. The typical alcoholic is a blue- or white-collar worker or homemaker and thus does not fit the common stereotype.

GENETICS OF ALCOHOLISM

Alcoholism is a multifactorial disorder in which both environmental and biologic factors contribute. The importance of genetic influences in alcoholism is supported by the higher risk for this disorder in the identical versus fraternal twin of an alcoholic and the fourfold increased risk for children of alcoholics even if adopted at birth and raised without knowledge of the problems of their biologic parents.

The evidence supporting genetic influences in alcoholism has stimulated a search for trait markers of a vulnerability toward the disorder. A 15-year follow-up of 453 men originally studied at age 20 has shown that subjects with alcoholic fathers demonstrated relatively lower levels of response to alcohol, including less intense subjective feelings of intoxication, less alcohol-related impairment in cognitive and psychomotor tests, and less intense alcohol-related changes in prolactin and cortisol secretion. This low level of response to alcohol at around age 20 was a powerful predictor of later alcoholism, explaining most of the relationship between a family history of this disorder and later alcohol problems. Additional genetically influenced characteristics that contribute to the risk of alcoholism appear to include some personality traits such as higher levels of impulsivity and sensation seeking, and several electrophysiologic measures such as the P300 wave of the event-related potential (Chap. 357), which might relate to cognitive styles or evidence of CNS disinhibition. All the genetic factors combined appear to explain up to 60% of the risk, with environmental influences contributing at least 40%.

NATURAL HISTORY

For the "average" alcoholic, the age of first drink and first minor problems (e.g., an argument with a friend while drunk or an alcoholic blackout) are similar to those in the general population. However, by the early to mid-twenties, most men and women moderate their drinking (perhaps learning from minor problems), whereas difficulties for alcoholics are likely to escalate, with the first major life problem from alcohol appearing in the mid-twenties to early forties. Once established, the course of alcoholism is likely to be one of exacerbations and remissions. As a rule, there is remarkably little difficulty in stopping alcohol use when problems develop, and this step is often followed by days

to months of carefully controlled drinking. Unfortunately, these periods are almost inevitably followed by escalations in alcohol intake and subsequent problems. The course is not hopeless, because between half and two-thirds of alcoholics maintain abstinence for extended periods after treatment. Even without formal treatment or self-help groups there is at least a 20% chance of long-term abstinence. However, should the alcoholic continue to drink, the life span is shortened by an average of 15 years, with the leading causes of death, in decreasing order, being heart disease, cancer, accidents, and suicide.

IDENTIFICATION OF THE ALCOHOLIC AND INTERVENTION

Physicians even in affluent areas should recognize that approximately 20% of patients have alcoholism. Therefore, it is important to pay attention to the alcohol-related symptoms and signs described above as well as laboratory tests that are likely to be abnormal in the context of regular consumption of 6 to 8 or more drinks per day. These include a high-normal or slightly elevatedMCV(e.g., ³91 fL),g-glutamyl transferase (GGT) (³30 units), serum uric acid [>416 umol/L (7 mg/dL)], carbohydrate-deficient transferrin (CDT) (³20 g/L), and triglycerides [³2.0 mmol/L (180 mg/dL)]. Mild and fluctuating hypertension (e.g., 140/95), repeated infections such as pneumonia, and otherwise unexplained cardiac arrhythmias should also raise the possibility that the patient is an alcoholic. Other disorders suggestive of alcoholism include cancer of the head and neck, esophagus, or stomach as well as cirrhosis, unexplained hepatitis, pancreatitis, bilateral parotid gland swelling, and peripheral neuropathy.

Once the likelihood of alcoholism is established, only a few moments are needed to gather the history of alcohol-related life problems. The patient and the spouse or another close family member should be asked about patterns of accidents, relationship difficulties, problems on the job, and driving-related difficulties, after which the role played by alcohol should be identified. All physicians should be able to take the time needed to gather such information. In addition, a simple 25-item form to be answered by the patient, the Michigan Alcohol Screening Test (MAST), is available to aid in identifying alcoholics. However, this is only a screening tool, and a careful face-to-face interview is still required for a meaningful diagnosis. The CAGE, which consists of asking about alcohol-related trouble *c*utting down on intake, being *a*nnoyed by criticisms, *g*uilt, or use of an "*e*ye-opener," can also be helpful as an initial screen.

After alcoholism is identified, the diagnosis must be shared with the patient. The presenting complaint can be used as an entree to the alcohol problem. For instance, the patient complaining of insomnia or hypertension could be told that these are clinically important symptoms and that physical findings and laboratory tests indicate that alcohol appears to have contributed to the complaints and is increasing the risk for further medical and psychological problems. The physician should share information about the course of alcoholism and explore possible avenues of attacking the problem. Some patients and family members will benefit from the opportunity to read additional material (see "Bibliography").

The process of intervention is rarely accomplished in one session. For the person who refuses to stop drinking at the first intervention, a logical step is to "keep the door open," establishing future meetings so that help is available as problems escalate. In the

meantime the family may benefit from counseling or referral to self-help groups such as Al-Anon (the Alcoholics Anonymous group for family members) and Alateen (for teenage children of alcoholics). The patient should be reminded that driving while intoxicated is dangerous and illegal.

THE ALCOHOL WITHDRAWAL SYNDROME

Once the brain has been repeatedly exposed to high doses of alcohol, any sudden decrease in intake can produce symptoms of withdrawal. As with all CNS depressants, the symptoms are generally the opposite of those produced by intoxication. Features include tremor of the hands (shakes or jitters); agitation and anxiety; autonomic nervous system overactivity such as an increase in pulse, respiratory rate, and body temperature; insomnia, possibly accompanied by bad dreams; and gastrointestinal upset. These withdrawal symptoms generally begin within 5 to 10 h of decreasing ethanol intake, peak in intensity on day 2 or 3, and improve by day 4 or 5. Anxiety, insomnia, and mild levels of autonomic dysfunction may persist at decreasing levels for 6 months or more as a protracted abstinence syndrome, which may contribute to the tendency to return to drinking.

At some point in their lives, between 2 and 5% of alcoholics experience withdrawal seizures ("rum fits"), usually within 48 h of stopping drinking. These are usually generalized (unless there is an underlying focal lesion), and any electroencephalographic abnormalities are mild and generally return to normal within several days.

The term *delirium tremens* (DTs) refers to delirium (mental confusion with fluctuating levels of consciousness) along with a tremor, severe agitation, and autonomic overactivity (e.g., marked increases in pulse, blood pressure, and respirations). Fortunately, this serious and potentially life-threatening complication of alcohol withdrawal is rare. Only 5 to 10% of alcohol-dependent individuals ever experience DTs; the chance of DTs during any single withdrawal is less than 1% but is higher if there has been a withdrawal seizure. DTs are most likely to develop in patients with concomitant severe medical disorders or evidence of underlying brain damage, and thus can usually be avoided if the underlying medical problems can be identified and treated.

TREATMENT

Acute Intoxication The first priority is to be certain that the vital signs are relatively stable without evidence of respiratory depression, cardiac arrhythmia, or potentially dangerous changes in blood pressure. Life-threatening problems require appropriate emergency care and hospitalization. The clinician must recognize that a variety of causes may produce obtundation or coma in the alcoholic patient. The possibility of intoxication with other drugs should be considered, and a blood or urine sample is indicated to screen for opioids or other CNS depressants such as benzodiazepines or barbiturates. A coexisting seizure disorder, head injury, meningitis, brain abscess, or other potentially life-threatening neurologic disorder may be present. Other medical conditions that must be considered include hypoglycemia, hepatic failure, or diabetic ketoacidosis.

Patients who are medically stable should be placed in a quiet environment and asked to lie on their side if fatigued in order to minimize the risk of aspiration. When the behavior indicates an increased likelihood of violence, hospital procedures should be followed, including planning for the possibility of a show of force with an intervention team. In the context of aggressiveness, patients should be clearly reminded in a nonthreatening way that it is the goal of the staff to help them to feel better and to avoid problems. If the aggressive behavior continues, relatively low doses of a short-acting benzodiazepine such as lorazepam (e.g., 1 mg by mouth) may be used and can be repeated as needed, but care must be taken so that the addition of this second CNS depressant does not destabilize vital signs or worsen confusion. An alternative approach is to use an antipsychotic medication (e.g., 5 mg of haloperidol liquid), but this has the potential danger of lowering the seizure threshold. If aggression escalates, the patient might require a short-term admission to a locked ward, where medications can be used more safely and vital signs more closely monitored.

Withdrawal The first, and most important, step is to perform a *thorough* physical examination in all alcoholics who are considering stopping drinking. It is necessary to evaluate organ systems likely to be impaired, including a search for evidence of liver failure, gastrointestinal bleeding, cardiac arrhythmia, and glucose or electrolyte imbalance.

The second step in treating withdrawal for even the typical well-nourished alcoholic is to give patients adequate nutrition and rest. All patients should be given oral multiple B vitamins, including 50 to 100 mg of thiamine daily for a week or more. Most patients enter withdrawal with normal levels of body water or mild overhydration, and intravenous fluids should be avoided unless there is evidence of significant recent bleeding, vomiting, or diarrhea. Medications can usually be administered orally.

The third step in treatment is to recognize that most withdrawal symptoms are caused by the rapid removal of a CNS depressant. Therefore, patients can be weaned by administering any drug of this class and gradually decreasing the levels over 3 to 5 days. While many CNS depressants are effective, the *benzodiazepines* have the highest margin of safety and are, therefore, the preferred class of drugs in the treatment of alcohol withdrawal. Benzodiazepines with short half-lives (Chap. 385) are especially useful for patients with serious liver impairment or evidence of preexisting encephalopathy or brain damage. On the other hand, short-half-life benzodiazepines, e.g., oxazepam or lorazepam, result in rapidly changing drug blood levels and must be given every 4 h to avoid abrupt fluctuations in blood levels that may increase the risk for seizures. Therefore, most clinicians use drugs with longer half-lives, such as diazepam or chlordiazepoxide. The goal is to administer enough drug on day 1 to alleviate most of the symptoms of withdrawal (e.g., the tremor and elevated pulse), and then to decrease the dose by 20% on successive days over a period of 3 to 5 days. The approach is flexible; the dose is increased if signs of withdrawal escalate, and the medication is withheld if the patient is sleeping or shows signs of increasing orthostatic hypotension. The average patient requires 25 to 50 mg of chlordiazepoxide or 10 mg of diazepam given orally every 4 to 6 h on the first day.

For the patient with DTs, treatment can be difficult and the condition is likely to run a course of 3 to 5 days regardless of the therapy employed. The focus of care is to

identify medical problems and correct them and to control behavior and prevent injuries. Many clinicians recommend the use of high doses of benzodiazepine (doses as high as 800 mg/day of chlordiazepoxide have been reported), a treatment that will decrease the agitation and raise the seizure threshold but probably does little to improve the confusion. Other clinicians recommend the use of antipsychotic medications, such as 20 mg or more per day of haloperidol, an approach less likely to exacerbate confusion but which may increase the risk of seizures. Antipsychotic drugs have no place in the treatment of mild withdrawal symptoms.

Generalized wtihdrawal seizures rarely require aggressive pharmacologic intervention beyond that given to the usual patient undergoing withdrawal, i.e., adequate doses of benzodiazepines. There is little evidence that anticonvulsants such as phenytoin are effective in drug-withdrawal seizures, and the risk of seizures has usually passed by the time effective drug levels are reached. *The rare patient with status epilepticus must be treated aggressively, as outlined in Chap. 361, initially with intravenous lorazepam.*

While alcohol withdrawal is often treated in a hospital, efforts at reducing costs have resulted in the development of outpatient detoxification for relatively mild abstinence syndromes. This is appropriate for patients in good physical condition who demonstrate mild signs of withdrawal despite low blood alcohol concentrations and for those without prior history ofDTs or withdrawal seizures. Such individuals still require a careful physical examination, evaluation of blood tests, and vitamin supplementation. Benzodiazepines can be given *in a 1- to 2-day supply* to be administered to the patient by a spouse or other family member four times a day. Patients are asked to *return daily* for evaluation of vital signs and to come to the emergency room if signs and symptoms of withdrawal escalate.

Rehabilitation of Alcoholics After completing alcoholic rehabilitation, 60% or more of middle-class alcoholics maintain abstinence for at least a year, and many for a lifetime. As is true for any long-term disorder for which treatment requires changes in life-style (e.g., diabetes or hypertension), therapeutic approaches include general supports that meet commonsense guidelines. Considering the lack of evidence for the superiority of any specific treatment type, it is best to keep interventions simple.

Maneuvers in rehabilitation fall into two general categories. First are attempts to help the alcoholic achieve and maintain a high level of motivation toward abstinence. These include education about alcoholism and instructing family and/or friends to stop protecting the person from the problems caused by alcohol. The second step is to help the patient to readjust to life without alcohol and to reestablish a functional lifestyle through counseling, vocational rehabilitation, and self-help groups such as Alcoholics Anonymous. The third component, called *relapse prevention*, helps the person to identify situations in which a return to drinking is likely, formulate ways of managing these risks, and develop coping strategies that increase the chances of a return to abstinence if a slip occurs.

There is no convincing evidence that inpatient rehabilitation is always more effective for the average alcoholic than is outpatient care. However, more intense interventions work better than those that are less intensive, and some alcoholics do not respond to outpatient care. The decision to hospitalize can be made if (1) the patient has medical

problems that are difficult to treat outside a hospital; (2) depression, confusion, or psychosis interferes with outpatient care; (3) the patient has such a severe life crisis that it is difficult to get his or her attention as an outpatient; (4) outpatient treatment has failed; or (5) the patient lives far from the treatment center. In any setting, the best predictors of continued abstinence include evidence of higher levels of life stability (e.g., supportive family and friends) and higher levels of functioning (e.g., job skills, higher levels of education, and absence of crimes unrelated to alcohol).

Whether the treatment begins in an inpatient or an outpatient setting, subsequent outpatient contact should be maintained for a minimum of 6 months and preferably a full year after abstinence is achieved. Counseling with an individual physician or through groups focuses on day-to-day living -- emphasizing areas of improved functioning in the absence of alcohol (i.e., why it is a good idea to continue to abstain) and helping the patient to manage free time without alcohol, develop a nondrinking peer group, and handle stresses on the job without alcohol.

The physician serves an important role in identifying the alcoholic, treating associated medical or psychiatric syndromes, overseeing detoxification, referring the patient to rehabilitation programs, and providing counseling. The physician is also responsible for selecting which (if any) medication might be appropriate during alcoholism rehabilitation. Patients often complain of continuing sleep problems or anxiety when acute withdrawal treatment is over, problems that may be a component of protracted withdrawal. Unfortunately, there is no place for hypnotics or antianxiety drugs in the treatment of most alcoholics after acute withdrawal has been completed. Regarding insomnia, patients should be reassured that the trouble in sleeping is normal after alcohol withdrawal and will improve over the subsequent weeks and months. They should then follow a rigid bedtime and awakening schedule and avoid any naps or the use of caffeine in the evenings. The sleep pattern will improve rapidly. Anxiety can be approached by helping the person to gain insight into the temporary nature of the symptoms and to develop strategies to achieve relaxation as well as using forms of cognitive therapy.

In addition, while the mainstay of alcoholic rehabilitation involves counseling, education, and cognitive techniques, several interesting medications are under active evaluation and might prove to be useful. The first is the opioid-antagonist drug naltrexone, which has been reported in several small-scale, short-term studies to decrease the probability of a return to drinking and to shorten periods of relapse. While this medication looks promising, longer-term large-scale trials in more diverse clinical settings will be required before the cost-effectiveness of naltrexone can be established. A second medication, acamprosate, has been tested in over 5000 patients in Europe, with results that appear similar to those reported for naltrexone. Currently, acamprosate is not available in the United States, although a long-term, trial of naltrexone, acamprosate, and their combination is in progress. A third medication, which has historically been used in the treatment of alcoholism, is the ALDH inhibitor disulfiram. Taken in doses of 250 mg/day, this drug produces an unpleasant (and potentially dangerous) reaction in the presence of alcohol, a phenomenon related to rapidly rising blood levels of the first metabolite of alcohol, acetaldehyde. However, few adequate double-blind controlled trials have demonstrated the superiority of disulfiram over placebo. Disulfiram has many side effects, and the reaction with alcohol can be dangerous, especially for patients with

heart disease, stroke, diabetes mellitus, and hypertension. Thus, most clinicians reserve this medication for patients who have a clear history of longer-term abstinence associated with prior use of disulfiram and for those who might take the drug under the supervision of another individual (such as a spouse), especially during discrete periods that they have identified as representing high-risk drinking situations for them (such as the Christmas holiday).

More data are required before any medication can be recommended for routine use in alcohol rehabilitation. However, additional support for alcoholics is available through Alcoholics Anonymous in almost every community. Alcoholics Anonymous is a self-help group of recovering alcoholics (men and women who have stopped drinking, perhaps many years ago) that offers an effective model of abstinence, provides a sober peer group, and makes crisis intervention available when the urge to drink escalates. No matter what type of rehabilitation program is planned, the alcoholic should be offered the option of joining Alcoholics Anonymous.

(Bibliography omitted in Palm version)

388. OPIOID DRUG ABUSE AND DEPENDENCE - *Marc A. Schuckit*, *David S. Segal*

The principal effects of the opioids (opiate-like drugs) are a damping of pain perception along with modest levels of sedation and euphoria. Drugs in this category include heroin, morphine, and codeine as well as many prescription analgesics and antitussive agents. Opioid drugs are widely used in medical practice, and, thus, dependence and abuse are not limited to the classic opiod-dependent person on the street.

Tolerance to any one opioid is likely to extend to the others (i.e., cross-tolerance is likely), and all opioids are associated with a similar pattern of drug-related problems. Each is capable of producing dependence as defined in the *Fourth Diagnostic and Statistical Manual* of the American Psychiatric Association (DSM-IV), including evidence of physical dependence, a diagnosis made in the context of a history of tolerance and/or withdrawal. The abstinence syndrome from any of the substances can be treated with administration of any of the others.

PHARMACOLOGY

The prototypic opiates, morphine and codeine (3-methoxymorphine), are taken directly from the milky juice of the poppy *Papaver somniferum*. The semisynthetic drugs produced from the morphine or thebane molecules include hydromorphone, diacetylmorphine (heroin), and oxycodone. The purely synthetic opioids, sharing many of the basic properties of opium and morphine, include meperidine, propoxyphene, diphenoxylate, fentanyl, buprenorphine, methadone, and pentazocine. Despite claims to the contrary, all these substances (including almost all prescription analgesics) are capable of producing euphoria as well as psychological and physical dependence when taken in high enough doses over prolonged periods.

The opioids produce their effects by binding to different types of opioid receptors throughout the body, including the central nervous system (CNS). Endogenous opioid peptides (i.e., enkephalins, endorphins, dynorphins, and others) have been identified that appear to be natural ligands for opioid receptors. These peptides have a distinct distribution in the CNS. The receptors with which opioid peptides interact are differentially engaged in production of the various opiate effects, such as analgesia, respiratory depression, constipation, and euphoria. Substances capable of antagonizing one or more of these actions include nalorphine, levallorphan, cyclazocine, butorphanol, buprenorphine, and pentazocine, each of which has mixed agonist and antagonist properties, as well as naloxone, nalmefene, and naltrexone, which are pure opiate antagonists. All antagonist drugs (including those with mixed agonist properties), can precipitate withdrawal symptoms if administered to a patient who is physically dependent on other opioids. The availability of relatively specific antagonists has helped identify different receptor subtypes, including u receptors, which influence some of the more classic opioid actions such as pain control, reinforcement, constipation, hormone levels, and respiration;k receptors, with possible similar functions along with sedation and effects on hormones; and dreceptors, thought to relate mostly to analgesia, mood, reinforcement, and breathing. The major features of tolerance, dependence, and withdrawal are thought to be mediated primarily by u receptors. All opioid receptors are coupled to inhibitory G proteins, which mediate their actions within cells (Chap. 386).

Opioid drugs are absorbed from the gastrointestinal system, the lungs, and/or the muscles. The most rapid and pronounced effects occur following intravenous administration, with only slightly less efficient absorption after smoking or inhaling the vapor ("chasing the dragon"), and the least intense actions are seen after absorption from the digestive tract. Most of the metabolism of opioids occurs in the liver, primarily through conjugation with glucuronic acid, and only small amounts are excreted directly in the urine or feces. The plasma half-lives of these drugs range from 2.5 to 3 h for morphine to more than 22 h for methadone and even longer for levomethadyl acetate (LAAM).

Street heroin is typically only 5 to 10% pure. The remainder consists of materials such as lactose and fruit sugars, quinine, powdered milk, phenacetin, caffeine, antipyrine, and strychnine, which are used to "cut" the drug and increase the profit margin. Any marked, unexpected increase in the purity of street drugs is likely to cause unintentional lethal overdoses in users expecting less effect from a "hit."

THE ACUTE AND CHRONIC EFFECTS OF OPIOID DRUGS

With the exception of overdose and physical dependence, most opioid effects are relatively benign and rapidly reversible. A major danger, however, comes through the use of contaminated needles by intravenous users, which increases the risk of hepatitis B and C, bacterial endocarditis, and infection with HIV (Chap. 309).

Effects on Body Systems Acute changes in the *gastrointestinal system* are the result of decreased motility with resulting constipation and anorexia. Chronic gastrointestinal problems in opioid-dependent individuals typically occur as a consequence of hepatitis in injection drug users.

Effects of opiods in the CNS include intoxication-induced nausea and vomiting (medulla), decreased pain perception (spinal cord, thalamus, and periaqueductal gray region), euphoria (limbic system), and sedation (reticular activating system). The adulterants added to street drugs may contribute to some of the more permanent nervous system damage, including peripheral neuropathy, amblyopia, myelopathy, and leukoencephalopathy. One study revealed abnormalities in cognitive function and brain computed tomography scans of opioid-dependent subjects; whether these abnormalities are due to the opioid itself, the adulterants, the consequences of dirty needles, or an unhealthy life-style is unknown. Acute opioid administration decreases levels of luteinizing hormone, with a subsequent reduction in testosterone, which might contribute to the decreased sex drive reported by most opioid-dependent people. Other hormonal changes include a decrease in the release of thyrotropin and increases in prolactin and possibly growth hormone (Chap. 328).

Acute changes in the *respiratory system* include respiratory depression, which results from a decreased response of the brainstem to carbon dioxide tension, a component of the drug overdose syndrome described below. At even low drug doses, this effect can be clinically significant in individuals with underlying pulmonary disease. *Cardiovascular* changes tend to be relatively mild, with no direct opiate effect on heart rhythm or myocardial contractility, but there is a potential problem from orthostatic hypotension, probably secondary to dilation of peripheral vessels. Bacterial infections of the lungs

and heart valves can occur from contaminated needles; the latter can result in emboli and thus an increased risk for stroke.

The Toxic Reaction or Overdose Syndrome High doses of opioids can result in a potentially lethal toxic reaction or overdose syndrome. While toxic reactions are seen with all opioids, the more potent drugs such as fentanyl (80 to 100 times more powerful than morphine) are especially dangerous. The typical syndrome, which occurs immediately with intravenous overdose, includes shallow respirations at a rate of two to four per minute, pupillary miosis (with mydriasis once brain anoxia develops), bradycardia, a decrease in body temperature, and a general absence of responsiveness to external stimulation. If this medical emergency is not treated rapidly, respiratory depression, cyanosis, cardiorespiratory arrest, and death can ensue. Postmortem examination reveals few specific changes except for diffuse cerebral edema. An "allergic-like" reaction to intravenous heroin, perhaps in part related to adulterants, can also occur and is characterized by decreased alertness, a frothy pulmonary edema, and an elevation in the blood eosinophil count.

The first step in managing overdose is to provide any needed respiratory or cardiovascular support including intubation for airway protection if needed. Definitive treatment for the typical opioid overdose is the administration of a narcotic antagonist such as naloxone in an initial dose of 0.4 mg to 2 mg intravenously, expecting a response in 1 to 2 min. This dose can be repeated every 2 to 3 min up to a dose of 10 mg. With the exception of overdoses with buprenorphene, if no response is seen after 10 mg, it is unlikely that an opioid overdose is responsible for the respiratory depression or coma. If an intravenous line is not available, the drug can be given intramuscularly. It is important to titrate the dose relative to the patient's symptoms. The goal is to ameliorate the respiratory depression but not provoke a severe withdrawal state. Because the effects of this drug diminish within 2 to 3 h, the individual must be monitored for at least 24 h after a heroin overdose and 72 h after an overdose of a longer-acting drug such as methadone. If there is little response to naloxone alone, the possibility of a concomitant overdose with a benzodiazepine should be considered and a challenge with intravenous flumazenil, 0.2 mg/min up to a maximum of 3 mg in an hour, might be used. Patients who are physically dependent on an opioid may experience a precipitous onset of an abstinence syndrome after administration of the opioid antagonist, but aggressive treatment of this syndrome is not appropriate until all vital signs are relatively stable.

As with any drug overdose, treatment of either the typical or the "allergic" type of opioid toxic reaction often requires continued supportive care until the drug effect subsides. Patients may require respiratory support (often with oxygen supplementation and positive-pressure breathing for the "allergic" type of overdose), intravenous fluids perhaps accompanied by pressor agents to support blood pressure, and gastric lavage to remove any remaining drug with care taken to use a cuffed endotracheal tube to prevent aspiration if the patient is not alert. It is important to evaluate and treat any possible anaphylactic reactions. Cardiac arrhythmias and/or convulsions, especially likely to be seen with codeine, propoxyphene, or meperidine, also need to be treated.

OPIOID ABUSE AND DEPENDENCE

Definition and Epidemiology Repeated opioid use to the point of developing multiple problems is a good indicator that future abuse and dependence are likely.DSM-IVcriteria for opioid dependence are the same as those for alcohol dependence (Chap. 387). An individual is dependent if within a 12-month period repeated difficulties occur in any three areas of functioning, including tolerance, withdrawal, use of greater amounts of opiates than intended, and use despite consequences. Patients who do not have dependence but demonstrate repeated difficulties with the law, impaired ability to meet obligations, use in hazardous situations, or continued use despite problems can be labeled as having abuse.

The use of opioids for intoxication is less prevalent than the use of alcohol, marijuana, and several other drugs. A 1997 national survey reported that almost 5% of men and women age 12 or above in the United States had used an opioid for intoxication, including almost 2% in the prior year and slightly less than 1% in the prior month. Focusing specifically on heroin, the lifetime prevalence was approximately 1%, with 0.3% having taken the drug in the prior year. Use patterns of these drugs were almost twice as high in another 1997 survey sampling 12th graders in high school. In all studies, prevalence rates were higher in males than females. None of the national surveys offered data regarding the prevalence of dependence.

Genetics While most data on the importance of genetic influences in substance use disorders apply to alcoholism, there are interesting findings regarding other drugs. One large study of over 3000 male twin pairs reported that there are genetic influences that relate uniquely to heroin dependence and also noted additional genetic factors related to an overall vulnerability toward substance-related problems. The genetic influences operate in the context of additional environmental factors that are likely to relate both to the family of upbringing and the general environment. Genetic factors might influence personality characteristics such as impulsivity and sensation-seeking or susceptibility to develop antisocial personality disorder. Genes relating to the actions of the drug on specific neurochemical systems such as dopamine are also potential candidates for an enhanced vulnerability toward developing opioid dependence.

Natural History Dependence on or abuse of opioids can be seen in at least three types of patients. First, a minority of people with nonfatal *chronic pain syndromes* (e.g., back, joint, and muscle disorders) misuse their prescribed drugs. If physical dependence is established, abstinence syndromes can then intensify the pain, promoting continued drug intake. Physicians can avoid contributing to physical dependence by helping the patient to accept the goal of minimization rather than disappearance of the pain and to recognize that discomfort may not be completely eliminated (Chap. 12). Analgesic medication should be only one component of treatment and limited to the oral administration of the least potent analgesic that is able to "take the edge off" the pain (e.g., ibuprofen or, if needed, propoxyphene). Behavior modification techniques, such as muscle relaxation and meditation, and carefully selected exercises should be used as appropriate to help increase function and decrease pain. Finally, nonmedicinal approaches, including electrical transcutaneous neurostimulation for muscle and joint disease, may be useful.

The second group at high risk are *physicians*, *nurses*, and *pharmacists*, primarily because of their easy access to substances of abuse. Physicians may begin to use

opioids to help them sleep or to reduce stress or physical aches and pains. This group appears to be at especially high risk for developing dependence on the highly potent drugs such as fentanyl. Because of the growing awareness of these problems, impaired-physician programs have been established in many hospitals and by most state medical societies. Such groups attempt to identify and aid substance-impaired physicians, giving them peer support and education to help them achieve abstinence before problems escalate to the point of licensure revocation. All doctors are advised never to prescribe opioids for themselves or for members of their family -- physicians deserve the same level of care and protection from future problems as their patients.

The third and most obvious group are those who buy street drugs to get high. While some of these men and women have prior histories of severe antisocial problems, most have a relatively high level of premorbid functioning. The typical person begins using opioids occasionally, often after experimenting with tobacco, then alcohol, then marijuana, and then brain depressants or stimulants. Occasional opiate use, or "chipping," might continue for some time, and some individuals never escalate their intake to the point of developing dependence.

Of course, opiate-dependent individuals are likely to continue to have experience with many other drugs. At least three of these often remain as problems during the course of opioid dependence. First, alcohol is typically used to moderate withdrawal problems, to enhance the opioid high, and as a substitute when the preferred drug is not readily available, including during methadone and other treatments. This pattern of problematic drinking, often meeting criteria for alcohol dependence, is present at some time in approximately half of opioid-dependent persons. The second drug, cocaine, appears to be taken for many of the same reasons as alcohol, and is often administered intravenously with the opioid in a mixture known as a "speedball." The third class of drugs misused in combination with opioids consists of the benzodiazepines, especially among people in methadone maintenance.

Once persistent opioid use is established, severe problems are likely to develop. At least 25% die within 10 to 20 years from suicide, homicide, accidents, or infectious diseases such as tuberculosis, hepatitis, or AIDS. The mortality rate has escalated in recent years in response to the AIDS epidemic among injection drug users, with an estimated 60% of these men and women carrying HIV (Chap. 309). At the same time, while the majority of opioid-dependent persons show frequent exacerbations and remissions, it is important to remember that approximately 35% achieve long-term, often permanent, abstinence. This remission is probably most often seen after the age of 40 but can occur at any point in the clinical course. While this favorable outcome can be observed in any opioid-dependent person, as is true with most drugs of abuse a better prognosis is associated with prior histories of marital and employment stability and fewer criminal activities unrelated to drugs.

TREATMENT

The key to diagnosis is to discard the erroneous stereotype that opioid-dependent men and women are always unemployed and homeless. Abuse or dependence is possible in any patient who demonstrates symptoms of what might be opioid withdrawal; anyone who has a chronic pain syndrome; physicians, nurses, and pharmacists or others with

easy access to opioids; and all patients who repeatedly seek out prescription analgesics. Therefore, it is important to take the time with *every* patient, especially those with complaints of pain, to gather a history that includes the patterns of opioid use and the list of doctors and clinics from which they have received prescriptions. If the chronic use of opioids is suspected, gathering further data from an additional informant such as a relative or close friend can be essential. Another indicator of an enhanced risk for opioid dependence is a history of pervasive antisocial problems beginning in the preteen years. Blood and urine screens can be used to identify opioids in patients in whom misuse is suspected, and clinicians should search for physical stigmata of misuse (e.g., needle marks).

After identifying opioid dependence, the next step is intervention. The need for active treatment of the abstinence syndrome can be presented, and the availability of help in establishing a drug-free life-style can be emphasized. The final decision, of course, rests with the patient. This approach to intervention is presented in relation to alcoholism in Chap. 387.

The Symptoms of Withdrawal Withdrawal symptoms, usually the opposite of the acute effects of the drug, include nausea and diarrhea, coughing, lacrimation, mydriasis, rhinorrhea, profuse sweating, twitching muscles, piloerection (or "goose bumps") as well as mild elevations in body temperature, respiratory rate, and blood pressure. In addition, diffuse body pain, insomnia, and yawning occur, along with intense drug craving. Drugs with a short half-life, such as morphine or heroin, cause symptoms typically within 8 to 16 h of the last dose (thus, many dependent individuals awake in mild withdrawal every morning); symptom intensity peaks within 36 to 72 h after discontinuation of the drug, and the acute syndrome disappears within 5 to 8 days. However, a protracted abstinence phase of mild symptoms (e.g., moodiness, slight changes in pupillary size, autonomic dysfunction, changes in sleep pattern) may persist for 6 or more months. These lingering symptoms, which can be relieved by administering an opioid, probably contribute to relapse.

Treatment of the Withdrawal Syndrome A thorough physical examination, including an assessment of neurologic function and a search for local and systemic infections, especially abscesses, is mandatory. Laboratory testing generally includes assessment of liver function and, in intravenous users, HIV status. Proper nutrition and rest must be initiated as soon as possible.

Optimal treatment of withdrawal requires administration of sufficient opioid medication on day 1 to decrease symptoms, followed by a more gradual withdrawal of the drug, usually over 5 to 10 days. Any opioid will work (all have some level of cross-tolerance), but for ease of administration, many physicians prefer to use a long-acting drug such as methadone. To estimate the first day's dose from the patient's history, 1 to 2 mg of methadone can be considered approximately equivalent to 3 mg of morphine, 1 mg of heroin, or 20 mg of meperidine. Most patients require between 10 and 25 mg of methadone orally twice on day 1, with higher doses given if prominent symptoms of withdrawal are not dampened. After several days of a stabilized drug dose, the opioid is then decreased by 10 to 20% of the original day's dose each day.

However, most states restrict the prescription of opioids to dependent persons, and, in

the absence of special permits, detoxification with opioids is often proscribed or limited. Thus, pharmacologic treatments often center on relief of symptoms of diarrhea with Imodium or a nonopioid drug, of "sniffles" with decongestants, and pain with nonopioid analgesics (e.g., ibuprofen). Comfort can be enhanced with thea$_2$-adrenergic agonist clonidine to decrease sympathetic nervous system overactivity. Given at doses of approximately 5 ug/kg (up to 0.3 mg given two to four times a day), clonidine decreases autonomic nervous system dysfunction and produces sedation. Blood pressure should be monitored closely. Some clinicians augment this regimen with low to moderate doses of benzodiazepines for 2 to 5 days to decrease agitation.

A special case of opioid withdrawal is seen in the newborn made passively dependent through the mother's drug abuse during pregnancy. Some level of withdrawal develops in 50 to 90% of children of heroin-dependent mothers. As few as 25% of infants of methadone-maintenance mothers show clinically relevant withdrawal symptoms, probably because of the longer half-life of this drug. The syndrome consists of irritability, crying, a tremor (in 80%), increased reflexes, increased respiratory rate, diarrhea, hyperactivity (in 60%), vomiting (40%), and sneezing/yawning/hiccuping (in 30%). The child usually has a low birth weight but may be otherwise unremarkable until the second day, when symptoms are likely to begin.

The treatment follows the same general steps used in the treatment of the physically dependent adult. The child must be carefully evaluated to rule out medical problems such as hypoglycemia, hypocalcemia, infections, and trauma; general support in a warm, quiet environment and regulation of electrolytes and glucose are also required. The infant with moderate to severe symptoms can be treated with any of the following: paregoric (0.2 mL orally every 3 to 4 h), methadone (0.1 to 0.5 mg/kg per day), phenobarbital (8 mg/kg per day), or diazepam (1 to 2 mg/kg every 8 h). Medication should be given in decreasing levels for 10 to 20 days. Dependent infants of mothers on methadone maintenance also benefit by breast feeding while the mother continues to take methadone.

Rehabilitation of Opioid-Dependent Persons Despite some differences in demographics, the same general rules for rehabilitation apply to opioid-dependent persons as to alcoholics. The basic strategy includes detoxification and family support, and the process can benefit from the use of reading materials or referral to self-help groups. It is also important to establish realistic patient goals and a program of counseling and education to increase motivation toward abstinence. A long-term commitment to rebuilding a life-style without the substance is essential for preventing recidivism.

Most rehabilitation approaches have common elements, regardless of the drug involved. Patients are educated about their responsibility for improving their lives, and *motivation for abstinence* is increased by providing information about the medical and psychological problems that can be expected if dependence continues. Patients and families are encouraged to *establish an opioid-free life-style* by learning to cope with chronic pain and develop realistic vocational planning (e.g., for pharmacists, physicians, and nurses). The dependent person is also encouraged to establish a drug-free peer group and to participate in self-help groups such as Narcotics Anonymous. Another important treatment component is *relapse prevention* aimed at identifying triggers for a

return to drugs and developing appropriate coping strategies.

Much of this advice and counseling can be given by the physician, but many clinicians refer patients to more formal drug programs, including methadone maintenance clinics, programs using narcotic antagonists, and therapeutic communities. Long-term follow-up of treated patients indicates that approximately one-third were completely drug free in the previous year; 60% were no longer using opioids, although some were misusing other substances. Individuals who stay in methadone maintenance or in therapeutic communities show significant improvement in antisocial behavior and employment status. In general, the best prognosis is for those individuals who are employed, who have higher levels of education, and who remain in treatment for at least 2 months. Dependence among health care providers, such as physicians, is treated similarly, but in addition a closely supervised "diversion" procedure is usually instituted and carried out for 1 to 2 years or more.

Methadone Maintenance Maintenance programs with methadone and the even longer-acting agentLAAMshould only be used in combination with education and counseling. It is important to note that drug maintenance is not aimed at "curing" opioid dependence; rather, it provides a substitute drug that is legally accessible, safer, can be taken orally, and has a long half-life so that it can be taken once a day. The goal is to help persons who have repeatedly failed in drug-free programs to improve functioning within the family and job, to decrease legal problems, and to improve health.

Methadone is a long-acting opioid that possesses almost all the physiologic properties of heroin. The recipient, who has been carefully screened to rule out prior psychiatric disorders, may be maintained on a relatively low dose (e.g., 30 to 40 mg/d); a better approach is to use a higher dose (80 to 120 mg/d), because it may be more effective in blocking heroin-induced euphoria and decreasing craving. There is some evidence that the higher methadone doses result in greater retention in treatment and consequently in lower levels of arrest and relapse to street drugs. Three-quarters or more of patients, especially those receiving the higher doses, are likely to remain heroin-free for 6 months or longer. Methadone is administered as an oral liquid given once a day at the program, with weekend doses taken by the patient at home. The longer-acting analogues, such asLAAM, can be given two or three times a week, with the dose of LAAM increased to as high as 80 mg three times a week if needed. After a period of maintenance (usually 6 months to 1 year or longer), the clinician can work closely with the patient to regulate the rate of drug decrease (by about 5% per week) if possible.

In the past, the British have used heroin maintenance with goals and guidelines similar to those of current methadone programs. There is no evidence that heroin maintenance has any advantages over methadone maintenance, but the heroin approach does add the risk that the drug will be easily sold on the streets. Treatment with mixed agonists-antagonists such as buprenorphine also appears beneficial, although results are not as good as with methadone.

Opioid Antagonists The opiate antagonists (e.g., naloxone) compete with heroin and other opioids for receptors, reducing the effects of the opioid agonists. Administered over long periods with the intention of blocking the "high" produced if the patient takes opioids, these drugs can be useful as part of an overall treatment approach that

includes counseling and support. The most widely used antagonist in rehabilitation is naltrexone; 50 mg per day antagonizes 15 mg of heroin for 24 h, and higher doses (125 to 150 mg) block the effects of 25 mg of intravenous heroin for up to 3 days. Naltrexone is free of agonist properties, produces no known withdrawal symptoms when stopped, and its side effects tend to be mild. To avoid precipitating a withdrawal syndrome, patients should be free of opioids for a minimum of 5 days before beginning treatment with this medication. In addition, they should first be challenged with 0.4 or 0.8 mg of the shorter-acting agent naloxone to be certain they are able to tolerate the long-acting antagonist. Following this procedure, a test dose of 10 mg of naltrexone can be given, with the expectation that any withdrawal symptoms will be seen in 0.5 to 2 h. Several variations of this approach can be used with detoxification from methadone maintenance, including a fairly rapid, medically supervised plan. Over a 10-day period, the daily dose should be increased to about 100 mg on Mondays and Wednesdays and 150 mg on Fridays. Unfortunately, despite the apparent advantages of this treatment approach, some patients are resistant to continuing care. In one study, only about 60% of the patients completed 6 days of naltrexone induction, and only 10% remained in the program at the end of 6 months. However, another study reported much higher rates of compliance, with almost a third achieving continuous abstinence for at least a year.

Drug-Free Programs Most existing halfway houses and recovery centers for opioid-dependent persons use some variant of the therapeutic community approach. This is an exception to the general preference for short-term residential (as opposed to outpatient) rehabilitation, since care can last a year or more while the person is taken out of the street culture and given a new life within the group. In this structure, members, including leaders who are themselves in the process of recovery, help participants gain insights into more successful strategies for coping with problems.

As is true for treatments of all substance-use disorders, it is likely that counseling, behavioral treatments, and relatively simple approaches to psychotherapy add significantly to a positive outcome. Most approaches focus on teaching participants to cope with stress, enhancing their understanding of personality attributes, teaching better cognitive styles, and, through the process of relapse prevention, addressing issues that might contribute to increased craving, easy access to drugs, or periods of decreased motivation. A combination of these therapies with the approaches described above appears to give the best results.

Finally, it is important to discuss prevention. Except for the terminally ill, physicians should carefully monitor opioid drug use in their patients, keeping doses as low as is practical and administering them over as short a period as the level of pain would warrant in the average person. Physicians must be vigilant regarding their own risk for opioid abuse and dependence, *never* prescribing these drugs for themselves. For the nonmedical intravenous drug-dependent person, all possible efforts must be made to prevent AIDS, hepatitis, bacterial endocarditis, and other consequences of contaminated needles both through methadone maintenance and by considering needle-exchange programs.

(Bibliography omitted in Palm version)

The abuse of cocaine and other psychostimulant drugs appears to be increasing in many metropolitan and rural areas throughout the world, according to a year 2000 report by the National Institute on Drug Abuse (NIDA). The number of deaths associated with these drugs has also increased. In several urban areas of the United States, use of these drugs has increased more sharply among women than men. Although enhanced legal enforcement as well as educational prevention procedures have attenuated, in part, the increase in psychostimulant abuse among youths in the United States, there appears to be an enhanced worldwide risk for psychostimulant abuse and dependence.

The initiation and continuation of drug abuse are determined by a complex interaction of the pharmacologic properties and relative availability of each drug, the personality and expectations of the user, and the environmental context in which the drug is used. Polydrug abuse, the concurrent use of several drugs with different pharmacologic effects, is increasingly common among individuals from all socioeconomic strata. There has been an alarming increase in particularly dangerous forms of polydrug abuse, such as the combined use of heroin and cocaine intravenously. There is no simple explanation for this change in polydrug use patterns. Drug abusers may attempt to attenuate one drug effect with another, as when heroin or alcohol is used to modulate the cocaine high. Sometimes one drug is used to enhance the effects of another, as with benzodiazepines and methadone, or cocaine plus heroin in methadone-maintained patients.

Chronic cocaine and psychostimulant abuse may cause a number of adverse health consequences, ranging from pulmonary disease to reproductive dysfunction. Preexisting disorders such as hypertension and cardiac disease may be exacerbated by drug abuse, and the combined use of two or more drugs may accentuate medical complications associated with abuse of one of them. The adverse health consequences of drug abuse are further complicated by AIDS.

Drug abuse increases the risk of exposure to HIV. Cocaine and psychostimulant abuse contribute to the risk for HIV infection in part by the adverse immunomodulatory effects of these drugs. In addition, concurrent use of cocaine and opiates (the "speedball") is frequently associated with needle-sharing by intravenous drug users. These individuals continue to represent the largest single group of persons with HIV infection in several major metropolitan areas in the United States as well as in urban areas in Scotland, Italy, Spain, Thailand, and China.

COCAINE

Cocaine is a stimulant and local anesthetic with potent vasoconstrictor properties. The leaves of the coca plant (*Erythroxylon coca*) contain approximately 0.5 to l% cocaine. The drug produces physiologic and behavioral effects when administered orally, intranasally (snorting), intravenously, or via inhalation following pyrolysis (smoking). Cocaine increases synaptic concentrations of the monoamine neurotransmitters dopamine, norepinephrine, and serotonin by binding to transporter proteins in presynaptic neurons and blocking reuptake. The reinforcing effects of cocaine are

related to effects on dopaminergic neurons in the mesolimbic system ([Chap. 386](#)).

Prevalence of Cocaine Use Cocaine has become widely available throughout the United States, and cocaine abuse occurs in virtually all social and economic strata of society. The prevalence of cocaine abuse in the general population has been accompanied by an increase in cocaine abuse by heroin-dependent persons, including those in methadone maintenance programs. Intravenous cocaine is often used concurrently with intravenous heroin -- a combination that purportedly attenuates the postcocaine "crash" and substitutes a cocaine "high" for the heroin "high" blocked by methadone.

Acute and Chronic Cocaine Intoxication There has been an increase in both intravenous administration and inhalation of pyrolyzed cocaine via smoking. Following intranasal administration, changes in mood and sensation are perceived within 3 to 5 min, and peak effects occur at l0 to 20 min. The effects rarely last>1 h. Inhalation of pyrolyzed materials includes inhaling crack/cocaine or smoking coca paste, a product made by extracting cocaine preparations with flammable solvents, and cocaine free-base smoking. Free-base cocaine, including the free base prepared with sodium bicarbonate (crack), is becoming increasingly popular because of the relative high potency of the compound and its rapid onset of action (8 to 10 s following smoking).

Cocaine produces a brief, dose-related stimulation and enhancement of mood and an increase in cardiac rate and blood pressure. Body temperature usually increases, and high doses of cocaine may induce lethal pyrexia or hypertension. Because cocaine inhibits reuptake of catecholamines at adrenergic nerve endings, the drug potentiates sympathetic nervous system activity. Cocaine has a short plasma half-life of approximately 45 to 60 min. Cocaine is metabolized primarily by plasma esterases, and cocaine metabolites are excreted in urine. The very short duration of euphorigenic effects of cocaine observed in chronic abusers is probably due to both acute and chronic tolerance. Frequent self-administration of the drug (two to three times per hour) is often reported by chronic cocaine abusers. Alcohol is used to modulate both the cocaine high and the dysphoria associated with the abrupt disappearance of cocaine's effects. A metabolite of cocaine, cocaethylene, has been detected in blood and urine of persons who concurrently abuse alcohol and cocaine. Cocaethylene induces changes in cardiovascular function similar to those of cocaine alone, and the pathophysiologic consequences of alcohol abuse plus cocaine abuse may be additive when both are used together.

The prevalent assumption that cocaine inhalation or intravenous administration is relatively safe is contradicted by reports of death from respiratory depression, cardiac arrhythmias, and convulsions associated with cocaine use. In addition to generalized seizures, neurologic complications may include headache, ischemic or hemorrhagic stroke, or subarachnoid hemorrhage. Disorders of cerebral blood flow and perfusion in cocaine-dependent persons have been detected with magnetic resonance spectroscopy (MRS) studies. Severe pulmonary disease may develop in individuals who inhale crack cocaine; this effect is attributed both to the direct effects of cocaine and to residual contaminants in the smoked material. Hepatic necrosis has been reported to occur following crack cocaine use.

Although men and women who abuse cocaine may report that the drug enhances libidinal drive, chronic cocaine use causes significant loss of libido and adversely affects reproductive function. Impotence and gynecomastia have been observed in male cocaine abusers, and these abnormalities often persist for long periods following cessation of drug use. Women who abuse cocaine have reported major derangements in menstrual cycle function including galactorrhea, amenorrhea, and infertility. Chronic cocaine abuse may cause persistent hyperprolactinemia as a consequence of disordered dopaminergic inhibition of prolactin secretion by the pituitary. Cocaine abuse by pregnant women, particularly the smoking of crack, has been associated with both an increased risk of congenital malformations in the fetus and perinatal cardiovascular and cerebrovascular disease in the mother. However, cocaine abuse per se is probably not the sole cause of these perinatal disorders, since many problems associated with maternal cocaine abuse, including poor nutrition and health care status as well as polydrug abuse, also contribute to risk for perinatal disease.

Protracted cocaine abuse may cause paranoid ideation and visual and auditory hallucinations, a state that resembles alcoholic hallucinosis. Psychological dependence on cocaine, as manifested by inability to abstain from frequent compulsive use, has also been reported. Although the occurrence of withdrawal syndromes involving psychomotor agitation and autonomic hyperactivity remains controversial, severe depression ("crashing") following cocaine intoxication may accompany drug withdrawal.

TREATMENT

Treatment of cocaine overdose is a medical emergency that is often best managed in an intensive care unit. Cocaine toxicity produces a hyperadrenergic state characterized by hypertension, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias. Intravenous diazepam in doses up to 0.5 mg/kg administered over an 8-h period has been shown to be effective for control of seizures. Ventricular arrhythmias have been managed successfully by administration of 0.5 to 1.0 mg of propranolol intravenously. Since many instances of cocaine-related mortality have been associated with concurrent use of other illicit drugs (particularly heroin), the physician must be prepared to institute effective emergency treatment for multiple drug toxicities.

Treatment of chronic cocaine abuse requires combined efforts by primary care physicians, psychiatrists, and psychosocial care providers. Early abstinence from cocaine use is often complicated by symptoms of depression and guilt, insomnia, and anorexia, which may be as severe as those observed in major affective disorders. Individual and group psychotherapy, family therapy, and peer group assistance programs are often useful for inducing prolonged remission from drug use. A number of medications used for the treatment of various psychiatric disorders have been administered to reduce the duration and severity of cocaine abuse and dependence. However, no available medication is both safe and highly effective for either cocaine detoxification or maintenance of abstinence. Some psychotherapeutic interventions are occasionally effective; however, no specific form of psychotherapy or behavioral modification is uniquely beneficial.

MARIJUANA AND CANNABIS COMPOUNDS

Cannabis sativa contains>400 compounds in addition to the psychoactive substance, delta-9-tetrahydrocannabinol (THC). Marijuana cigarettes are prepared from the leaves and flowering tops of the plant, and a typical marijuana cigarette contains 0.5 to 1 g of plant material. Although the usual THC concentration varies between 10 and 40 mg, concentrations>100 mg per cigarette have been detected. Hashish is prepared from concentrated resin of *C. sativa* and contains a THC concentration of between 8 to 12% by weight. "Hash oil," a lipid-soluble plant extract, may contain a THC concentration of 25 to 60% and may be added to marijuana or hashish to enhance its THC concentration. Smoking is the most common mode of marijuana or hashish use. During pyrolysis,>150 compounds in addition to THC are released in the smoke. Although most of these compounds do not have psychoactive properties, they do have potential physiologic effects.

THCis quickly absorbed from the lungs into blood and is then rapidly sequestered in tissues. It is metabolized primarily in the liver, where it is converted to 11-hydroxy-THC, a psychoactive compound, and >20 other metabolites. Many THC metabolites are excreted through the feces at a rate of clearance that is relatively slow in comparison to that of most other psychoactive drugs.

Specific cannabinoid receptors (CB$_1$ and CB$_2$) have been identified in the central nervous system, including the spinal cord, and in the peripheral nervous system. High densities of these receptors have been found in the cerebral cortex, basal ganglia, and hippocampus. B lymphocytes also appear to have cannabinoid receptors. A naturally occurringTHC-like ligand has been identified in the nervous system, where it is widely distributed.

Prevalence of Marijuana Use Marijuana is the most commonly used illegal drug in the United States. Use is particularly prevalent among adolescents; studies suggest that ~40% of high school students in the United States have used marijuana. Marijuana is relatively inexpensive and is considered by many persons to be less hazardous than the use of other controlled drugs and substances. Very potent forms of marijuana (sinsemilla) are now available in many communities, and concurrent use of marijuana with crack/cocaine and phencyclidine is increasing. Marijuana abuse by individuals from all social strata has been increasing.

Acute and Chronic Marijuana Intoxication Acute intoxication from marijuana and cannabis compounds is related to both the dose ofTHC and the route of administration. THC is absorbed more rapidly from marijuana smoking than from orally ingested cannabis compounds. Acute marijuana intoxication usually consists of a subjective perception of relaxation and mild euphoria resembling mild to moderate alcohol intoxication. This condition is usually accompanied by some impairment in thinking, concentration, and perceptual and psychomotor function. Higher doses of cannabis may produce behavioral effects analogous to severe alcohol intoxication. Although the effects of acute marijuana intoxication are relatively benign in normal users, the drug can precipitate severe emotional disorders in individuals who have antecedent psychotic or neurotic problems. As with other psychoactive compounds, both set (user's expectations) and setting (environmental context) are important determinants of the type and severity of behavioral intoxication.

As is true of alcoholics, chronic marijuana abusers may lose interest in common socially desirable goals and steadily devote more time to drug acquisition and use. However, THC does not cause a specific and unique "amotivational syndrome." The range of symptoms sometimes attributed to marijuana use is difficult to distinguish from mild to moderate depression and the maturational dysfunctions often associated with protracted adolescence. Chronic marijuana use has also been reported to increase the risk of psychotic symptoms in individuals with a past history of schizophrenia.

Physical Effects of Marijuana Conjunctival injection and tachycardia are the most frequent immediate physical concomitants of smoking marijuana. Tolerance for marijuana-induced tachycardia develops rapidly among regular users; angina may be precipitated by marijuana smoking in persons with a history of coronary insufficiency. Exercise-induced angina may be increased after marijuana use to a greater extent than after tobacco cigarette smoking. Patients with cardiac disease should be strongly advised not to use cannabis compounds.

Significant decrements in pulmonary vital capacity have been found in regular daily marijuana smokers. Because marijuana smoking typically involves deep inhalation and prolonged retention of marijuana smoke, marijuana smokers may develop chronic bronchial irritation. Impairment of single-breath carbon monoxide diffusion capacity (DL_{co}) is greater in persons who smoke both marijuana and tobacco than in tobacco smokers. Despite the well-documented association between tobacco smoking and lung cancer, at present there is no direct evidence that marijuana smoking induces lung cancer. However, heavy marijuana use among Americans may be too recent to permit detection of this problem.

Although marijuana has also been associated with adverse effects on a number of other systems, many of these studies await replication and confirmation. A reported correlation between marijuana use and decreased testosterone levels in males has not been confirmed. Decreased sperm count and sperm motility and morphologic abnormalities of spermatozoa following marijuana use have also been reported. Administration of high doses of marijuana to female rhesus monkeys suppresses pituitary gonadotropins and gonadal steroids. Prospective studies demonstrated a correlation between impaired fetal growth and development and heavy marijuana use during pregnancy. Marijuana has also been implicated in derangements of the immune system; in chromosomal abnormalities; and in inhibition of DNA, RNA, and protein synthesis; however, these findings have not been confirmed or related to any specific physiologic effect in humans.

Tolerance and Physical Dependence Habitual marijuana users rapidly develop tolerance to the psychoactive effects of marijuana and often smoke more frequently and try to secure more potent cannabis compounds. Tolerance for the physiologic effects of marijuana develops at different rates; e.g., tolerance develops rapidly for marijuana-induced tachycardia but more slowly for marijuana-induced conjunctival injection. Tolerance to both behavioral and physiologic effects of marijuana decreases rapidly upon cessation of marijuana use.

Withdrawal signs and symptoms have been reported in chronic cannabis users, with the severity of symptoms related to dosage and duration of use. These include tremor,

nystagmus, sweating, nausea, vomiting, diarrhea, irritability, anorexia, and sleep disturbances. Withdrawal signs and symptoms observed in chronic marijuana users are usually relatively mild in comparison to those observed in heavy opiate or alcohol users and rarely require medical or pharmacologic intervention. More severe and protracted abstinence syndromes may occur after sustained use of high potency cannabis compounds.

Therapeutic Use of Marijuana Marijuana, administered as cigarettes or as a synthetic oral cannabinoid (dronabinol), has been proposed to have a number of properties that may be clinically useful in some situations. These include antiemetic effects in chemotherapy recipients, appetite-promoting effects in AIDS, reduction of intraocular pressure in glaucoma, and reduction of spasticity in multiple sclerosis and other neurologic disorders. With the possible exception of AIDS-related cachexia, none of these attributes of marijuana compounds is clearly superior to other readily available therapies. Furthermore, any therapeutic benefit of marijuana must be balanced against the many unhealthy psychoactive effects associated with its use.

METHAMPHETAMINE

The abuse of methamphetamine, also referred to as "meth," "speed," "crank," "chalk," "ice," "glass," or "crystal," has been declining in many metropolitan areas and communities throughout the United States. This decrease is attributed in part to drug seizures and the closures of clandestine laboratories that produce methamphetamine illegally. Prevention programs focusing upon methamphetamine abuse have also increased.

Most persons who abuse amphetamine self-administer the drug orally, although there have been reports of methamphetamine administration by inhalation and intravenous injection. Individuals who abuse or become dependent upon methamphetamine state that use of this drug induces feelings of euphoria and decreases fatigue associated with aversive life situations. Adverse physiologic effects observed as a consequence of methamphetamine abuse include headache, difficulty concentrating, diminished appetite, abdominal pain, vomiting or diarrhea, disordered sleep, paranoid or aggressive behavior, and psychosis. Severe, life-threatening toxicity may present as hypertension, cardiac arrythmia or failure, subarachnoid hemorrhage, ischemic stroke, intracerebral hemorrhage, convulsions, or coma. Amphetamines increase the release of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) from presynaptic neurons. It is thought that the euphoric and reinforcing effects of this class of drugs are mediated through dopamine and the mesolimbic system, whereas the cardiovascular effects are related to norepinephrine. Magnetic resonance spectroscopy studies suggest that chronic abuse may injure the frontal areas and basal ganglia of the brain.

Therapy of acute methamphetamine overdose is largely symptomatic. Ammonium chloride may be useful to acidify the urine and enhance clearance of the drug. Hypertension may respond to sodium nitroprusside or a-adrenergic antagonists. Sedatives may reduce agitation and other signs of central nervous system overactivity. Treatment of chronic methamphetamine dependence may be accomplished in either an inpatient or outpatient setting using strategies similar to those described above for cocaine abuse.

MDMA (3,4-methylenedioxymethamphetamine), or *Ecstasy*, is a derivative of methamphetamine. Ecstasy is usually taken orally but may be injected or inhaled. In addition to amphetamine-like effects, MDMA can induce vivid hallucinations and other perceptual distortions. These toxicities are similar to those of lysergic acid diethylamide (LSD) and may be mediated through the release of serotonin.

LYSERGIC ACID DIETHYLAMIDE

The discovery of the psychedelic effects of LSD in 1947 led to an epidemic of LSD abuse during the 1960s. Imposition of stringent constraints on the manufacture and distribution of LSD (classified as a Schedule I substance by the U.S. Food and Drug Administration), as well as public recognition that psychedelic experiences induced by LSD were a health hazard, have resulted in a reduction in LSD abuse. The drug still retains some popularity among adolescents and young adults, however, and there are indications that LSD use among young persons has been increasing in some communities in the United States.

LSD is a very potent drug; oral doses as low as 20 ug may induce profound psychological and physiologic effects. Tachycardia, hypertension, pupillary dilation, tremor, and hyperpyrexia occur within minutes following oral administration of 0.5 to 2 ug/kg. A variety of bizarre and often conflicting perceptual and mood changes, including visual illusions, synesthesias, and extreme lability of mood, usually occur within 30 min after LSD intake. The action of LSD may persist for 12 to 18 h, even though the half-life of the drug is only 3 h.

Tolerance develops rapidly for LSD-induced changes in psychological function when the drug is used one or more times per day for 4 or more days. Abrupt abstinence following continued use does not produce withdrawal signs or symptoms. There have been no clinical reports of death caused by the direct effects of LSD.

The most frequent medical emergency associated with LSD use is panic episode (the "bad trip"), which may persist up to 24 h. Management of this problem is best accomplished by supportive reassurance ("talking down") and, if necessary, administration of small doses of anxiolytic drugs. Adverse consequences of chronic LSD use include risk for schizophreniform psychosis and derangements in memory function, problem solving, and abstract thinking. Treatment of these disorders is best carried out in specialized psychiatric facilities.

PHENCYCLIDINE

Phencyclidine (PCP), a cyclohexylamine derivative, is widely used in veterinary medicine to briefly immobilize large animals and is sometimes described as a dissociative anesthetic. PCP binds to ionotropic *n*-methyl-*d*-aspartate (NMDA) receptors in the nervous system, blocking ion current through these channels. PCP is easily synthesized; its abusers are primarily young people and polydrug users. It is used orally, by smoking, or by intravenous injection. It is also used as an adulterant in THC, LSD, amphetamine, or cocaine. The most common street preparation, *angel dust*, is a white granular powder that contains 50 to 100% of the drug. Low doses (5 mg) produce

agitation, excitement, impaired motor coordination, dysarthria, and analgesia. Users may have horizontal or vertical nystagmus, flushing, diaphoresis, and hyperacusis. Behavioral changes include distortions of body image, disorganization of thinking, and feelings of estrangement. Higher doses of PCP (5 to 10 mg) may produce hypersalivation, vomiting, myoclonus, fever, stupor, or coma. PCP doses of ³10 mg cause convulsions, opisthotonus, and decerebrate posturing, which may be followed by prolonged coma.

The diagnosis of PCP overdose is difficult because the patient's initial symptoms may suggest an acute schizophrenic reaction. Confirmation of PCP use is possible by determination of PCP levels in serum or urine; PCP assays are available at most toxicologic centers. PCP remains in urine for 1 to 5 days following high-dose intake.

PCP overdose requires life-support measures, including treatment of coma, convulsions, and respiratory depression in an intensive care unit. There is no specific antidote or antagonist for PCP. PCP excretion from the body can be enhanced by gastric lavage and acidification of urine. Death from PCP overdose may occur as a consequence of some combination of pharyngeal hypersecretion, hyperthermia, respiratory depression, severe hypertension, seizures, hypertensive encephalopathy, and intracerebral hemorrhage.

Acute psychosis associated with PCP use should be considered a psychiatric emergency since patients may be at high risk for suicide or extreme violence toward others. Phenothiazines should not be used for treatment because these drugs potentiate PCP's anticholinergic effects. Haloperidol (5 mg intramuscularly) has been administered on an hourly basis to induce suppression of psychotic behavior. PCP, like LSD and mescaline, produces vasospasm of cerebral arteries at relatively low doses. Chronic PCP use has been shown to induce insomnia, anorexia, severe social and behavioral changes, and, in some cases, chronic schizophrenia.

POLYDRUG ABUSE

Although drug abusers often report a preference for a particular drug, such as alcohol or opiates, the concurrent use of other drugs is common. Multiple drug use often involves substances that may have different pharmacologic effects from the preferred drug. Concurrent use of dissimilar compounds such as stimulants and opiates or stimulants and alcohol is not unusual. The diversity of reported drug use combinations suggests that achieving some perceptible change in state, rather than any particular direction of change (stimulation or sedation), may be the primary reinforcer in polydrug use and abuse. There is also evidence that intoxication with alcohol or opiates is associated with increased tobacco smoking. There is relatively little systematic information available about multiple drug abuse interactions. However, the combined use of cocaine, heroin, and alcohol increases the risk for toxic effects and adverse medical consequences over risks associated with use of a single drug. One determinant of polydrug use patterns is the relative availability and cost of the drugs. There are many examples of situationally determined drug-use patterns. For example, alcohol abuse, with its attendant medical complications, is one of the most serious problems encountered in former heroin addicts participating in methadone maintenance programs.

The physician must recognize that perpetuation of polydrug abuse and drug dependence is not necessarily a symptom of an underlying emotional disorder. Neither alleviation of anxiety nor reduction of depression accounts for initiation and perpetuation of polydrug abuse. Severe depression and anxiety are as frequently the consequences of polydrug abuse as they are the antecedents. There is also evidence that some of the most adverse consequences of drug use may be reinforcing and contributing to the continuation of polydrug abuse.

TREATMENT

Adequate treatment of polydrug abuse, as well as other forms of drug abuse, requires innovative programs of intervention. The first step in successful treatment is detoxification, a process that may be difficult because of the abuse of several drugs with different pharmacologic actions (e.g., alcohol, opiates, and cocaine). Since patients may not recall or may deny simultaneous multiple drug use, diagnostic evaluation should always include urinalysis for qualitative detection of psychoactive substances and their metabolites. Treatment of polydrug abuse often requires hospitalization or inpatient residential care during detoxification and the initial phase of drug abstinence. When possible, specialized facilities for the care and treatment of chemically dependent persons should be used. Outpatient detoxification of polydrug abuse patients is likely to be ineffective and may be dangerous.

As in the treatment of alcohol abuse, no single therapeutic modality has been shown to be uniquely effective in inducing remission. Polydrug abuse is a chronic disorder with an unpredictable pattern of remission and recrudescence. Even temporary remissions with attendant physical, social, and psychological improvements are preferable to the continuation or progressive acceleration of polydrug abuse and its related adverse medical and interpersonal consequences. In polydrug abuse, as in many chronic disorders, definitive "cures" rarely occur. The concerned physician should continue to assist polydrug abuse patients throughout the cyclic oscillations of this complex behavior disorder, recognizing that resumption of drug use may be the rule rather than the exception.

(Bibliography omitted in Palm version)

390. NICOTINE ADDICTION - *David M. Burns*

The use of tobacco leaf to create and satisfy nicotine addiction was introduced to Columbus by Native Americans and spread rapidly to Europe. The use of tobacco as cigarettes, however, is predominantly a twentieth century phenomenon, as is the epidemic of disease caused by this form of tobacco.

Nicotine is the principal constituent of tobacco responsible for its addictive character. Addicted smokers regulate their nicotine intake and blood levels by adjusting the frequency and intensity of their tobacco use both to obtain the desired psychoactive effects and avoid withdrawal.

Unburned cured tobacco contains nicotine, carcinogens, and other toxins capable of causing gum disease and oral cancer. When tobacco is burned, the resultant smoke contains, in addition to nicotine, carbon monoxide and >4000 other compounds that result from volatilization, pyrolysis, and pyrosynthesis of tobacco and various chemical additives used in making different tobacco products. The smoke is composed of a fine aerosol, with a particle size distribution predominantly in the range to deposit in the airways and alveolar surfaces of the lungs, and a vapor phase. The bulk of the toxicity and carcinogenicity of the smoke resides in the aerosolized particulate phase, which contains a large number of toxic constituents and >40 carcinogenic compounds. The aggregate of particulate matter, after subtracting nicotine and moisture, is referred to as tar. The vapor phase contains carbon monoxide, respiratory irritants, and ciliotoxins as well as many of the volatile compounds responsible for the distinctive smell of cigarette smoke.

The alkaline pH of smoke from blends of tobacco utilized for pipes and cigars allows sufficient absorption of nicotine across the oral mucosa to satisfy the smoker's need for this drug. Therefore, smokers of pipes and cigars tend not to inhale the smoke into the lung, confining the toxic and carcinogenic exposure (and the increased rates of disease) largely to the upper airway for most users of these products. The acidic pH of smoke generated by the tobacco used in cigarettes dramatically reduces absorption of nicotine in the mouth, necessitating inhalation of the smoke into the larger surface of the lungs in order to absorb quantities of nicotine sufficient to satisfy the smoker's addiction. The shift to using tobacco as cigarettes, with resultant increased deposition of smoke in the lung, has created the epidemic of heart disease, lung disease, and lung cancer that dominates the current disease manifestations of tobacco use.

DISEASE MANIFESTATIONS OF CIGARETTE SMOKING

Over 400,000 individuals die prematurely each year in the United States from cigarette use; this represents approximately one out of every five deaths in the United States. Approximately 40% of cigarette smokers will die prematurely due to cigarette smoking unless they are able to quit.

The major diseases caused by cigarette smoking are listed in Table 390-1, with the relative risks for each disease listed for male and female current smokers. The incidence of smoking-related diseases is proportionately greater in younger than in older smokers, particularly for coronary artery disease and stroke. At older ages, the

background rate of disease in nonsmokers increases, diminishing the fractional contribution of smoking and the relative risk; however, absolute excess rates of disease mortality found in smokers compared to nonsmokers increase with increasing age. The organ damage caused by smoking and the number of smokers who die from smoking are both greater among the elderly, as one would expect from a process of cumulative injury.

Cardiovascular Diseases Cigarette smokers are more likely than nonsmokers to develop large vessel atherosclerosis as well as small vessel disease. Approximately 90% of peripheral vascular disease in the nondiabetic population can be attributed to cigarette smoking, as can approximately 50% of aortic aneurysms. In contrast, 20 to 30% of coronary artery disease and approximately 10% of occlusive cerebrovascular disease are caused by cigarette smoking. There is a multiplicative interaction between cigarette smoking and other cardiac risk factors such that the increment in risk produced by smoking among individuals with hypertension or elevated serum lipids is substantially greater than the increment in risk produced by smoking for individuals without these risk factors.

In addition to its role in promoting atherosclerosis, cigarette smoking also increases the likelihood of myocardial infarction and sudden cardiac death by promoting platelet aggregation and vascular occlusion. Reversal of these effects may explain the rapid benefit of smoking cessation for a new coronary event demonstrable among those who have survived a first myocardial infarction. This effect may also explain the substantially higher rates of graft occlusion among continuing smokers following vascular bypass surgery for cardiac or peripheral vascular disease, as well as the high failure rate of angioplasty procedures among continuing smokers.

Cessation of cigarette smoking reduces the risk of a second coronary event within 6 to 12 months after quitting, and rates of first myocardial infarction or death from coronary heart disease also decline within the first few years following cessation. After 15 years of cessation, the risk of a new myocardial infarction or death from coronary heart disease in former smokers is similar to that in those who have never smoked.

Cancer Cancers of the lung, larynx, oral cavity, esophagus, pancreas, kidney, and urinary bladder are caused by cigarette smoking. In addition, there is evidence suggesting that cigarette smoking may play a role in increasing the risk of cervical and stomach cancer. There is conflicting evidence on the relationship of cigarette smoking and cancer of the breast, but overall there does not appear to be a causal link. There is a lower risk of uterine cancer among postmenopausal women who smoke.

The risks of cancer increase with the increasing number of cigarettes smoked per day and the duration of smoking, and there are synergistic interactions between cigarette smoking and alcohol use for cancer of the oral cavity, esophagus, and possibly lung. Several occupational exposures also synergistically increase lung cancer risk among cigarette smokers, most notably occupational asbestos and radon exposure.

Cessation of cigarette smoking reduces the risk of developing cancer relative to continuing smoking, but even 20 years after cessation there is a modest persistent increased risk of developing lung cancer.

Respiratory Disease Cigarette smoking is responsible for>90% of chronic obstructive pulmonary disease. Within 1 to 2 years of beginning to smoke regularly, many young smokers will develop inflammatory changes in their small airways, although lung function measures of these changes do not predict development of chronic airflow obstruction. After³20 years of smoking, pathophysiologic changes in the lungs develop and progress proportional to smoking intensity and duration. Chronic mucous hyperplasia of the larger airways results in a chronic productive cough in as many as 80% of smokers over age 60. Chronic inflammation and narrowing of the small airways and/or enzymatic digestion of alveolar walls resulting in pulmonary emphysema can result in reduced expiratory airflow sufficient to produce clinical symptoms of respiratory limitation in approximately 15% of smokers.

Changes in the small airways of young smokers will reverse after 1 to 2 years of cessation. There may also be a small increase in measures of expiratory airflow following cessation among individuals who have developed chronic airflow obstruction, but the major change following cessation is a slowing of the rate of decline in lung function with advancing age rather than a return of lung function toward normal.

Pregnancy Cigarette smoking is associated with several maternal complications of pregnancy: premature rupture of membranes, abruptio placentae, and placenta previa; there is also a small increase in the risk of spontaneous abortion among smokers. Infants of smoking mothers are more likely to experience preterm delivery, have a higher perinatal mortality, are small for their gestational age, are more likely to die of sudden infant death syndrome, and appear to have a developmental lag for at least the first several years of life.

Other Conditions Smoking delays healing of peptic ulcers; increases the risk of osteoporosis, senile cataracts, and macular degeneration; and results in premature menopause, wrinkling of the skin, gallstones and cholecystitis in women, and male impotence.

Environmental Tobacco Smoke Long-term exposure to environmental tobacco smoke increases the risk of lung cancer and coronary artery disease among nonsmokers. It also increases the incidence of respiratory infections, chronic otitis media, and asthma in children as well as causing exacerbation of asthma in children.

PHARMACOLOGIC INTERACTIONS

Cigarette smoking may interact with a variety of other drugs in ways that may have clinically significant implications (Table 390-2). Cigarette smoking induces the cytochrome P450 system, which may alter the metabolic clearance of drugs such as theophylline. This effect may result in more drug toxicity among nonsmokers on fixed drug dosage schedules and in inadequate serum levels in smokers as outpatients when the dosage is established in the hospital under nonsmoking conditions. Correspondingly, serum levels may rise when smokers are hospitalized and not allowed to smoke. Smokers may also have higher first-pass clearance for drugs such as lidocaine, and the stimulant effects of nicotine may reduce the effect of benzodiazepines or beta blockers.

OTHER FORMS OF TOBACCO USE

Other major forms of tobacco use are moist snuff deposited between the cheek and gum, chewing tobacco, pipes and cigars, and recently bidi (tobacco wrapped in tendu or temburni leaf and commonly used in India) and clove cigarettes. Oral tobacco use leads to gum disease and can result in oral cancer. All forms of burned tobacco generate toxic and carcinogenic smoke similar to that of cigarette smoke. The differences in disease consequences of use relate to frequency of use and depth of inhalation. The risk of upper airway cancers is similar among cigarette and cigar smokers, while those who have smoked only cigars have a much lower risk of lung cancer, heart disease, and chronic obstructive pulmonary disease. However, cigarette smokers who switch to pipes or cigars do tend to inhale the smoke, increasing their risk; and it is likely that comparable inhalation and frequency of exposure to tobacco smoke from any of these forms of tobacco use will lead to comparable disease outcomes.

Recent prevalence-of-use data have suggested a resurgence of cigar and bidi use among adolescents of both genders, raising concerns that these older forms of tobacco use are once again causing a public health concern.

LOWER TAR AND NICOTINE CIGARETTES

Since the bulk of the toxicity of cigarette smoke is contained in the tar, and since nicotine is the principal addictive agent in cigarettes, it has been suggested that cigarettes that deliver less tar and nicotine to the smoker might be safer. Studies of smokers of low-yield cigarettes suggest that there may be a 10 to 20% reduction in the risk of developing lung cancer among those who reduce the nominal tar yield of their cigarettes by³50%. However, this benefit is only evident if smokers do not compensate for the lower nicotine delivery with an increased intensity of smoking, and most studies show that smokers of low-yield cigarettes do compensate. Because of their addiction to nicotine, most smokers tend to preserve their intake of nicotine, and correspondingly their tar intake, when they shift to lower nicotine cigarettes.

Newer, very low yield cigarettes commonly use vents in the filters or other engineering designs to reduce the tar and nicotine when the cigarette is smoked by machine. However, the delivery of tar and nicotine is much higher when these cigarettes are smoked by actual smokers. Current evidence suggests that if there is any disease-reduction benefit for smokers of low-yield cigarettes, it is too small to be clinically meaningful, and individuals should be discouraged from thinking of low-yield cigarettes as a substitute for cessation.

CESSATION

The process of stopping smoking is often a cyclical one, with the smoker sometimes making multiple attempts to quit and failing before finally being successful. Approximately 70 to 80% of smokers would like to quit smoking, approximately one-third of current smokers attempt to quit each year, and ³90% of these unassisted quit attempts fail. Smokers have been categorized into those who are not thinking about quitting (precontemplation), those who are thinking about quitting (contemplation), and

those who are in the action phase of quitting. A useful conceptualization of the cessation process is one where smokers cycle through the stages of cessation; each time smokers go around the cycle, a few more smokers become successful in their cessation efforts. One goal of clinician-based smoking interventions then becomes moving smokers from one stage of the cessation cycle to another, and efforts can be focused on moving the smoker to the next stage rather than focusing exclusively on immediate cessation.

The move from thinking about quitting to making a quit attempt is often triggered by a variety of environmental stimuli independent of physician control. The cost of cigarettes can be a powerful trigger for cessation attempts. Media campaigns, particularly when coupled with cessation events, are also able to trigger cessation attempts in large numbers of smokers. Changes in workplace rules to restrict smoking in the workplace have been associated with quit attempts in substantial numbers of workers. However, physician advice to quit, particularly around an acute illness, is also a powerful trigger for cessation activity, with up to half of patients who are advised to quit making a cessation effort.

Telephone counseling and nicotine-replacement therapy are all useful enhancers of long-term cessation success. Clinic-based cessation programs have a substantial benefit for long-term cessation for those who can be recruited to participate, and physician recommendation can double the fraction of smokers who are willing to participate in these programs.

PREVENTION

Approximately 90% of individuals who will become cigarette smokers initiate the behavior during adolescence. Factors that promote adolescent initiation are parental or older generation cigarette smoking, tobacco advertising and promotional activities, the availability of cigarettes, and the social acceptability of smoking. The need for an enhanced self-image and to imitate adult behavior is greatest for those adolescents who have the least external validation of their self-worth, which may explain in part the enormous differences in adolescent smoking prevalence by socioeconomic and school performance strata.

Prevention of smoking initiation must begin early, preferably in the elementary school years. Physicians who deal with adolescents should be sensitive to the prevalence of this problem in their patient population. Effective physician-based interventions for adolescent smokers remain to be developed, but current clinical guidelines suggest that physicians should ask all adolescents whether they have experimented with tobacco or currently use tobacco, reinforce the facts that most adolescents and adults do not smoke, and explain that all forms of tobacco are both addictive and harmful.

GENETIC CONSIDERATIONS

Several genes have been associated with nicotine addiction. Some reduce the clearance of nicotine, and others have been associated with an increased likelihood of becoming dependent on tobacco and other drugs as well as a higher incidence of depression. Genetic alterations that involve the neurotransmitter dopamine, and

possibly the serotoninergic and cholinergic neuroregulatory pathways, are being explored for their contribution to development of addiction to tobacco and other substances. The precise role these genetic differences play in development and maintenance of nicotine addiction remains to be determined, but it is unlikely that genetic factors are the principal determinants of addiction. Rates of smoking initiation among males, and corresponding rates of nicotine addiction, have dropped by almost 50% since the mid-1950s, suggesting that factors other than genetics are the principal determinants of whether individuals will become addicted. It is more likely that genetic polymorphism represents a range of biologic susceptibility conditioning the intensity of cigarette use and the probability that experimentation with tobacco as an adolescent leads to addiction as an adult.

PHYSICIAN INTERVENTION

Physicians can make a clear difference in promoting successful cessation among their smoking patients, and the Agency for Health Care Policy and Research (AHCPR) has developed clinical guidelines for health care system-based smoking cessation (Table 390-3). All patients should be asked whether they smoke, their past experience with quitting, and whether they are currently interested in quitting. Those who are not interested in quitting should be encouraged and motivated to quit; provided a clear, strong, and personalized physician message that smoking is an important health concern; and offered assistance if they become interested in quitting in the future. There is a relationship between the amount of assistance a patient is willing to accept, and the success of the cessation attempt. A quit date should be negotiated, usually not the day of the visit but within the next few weeks, and a follow-up contact by office staff around the time of the quit date should be provided.

There are a variety of nicotine-replacement products, including over the counter nicotine patch and gum, as well as nicotine nasal and oral inhalers available by prescription. Clonidine and, more recently, antidepressants such as bupropion have also been shown to be effective; some evidence supports the combined use of nicotine-replacement therapy and antidepressants. Nicotine-replacement therapy is provided in different dosages for use with smokers of different numbers of cigarettes per day. Antidepressants are more effective in those with a history of depression symptoms. At this time there are few clear indications favoring the use of one agent over another as initial therapy. Current recommendations are to offer pharmacologic treatment to all who will accept it and to provide counseling and other support to the patient as a part of the cessation attempt. Cessation advice alone is likely to increase success by 50% compared with no intervention; a more comprehensive approach with advice, pharmacologic assistance, and counseling can increase cessation success by almost threefold.

In order for physicians to incorporate cessation assistance into their practice successfully, it is essential to change the infrastructure in which the physician practices. The following are simple changes: (1) including questions on smoking and interest in cessation on patient-intake questionnaires, (2) asking patients whether they smoke as part of the initial vital sign measurements made by office staff, (3) listing smoking as a problem in the medical record, and (4) automating follow-up contact with the patient on their quit date. These changes are essential to institutionalizing smoking intervention

within the practice setting; without this institutionalization, the best intentions of physicians to intervene with their patients who smoke are often lost in the time crush of a busy practice.

(Bibliography omitted in Palm version)

PART FIFTEEN - ENVIROMENTAL AND OCCUPATIONAL HAZARDS

SECTION 1 - SPECIFIC ENVIRONMENTAL AND OCCUPATIONAL HAZARDS

391. SPECIFIC ENVIRONMENTAL AND OCCUPATIONAL HAZARDS - *Howard Hu, Frank E. Speizer*

It cannot be overemphasized that an appropriate environmental/occupational history is an essential part of the medical workup of many chronic diseases. The general approach to the patient whose illness may have been caused or exacerbated by environmental or occupational hazards is detailed in Chap. 5.

The term *hazards* in this context is generally synonymous with *toxins* and *toxic exposures* and encompasses chemical factors as well as other risks posed by the physical environment and by selected natural phenomena. These hazards may exist in the general environment or in the workplace. Strictly speaking, smoking, alcohol ingestion, nutritional factors, and infectious agents can also be considered chemical or environmental hazards.

Once a specific hazard has been identified as a factor in the pathogenesis of an illness or as an imminent threat, the clinical approach must include the development of a strategy for preventing further exposure and for treating the specific manifestations of the illness, using antidotes and supportive measures. In the following chapters, specific hazards are considered, including acute poisoning and drug overdose; heavy metal poisoning; disorders caused by venoms, bites, and stings; drowning and near-drowning; electrical injuries; and radiation injury. The health effects of ambient air pollution, occupational respiratory exposures, passive smoking, and assorted toxic air pollutants are discussed briefly in Chap. 254. Space does not allow specific discussion in this text of many other important categories of hazards, such as organic solvents; chemicals used in the plastics, synthetic textiles, and rubber industries; and pesticides. The reader should consult other detailed texts or electronic information sources for clinical data on these topics. In this volume, however, brief attention is focused on several selected issues in light of recent developments in research that have enhanced our understanding of the way these hazards may interact with human behavior and consequently pose increased risks to both individuals and society.

HAZARDOUS WASTE AND GROUNDWATER CONTAMINATION

The term *hazardous waste* embodies toxic chemicals, radioactive materials, and biologic or infectious wastes. In many communities, hazardous waste has emerged as a major public health concern. In the United States, some 50,000 sites (defined by specific criteria) have been estimated to contain hazardous chemicals; 1000 or so of these have been included as "Superfund sites" on a National Priority List drawn up by the Environmental Protection Agency (EPA). New or unrecognized sites are likely to exist as well. These sites may require long-term remedial action. The spectrum of substances contained at the sites is wide and theoretically may include any of some 30,000 chemicals that are commonly used in commerce. However, the EPA keeps fewer than 200 chemicals on a special hazardous substance list in light of their toxicity, the frequency with which they are encountered, and other factors. One difficulty in

anticipating risks associated with hazardous waste sites is that the substances are usually present in mixtures whose composition is seldom fully known. In addition, with respect to toxicity, chemicals may interact with one another in an additive, protective, or synergistic fashion, and little knowledge exists on which to base predictions regarding the interactions of these complex mixtures.

Waste-site employees and the surrounding community can incur hazardous exposures through the inhalation of toxic vapors or dusts emanating directly from a waste site or an on-site incinerator; the ingestion of water contaminated by surface runoff or by material leaching through soil into surface water or groundwater; the ingestion of contaminated plants, fish, or other wildlife; or direct contact. This last risk is particularly likely for children, who may enter a poorly secured site. Perhaps the exposure of greatest concern to community residents has been the contamination of groundwater by volatile organic compounds or solvents (VOCs); together, the widespread detection of low levels of VOCs in groundwater and the several studies suggesting an association between heavy VOC contamination of drinking water and cancer probably account for the high priority given in public opinion polls to avoiding cancer risks. A 1983 study found that 11 of the 20 chemicals most commonly detected at National Priority List waste sites were VOCs (Table 391-1).

Current regulatory policy rests on the assumption that there is no threshold below which a carcinogen exerts no effect or risk. Thus, once a substance is identified as a probable carcinogen (see below), it is regulated to a concentration that is believed to be accompanied by an acceptable level of risk. Clearly, great uncertainty exists regarding methods used to classify drinking-water carcinogens and to extrapolate the risks related to exposure to these substances. Regardless, VOC contamination in groundwater is likely to continue to be a high-priority issue in the public arena.

ENVIRONMENTAL CARCINOGENS

Based on studies and reviews of the literature by the International Agency for Research on Cancer, enough evidence exists to classify around 60 substances and processes as probably or definitely carcinogenic in humans (Table 391-2). Some processes are deemed carcinogenic on the basis of epidemiologic evidence, even though the specific causative agent cannot always be clearly identified. Tumor promoters are not distinguished from tumor initiators in this listing, and the chemical structures and modes of action are diverse. Around 150 additional agents and processes have been designated as possibly carcinogenic on the basis of studies of bacteria and animals as well as human epidemiologic studies. The extent to which inferences can be made from nonhuman studies is controversial but certainly depends on minimal standards in the execution of such studies. For example, the Interagency Regulatory Liaison Group recommends that for a carcinogen assay to be considered positive, the test must have been performed on at least 50 animals of each sex in two different species with at least three dose groups (control and two dose levels) over the lifetime of the animals.

BUILDING-RELATED ILLNESSES

Reports of discomfort and symptoms in relation to office environments began in the United States in the 1970s. Research has led to the recognition that some

building-related illnesses have a clear etiology; these illnesses include hypersensitivity diseases, infections, and exacerbations of asthma due to airborne irritants. However, the majority of such complaints, particularly those of mucous membrane irritation, fatigue, and headache, have no clear etiology. Terms such as *sick-building syndrome* (SBS; also called *tight-building syndrome*) and *nonspecific building-related illnesses* have been used to designate this constellation of symptoms, which have been found in most investigations to occur most often in sealed buildings with centrally controlled mechanical ventilation. Early characterizations of SBS as mass psychogenic illness have not been borne out in the majority of cases by subsequent epidemiologic investigations. Since indoor air-exchange rates were sharply reduced in the 1970s to conserve energy, current hypotheses focus on inadequate dilution of irritants arising from building materials (such as formaldehyde-containing particle board), office supplies (such as carbonless copy paper and photocopy developer solution), toxins from mold and bacterial endotoxin, and personal care products used by occupants as risk factors for SBS. Confirmation of these hypotheses and further characterization of SBS await additional research.

MULTIPLE-CHEMICAL SENSITIVITY

The multiple-chemical sensitivity (MCS) syndrome is a diagnosis that has increasingly been given to patients with a wide variety of symptoms that they attribute to exposure at very low levels to a number of commonly encountered chemicals. The syndrome usually begins after a well-defined environmental event, such as a reaction to a more clearly toxic dose of an organic solvent, pesticide, or respiratory irritant. Some cases of MCS begin as SBS. Affected persons commonly report symptoms such as fatigue, malaise, headache, dizziness, lack of concentration, memory loss, and "spaciness" -- symptoms that overlap somewhat with those of other diagnoses of uncertain etiology, such as chronic fatigue syndrome. The pathogenesis of MCS is obscure, and no proven methods exist for its diagnosis, evaluation, and treatment. Case series suggesting a high prevalence of affective disorders indicate that psychological factors may play a role in causing MCS and/or in determining its severity; however, evidence does not support MCS as a purely psychogenic illness. A few studies of MCS patients suggest that the biologic mechanism of MCS may involve neurogenic inflammation of the nasal mucosa (as indicated by abnormal rhinolaryngoscopic findings) linked to central nervous system dysfunction (as indicated by alterations seen on single photon emission computed tomography); however, well-controlled research remains sparse, and no firm conclusions can be drawn. Other than the ruling out of other treatable conditions and the avoidance of exacerbating exposures, no specific recommendations for the management of MCS patients can yet be made. A panel of European scientists convened by the World Health Organization recommended that the designation *MCS* be replaced by the term *idiopathic environmental illness* (IEI).

PERSISTENT ORGANIC POLLUTANTS

Persistent organic pollutants (POPs) are a class of chemical compounds that tend to travel thousands of miles if released into the atmosphere, to accumulate in the food chain, and to persist in the environment as well as in human tissues (principally fat cells). Although the list of POPs is long, 12 have been identified as particularly important: nine pesticides (aldrin, chlordane, DDT, dieldrin, endrin, heptachlor,

hexachlorobenzene, mirex, and toxaphene), dioxins and furans (byproducts of incineration), and polychlorinated biphenyls (PCBs, fluids used mainly as dielectrics in transformers). The persistence and lipid solubility of these compounds allow them to bioconcentrate several thousand-fold as they are passed up the food chain to humans. High levels of exposure to a number of POPs have been shown to contribute to birth defects, infertility, immunosuppression, impaired cognitive development, and some types of cancers. These effects have been linked to the potential of POPs to act as endocrine disruptors -- i.e., hormonal mimics. The further production and use of most POPs have been banned, but concern remains over the possible low-level effects of POPs that persist in the environment and in human tissues. Concern has been raised, for example, that population exposures to POPs are contributing to worldwide declines in sperm density and increased rates of congenital hypospadias and testicular and breast cancer; epidemiologic studies testing these theories have yielded mixed results, however, and more research is needed.

GLOBAL CLIMATIC CHANGES

An increasing body of evidence indicates that human activities are responsible for global climatic changes, which, in turn, may be directly or indirectly increasing human exposure to environmental hazards. The depletion of stratospheric ozone by chlorinated fluorocarbons, with a consequent increase in ultraviolet radiation exposure, has been firmly established. Increased risks of skin cancers and cataracts are accepted as results of this phenomenon. Less clear is whether the immunosuppressive effects of ultraviolet radiation detected in animals and in vitro have significant clinical impacts on human resistance to infection. Although uncertainties in climate modeling persist, an increasing if not overwhelming amount of evidence indicates that anthropogenic greenhouse gases are fostering global warming. A prominent concern is that global warming can abet the introduction and dissemination of serious infectious diseases, such as mosquito-borne infections (malaria, dengue, and viral encephalitis) and waterborne infectious and toxin-related illnesses (cholera, shellfish poisoning). The World Health Organization has identified global warming as one of the largest public health challenges facing the twenty-first century.

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392. DROWNING AND NEAR-DROWNING - *Jerome H. Modell*

It is an unexpected tragedy when a previously healthy person dies or is exposed to severe cerebral hypoxia and suffers permanent brain damage. For many years, drowning was considered a "fight for survival": Arms flailing and screaming for help, a person who could not swim struggled to remain on the surface of the water to reach safety. This situation, however, is rarely reported by persons at the scene of aquatic emergencies. Furthermore, no single set of circumstances comprises drowning or near-drowning. It may be a secondary event following such precursors as head or spinal trauma; hypoxia-induced unconsciousness; or unconsciousness due to preexisting cardiovascular disease, sudden cardiac death, or myocardial infarction. The initiating event is usually unknown, so the drowned or near-drowned victim must be treated based on probable physiologic effects of the near-drowning itself. If survival with normal brain function is to occur, a thorough understanding of the pathophysiology of drowning and an organized approach to therapy are imperative.

PATHOPHYSIOLOGY OF DROWNING

Approximately 90% of near-drowning victims aspirate fluid into their lungs. In those who do not aspirate fluid, hypoxemia results simply from breath holding, laryngospasm, or apnea. In those who do aspirate, the volume and the composition of the fluid determine the physiologic basis of the hypoxemia. Freshwater aspiration alters the surface tension properties of pulmonary surfactant and makes alveoli unstable, which causes a decreased ventilation/perfusion ratio. Some alveoli collapse and become atelectatic, which produces a true or absolute intrapulmonary shunt, while others are poorly ventilated and produce a relative shunt; in either case, significant pulmonary venous admixture occurs. Fresh water in the alveoli is hypotonic and is rapidly absorbed and redistributed throughout the body. While some have proposed that water continues to enter the lungs after death, at autopsy the lungs of victims who died in the water frequently contain little water. Also, it has been shown experimentally that if a dead body is submerged in tagged or colored water, water is not found in the lungs at autopsy. These findings support the premise that active respiration determines the volume of water aspirated.

Hypertonic seawater pulls additional fluid from the plasma into the lungs, and thus the alveoli are fluid-filled but perfused, which causes substantial pulmonary venous admixture. With both types of water, pulmonary edema may occur secondary to events such as fluid shifts, a change in capillary permeability, or cerebral hypoxia, which causes neurogenic pulmonary edema. Regardless of the cause, pulmonary edema adds to the ventilation/perfusion abnormality.

Water that is grossly contaminated with bacteria or that contains particulate matter may complicate the picture. Particulate matter can obstruct the smaller bronchi and respiratory bronchioles. Grossly contaminated water increases the risk of severe pulmonary infection. Neither problem is sufficiently common, however, to justify recommending specific therapy routinely for all victims.

At least 85% of near-drowned victims are thought to aspirate 22 mL/kg of water or less, which does not result in a clinically significant alteration of blood volume or serum

electrolyte concentrations. After resuscitation, by the time blood is analyzed, serum electrolyte concentrations are usually normal or close to normal. Significant changes are documented in only approximately 15% of those who cannot be resuscitated and only rarely in those who are resuscitated. These findings suggest that either a small amount of water was aspirated, fluid was rapidly redistributed, or both. Therefore, electrolyte disturbance rarely needs treatment. When a large quantity of water is aspirated, seawater causes hypovolemia, which concentrates extracellular electrolytes, and fresh water causes acute hypervolemia. If enough water is aspirated that plasma becomes severely hypotonic and the patient is hypoxemic, red cell membranes can rupture, and plasma hemoglobin and serum potassium concentrations increase significantly. However, this development has been reported only rarely. With rapid redistribution of fluid and development of pulmonary edema, even freshwater victims frequently demonstrate hypovolemia by the time they reach the hospital.

Hypercarbia, which is associated with apnea and/or hypoventilation, is less often documented by blood gas analysis than is hypoxemia. While hypoxemia due to pulmonary venous admixture persists in all near-drowned victims who aspirate water, hypercarbia is usually corrected sooner with artificial mechanical ventilation and improved minute ventilation and, thus, is reported in only a small percentage of victims evaluated at the hospital. Besides hypoxemia, metabolic acidosis also persists in most patients. Abnormal cardiovascular function, usually ascribed to hypoxemia, is brief with effective, timely therapy. Abnormality in renal function is uncommon, but when it does occur, it too is secondary to hypoxemia, altered renal perfusion, or, in extremely rare circumstances, significant hemoglobinuria.

TREATMENT

The first step is retrieving the victim from the water, and, if necessary, performing artificial ventilation and circulation. The American Heart Association recommends that an abdominal thrust not be used routinely in victims of submersion. This recommendation was upheld by a special committee of the Institute of Medicine convened in 1994 specifically to evaluate the efficacy of an abdominal thrust in the treatment of near-drowned victims. In these patients, an abdominal thrust may lead to regurgitation of gastric contents and, thus, to aspiration of the vomitus. Further, an abdominal thrust may delay ventilatory or circulatory resuscitation. Therefore, an abdominal thrust should be used only when the airway is obstructed with a foreign body or when the victim fails to respond to mouth-to-mouth ventilation.

Because emergency services and intensive pulmonary and cardiovascular care have improved during the past 25 years, central nervous system depression now presents the major therapeutic challenge in near-drowning. The rate of survival with normal cerebral function varies considerably in retrospective studies. Some factors that adversely influence survival are prolonged submersion, delay in initiation of effective cardiopulmonary resuscitation, severe metabolic acidosis (pH< 7.1), asystole upon arrival at a medical facility, fixed dilated pupils, and a low Glasgow coma score (<5). None of these predictors is absolute, however, and, when maximally treated, normal survivors have been reported in all of the above categories. Absence of cortical evoked potentials does indicate irreversibility of the cerebral hypoxic lesion; this test, however, cannot be done in the field to guide rescuers. A comparison of outcomes between one

institution that added brain preservation techniques to intensive pulmonary and circulatory treatment and another institution that did not found no significant differences.

Hypothermia appears to be protective, but only if it occurs early, at the time of the accident, in which case it increases the victim's chance of cerebral salvage after relatively long periods of acute hypoxia and cardiac arrest. While hypothermia prolongs tolerance to hypoxia, it also can precipitate fatal cardiac arrhythmia; thus, its occurrence can be helpful on the one hand and harmful on the other. The diving reflex produces bradycardia, breath holding, and circulatory redistribution when the face is submerged in cold water. However, the effect of the diving reflex in explaining cerebral recovery after prolonged immersion has not been specifically documented.

Significant pulmonary venous admixture usually persists even after successful resuscitation; therefore, supplemental oxygen should be administered until arterial blood gas analysis confirms that oxygen is no longer needed. Intravenous access should be established as soon as possible. The trachea should be intubated if necessary for airway maintenance or to facilitate mechanical ventilatory support. Electrocardiographic monitoring will facilitate prompt treatment of cardiac arrhythmia.

Victims should be transported to a hospital for definitive testing of the adequacy of ventilation and blood gas exchange, cardiac activity, and effective circulating blood volume. Other variables, such as serum electrolyte concentrations, renal function, and cerebral status, should be analyzed as indicated.

The single most effective treatment for hypoxemia, regardless of cause, is mechanical ventilatory support including continuous positive airway pressure (CPAP). After freshwater aspiration, improvement in ventilation/perfusion matching is more consistent when CPAP is combined with mechanical inflation of the lung than with spontaneous respiration. The question of whether CPAP should be combined with spontaneous respiration or with mechanical ventilation should be decided by whether the specific patient can perform the necessary work of breathing, adequately eliminate carbon dioxide, and adequately match ventilation/perfusion ratios. Positive airway pressure should be withdrawn gradually as the lungs stabilize and ventilation/perfusion ratio returns toward normal.

The pH in near-drowned victims is commonly significantly acidotic, which, in turn, can depress cardiac function. The metabolic component of the acidosis, if it results in a pH< 7.20, should be corrected pharmacologically, although there is some disagreement on this point. With cardiovascular instability, cannulation of the pulmonary artery with a Swan-Ganz catheter or evaluation by transesophageal echocardiography is indicated. Many patients will be hypovolemic from loss of fluid into the lung as pulmonary edema or from decreased venous return secondary to increased intrathoracic pressure during mechanical ventilatory support.

Because recovery after long periods of submersion under frigid conditions has been reported, body temperature should be taken into account before a decision is made to terminate therapy. The body temperature of victims depends not only on the temperature of the water from which they are retrieved but also on how well they were insulated by clothing. The volume of water actually aspirated is also important, because

a large volume, if distributed before cardiac arrest occurs, can produce rapid central cooling. Thus, cold water can be protective when it produces total-body hypothermia, which decreases metabolic oxygen requirement. On the other hand, cold water may also contribute to the accident if hypothermia occurs before total submersion, and severe, or even fatal, cardiac arrhythmia results. Several methods of rewarming hypothermic victims have been advocated, but any technique that increases oxygen utilization, such as shivering, should be avoided.

Regardless of the conditions surrounding a drowning or near-drowning, treatment should adhere to the following sequence of priorities (Fig. 392-1):

1. Remove the victim from the water as soon as possible and stabilize the patient's head and neck if trauma is suspected.

2. Immediately follow the ABCs of cardiopulmonary resuscitation -- even in the water if this does not endanger the rescuer.

3. If the patient is unconscious, protect the airway as needed with endotracheal intubation.

4. Establish venous access as soon as possible.

5. Provide supplemental oxygen and ventilatory support until each is no longer needed. This can be judged from analysis of arterial blood for oxygen tension, carbon dioxide tension, and pH.

6. Monitor cardiac rhythm with an electrocardioscope as soon as possible.

7. Monitor body temperature and restore it to normal.

8. If the patient has persistent respiratory insufficiency, provide intensive pulmonary support withCPAP and mechanical ventilation therapy as necessary.

9. If the patient has cardiovascular instability, evaluate cardiac output and effective circulatory volume by invasive monitoring, and measure serum electrolyte concentrations. Intravenous fluid replacement should be provided as necessary.

10. Evaluate and treat renal function and cerebral status as indicated.

Glucocorticoid therapy, prophylactic antibiotic therapy, and monitoring of intracranial pressure are no longer recommended.

ACCIDENT PREVENTION

Because drowning begins as an accident that results in a medical problem, the definitive strategy is to prevent the accident. For those victims in whom the accident is secondary to a medical condition, as in persons susceptible to syncope or seizure, the only way to prevent the accident is to identify those who ought to avoid the water or to encourage them to use the buddy system. For young children, early swimming lessons, vigilant

caretakers, and stringent laws governing pool enclosures are needed. Those who teach parenting classes should routinely warn parents about the risk of toddlers' drowning in such household fixtures as toilets, buckets of water, and even washing machines. Preventing accidents during boating, athletics, and other water-related recreational activities requires public education. Rules associated with these activities to maximize safety and judicious, responsible behavior should be portrayed as life-saving measures. Similarly, drinking alcohol, a "ubiquitous catalyst" to drowning, should be portrayed as life-threatening whenever water is nearby.

(Bibliography omitted in Palm version)

393. ELECTRICAL INJURIES - *Raphael C. Lee*

EPIDEMIOLOGY

Electrical injury occurs when the body experiences levels of current that alter electrophysiologic function or cause tissue damage. Most commonly, such injuries result from contact with commercial electrical power sources in the home and workplace. Microwave, radiofrequency, light irradiation, and other injuries are less common. Ionizing electromagnetic fields (radiation) involve atomic absorption and free radical production, leading to biochemical alterations.

Electrical shock is one of the leading causes of work related injury, comprising 7% of all workplace fatalities. The exact incidence is unknown because many victims don't report minor injuries. The economic impact of industrial electrical injury in the United States is estimated to be in excess of $1 billion annually. Approximately one-third of high-power electrical injuries occur in the construction industry, one-third occur in the utility and petrochemical industries, and one-third are non-work related. More than 90% of the injuries occur in males, most commonly between the ages of 20 and 34. The extremities are nearly always involved, and limb amputation may be required.

Most injuries are due to low-voltage (<1000 V) electrical shock. Low-voltage power-frequency electrical shocks usually occur in and around the home. The household electric power in the United States is 120 V, AC 60-cycle current. In Europe it is 220 V. Low-voltage shocks carry a significant risk of electrocution due to cardiac arrest because they may cause muscle spasm that results in prolonged contact. Roughly 3 to 4% of all United States hospital burn unit admissions are for electrical injury, mostly a result of high-voltage (>1000 V) shocks. Extensive tissue damage, rather than electrocution, is characteristic of high-voltage shocks.

PATHOPHYSIOLOGY

The term *direct current* (DC) is used to indicate a field frequency of zero (i.e., constant voltage gradient), and *alternating current* (AC) indicates that the field is changing direction (i.e., alternating polarity) with time. DC electrical power passes through the body on direct electrical contact. AC current can be carried by direct contact, capacitive coupling, and magnetic induction.

Tissue damage can result from exposure to harmful levels of current at any frequency in the electromagnetic spectrum that ranges fromDC toz-hertz (ionizing irradiation). The tissue effects of electricity depend as much on the frequency as on the magnitude of current.Table 393-1 presents a classification of electrical injury according to frequency range. Commercial electrical power operates in the narrow frequency range of DC to 150 Hz in the low frequency regime. An electrical shock in this frequency range is most common.

When the voltage is<1000 V, direct mechanical contact is usually required for electrical contact. For high voltages (>1000 V), arcing usually initiates the electrical contact. On direct electrical contact, the electron flow in the metal conductor or arc is converted at the skin surface into electrolyte ions that carry the current through the body. This

electrochemical process generates heat and toxic chemical by-products that contribute to contact area injury. In high-voltage contacts, exposure to the expanding arc, an excellent conductor, brings the victim into the electrical circuit. The arc can reach very high temperatures, leading to skin burns or clothing ignition. At higher frequencies (>10 MHz) electrical power can couple electrical energy across an air gap into the body without charge transport across the skin surface (capacitive coupling).

Low-frequency electricity causes tissue injury primarily by permeabilizing cell membranes, electroconformational denaturation of cell membrane proteins, and thermal denaturation of tissue proteins. Factors that determine the anatomic pattern, the extent of tissue injury, and the relative contribution of heat versus direct electrical damage include the amount of current, anatomic location, and the contact duration. The type of clothing, the use of protective gear, and the power capability of the electrical source also contribute to the wide range of clinical manifestations in victims of electrical shock. In addition, a very high-energy electrical arc can produce a strong thermoacoustic blast force leading to barotrauma. Associated falls and skin burns are frequent, exacerbating the injury. Cataracts characteristically occur after rapid and brief exposure of the eyes to hot gases and arc-mediated electrical current. The latency period for development of cataracts averages approximately 6 months.

Peripheral nerve and skeletal muscle tissues are most vulnerable to membrane damage by applied electrical currents. The "no-let-go" phenomenon results from the passage of more than 14 to 16 mA longitudinally through the forearm that induces tetanic contractions of muscles controlling handgrip. The resulting involuntary muscle spasm may lead to joint dislocations and spine fractures. When current of >50 mA is passed hand-to-hand or hand-to-foot, there is enough induced depolarization of myocardial membranes to cause cardiac arrhythmias, particularly if the induced depolarization occurs during early myocardial repolarization. Disruption of extremity skeletal muscle and nerve cell membranes by the process of electroporation results when more than 0.5 to 1 A is passed through the extremity. Electroporation damage accumulates on the time scale of milliseconds, leading to lethal cellular injury. With more prolonged contacts in the range of seconds, thermal damage in the subcutaneous tissues becomes substantial. Because the vulnerability to supraphysiologic temperature exposure is similar regardless of tissue type, all tissues in the current path are burned when pathologic levels of heating occur. Extensive disruption of cell membranes leads to release of myoglobin and hemoglobin, which enter the circulation. Acute renal failure can result from intrarenal crystalization of these molecules. Acute renal failure superimposed on extensive tissue injury has a very high mortality rate.

DIAGNOSIS

For the more common low-frequency electrical injuries, at least two skin contact wounds are present. Differences in wound size and topography are largely determined by the surface contact area, the shape of the objects that conducted the current through the victim, and the duration of contact.

Cardiac arrhythmias and most respiratory disturbances must be rapidly detected by examination of the pulse, chest, and electrocardiogram. The next priority is to determine the location and extent of tissue damage. Injured skeletal muscle and nerves are often

found beneath undamaged skin. Lateral spine x-rays or computed tomography (CT) are needed to rule out unstable spine fracture patterns. X-ray images of the extremities involved are also important to rule out skeletal fractures or joint dislocations. Blood chemistries should be immediately evaluated and monitored. Metabolic acidosis and elevated serum potassium levels may exist as consequences of extensive skeletal muscle injury. Serum CPK levels will rise over several hours if there is significant rhabdomyolysis.

Tissue edema begins to form because of increased vascular permeability and the release of intracellular contents into the extravascular space. Muscle compartment syndrome and compression neuropathies are common manifestations. If available, magnetic resonance imaging (MRI) scans can rapidly localize tissue edema. Where severe heating has coagulated the blood vessels, tissue injury may exist in the absence of edema. Muscle compartment fluid pressures should be measured where edema is present. If MRI is not available, then the muscle compartments in the current path between contact points should be monitored for elevated interstitial fluid pressure. Elevated compartment pressures may evolve during resuscitation. Muscle compartment fluid pressures >30 cmH$_2$0 are indications for fasciotomy. It may be necessary to check the pressures every 8 h for 24 h. Radionucleotide scanning with **99m**Tc-pyrophosphate can also be useful to detect tissue damage. These scans, however, take 4 to 6 h to complete and are mostly useful in the less severe injuries. If there is a history of loss of consciousness, CT of the head is indicated.

TREATMENT

The first priority is to disconnect the patient from the electrical power source. When high-capacity circuits are involved, disconnection must not be attempted before the circuit is deenergized. Cervical spine fracture should be assumed until proven otherwise. Critical initial considerations are evaluation and support of vital organ function and, secondarily, assessment of the extent of injury. After very-high voltage trauma, prolonged cardiopulmonary resuscitation (CPR) may be necessary before the stunned myocardium regains the ability to sustain a coordinated rhythm.

Patients with significant wounds and tissue injury as well as those with vital organ injury require hospital admission. It is unlikely for cardiac arrhythmias to develop if cardiac injury is not detectable on initial presentation. Peripheral nerve injury invariably occurs even in minor shocks and usually resolves over several days. If symptoms persist, however, they may be controlled with cyclooxygenase inhibitors alone or with antioxidants. Small wounds can be managed by cleaning and applying topical antibiotics. Major neuropsychological and stress disorders often follow a terrifying "no-let-go" experience. Management often involves psychiatric consultation.

For more substantial trauma, a Foley catheter and large bore peripheral intravenous lines delivering normal saline at a rate sufficient to generate a 30 to 50 mL/h urine output are essential. If the urine is visibly pigmented with myoglobin or hemoglobin, the output should be doubled and alkalinized to a pH >6 by adding bicarbonate to the intravenous solutions until the urine has cleared. In the most severe injuries, hyperpermeability of peripheral capillaries may result in rapid interstitial (third space) fluid accumulation. In such cases, it may be necessary to increase blood oxygen levels

and add dextran to resuscitation fluids.

Cardiac arrhythmias must be immediately controlled by antiarrhythmic drugs simultaneously with the correction of serum pH and electrolyte abnormalities. Brain injury-related seizures must be controlled with antiepileptic agents. Patients who have lost central nervous system (CNS) control of respiration or airways should be intubated and mechanically ventilated. A paralyzed ventilated patient may need monitoring by electroencephalogram (EEG) to assess seizure control. Appropriate management of corneal burns or abrasions, tympanic membrane rupture, and closed head injury should be instituted.

Large skin burn wounds are often present because of arc-mediated contacts and clothing ignition. Care should be taken to prevent rapid loss of body heat through open wounds. Tetanus prophylaxis should be administered.

Perfusion of devascularized tissue must be quickly restored. Diminished pulses or decreased tissue oxygen by transcutaneous pulse oximetry are indications for escharotomy releases. Fasciotomy is often required. The classic clinical signs of pain in acute compartment syndrome cannot be relied on because of associated nerve injury. In addition to decompression of extremity muscle compartments, decompression of nerve within edematous fibrous and osseous conduits (e.g., carpal tunnel, Guyon's canal, and tarsal tunnel) should be carried out to help prevent compression neuropathy. Care to avoid tissue drying or desiccation is important. Debridement of nonviable subcutaneous tissue should be performed as soon as a general anesthetic can be safely administered.

Anaerobic bacterial infection of devascularized skeletal muscle is a common complication. Intravenous penicillin G and/or hyperbaric oxygen as prophylactic antibiotics are sometimes utilized but have unproven value. Radiographs taken to rule out fractures may reveal air bubbles in the subcutaneous tissues. This gas results from tissue boiling when prolonged Joule heating has occurred.

Rehabilitation into society and gainful employment are the ultimate objectives. For severely injured victims these goals require functional muscle and nerve reconstruction as well as correction of scar contractures. Psychological and neurocognitive problems are expected and require treatment by experts. Persistent peripheral neurologic problems are also common and often require detailed evaluation and therapeutic intervention.

LIGHTNING INJURIES

Lightning injury is a powerful manifestation of arc-mediated electrical contact. Arcing occurs when the voltage gradient in air exceeds 2 million V/m. The arc consists of a hot ionized gas of subatomic particles that is highly conductive. Peak lightning currents reach into the range of 30,000 to 50,000 A for a duration of 5 to 10 us. Lightning arc temperatures reach up to 30,000°K, which generates thermoacoustic blast waves, commonly called thunder. Peak blast pressures reach 4 or 5 atm in the immediate vicinity of a lightning strike, and up to 1 or 2 atm 1 m away. Substantial barotrauma can result.

Like radiofrequency current, lightning current flows along the surfaces of conducting objects. Initially, the flow of an enormous current through the lightning strike generates a very large surrounding magnetic field pulse. This magnetic field pulse can induce current flow in the body, enough to disrupt cardiac and CNS function. When lightning current enters the ground, it spreads out radially, which sets a large current traveling along the surfaces of the ground. A substantial voltage drop can occur between the feet of a nearby individual. The voltage drops between widely separated feet can reach 1500 to 2000 V and can induce a 2 to 3 A current flow in the legs for a 10-us period.

Victims of direct lightning strikes experience a multimodal injury. Superficial burns on the skin represent the current path along the skin surface. The intense brief shock pulse seems to arrest all electrophysiologic processes. The victim appears lifeless. Prolonged CPR may be necessary. Muscle and nerve necrosis is rare in survivors. Deeper injury results when the victim is in contact with a large conducting object such as a truck or fence that has been struck by lightning, which then discharges over several milliseconds through the victim.

Delay in resuscitation is the most common cause of death. Bystanders are usually afraid to touch the victim while precious minutes pass. However, unless the victim is on an insulating platform, there is no residual electric charge on the body afer several milliseconds. When needed, CPR should be given without hesitation. Victims should be cared for in an intensive care unit until life-threatening CNS and cardiac injuries are ruled out. Late neurologic and ophthalmologic sequelae often develop.

(Bibliography omitted in Palm version)

394. RADIATION INJURY - *Stephen M. Hahn, Eli Glatstein*

All human beings are constantly exposed to ionizing radiation. Environmental sources include the cosmic radiation from space and radiation from the ground and from inhaled and ingested materials. Airline travel and mining both increase exposure to the background radiation. For example, air travel at 30,000 ft exposes individuals to a dose equivalent of 0.5 mrem/h. Radiation originating in the body comes mainly from radioactive potassium, which emits beta and gamma rays. Lungs are exposed to irradiation from inhaled air, which contains small amounts of radioactive radon. The cosmic exposure contributes approximately 28 mrem per year. The ground and internal sources contribute approximately 26 and 27 mrem per year, respectively. The most prominent man-made sources of radiation include x-ray equipment, nuclear weapons, and radioactive medications.

TERMINOLOGY AND DEFINITIONS

The first major unit of radiation exposure was the roentgen (R), defined as an amount of x-rays or gamma rays that produces a specific amount of ionization in a unit of air under standard temperature and pressure (Table 394-1); this quantity can be measured directly in an ionization chamber. The rad, or *r*adiation *a*bsorbed *d*ose, is defined as 100 ergs/g of tissue. Thus, the rad represents a net deposition of energy in a three-dimensional volume, because x-rays attenuate as they traverse tissue. The rad has been replaced by the Systeme Internationale (SI) unit of the gray (Gy), which represents 100 rad. Roentgens and rads can be converted by means of various tables; the relation between them depends on photon energy.

The above definitions reflect physical variables. The unit that reflects the biologic response and that can be used to compare the effects of various types of radiation is the unit of *dose equivalence*, the rem (*r*oentgen *e*quivalent in *m*an). The rem has been replaced by the SI unit, the sievert (Sv), which equals 100 rem. These units reflect the exposure or absorption dose multiplied by a biologic factor that represents the biologic effectiveness of the specific type of radiation (see below).

TYPES OF IONIZING RADIATION

The absorption of energy from radiation in tissue often leads to excitation or ionization. Excitation involves elevation of an electron in an atom or molecule to a higher energy state without actual ejection of the electron. Ionization involves actual ejection of one or more electrons from the atom. Ionizing radiation is subclassified as electromagnetic (photon) or particulate radiation (Table 394-2). X-rays and gamma rays are examples of electromagnetic photon radiation. They differ only in their source: X-rays are produced mechanically, by making electrons strike a target, which causes the electrons to give up their kinetic energy as x-rays, while gamma rays are produced by nuclear disintegration of radioactive isotopes.

X-rays can be thought of as packets of energy, or photons. X-rays have no mass or charge, travel in straight lines, and attenuate continuously as they traverse tissue. Gamma rays have similar properties. Each photon contains an amount of energy equal to *hn*, where *h* is Planck's constant. The critical difference between nonionizing and

ionizing radiation is the energy of individual photons, not the energy of the total dose.

Types of *particulate radiation* include electrons, protons, alpha particles, neutrons, negative pi-mesons, and heavy charged ions; these have discrete mass and charge (except for neutrons, which lack charge; Table 394-2). *Electrons*, or *beta particles*, are small and negatively charged and can be accelerated to close to the speed of light. They decelerate fairly rapidly in tissue and penetrate it to only a limited depth. Thus, electron beams are often used to treat superficial problems. *Protons* are positively charged and have a mass about 2000 times that of an electron. Protons stop abruptly, depending on their energy; in the process of sudden deceleration, most of their energy is given up, which tends to cause ionization just before the proton stops. This region of enhanced ionization, sometimes called the Bragg peak, means that proton beams exert their effects in a relatively compact region. *Alpha particles* are helium nuclei, consisting of two protons and two neutrons. The mass and charge are great enough that these particles do not penetrate far through matter unless they have tremendous energy; even a piece of paper is enough to protect against most alpha particles. Because these particles are charged, they can be accelerated in electrical fields.

Neutrons are similar in mass to protons (having an atomic mass of 1), but they are not charged and therefore cannot be accelerated in an electrical field. Neutron beams are produced by colliding charged particles into a suitable target or are emitted as a fission product of heavy radioactive atoms. *Heavy charged ions* are nuclei of heavier elements that have a positive charge owing to the stripping away of some or all of the orbiting electrons.

Equal doses of different types of radiation do not necessarily produce equal biologic effects; thus 1 Gy of neutrons produces a greater biologic effect than 1 Gy of x-rays. The biologic effects produced by a given dose of radiation can be quantified by the relative biologic effectiveness (RBE) value, which relates them to the effects produced by 250-kV photon radiation as a standard. In general, the greater the RBE value for a given type of radiation, the greater the biologic effect. The RBE value will be greater for more densely ionizing radiation, such as neutrons. The RBE value depends on the linear energy transfer (see below), the dose, the dose rate, and the nature of the biologic system.

The linear energy transfer (LET) is the amount of ionization occurring per unit length of the radiation track. It is usually expressed as kilovolts per micron and increases with the square of the charge of the incident particle. High-LET radiation is biologically different from low-LET (i.e., conventional) radiation: Hypoxic and oxygenated cells respond similarly to high-LET irradiation, whereas it takes about three times as much low-LET radiation to produce a given killing effect in hypoxic cells as in oxygenated cells. It is thought that low-LET radiation must produce multiple hits on DNA to destroy a cell, whereas high-LET radiation need produce only a single hit on DNA to kill a cell. Representative values of LET andRBE are given in Table 394-3.

Radiation, especially x-rays, is absorbed and causes ionization in three major ways: the *photoelectric effect*, the *Compton effect*, and *pair production*. At low energies (30 to 100 keV), as in diagnostic radiology, the photoelectric effect is important. In this process, the incident photon interacts with an electron in one of the outer shells of an atom (typically

K, L, or M). If the energy of the photon is greater than the binding energy of the electron, then the electron is expelled from the orbit with a kinetic energy that is equal to the energy of the incident photon minus the binding energy of the electron. The photoelectric effect varies as a function of the cube of the atomic number of the material exposed (Z_3); this fact explains why bone is visualized much better than soft tissue on radiographs.

At higher energies, as used in therapeutic radiology, the Compton effect dominates. In this process, the incident photon interacts with an electron in an orbital shell. Part of the incident photon energy appears as kinetic energy of electrons, and the residual energy continues as a less energetic deflected photon.

At energy levels above 1.02 MeV, the photons may be absorbed through pair production. In this process, both a positron and an electron are produced in the absorbing material. A positron has the same mass as an electron but has a positive instead of a negative charge. The positron travels a very short distance in the absorbing medium before it interacts with another electron. When that happens, the entire mass of both particles is converted to energy, with the emission of two photons in exactly opposite directions.

BIOLOGIC EFFECTS OF RADIATION

Radiation must produce double-strand breaks in DNA to kill a cell, owing partly to the high capacity of mammalian cells for repairing single-strand damage. Radiation can also produce effects indirectly by interacting with water (which makes up approximately 80% of a cell's volume) to generate free radicals, which can damage the cell. Free radicals are highly reactive chemical entities that lack a stable number of outer-shell electrons. A free radical is not stable and has a life span of a fraction of a second. It is estimated that most x-ray-induced cell damage is due to the formation of hydroxyl radicals, as follows:

The result of radiation damage is cell death. The biologic effects on epithelial cell reproduction are typically expressed only when the damaged cells attempt to divide. Another biologic effect is the induction of cancerous growth by mutation many years after radiation exposure. Patients who receive radiation have a significant risk of neoplasm two to three decades after their exposure; this risk is significantly higher than that of the population as a whole.

RADIATION-INDUCED CHROMOSOME ABERRATIONS

Chromosome breaks can occur when cells are irradiated. The broken ends of chromosomes can combine with broken ends of different chromosomes. These abnormal combinations are most readily seen during mitosis. Chromosome abnormalities typically occur in cells irradiated in the G1 phase of the cell cycle, before the doubling of genetic material. If cells are irradiated in the G2 phase, chromatid aberrations may result. The frequency of chromosomal aberrations in peripheral circulating lymphocytes correlates with the dose received. The dose can be estimated by comparing the chromosomal changes to in vitro cultures exposed to controlled doses

of irradiation. The minimum dose that can be detected by peripheral lymphocyte analysis is about 0.1 to 0.2 Sv (10 to 20 rem). Lymphocyte analysis may provide evidence of recent total-body exposure.

CELL SURVIVAL CURVE

The dose-response curve for all mammalian cells appears to have a linear-quadratic relationship. In simple terms, the mathematical model that explains the relationship between the dose and the fraction of surviving cells has both linear and exponential components. The linear component results from double-stranded chromosomal breaks produced by single hits. The exponential component represents breaks produced by multiple hits. Figure 394-1 shows the shape of a typical survival curve for mammalian cells exposed to radiation. The fraction of cells surviving is plotted on a semilogarithmic scale. For x-rays or gamma rays, the dose-response curve has a shoulder that is followed by a straight line curve as the dose is increased. The shoulder represents the cell's ability to repair sublethal injury. For alpha particles or lower energy neutrons, the dose-response curve is a straight line from the origin. Thus, the survival rate is an exponential function of the dose.

In all mammalian cell lines studied, increases in the radiation dose decrease the survival rate of cells. However, a number of factors may contribute to a relative resistance to radiation in human tumors in vivo, including hypoxia and expression of particular oncogenes, such as *ras*. The biologic basis for radiation resistance has not been fully defined.

Four important processes that occur after radiation exposure can be summarized as the "four R's" of radiobiology. The first is *repair*. Repair is temperature dependent and is thought to represent the enzymatic mechanisms for healing intracellular injury. The second R is *reoxygenation*, a process whereby oxygen (and other nutrients) are actually better distributed to viable cells following radiation injury and cell killing. The third R is *repopulation*, the ability of the cell population to continue to divide and to replace dying and dead cells. The fourth R is *redistribution*, which reflects the variability of a cell's radiosensitivity over the cell cycle. Radiosensitivity can vary through the cell cycle by as much as a factor of 3. The G1 phase has the most variable length of all the phases of the cell cycle. For most cell lines, cells that have a short G1 period are most sensitive at the G2/mitosis interface, less sensitive in G1, and most resistant toward the end of the synthesis (S) period.

Radiation therapy is effective in cancer treatment when it exerts greater cytotoxic effects on tumor cells than on normal tissues. A major determinant of the therapeutic index is exploiting differences in the four R's between tumor cells and normal tissues by delivering the radiation in dose fractions.

CLINICAL FINDINGS ON FRACTIONATION

The clinical radiation response may be related to the interactions of various growth factors and cytokines. For example, radiation can induce growth factors and cytokines such as tumor necrosis factor (TNF), interleukin (IL) 1. TNF can induce proliferation of fibroblasts and enhance the inflammatory response. TNF and IL-1 have been shown to

radioprotect hematopoietic cells in vitro by increasing the D_0 of the cell survival curve. TNF also enhances killing of a human tumor cell line by irradiation. TNF may produce radioprotection or radiosensitization depending on the cell type. Efforts to modulate radiation effects with TNF remain experimental. Other factors implicated in the radiation response are basic fibroblast growth factor and platelet-derived growth factorb, which may be associated with late effects of radiation on vessels.

The degree and the duration of functional recovery of normal tissues are related to the number of stem cells surviving after irradiation. If the stem cells are destroyed in the irradiated volume and replacement from adjacent tissues is inadequate, radiation injury will persist. True late effects develop independent of early reactions; they occur despite recovery from acute radiation injury.

Table 394-4 shows the frequency of radiation tolerance seen with fractionated radiotherapy at 5 years of follow-up. These numbers are rough estimates at best. The clinical manifestations of irradiation will depend on the volume of the organ irradiated, the total dose, the dose per fraction, and the length of time taken to deliver the dose. Dose per fraction is the most important factor determining normal tissue effects. In addition, the cellular consequences of treatment can be progressive over time. Thus, length of follow-up is also crucial in judging clinical sequelae.

Central Nervous System Traditionally, the central nervous system (CNS) has been described as relatively resistant to radiation-induced changes. When the human brain is treated with standard fractionation (1.8 to 2.0 Gy/d), acute reactions are seldom observed.

Subacute CNS reactions to radiation treatment are more common. The clinical manifestations may include *Lhermitte's sign*, which is a self-limited paresthesia occurring with flexion of the neck. It is believed to be due to transient demyelination of the spinal cord following significant radiation exposure. It can be seen 1 to 3 months after completion of radiation treatment to the spinal cord. The frequency of Lhermitte's sign varies according to the type of radiation therapy and can be as high as 15% after mantle-field radiation. Mild encephalopathy and focal neurologic changes can occur after irradiation limited to the cranium. If radiation treatments to the brain are given at the same time that chemotherapeutic agents are administered, the effects can be more severe, presumably reflecting altered permeability to the drugs. The effect of cranial irradiation is believed to be secondary to radiation effects on the replicating oligodendrocytes and possibly on the microvasculature. Both clinical and radiologic changes may simulate tumor progression and can often pose diagnostic and treatment dilemmas.

Postirradiation pathology and associated clinical symptoms typically begin 6 to 36 months after radiation therapy and are related to the total dose and volume treated. Fraction size appears to be the most important variable affecting the rate of postirradiation brain necrosis. Neurocognitive changes can also be seen in children after cranial irradiation. The important pretreatment factors that predict the degree of late CNS effects include the age at which cranial irradiation was given and neurocognitive functional level at the time of treatment.

A unique late effect of cranial irradiation combined with chemotherapy, known as *leukoencephalopathy*, has been described in some patients. Leukoencephalopathy is a necrotizing reaction usually noted 4 to 12 months after combined treatment with methotrexate and cranial irradiation. Dementia and dysarthria may progress to seizures, ataxia, or death.

Transverse myelitis after radiation treatment is a spinal cord reaction similar to cerebral necrosis. This syndrome consists of progressive and irreversible leg weakness and loss of bladder function and sensation referrable to a single spinal cord level. Flaccid paralysis eventually occurs. Symptoms can occur as early as 6 months after radiation treatment, but the usual time to onset is 12 to 24 months. Lhermitte's sign does not correlate with transverse myelitis.

Skin Skin reaction can be seen within 2 weeks of fractionated radiotherapy, a delay that correlates with the time required for cells to move from the basal to the keratinized layer of skin. The severity of the reaction depends on the skin dose per fraction and the total dose delivered to an area of skin. Erythema is observed, soon followed by dry desquamation. The skin at this time can be erythematous, warm, and sometimes edematous. The vessels in the upper dermis are dilated, and inflammatory infiltration with granulocytes, macrophages, eosinophils, plasma cells, and lymphocytes is noted.

When a severe skin reaction occurs, it is usually located where the beam strikes the skin tangentially. *Moist desquamation* consists of eruption of the epidermal layer. Healing is through reepithelialization from cells of less affected basal layers. When skin reactions are severe, treatment interruptions are needed to permit healing.

Dry desquamation is treated conservatively. Symptoms of dryness can be alleviated by advising the patient to wear only cotton fabric next to the affected skin and to refrain from the use of irritants of any kind. If treatment becomes necessary, hydrophilic agents that do not contain heavy metals are recommended. Petroleum jellies should not be used, as they may trap bacteria and increase the chance of infection. Moist desquamation is best managed by leaving the affected area dry and open to air.

A chronic reaction to radiation can be seen starting 6 to 12 months after irradiation. The epidermis is usually atrophic and may be more easily injured than normal skin. Interstitial fibrosis may also be increased. Hyperpigmentation of irradiated skin outlining the treatment field can be seen within a couple of months after completion of irradiation. This will fade gradually. The skin becomes thin, and hair loss may be permanent. Radiation therapy can induce second malignancies, which tend to be more aggressive than cancers arising in patients without significant radiation exposure.

Heart and Blood Vessels When cardiac disease appears after radiation treatment, it is often difficult to tell to what extent the radiation treatment was causative. The pathogenesis of atherosclerotic heart disease is multifactorial. Exposure of a large heart volume to high-dose radiation therapy accelerates the development of coronary artery disease. Acute "pericarditis" may result from cardiac irradiation. The symptoms may include chest pain and fever, with or without pericardial effusion. This syndrome is usually self-limited and typically manifests itself a few months after treatment. Asymptomatic pericardial effusion may be the most common manifestation of

radiation-induced heart disease. It is usually detected by chest x-ray and confirmed by an echocardiogram.

Most patients with symptomatic radiation-induced constrictive pericarditis will have received more than 40 Gy to a large portion of the heart. The risk increases significantly with cardiac doses greater than 50 Gy.

Chronic cardiac changes may have their onset from 6 months to several years after irradiation. The clinical symptoms may indicate chronic constrictive disease due to pericardial, myocardial, and endocardial fibrosis -- a pancarditis. The clinical signs may include dyspnea, chest pain, venous distention, pleural effusion, and paradoxical pulse.

Lung The clinical symptoms of radiation pneumonitis can be separated into early and late phases. During the early phase, clinical manifestations may include dyspnea, cough, and fever. Shortness of breath is relatively infrequent. It is more common to observe only the radiologic changes on a chest x-ray, without clinical symptoms. The clinical signs and symptoms of radiation pneumonitis may appear in 3 to 6 weeks if a large region of lung is irradiated to a dose above 25 Gy. An infiltrate outlining the treatment field may become evident on the chest x-ray. Radiation changes should not occur outside the treated field. Computed tomography can often help in distinguishing radiation pneumonitis from other causes of the infiltrate. The incidence of radiation pneumonitis can be reduced with careful treatment planning designed to lower the total dose given to the treated lung volume. Permanent scarring that results in respiratory compromise may develop if the dose and the volume of lung irradiated are excessive. Dyspnea and cough may be severe and debilitating.

Patients with symptoms of radiation pneumonitis may respond rapidly to glucocorticoids, but the medication has little effect on fibrotic changes. Glucocorticoids must be tapered very slowly to avoid rebound exacerbation of symptoms, which can prove lethal for some patients. Prophylactic administration of glucocorticoids is of no proven merit. Supportive care includes bronchodilators and oxygen at the lowest possible FI_{O2}.

Digestive Tract Pathologic changes of the epithelial layer occur early during radiation treatments. The underlying submucosa may become edematous, with dilation of capillaries. Recovery from radiation damage can be expected within a few weeks after completion of radiation therapy, provided that sufficient numbers of stem cells are left. The radioresponsiveness of the aerodigestive tract, like that of other structures, is not uniform but varies according to the location.

Patients often have symptoms from radiation exposure that are similar to other forms of acute gastritis. The clinical signs include epigastric pain, loss of appetite, nausea, and vomiting. Decreased gastric acidity is observed after 15 to 20 Gy of fractionated radiation therapy. The tolerance of the stomach to radiation is also aggravated by addition of systemic chemotherapy, such as 5-fluorouracil.

The germinal centers of the bowel mucosa are in the crypts of Lieberkuhn. Newly formed cells move upward along the walls of the crypts as transitional cells, undergoing maturation. The epithelial lining of the small bowel is the most rapidly renewed system in the human body and is completely renewed in 3 to 6 days. Within 12 to 24 h after the

first dose of radiation therapy, pathologic evidence of dead cells are seen in the mucosal lining. Complete denudation of the mucosal surface rarely occurs during a regular course of radiation treatment because of the high capacity of the mucosa for regeneration. However, a focal area of erosion may be seen. The histologic appearance may be nearly normal within 2 to 3 weeks after radiation therapy.

Clinical manifestations of acute radiation enteropathy are nausea and vomiting, diarrhea, and cramping pain. Relevant factors contributing to the pathogenesis of diarrhea include malabsorption and alterations in the intestinal bacterial flora. The severity of symptoms, as in other anatomic areas, is proportional to the irradiated volume and the total dose.

Symptoms of chronic radiation enteropathy include diarrhea, abdominal cramping, nausea, malabsorption, vomiting, and obstruction. Progressive fibrosis, perforation, fistula formation, and stenosis of the irradiated portion of the bowel can occur during the chronic phase of radiation enteropathy. Most clinical manifestations of chronic changes occur between 6 months and 5 years after radiation therapy.

Conservative noninvasive treatment can frequently control gastrointestinal symptoms. A low-residue or elemental diet may be beneficial. When nonsurgical treatment fails to relieve severe symptoms, surgical intervention is often indicated.

Bladder Radiation injury to the bladder generally becomes symptomatic 3 to 6 weeks after the start of treatment, and symptoms usually subside 3 to 4 weeks after completion of radiation therapy. Patients often complain of increased frequency and dysuria. Cystoscopy often shows diffuse mucosal changes similar to those of acute cystitis. Sometimes desquamation and ulceration can be seen. Without infection, urinary symptoms are managed symptomatically. Concurrent chemotherapy with cytotoxic agents such as cyclophosphamide increases the severity of the acute bladder reaction.

The late effects of high radiation doses to the bladder may include interstitial fibrosis, telangiectasia, and ulceration. The blood vessels may be dilated and prone to rupture, resulting in painless hematuria. These changes are often difficult to distinguish from tumor recurrence and progression. A contracted bladder may result from doses in excess of 60 Gy.

Testes and Ovaries In general, type B spermatogonia are exquisitely sensitive to the effects of radiation. The type A spermatogonia are thought to be more resistant because their longer cell cycle time allows considerable variation in radiosensitivity among different phases of the cell cycle. Sertoli cells and Leydig cells are less radiosensitive than the spermatogonia. Elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have been observed after as little as 75 cGy. Doses as low as 10 cGy to the testicles may result in injury to the type B spermatogonia. The single dose required for permanent sterilization on normal human males is believed to be between 6 and 10 Gy. In normal human males, sperm count recovery requires 9 to 18 months after a fractionated dose of 8 to 100 cGy.

The radiation dose necessary to induce ovarian failure is age-dependent. A single dose of 3 to 4 Gy can induce amenorrhea in almost all women over 40 years of age. In young

women, oogenesis is much less sensitive to radiation than is spermatogenesis in men.

ACUTE TOTAL-BODY IRRADIATION

The data regarding the acute effects of total-body irradiation on humans come primarily from Japanese survivors of the atomic bomb, Marshallese exposed to radioactive fall-out in 1954, and persons exposed to radiation from the Chernobyl nuclear accident. Early symptoms of acute total-body irradiation, known as the *prodromal radiation syndrome*, last for a limited time. Clinical manifestations depend on the total-body dose. At doses >100 Gy, death usually occurs 24 to 48 h later from neurologic and cardiovascular failure. This is known as the *cerebrovascular syndrome*. Because cerebrovascular damage causes death very quickly, the failures of other systems do not have time to develop.

At doses between 5 and 12 Gy, death may occur in a matter of days as a result of the *gastrointestinal syndrome*. The symptoms during this period may include nausea, vomiting, and prolonged diarrhea for several days leading to dehydration, sepsis, and death. A total-body dose >10 Gy is uniformly fatal unless supportive therapy (fluid, electrolytes, blood products, and antibiotics) is given. The process of intestinal denudation depends on the dose and may take between 3 and 120 days. Death from intestinal denudation usually occurs before the full effects of radiation on the blood-forming elements are seen.

At total-body doses between 2 and 8 Gy, death may occur 2 to 4 weeks after exposure from bone marrow failure, the *hematopoietic syndrome*. The full effect of radiation is not apparent until the mature hematopoietic cells are depleted. Clinical symptoms during this period may include chills, fatigue, and petechial hemorrhage. Peripheral blood lymphopenia develops during the first 12 to 48 h after any significant exposure. Beyond 5 to 6 Gy, the rate and magnitude of the drop are not well correlated to radiation exposure. Some stem cells may survive acute exposure to^{3}10 Gy. Death is from infection or bleeding and usually occurs before anemia can develop (red blood cell half-life is 100 to 120 days).

The LD$_{50/60}$(the dose at which 50% of the population is dead by 60 days) is around 3.25 Gy if support is not given. There is considerable variability in the total-body dose tolerated. The very young and the old are more radiosensitive than middle-aged and young adult individuals. Females in general appear to be more tolerant of radiation than males. Persons exposed to<2 Gy will require little or no therapy but should probably be observed closely with daily blood counts for a few days.

The role of bone marrow transplantation for patients exposed to acute total-body irradiation is debated. At doses<8 Gy, the patient is likely to survive with supportive care. Most people exposed to doses higher than 10 Gy will die from the gastrointestinal syndrome. Therefore, 8 to 10 Gy may be the dose range in which bone marrow transplantation could have a role, although the Chernobyl experience did not confirm this prediction. Estimating the dose received by a given patient after radiation exposure is difficult. However, exposure estimation must be done quickly because bone marrow transplantation is most effective if it is performed within the first 3 to 5 days after exposure.

RADIATION AND CANCER INDUCTION

Some nonlethal changes in DNA sequences caused by irradiation may cause malignant transformations. Thus, it is not surprising that second neoplasms can be caused by exposure to ionizing radiation. However, paradoxically, this risk is actually less with doses above a certain level. Whether there is a "safe" dose that will not have any adverse biologic effect is unclear. Estimates of the risk of developing cancer after low-level exposure to ionizing radiation are often derived by extrapolation from the risks for higher doses and acute exposures. Predicted risks of cancer are, therefore, prone to modification depending on the assumptions made about the data available for analysis.

Throughout the history of human exposure to ionizing radiation, increased rates of cancer have been noted after exposure to radiation. The populations studied include survivors of the atomic bomb during World War II; radium watch-dial painters who shaped their brush tips with their tongues; and patients who underwent multiple fluoroscopic examinations for tuberculosis, received spinal irradiation for ankylosing spondylitis, and received breast irradiation for postpartum mastitis; and others. Exposure to ionizing radiation at an earlier age appears to increase the chance of developing radiation-induced carcinomas. However, the radiation-induced cancers have an age of onset similar to that of the native cancers, and the available data argue against radiation as the only cause of the increased incidence of cancers seen after exposure to radiation.Table 394-5 shows examples of cancer observed in specific situations.

Because a safe dose of radiation is unknown at present, it is prudent to avoid routine exposures to ionizing irradiation.

ACKNOWLEDGEMENT

(Bibliography omitted in Palm version)

395. HEAVY METAL POISONING - *Howard Hu*

Metals constitute a major category of toxins that pose a significant threat to health through occupational as well as environmental exposures. One indication of their importance relative to other potential hazards is their ranking by the U.S. Agency for Toxic Substances and Disease Registry, which lists all hazards present in toxic waste sites according to their prevalence and the severity of their toxicity. The first, second, third, and sixth hazards on the list are heavy metals: lead, mercury, arsenic, and cadmium, respectively. This chapter offers specific information on the sources and metabolism of each of these metals as well as on the toxic effects produced by each and the appropriate treatment for poisoning by each.

The intrinsic atomic stability of metals allows their relatively easy tracing and measurement in biologic material, although the clinical significance of the levels measured is not always clear. Metals are inhaled primarily as dusts and fumes (the latter defined as tiny particles generated by combustion). Metal poisoning can also result from exposure to vapors (e.g., mercury vapor in the manufacture of fluorescent lamps). When metals are ingested in contaminated food or drink or through hand-to-mouth activity (implicated especially often in children), their gastrointestinal absorption varies greatly with the specific chemical form of the metal and the nutritional status of the host. Once a metal is absorbed, blood is the main medium for its transport, with the precise kinetics dependent on diffusibility, binding forms, rates of biotransformation, availability of intracellular ligands, and other factors. Some organs (such as bone, liver, and kidney) sequester metals in relatively high concentrations for years. Most metals are excreted through renal clearance and gastrointestinal excretion; some proportion is also excreted through salivation, perspiration, exhalation, lactation, skin exfoliation, and loss of hair and nails.

Some metals, such as copper and selenium, are essential to normal metabolic function as trace elements (Chap. 75) but are toxic at high levels of exposure. Others, such as lead and mercury, are xenobiotic and theoretically are capable of exerting toxic effects at any level of exposure. Indeed, much research is currently focused on the contribution of low-level xenobiotic metal exposure to chronic diseases and to subtle changes in health that may have significant public health consequences.

The most important component of treatment for metal toxicity is the termination of exposure. Another component is the use of *chelating agents*, which are used to bind metals into stable cyclic compounds with relatively low toxicity and to enhance their excretion. The principal chelating agents are dimercaprol (British Anti-Lewisite, BAL), edetate (EDTA), succimer (DMSA, dimercaptosuccinic acid), and penicillamine; their specific use depends on the metal involved and the clinical picture. Activated charcoal does not bind metals and thus is of limited usefulness in cases of acute metal ingestion.

Besides the four metals discussed in detail in this chapter, several others deserve mention. *Aluminum* contributes to the encephalopathy occurring in patients with severe renal disease who are undergoing dialysis (Chap. 341). High levels of aluminum are found in the neurofibrillary tangles in the cerebral cortex and hippocampus of patients with Alzheimer's disease as well as in the drinking water and soil of areas with an unusually high incidence of Alzheimer's disease. The experimental and epidemiologic

evidence for the aluminum-Alzheimer's disease link is so far relatively weak, however, and it cannot be concluded that aluminum is a causal agent or a contributing factor in neurodegenerative disease. Hexavalent *chromium* is corrosive and sensitizing. Workers in the chromate and chrome pigment production industries have consistently had an excess risk of lung cancer. The introduction of *cobalt* chloride as a fortifier in beer led to outbreaks of fatal cardiomyopathy among heavy consumers. Occupational exposure (e.g., of some miners, dry-battery manufacturers, and arc welders) to *manganese* can cause a Parkinsonian syndrome within 1 to 2 years, including gait disorders; postural instability; a masked, expressionless face; tremor; and psychiatric symptoms. With the introduction of methylcyclopentadienyl manganese tricarbonyl (MMT) as a gasoline additive, concern has arisen over the toxic potential of environmental manganese exposure. *Nickel* exposure induces an allergic response, and inhalation of nickel compounds with low aqueous solubility (such as nickel subsulfide and nickel oxide) in occupational settings is associated with an increased risk of cancer of the lung. Overexposure to *selenium* may cause local irritation of the respiratory system and eyes, gastrointestinal irritation, liver inflammation, loss of hair, depigmentation, and peripheral nerve damage. Workers exposed to certain organic forms of *tin* (particularly trimethyl and triethyl derivatives) have developed psychomotor disturbances, including tremor, convulsions, hallucinations, and psychotic behavior.

Finally, *thallium*, which is a component of some insecticides, metal alloys, and fireworks, is absorbed through the skin as well as through ingestion and inhalation. Severe poisoning follows a single ingested dose of >1 g or>8 mg/kg. Nausea and vomiting, abdominal pain, and hematemesis precede confusion, psychosis, organic brain syndrome, and coma. Thallium is radiopaque. Induced emesis or gastric lavage is indicated within 4 to 6 h of acute ingestion; Prussian blue prevents absorption and is given orally at 250 mg/kg in divided doses. Unlike other types of metal poisoning, thallium poisoning may be less severe when activated charcoal is used to interrupt its enterohepatic circulation. Other measures include forced diuresis, treatment with potassium chloride (which promotes renal excretion of thallium), and peritoneal dialysis.

LEAD

SOURCE

Lead has been mined and used in industry and in household products for centuries. The dangers of lead toxicity, the clinical manifestations of which are termed *plumbism*, have been known since ancient times. The twentieth century saw both the greatest-ever exposure of the general population to lead and an extraordinary amount of new research on lead toxicity.

Populations are exposed to lead chiefly via paints, cans, plumbing fixtures, and leaded gasoline. The intensity of these exposures, while decreased by regulatory actions, remains high in some segments of the population because of the deterioration of lead paint used in the past and the entrainment of lead from paint and vehicle exhaust into soil and house dust. Many other environmental sources of exposure exist, such as leafy vegetables grown in lead-contaminated soil, improperly glazed ceramics, lead crystal, and certain herbal folk remedies. Many industries, such as battery manufacturing, demolition, painting and paint removal, and ceramics, continue to pose a significant risk

of lead exposure to workers and surrounding communities.

New research on lead toxicity has been stimulated by advances in toxicology and epidemiology as well as by a shift of emphasis in toxicology away from binary outcomes (life/death; 50% lethal dose) to grades of function, such as neuropsychological performance, indices of behavior, blood pressure, and kidney function.

Tests for levels of lead in blood have facilitated both research on lead and surveillance of individuals at risk. Blood lead is now measured with stringent quality controls in commercial laboratories throughout the United States. Measurement of the blood lead levels of children 6 months to 5 years of age is mandated by some states, and the U.S. Occupational Safety and Health Administration (OSHA) requires the testing of workers who may be exposed to lead in the course of their jobs.

METABOLISM

Elemental lead and inorganic lead compounds are absorbed through ingestion or inhalation. Organic lead (e.g., tetraethyl lead, the lead additive to gasoline) is absorbed to a significant degree through the skin as well. Pulmonary absorption is efficient, particularly if particle diameters are<1 um (as in fumes from burning lead paint). Children absorb up to 50% of the amount of lead ingested, whereas adults absorb only ~10 to 20%. Gastrointestinal absorption of lead is enhanced by fasting and by dietary deficiencies in calcium, iron, and zinc; such absorption is minimal, however, for lead in the form of lead sulfide, a common constituent of mining waste. Lead is absorbed into blood plasma, where it equilibrates rapidly with extracellular fluid, crosses membranes (such as the blood-brain barrier and the placenta), and accumulates in soft and hard tissues. In the blood, ~95 to 99% of lead is sequestered in red cells, where it is bound to hemoglobin and other components. As a consequence, lead is usually measured in whole blood rather than in serum. The largest proportion of absorbed lead is incorporated into the skeleton, which contains>90% of the body's total lead burden. Lead is excreted mainly in the urine (in a process that depends on glomerular filtration and tubular secretion) and in the feces. Lead also appears in hair, nails, sweat, saliva, and breast milk. The half-life of lead in blood is ~25 days; in soft tissue, ~40 days; and in the nonlabile portion of bone,>25 years. Thus, blood lead levels may decline significantly while the body's total burden of lead remains heavy.

The toxicity of lead is probably related to its affinity for cell membranes and mitochondria, as a result of which it interferes with mitochondrial oxidative phosphorylation and sodium, potassium, and calcium ATPases. Lead impairs the activity of calcium-dependent intracellular messengers and of brain protein kinase C. In addition, lead stimulates the formation of inclusion bodies that may translocate the metal into cell nuclei and alter gene expression.

CLINICAL TOXICOLOGY

Symptomatic lead poisoning in childhood generally develops at blood lead levels>3.9 umol/L (80 ug/dL) and is characterized by abdominal pain and irritability followed by lethargy, anorexia, pallor (resulting from anemia), ataxia, and slurred speech. Convulsions, coma, and death due to generalized cerebral edema and renal failure

occur in the most severe cases. Subclinical lead poisoning [blood lead level>1.4 umol/L (> 30 ug/dL)] can cause mental retardation and selective deficits in language, cognitive function, balance, behavior, and school performance despite the lack of discernible symptoms. Epidemiologic studies and meta-analyses of studies regarding lead's effect on the intellectual function of children indicate that cognition is probably impaired in a dose-related fashion at blood lead levels well below 1.4 umol/L (30 ug/dL) and that no threshold for this effect is likely to exist above the lowest measurable blood lead level of 0.05 umol/L (1 ug/dL). The impact is greatest when the exposure is of long duration and has been most apparent when it takes place around the age of 2 years; however, the impact of fetal lead exposure remains to be clarified, particularly in view of the observation that maternal bone lead stores can be mobilized to a significant degree during pregnancy, with consequent exposure of the fetus.

In adults, symptomatic lead poisoning, which usually develops when blood lead levels exceed 3.9 umol/L (80 ug/dL) for a period of weeks, is characterized by abdominal pain, headache, irritability, joint pain, fatigue, anemia, peripheral motor neuropathy, and deficits in short-term memory and the ability to concentrate. Encephalopathy is rare. A "lead line" sometimes appears at the gingiva-tooth border after prolonged high-level exposure. Some individuals develop these symptoms and signs at lower blood lead levels [1.9 to 3.9 umol/L (40 to 80 ug/dL)] and/or with briefer periods of exposure. Chronic subclinical lead exposure is associated with interstitial nephritis, tubular damage (with tubular inclusion bodies), hyperuricemia (with an increased risk of gout), and a decline in glomerular filtration rate and chronic renal failure. Epidemiologic evidence also suggests that blood lead levels in the range of 0.34 to 1.7 umol/L (7 to 35 ug/dL) are associated with increases in blood pressure, decreases in creatinine clearance, and decrements in cognitive performance that are too small to be detected as a lead effect in individual cases but nevertheless may contribute significantly to the causation of chronic disease.

An additional issue for both children and adults is whether lead that has accumulated in bone and lain dormant for years can pose a threat later in life, particularly at times of increased bone resorption such as pregnancy, lactation, and senile osteoporosis. Elevation of the bone lead level appears to be a risk factor for anemia, hypertension, cardiac conduction delays, and impairment of cognitive function. Hyperthyroidism has been reported to cause lead toxicity in adults by mobilizing stores of bone lead acquired during childhood.

Genetic polymorphisms, such as variants of the gene that codes for aminolevulinic acid dehydratase (a critical enzyme in the production of heme) or the C282Y hemochromatosis gene, may confer differences in susceptibility to lead retention and toxicity; ~15% of Caucasians have a variant form of one of these genes. This issue is the focus of continued research.

LABORATORY FINDINGS

In 1991, the Centers for Disease Control and Prevention designated 0.48 umol/L (10 ug/dL) as the blood lead level of concern in children. A specific set of interventions is recommended when the level exceeds this value. OSHA requires the regular measurement of blood lead in lead-exposed workers and the maintenance of blood lead

levels<1.9 umol/L (40 ug/dL). Concentrations of heme precursors (such as d-aminolevulinic acid) in plasma and urine are sometimes increased at blood lead levels as low as 0.73 umol/L (15 ug/dL). Levels of protoporphyrin (free erythrocyte or zinc) rise -- although not consistently -- once blood lead levels have exceeded 1.2 umol/L (25 ug/dL) for several months. Lead-associated anemia is usually normocytic and normochromic and may be accompanied by basophilic stippling. Lead-induced peripheral demyelination is reflected by prolonged nerve conduction time and subsequent paralysis, usually of the extensor muscles of the hands and feet (wristdrop and footdrop). An increased density at the metaphyseal plate of growing long bones (lead lines) can develop in children and resemble those seen in rickets. Children with high-level lead exposure sometimes develop Fanconi's syndrome, pyuria, and azotemia. Adults chronically exposed to lead can develop elevated serum creatinine levels, decreased creatinine clearance rates, and chronic changes and intranuclear inclusion bodies (detected at renal biopsy). Deficits may be apparent in neuropsychometric tests of both children and adults; these abnormalities by themselves are not pathognomonic. Bone lead levels measured in vivo by K-x-ray fluorescence, a technique adapted for this purpose, are more sensitive than blood lead levels as a predictor of hypertension, cognitive impairments, and reproductive toxicity in epidemiologic studies; however, measurement of bone lead levels has not yet been shown to be of clinical value and is not widely available.

TREATMENT

It is absolutely essential to prevent further exposure of affected individuals to lead. Cases of lead poisoning should be reported to OSHA (if the exposure is occupational) and to local boards of health so that home evaluations can be performed. Pharmacologic treatment for lead toxicity entails the use of chelating agents, principally edetate calcium disodium (CaEDTA), dimercaprol, penicillamine, and succimer, which is given orally and has relatively few side effects. Chelation is recommended for the treatment of all children whose blood lead levels are >2.7 umol/L (55 ug/dL), with the addition of dimercaprol if lead encephalopathy is found. Chelation is also recommended for children if blood lead levels are between 1.2 and 2.7 umol/L (25 and 55 ug/dL) and the total amount of lead excreted in urine during the 8 h after a single dose of edetate calcium disodium exceeds 9.7 umol/L (200 ug/dL). Chelation is recommended for adults if blood lead levels exceed 3.9 umol/L (80 ug/dL) or if these levels exceed 2.9 umol/L (60 ug/dL) and symptoms have developed. The ability of chelation to improve subclinical outcomes (such as performance on psychometric testing) at lower levels of blood lead in both children and adults is the subject of current research.

MERCURY

SOURCE

Metallic mercury (Hg_0) is used in thermometers, dental amalgams, and some batteries. Mercurous mercury (Hg_+) and mercuric mercury (Hg_{2+}) can be combined with other chemicals, such as carbon, chlorine, or oxygen, to form inorganic or organic mercury compounds. All three forms of mercury are toxic to various degrees. Organic mercury compounds are slowly broken down into inorganic compounds; conversely, inorganic mercury can be converted by microorganisms in soil and water into the organic

compound methyl mercury. Fish, particularly tuna and swordfish, can concentrate methyl mercury at high levels; such contamination of fish by industrial runoff and their subsequent ingestion was responsible for the Minamata Bay epidemic of mercury poisoning in Japan in 1955. Occupational exposure to inorganic mercury compounds continues in some chemical, metal-processing, electrical-equipment, automotive, and building industries and in medical and dental services. Environmental exposure probably takes place most commonly through ingestion of contaminated fish and through inhalation of the vapor generated by ordinary dental amalgam, which typically contains ~50% metallic mercury. There is also concern about exposure to drinking water contaminated by toxic waste sites included on the National Priority List, almost half of which contain mercury, and about the inhalation of fumes from incinerators burning mercury-contaminated waste products. Such incineration can also lead to environmental mercury contamination, methylation of the contaminating mercury by environmental bacteria, concentration of the resultant organic mercury compounds up the food chain, and consequent human exposure (particularly to contaminated fish). Ironically, the medical/hospital industry has been identified as a major incinerator of mercury-contaminated waste.

METABOLISM

Elemental mercury is not well absorbed by the gastrointestinal tract and is excreted almost entirely in the feces after being ingested; however, when left standing, mercury is volatilized at room temperature into a vapor that is well absorbed by the lungs. Once absorbed, mercury in this form is lipid soluble, crosses the blood-brain barrier and the placenta, and can be oxidized by catalase and hydrogen peroxide into mercuric chloride, which is retained by the kidney and brain for years. Elemental mercury in blood has a half-life of ~60 days and is excreted mainly in the urine and feces.

The gastrointestinal and dermal absorption of inorganic mercury is significant. Large overdoses disrupt gastrointestinal barriers, further enhancing absorption. Once absorbed, inorganic mercury breaks down into metallic and mercuric mercury. Relatively little of this mercury crosses the blood-brain barrier; most is excreted in the urine or feces, with a half-life of 40 days, or is retained by the kidneys as mercuric mercury.

Organic mercury, particularly methyl mercury, can evaporate and undergo pulmonary absorption. Forms that are ingested (e.g., in contaminated fish) are well absorbed. Only small amounts are absorbed through the skin. Absorbed organic mercury is lipid soluble, readily crosses the blood-brain barrier and the placenta, appears in breast milk, and concentrates in the kidneys and central nervous system. Methyl mercury is acetylated in the liver, excreted in bile, reabsorbed, and then excreted in urine. Methyl mercury can also be conjugated with cysteine or glutathione. Only 1% of organic mercury is excreted unchanged into urine. The half-life of organic mercury compounds is in the range of 70 days. Exposure to mercury in any form stimulates the kidney to produce metallothionein, a metal-binding protein that affords partial protection against mercury toxicity.

CLINICAL TOXICOLOGY

Inhalation of metallic mercury vapor is the form of mercury exposure that has been best

studied in terms of toxicity. High levels of exposure are most likely in an occupational setting in which mercury vapors are generated by heat-induced volatilization of metallic mercury. Cough, dyspnea, and tightness or burning pain in the chest are common symptoms that may be accompanied by diffuse infiltrates or a pneumonitis-like appearance on chest x-ray. Respiratory distress, pulmonary edema, lobar pneumonia, fibrosis, and desquamation of the bronchiolar epithelium can occur in relatively severe cases and have sometimes led to death. Acute inhalation of mercury vapor can also cause neurologic toxicity manifested by tremors (beginning in the hands), emotional lability, headaches, and polyneuropathy. Chronic exposure to metallic mercury produces a characteristic intention tremor and mercurial *erethism*, a constellation of findings including excitability, memory loss, insomnia, timidity, and sometimes delirium that was described in workers with occupational exposure in the felt-hat industry -- hence the expression "mad as a hatter." Dentists with occupational exposure to mercury score below normal on neurobehavioral tests of motor speed, visual scanning, verbal and visual memory, and visuomotor coordination. Low-level exposure from dental amalgams may also be associated with adverse immunologic reactions in individuals with certain major human leukocyte antigen genotypes; further research is needed in this area.

Acute high-dose ingestion of inorganic mercury causes severe gastrointestinal corrosion with nausea, vomiting, hematemesis, and abdominal pain; acute renal failure, cardiovascular collapse, and shock may ensue. The lethal dose of inorganic mercury is estimated to be in the range of 10 to 42 mg/kg. Lower levels of exposure cause milder forms of gastrointestinal inflammation, gingivitis and loosening of the teeth, increased blood pressure and tachycardia, and the nephrotic syndrome. Symptoms similar to erethism may develop. Skin exposure to mercuric salts can cause exfoliative dermatitis.

Ingestion of organic mercury compounds is followed by diarrhea, tenesmus, and blisters of the upper gastrointestinal tract. The fatal dose of organic mercury is estimated at 10 to 60 mg/kg. People who ingested flour contaminated with *N*-(ethylmercuri)-*p*-toluenesulfonanilide developed bradycardia, QT prolongation, ST-segment depression, and T-wave inversions. The neurotoxicity resulting from organic mercury exposure is characterized by paresthesia; impaired peripheral vision, hearing, taste, and smell; slurred speech; unsteadiness of gait and limbs; muscle weakness; irritability; memory loss; and depression. In general, such symptoms begin at doses>1.7 mg/kg. Autopsy findings suggest that lesions in the basal ganglia and gray matter of the cortex and cerebellum are chiefly responsible for these symptoms. Organic mercury exposure, primarily through the ingestion of grain treated with mercuric fungicides or of contaminated fish, is also associated with an increased risk of fetal toxicity. After the 1955 mercury poisoning outbreak in Minamata, Japan, exposed mothers gave birth to infants with mental retardation; retention of primitive reflexes; cerebellar symptoms; dysarthria; hyperkinesia; hypersalivation; atrophy of the cerebral cortex, corpus callosum, and cerebellum; and abnormal neuronal cytoarchitecture. This last change may reflect derangement of neuronal migration during fetal development.

Worthy of special note is dimethylmercury, a "supertoxic" compound encountered exclusively in laboratory settings. The physical properties of dimethylmercury permit transdermal absorption (against which latex gloves do not afford protection) as well as volatilization with inhalation. Exposure to ~400 mg (an amount equivalent to a few drops) is lethal, with cerebellar degeneration as a prominent feature.

Exposure of children to mercury in any of its forms can cause a particular syndrome known as *acrodynia*, or pink disease. This condition is characterized by flushing, itching, swelling, tachycardia, elevated blood pressure, excessive salivation or perspiration, irritability, weakness, morbilliform rashes, and desquamation of the palms and soles.

LABORATORY FINDINGS

Levels of mercury in blood and urine should not exceed 180 nmol/L (3.6 ug/dL) and 0.7 umol/L (15 ug/L), respectively. Symptoms may develop when blood and urine mercury levels exceed 1 umol/L (20 ug/dL) and 3 umol/L (60 ug/L), respectively. If a baseline 24-h urinary mercury value is low, repetition of the measurement after a single 2-g oral dose of succimer may be useful in documenting elevated renal mercury burdens in retired mercury-exposed workers; an increase of>20 ug in a 24-h urine sample suggests previous exposure. Levels in hair may be used as a dosimeter for chronic organic mercury exposure; neurobehavioral dysfunction in children may occur if the maternal mercury concentration in hair exceeds 30 nmol/g (6 ug/g).

TREATMENT

Acute ingestion of mercuric salts can be treated by induced emesis or gastric lavage. Polythiol resins can be administered orally to bind mercury in the gastrointestinal tract. The most effective chelating agents are dimercaprol, succimer, and penicillamine, which have active mono- or dithiol groups. Acute inorganic mercury poisoning can be treated with dimercaprol at a dose not exceeding 24 mg/kg per day and given intramuscularly in divided doses. Therapy is usually given in 5-day courses separated by several days of rest. The *N*-acetyl form of penicillamine is also useful at a dose of 30 mg/kg per day in divided doses. Peritoneal dialysis, hemodialysis, and extracorporeal regional complexing hemodialysis with succimer have all been used with some success in the treatment of patients with renal failure.

Chronic inorganic mercury poisoning is best treated with *N*-acetyl penicillamine.

ARSENIC

SOURCE

Significant exposure to arsenic occurs through both anthropogenic and natural sources. Arsenic is released into the air by volcanoes and is a natural contaminant of some deep-water wells. Occupational exposure to arsenic is common in the smelting industry (in which arsenic is a byproduct of ores containing lead, gold, zinc, cobalt, and nickel) and is increasing in the microelectronics industry (in which gallium arsenide is responsible). Low-level arsenic exposure continues to take place in the general population (as do some cases of high-dose poisoning) through the commercial use of inorganic arsenic compounds in common products such as wood preservatives, pesticides, herbicides, fungicides, and paints; through the consumption of foods and the smoking of tobacco treated with arsenic-containing pesticides; and through the burning of fossil fuels in which arsenic is a contaminant. Arsenic was also a major ingredient of Fowler's solution and continues to be found in some folk remedies.

METABOLISM

The toxicity of an arsenic-containing compound depends on its valence state (zero-valent, trivalent, or pentavalent), its form (inorganic or organic), and the physical aspects governing its absorption and elimination. In general, inorganic arsenic is more toxic than organic arsenic, and trivalent arsenite is more toxic than pentavalent and zero-valent arsenic. The normal intake of arsenic by adults occurs primarily through ingestion and averages ~50 ug/d (range, 8 to 104 ug/d). Most (~64%) of this amount is accounted for by organic arsenic from fish, seafood, and algae; the specific arsenic compounds obtained from these sources are arsenobentaine and arsenocholine, which are relatively nontoxic and are rapidly excreted in unchanged form in the urine. After absorption, inorganic arsenic accumulates in the liver, spleen, kidneys, lungs, and gastrointestinal tract. It is then rapidly cleared from these sites but leaves a residue in keratin-rich tissues such as skin, hair, and nails. Arsenite (+5) undergoes biomethylation in the liver to the less toxic metabolites methylarsenic acid and dimethylarsenic acid; biomethylation can quickly become saturated, however, and the result is the deposition of increasing doses of inorganic arsenic in soft tissues. Arsenic, particularly in its trivalent form, inhibits critical sulfhydryl-containing enzymes. In the pentavalent form, the competitive substitution of arsenic for phosphate can lead to rapid hydrolysis of the high-energy bonds in compounds such as ATP.

CLINICAL TOXICOLOGY

Acute arsenic poisoning from ingestion results in increased permeability of small blood vessels and inflammation and necrosis of the intestinal mucosa; these changes manifest as hemorrhagic gastroenteritis, fluid loss, and hypotension. Delayed cardiomyopathy accompanied by electrocardiographic abnormalities may develop. Symptoms include nausea, vomiting, diarrhea, abdominal pain, delirium, coma, and seizures. A garlicky odor may be detectable on the breath. Acute tubular necrosis and hemolysis may develop. The reported lethal dose of arsenic ranges from 120 to 200 mg in adults and is 2 mg/kg in children. Arsine gas causes severe hemolysis within 3 to 4 h of exposure and can lead to acute tubular necrosis and renal failure.

In chronic arsenic poisoning, the onset of symptoms comes at 2 to 8 weeks. Typical findings are skin and nail changes, such as hyperkeratosis, hyperpigmentation, exfoliative dermatitis, and Mees' lines (transverse white striae of the fingernails); sensory and motor polyneuritis manifesting as numbness and tingling in a "stocking-glove" distribution, distal weakness, and quadriplegia; and inflammation of the respiratory mucosa. Epidemiologic evidence has linked chronic consumption of water containing arsenic at concentrations in the range of 10 to 1820 ppb with diabetes, vasospasm, and peripheral vascular insufficiency culminating in "blackfoot disease," a gangrenous condition affecting the extremities. Chronic arsenic exposure has also been associated with a greatly elevated risk of skin cancer and possibly of cancers of the lung, liver (angiosarcoma), bladder, kidney, and colon.

LABORATORY FINDINGS

When acute arsenic poisoning is suspected, an x-ray of the abdomen may reveal

ingested arsenic, which is radiopaque. The serum arsenic level may exceed 0.9 umol/L (7 ug/dL); however, arsenic is rapidly cleared from the blood. Electrocardiographic findings may include QRS complex broadening, QT prolongation, ST-segment depression, T-wave flattening, and multifocal ventricular tachycardia. Urinary arsenic should be measured in 24-h specimens collected after 48 h of abstinence from seafood ingestion; normally, levels of total urinary arsenic excretion are<0.67 umol/d (50 ug/d). Arsenic may be detected in the hair and nails for months after exposure. Abnormal liver function, anemia, leukocytosis or leukopenia, proteinuria, and hematuria may be detected. Electromyography may reveal features similar to those of Guillain-Barre syndrome.

TREATMENT

Vomiting should be induced with ipecac in the alert patient with acute arsenic ingestion. Gastric lavage may be useful; activated charcoal with a cathartic (such as sorbitol) may be tried, although its efficacy is not clear. Aggressive therapy with intravenous fluid and electrolyte replacement in an intensive-care setting may be life-saving. Dimercaprol is the chelating agent of choice and is administered intramuscularly at an initial dose of 3 to 5 mg/kg on the following schedule: every 4 h for 2 days, every 6 h on the third day, and every 12 h thereafter for 10 days. (An oral chelating agent may be substituted.) Succimer is sometimes an effective alternative, particularly if adverse reactions to dimercaprol develop (such as nausea, vomiting, headache, increased blood pressure, and convulsions). In cases of renal failure, doses should be adjusted carefully, and hemodialysis may be needed to remove the chelating agent-arsenic complex. Arsine gas poisoning should be treated supportively with the goals of maintaining renal function and circulating red-cell mass. Other than the avoidance of additional exposure, specific treatment is not of proven benefit in chronic arsenic toxicity. Recovery, particularly from the resulting peripheral neuropathy, may take months and may never be complete.

CADMIUM

SOURCE

Environmental exposure to cadmium can result from the ingestion of basic foodstuffs, especially grains, cereals, and leafy vegetables, which readily absorb cadmium occurring naturally or in soil contaminated by sewage sludge, fertilizers, and polluted groundwater. Serious cadmium poisoning can follow the contamination of food and water by mining effluents, as took place in the 1946 outbreak of *itai-itai* ("ouch-ouch") disease (so named because cadmium-induced bone toxicity caused painful bone fractures) in the Jintzu River basin in Japan. Airborne cadmium can be released during smelting or during the incineration of municipal waste containing plastics and nickel-cadmium batteries. Cigarette smoke contains cadmium. Occupational exposure takes place in the metal-plating, pigment, battery, and plastics industries.

METABOLISM

The normal daily intake of cadmium through ingestion or inhalation is from 20 to 40 ug, although only 5 to 10% of this amount is absorbed. Most absorbed cadmium is concentrated in the liver and kidneys. In erythrocytes and soft tissues, cadmium is

bound to metallothionein, a low-molecular-weight protein that mitigates the toxicity of the unbound ion. This complex is filtered at the glomerulus but is then reabsorbed by the proximal tubules. The lack of an effective elimination pathway is responsible for cadmium's biologic half-life of 10 to 30 years. The toxicity of cadmium may involve its binding to key cellular sulfhydryl groups, its competition with other metals (zinc and selenium) for inclusion in metalloenzymes, and its competition with calcium for binding sites on regulatory proteins such as calmodulin.

CLINICAL TOXICOLOGY

Acute high-dose cadmium inhalation can cause severe respiratory irritation with pleuritic chest pain, dyspnea, cyanosis, fever, tachycardia, nausea, and life-threatening noncardiogenic pulmonary edema. The onset of symptoms may be delayed from 4 to 24 h. Acute exposure through ingestion can cause severe nausea, vomiting, salivation, abdominal cramps, and diarrhea. Single lethal oral doses have reportedly ranged from 350 to 8900 mg. Chronic effects of cadmium exposure are dose-dependent and include anosmia, yellowing of the teeth, emphysema, minor changes in liver function, microcytic hypochromic anemia unresponsive to iron therapy, renal tubular dysfunction characterized by proteinuria and increased urinary excretion of b_2-microglobulin, and (with prolonged poisoning) osteomalacia leading to bone lesions and pseudofractures. In follow-up studies of occupationally exposed workers, b_2-microglobulinuria was found to be irreversible. Associations with hypertension, prostate cancer, and lung cancer have been suggested by some studies but await confirmation. In one study of men and women living in an area moderately contaminated with cadmium, higher body cadmium burdens were found to be a significant risk factor for lower bone density, a higher incidence of fractures, and a faster decline in height. These changes may be related to cadmium's calciuric effect on the kidney.

LABORATORY FINDINGS

The daily level of excretion of cadmium by persons without known cadmium exposures is usually<10 nmol/L (1 ug/L or 1 ug/g of creatinine). This level increases somewhat with age and smoking. Toxicity, including renal dysfunction, is considered unlikely until the urinary cadmium level exceeds 100 nmol/L (10 ug/g of creatinine). Serum cadmium levels reflect recent rather than chronic exposure and generally are <30 nmol/L (0.3 ug/dL) in unexposed persons. A blood level >500 nmol/L (5 ug/dL) is considered toxic. An increased urinary concentration of b_2-microglobulin is the most sensitive indicator of an elevated cadmium dose and of nephropathy but may also be detected in other renal diseases, such as chronic pyelonephritis.

TREATMENT

There is no effective treatment for cadmium poisoning. Chelation therapy is not useful, and dimercaprol is contraindicated as this agent may exacerbate nephrotoxicity. Avoidance of further exposure and supportive therapy (including vitamin D if osteomalacia exists) are the mainstays of management.

(Bibliography omitted in Palm version)

396. POISONING AND DRUG OVERDOSAGE - *Christopher H. Linden, Michael J. Burns*

Poisoning refers to the development of dose-related adverse effects following exposure to chemicals, drugs, or other xenobiotics. To paraphrase Paracelsus, the dose makes the poison. In excessive amounts, substances that are usually innocuous, such as oxygen and water, can cause poisoning. Conversely, in small doses, substances commonly regarded as poisons, such as arsenic and cyanide, can be consumed without ill effect. There is, however, substantial individual variability in the response to, and disposition of, a given dose (Chaps. 70 and71). Some of this variability is genetic, and some is acquired on the basis of enzyme induction, inhibition, or because of tolerance. Poisoning may be local (e.g., skin, eyes, or lungs) or systemic depending on the chemical and physical properties of the xenobiotic, its mechanism of action, and the route of exposure. The severity and reversibility of poisoning also depend on the functional reserve of the individual or target organ, which is influenced by age and preexisting disease. All of these factors must be considered when attempting to predict the effects of a particular exposure.

EPIDEMIOLOGY

In the United States, exposure to xenobiotics results in over 5 million requests for medical advice or treatment each year. Most exposures are acute, accidental, involve a single agent, occur in the home, result in minor or no toxicity, and involve children under 6 years of age. Common routes of exposure are ingestion (74%), dermal (8.2%), inhalation (6.7%), ocular (6%), bites and stings (3.9%), and parenteral injections (0.3%). Exposures most frequently involve cleaning agents, analgesics, cosmetics, plants, cough and cold preparations, and bites and envenomations (Chaps. 397 and398). Pharmaceuticals are involved in 41% of exposures and 75% of serious or fatal poisonings.

Accidental exposures can result from the improper use of chemicals at work or play; product mislabeling; label misreading; mistaken identification of unlabeled chemicals; uninformed self-medication; and dosing errors by nurses, parents, pharmacists, physicians, and the elderly. Excluding the recreational use of ethanol, attempted suicide is the most common reason for intentional exposure. Unintended poisonings may result from the intentional use of drugs for psychotropic effects (abuse) or excessive self-dosing (misuse).

About 5% of exposures require hospitalization. They account for 5 to 10% of all ambulance transports, emergency room visits, and intensive care unit admissions. Up to 30% of psychiatric admissions are prompted by attempted suicide via overdosage.

Overall, the mortality rate is low: 0.03% of all exposures. It is much higher (1 to 2%) in hospitalized patients with nonaccidental (suicidal) overdose, who account for the majority of serious poisonings. Carbon monoxide poisoning is the leading cause of death; patients with such poisoning are typically dead when discovered and are

included in medical examiner but not hospital or poison center statistics. Drug-related fatalities are most commonly due to analgesics, antidepressants, sedative-hypnotics, neuroleptics, stimulants and street drugs, cardiovascular drugs, anticonvulsants, antihistamines, and asthma therapies. Nonpharmaceutical agents most often implicated in fatal poisoning include alcohols and glycols, gases and fumes, chemicals, cleaning substances, pesticides, and automotive products.

DIAGNOSIS

Although poisoning can mimic other illnesses, the correct diagnosis can usually be established by the history, physical examination, routine and toxicologic laboratory evaluations, and characteristic clinical course. The *history* should include the time, route, duration, and circumstances (location, surrounding events, and intent) of exposure; the name and amount of each drug, chemical, or ingredient involved; the time of onset, nature, and severity of symptoms; the time and type of first aid measures provided; and the medical and psychiatric history.

In many cases the victim is confused, comatose, unaware of an exposure, or unable or unwilling to admit to one. Suspicious circumstances include unexplained illness in a previously healthy person; a history of psychiatric problems (particularly depression); recent changes in health, economic status, or social relationships; and onset of illness while working with chemicals or after ingesting food, drink (especially ethanol), or medications. Patients who become ill soon after arriving from a foreign country or being arrested for criminal activity should be suspected of "body packing" or "body stuffing" (ingesting or concealing illicit drugs in a body cavity). Relevant history may be available from family, friends, paramedics, police, pharmacists, physicians, and employers, who should be questioned regarding the patient's habits, hobbies, behavior changes, available medications, and antecedent events. A search of clothes, belongings, and place of discovery may reveal a suicide note or a container of drugs or chemicals. The imprint code on pills and the label on chemical products may be used to identify the ingredients and potential toxicity of a suspected poison by consulting a reference text, a computerized database, the manufacturer, or a regional poison information center.

In the absence of a history of exposure, the *clinical course* may suggest a diagnosis of poisoning. Poisoning typically evolves and resolves more rapidly than other disorders. Signs and symptoms characteristically develop within an hour of acute exposure, peak within several hours, and resolve over hours to days. However, the absence of signs and symptoms soon after an overdose does not rule out a poisoning.

The *physical examination* should focus initially on the vital signs, cardiopulmonary system, and neurologic status. On the basis of the pulse, blood pressure, respiratory rate, temperature, and mental status, the physiologic state can be characterized as excited, depressed, discordant, or normal. A differential diagnosis can then be formulated (Table 396-1). Examination of the eyes (for nystagmus, pupil size and reactivity), abdomen (for bowel activity and bladder size), and skin (for burns, bullae, color, warmth, moisture, pressure sores, and puncture marks) may narrow the diagnosis to a particular disorder. Grading the severity of poisoning (Table 396-2) is useful for assessing the clinical course and response to treatment.

The patient should also be examined for evidence of trauma and underlying illnesses. Except with carbon monoxide, theophylline, and drugs that cause hypoglycemia or hypoxia, seizures and neurologic manifestations of poisoning are nonfocal. Hence, focal findings should prompt evaluation for a structural central nervous system (CNS) lesion. When the history is unclear, all orifices should be examined for the presence of chemical burns and drug packets. The odor of breath or vomitus and the color of nails, skin, or urine may provide diagnostic clues.

Laboratory assessment may be helpful in the differential diagnosis of poisoning (Fig. 396-1). An increased anion-gap metabolic acidosis is characteristic of advanced methanol, ethylene glycol, and salicylate intoxication but can occur with other agents (Table 396-1) and in any poisoning that results in hepatic, renal, or respiratory failure, seizures, or shock. The serum lactate concentration is low (less than the anion gap) in the former and high (nearly equal to the anion gap) in the latter. An abnormally low anion gap can be due to elevated blood levels of bromide, calcium, iodine, lithium, magnesium, or nitrate. An increased osmolal gap -- the difference between the serum osmolality (measured by freezing point depression) and that calculated from the serum sodium, glucose, and blood urea nitrogen (BUN) of>10 mmol/L -- suggests the presence of a low-molecular-weight solute such as an alcohol, glycol, or ketone or an unmeasured electrolyte or sugar. The osmolal gap can also provide an estimate of the amount of anion present (Table 396-3). Ketosis suggests acetone, isopropyl alcohol, or salicylate poisoning. Hypoglycemia may be due to poisoning withb-adrenergic blockers, ethanol, insulin, oral hypoglycemic agents, quinine, and salicylates, whereas hyperglycemia can occur in poisoning with acetone, b-adrenergic agonist, calcium channel blockers, iron, theophylline, or Vacor. Hypokalemia can be caused by barium, a b-adrenergic agonist, a diuretic, theophylline, or toluene; hyperkalemia suggests poisoning with ana-adrenergic agonist, ab-adrenergic blocker, cardiac glycosides, or fluoride.

Radiologic studies may also be useful for diagnostic purposes. Pulmonary edema (adult respiratory distress syndrome, or ARDS) can be caused by poisoning with carbon monoxide, cyanide, an opioid, paraquat, phencyclidine, a sedative-hypnotic, or salicylate; by inhalation of irritant gases, fumes, or vapors (ammonia, metal oxides, mercury); or by prolonged anoxia, hyperthermia, or shock. Aspiration pneumonia is common in patients with coma, seizures, and petroleum distillate ingestion. Radiopaque densities may be visible on abdominal x-rays following the ingestion of calcium salts, chloral hydrate, chlorinated hydrocarbons, heavy metals, illicit drug packets, iodinated compounds, potassium salts, psychotherapeutic agents, lithium, phenothiazines, enteric-coated tablets, or salicylates.

Theelectrocardiogram (ECG) can be useful to assist with the differential diagnosis and to guide treatment. Bradycardia and atrioventricular (AV) block may occur in patients poisoned bya-adrenergic agonists, antiarrhythmic agents, beta blockers, calcium channel blockers, cholinergic agents (carbamate and organophosphate insecticides), cardiac glycosides, lithium, magnesium, or tricyclic antidepressants. QRS- and QT-interval prolongation may be caused by hyperkalemia and by membrane-active drugs (Table 396-1). Ventricular tachyarrhythmias may be seen in poisoning with cardiac glycosides, fluorides, membrane-active drugs, sympathomimetics, or agents that cause hyperkalemia or potentiate the effects of endogenous catecholamines (e.g.,

chloral hydrate, aliphatic and halogenated hydrocarbons).

Analysis of urine and blood (and occasionally of gastric contents and chemical samples) may be useful to confirm or rule out suspected poisoning. Interpretation of laboratory data requires knowledge of the tests used for screening and confirmation (thin-layer, gas-liquid, or high-performance liquid chromatography; colorimetric and fluorometric assays; enzyme-multiplied and radioimmunoassays; gas chromatography; mass spectrometry), their sensitivity (limit of detection) and specificity, the preferred biologic specimen for analysis, and the optimal time of specimen sampling. Personal communication with the laboratory is essential. A negative result on a screen may mean the substance is not detectable by the test used or that its concentration is too low for detection at the time of sampling. In the latter case, repeating the test at a later time may yield a positive result.

Although some rapid screening tests for a limited number of drugs of abuse are available, comprehensive screening tests require 2 to 6 h for completion, and immediate management must be based on the history, physical examination, and routine ancillary tests. In addition, when the patient is asymptomatic, or when the clinical picture is consistent with the reported history, qualitative screening is neither clinically useful nor cost-effective. It is of greatest value in patients with severe or unexplained toxicity who have coma, seizures, cardiovascular instability, metabolic or respiratory acidosis, and nonsinus cardiac rhythms. Quantitative analysis is useful for poisoning with acetaminophen, acetone, alcohol (including ethylene glycol), antiarrhythmics, anticonvulsants, barbiturates, digoxin, heavy metals, lithium, paraquat, salicylate, and theophylline, as well as for carboxyhemoglobin and methemoglobin. Results can often be available within an hour.

The *response to antidotes* may be useful for diagnostic purposes. Resolution of altered mental status and abnormal vital signs within minutes of intravenous administration of dextrose, naloxone, or flumazenil is virtually diagnostic of hypoglycemia, narcotic poisoning, and benzodiazepine intoxication, respectively. The prompt reversal of acute dystonic (extrapyramidal) reactions following an intravenous dose of benztropine or diphenhydramine confirms a drug etiology. Although the reversal of both central and peripheral manifestations of anticholinergic poisoning by physostigmine is diagnostic, this antidote may cause arousal in patients with CNS depression of any etiology.

TREATMENT

General Principles Treatment goals include support of vital signs, prevention of further poison absorption, enhancement of poison elimination, administration of specific antidotes, and prevention of reexposure (Table 396-4). Specific treatment depends on the identity of the poison, the route and amount of exposure, the time of presentation relative to the time of exposure, and the severity of poisoning. Knowledge of the offending agents' pharmacokinetics and pharmacodynamics is essential.

During the *pretoxic phase*, prior to the onset of poisoning, decontamination is the highest priority, and treatment is based solely on the history. The maximum potential toxicity based on the greatest possible exposure should be assumed. Since decontamination is more effective when accomplished soon after exposure, the initial

history and physical examination should be focused and brief. It is also advisable to establish intravenous access and initiate cardiac monitoring, particularly in patients with potentially serious ingestions or unclear histories.

When an accurate history is not obtainable, and a poison causing delayed toxicity or irreversible damage is suspected, blood and urine should be sent for toxicologic screening and, if indicated, for quantitative analysis. During absorption and distribution, blood levels may be greater than those in tissue and may not correlate with toxicity. However, high blood levels of agents whose metabolites are more toxic than the parent compound (acetaminophen, ethylene glycol, or methanol) may indicate the need for additional interventions (antidotes, dialysis).

Most patients who remain or become asymptomatic 4 to 6 h after ingestion will not develop subsequent toxicity and can be discharged safely. Longer observation may be necessary for patients who have ingested agents that slow gastric emptying and intestinal motility as this will delay dissolution, absorption, and distribution characteristics. Extended observation may also be indicated for agents that are converted in the body to toxic metabolites (Table 396-1).

During the *toxic phase*, the time between the onset of poisoning and the peak effects, management is based primarily on clinical and laboratory findings. *Effects after an overdose begin sooner, peak later, and last longer than they do after a therapeutic dose*. Resuscitation and stabilization are the first priority. All symptomatic patients should have an intravenous line, oxygen saturation determination, cardiac monitoring, and continuous observation. Baseline laboratory, ECG, and x-ray evaluation may also be appropriate. Intravenous glucose (unless documented to be normal), naloxone, and thiamine should be considered in patients with altered mental status, particularly those with soma or seizures. Decontamiation may also be appropriate.

Measures that enhance poison elimination may shorten the duration of toxicity and lessen its severity. However, the risks must be weighed against the benefits. Diagnostic certainty (usually via laboratory confirmation) is generally a prerequisite. Intestinal dialysis with repetitive doses of activated charcoal is usually safe and can enhance the elimination of many poisons. Diuresis and chelation therapy enhance the elimination of a relatively small number of poisons, and their use is associated with potential complications. Extracorporal methods are effective in removing many poisons, but their expense and risk make their use reasonable only in patients who would otherwise have an unfavorable outcome.

During the *resolution phase* of poisoning, supportive care and monitoring should continue until clinical, laboratory, and ECG abnormalities have resolved. Since chemicals are eliminated from the blood before tissues, blood levels are usually lower than tissue levels during this phase and may not correlate with toxicity. This is particularly true when extracorporeal elimination procedures are used. Redistribution from tissues may cause a rebound increase in the blood level after termination of these procedures. When a metabolite is responsible for toxic effects, continued treatment of an asymptomatic patient might be necessary because of a potentially toxic blood level (acetaminophen, ethylene glycol, and methanol).

Supportive Care The goal of supportive therapy is to maintain physiologic homeostasis until detoxification is accomplished and to prevent and treat secondary complications such as aspiration, bedsores, cerebral and pulmonary edema, pneumonia, rhabdomyolysis, renal failure, sepsis, thromboembolic disease, and generalized organ dysfunction due to prolonged hypoxia or shock.

Admission to an intensive care unit is indicated for the following: patients with severe poisoning (coma, respiratory depression, hypotension, cardiac conduction abnormalities, cardiac arrhythmias, hypothermia or hyperthermia, seizures); those needing close monitoring, antidotes, or enhanced elimination therapy; those showing progressive clinical deterioration; and those with significant underlying medical problems. Patients with mild to moderate toxicity can be managed on a general medical service, intermediate care unit, or emergency department observation area, depending on the anticipated duration and level of monitoring needed (intermittent clinical observation versus continuous clinical, cardiac, and respiratory monitoring). Patients who have attempted suicide require continuous observation and measures to prevent self-injury until they are thought unlikely to make further attempts.

Respiratory care Endotracheal intubation for protection against the aspiration of gastrointestinal contents is of paramount importance in patients with CNS depression or seizures as this complication can increase morbidity and mortality. Mechanical ventilation may be necessary for patients with respiratory depression or hypoxia and to facilitate therapeutic sedation or paralysis in order to prevent hyperthermia, acidosis, and rhabdomyolysis associated with neuromuscular hyperactivity. Since clinical assessment of respiratory function is often inaccurate, the need for oxygenation and ventilation is best determined by oximetry or arterial blood gas analysis. The gag reflex is not a reliable indicator of the need for intubation. A patient may maintain airway patency while being stimulated but not if left unattended. Those who cannot respond to voice or who are unable to sit and drink fluids without assistance are best managed by prophylactic intubation.

Drug-induced pulmonary edema is usually noncardiac rather than cardiac in origin. Profound CNS depression and cardiac conduction abnormalities suggest the latter etiology. Measurement of pulmonary artery pressure may be necessary to establish etiology and direct appropriate therapy. Extracorporeal measures (membrane oxygenation, venoarterial perfusion, cardiopulmonary bypass), partial liquid (perfluorocarbon) ventilation, and hyperbaric oxygen therapy may be appropriate for severe but reversible respiratory failure.

Cardiovascular therapy Maintenance of normal tissue perfusion is critical to allow for complete recovery once the offending agent has been eliminated. If hypotension is unresponsive to volume expansion, treatment with norepinephrine, epinephrine, or high-dose dopamine may be necessary (Chap. 38). Intraaortic balloon pump counterpulsation and venoarterial or cardiopulmonary perfusion techniques should be considered for severe but reversible cardiac failure. Bardyarrhythmias associated with hypotension generally should be treated as described in Chap. 229. Glucagon and calcium may be effective in both beta blocker and calcium channel blocker poisoning. Antibody therapy may be indicated for cardiac glycoside poisoning.

Supraventricular tachycardia associated with hypertension and CNS excitation is almost always due to agents that cause generalized physiologic excitation (Table 396-1). Most cases are mild or moderate in severity and require only observation or nonspecific sedation with a benzodiazepine. For cases that are severe or associated with hemodynamic instability, chest pain, or ECG evidence of ischemia, specific therapy is indicated. For patients with sympathetic hyperactivity, treatment with a combined alpha and beta blocker (labetalol), a calcium channel blocker (verapamil or diltiazem), or a combination of a beta blocker and a vasodilator (esmolol and nitroprusside) is preferred. For those with anticholinergic poisoning, physostigmine is the treatment of choice. Supraventricular tachycardia without hypertension is generally secondary to vasodilation or hypovolemia and responds to fluid administration.

Lidocaine and phenytoin are generally safe for ventricular tachyarrhythmias, but beta blockers can be hazardous unless the arrhythmia is clearly due to sympathetic hyperactivity. For ventricular tachyarrhythmias due to tricyclic antidepressants and probably other membrane-active agents (Table 396-1), class IA, IC, and III antiarrhythmic agents are contraindicated (because of similar electrophysiologic effects), but sodium bicarbonate may be helpful. Magnesium sulfate and overdrive pacing (by isoproterenol or a pacemaker) may be useful in patients with torsade de pointes and prolonged QT intervals. Magnesium and antidigoxin antibodies should be considered in patients with severe cardiac glycoside poisoning. Invasive (esophageal or intracardiac) ECG recording may be necessary to determine the origin (ventricular or supraventricular) of wide-complex tachycardias (Chap. 230). If the patient is hemodynamically stable, however, it may be prudent to observe rather than to treat with another potentially proarrhythmic agent. Arrhythmias may be resistant to drug therapy until underlying acid-base, electrolyte, oxygenation, and temperature derangements are corrected.

Central nervous system therapies Neuromuscular hyperactivity and seizures can lead to hyperthermia, lactic acidosis, and rhabdomyolysis, with their attendant complications, and should be treated aggressively. Seizures caused by excessive stimulation of catecholamine receptors (sympathomimetic or hallucinogen poisoning and drug withdrawal), or decreased activity of g-aminobutyric acid (GABA) (isoniazid poisoning) or glycine (strychnine poisoning) receptors are best treated with enhancers of GABA effects such as benzodiazepines or barbiturates. Since benzodiazepines and barbiturates act by slightly different mechanisms (the former increases the frequency and the latter increases the duration of chloride channel opening in response to GABA), therapy with both may be effective when neither is effective alone. Seizures caused by isoniazid, which inhibits the synthesis of GABA, may require high doses of pyridoxine (which facilitates the synthesis of GABA). Seizures resulting from membrane destabilization (beta blocker or cyclic antidepressant poisoning) may require a membrane-active anticonvulsant such as phenytoin as well as GABA enhancers. For poisons with central dopaminergic effects (phencyclidine), an agent with opposing activity, such as haloperidol, may be useful. In anticholinergic and cyanide poisoning, specific antidotal therapy may be necessary. The treatment of seizures secondary to ischemia, edema, or metabolic abnormalities should include correction of the underlying cause. Neuromuscular paralysis is indicated in refractory cases. Electroencephalographic (EEG) monitoring and continuing treatment of seizures are necessary to prevent permanent neurologic damage.

Other measures Temperature extremes, metabolic abnormalities, hepatic and renal dysfunction, and secondary complications should be treated by standard therapies.

Prevention of Poison Absorption

Gastrointestinal Decontamination Whether or not to perform gastrointestinal decontamination, and which procedure to use, depends on the time since ingestion; the existing and predicted toxicity of the ingestant; the availability, efficacy, and contraindications of the procedure; and the nature, severity, and risk of complications. In animal and human volunteer studies, the efficacy of activated charcoal, gastric lavage, and syrup of ipecac decreases with time, and there are insufficient data to support or exclude a beneficial effect when they are used more than 1 h after ingestion. Due to the lack of clinical studies using control groups without treatment, the efficacy of these procedures for improving the outcome of overdose patients has not been established.

The average time from ingestion to presentation for treatment is over 1 h for children and over 3 h for adults. Most patients will recover from poisoning uneventfully with good supportive care alone, but complications of gastrointestinal decontamination, particularly aspiration, can prolong this process. Hence, gastrointestinal contamination should be performed selectively, not routinely, in the management of overdose patients. It is clearly unnecessary when predicted toxicity is minimal or the time of expected maximal toxicity has passed without significant effect.

Activated charcoal has comparable or greater efficacy, fewer contraindications and complications, is less aversive and invasive than ipecac or gastric lavage, and is the preferred method of gastrointestinal decontamination in most situations.

Activated charcoal is prepared as a suspension in water, either alone or with a cathartic. It is given orally via a nippled bottle (for infants), or via a cup, straw, or small-bore nasogastric tube. The recommended dose is 1 g/kg body weight, using 8 mL of diluent per gram of charcoal if a premixed formulation is not available. Palatability may be increased by adding a sweetener (sorbitol) or a flavoring agent (cherry, chocolate, or cola syrup) to the suspension. Charcoal adsorbs ingested poisons within the gut lumen, allowing the charcoal-toxin complex to be evacuated with stool. The complex can also be removed from the stomach by induced emesis or lavage. In vitro, charcoal adsorbs³90% of most substances when given in an amount equal to 10 times the weight of the substance. Charged (ionized) chemicals such as mineral acids, alkalis, and highly dissociated salts of cyanide, fluoride, iron, lithium, and other inorganic compounds are not well adsorbed by charcoal. In animal and human volunteer studies, charcoal decreases the absorption of ingestants by an average of 73% when given within 5 min of ingestant administration, 51% when given at 30 min, and 36% at 60 min. Charcoal is at least equally as effective as ipecac syrup or gastric lavage. Experimentally, lavage followed by charcoal is more effective than charcoal alone, and charcoal before and after lavage is more effective than charcoal alone or charcoal after lavage. In the treatment of poisoned patients, however, charcoal alone generally results in a better clinical outcome than either treatment with ipecac followed by charcoal or lavage followed by charcoal. Side effects of charcoal include nausea, vomiting, and diarrhea or constipation. Charcoal may also prevent the absorption of orally administered

therapeutic agents. Complications include mechanical obstruction of the airway, aspiration, vomiting, and bowel obstruction and infection caused by inspissated charcoal. Charcoal is not recommended for patients who have ingested corrosives because it obscures endoscopy.

Gastric lavage is performed by sequentially administering and aspirating about 5 mL fluid per kilogram of body weight through a no. 28 French orogastric tube in children and a no. 40 French tube in adults. Except for infants, tap water is acceptable. The patient should be placed in Trendelenburg and left lateral decubitus positions to prevent aspiration (even if an endotracheal tube is in place). Lavage decreases ingestant absorption by an average of 52% if performed within 5 min of ingestion administration, 26% if performed at 30 min, and 16% if performed at 60 min. Its efficacy is similar to that of ipecac. Significant amounts of ingested drug are recovered in one-tenth of patients. Aspiration is a common complication (occurring in up to 10% of patients), especially when lavage is perfomed improperly. Serious complications (tracheal lavage, esophageal and gastric perforation) occur in approximately 1% of patients. For this reason, the physician should personally insert the lavage tube and confirm its placement, and the patient must be cooperative or adequately restrained (with pharmacologic sedation if necessary) during the procedure. Gastric lavage is contraindicated in corrosive or petroleum distillate ingestions because of the respective risks of gastroesophageal perforation and aspiration-induced hydrocarbon pneumonitis.

Syrup of ipecac can be used for the home management of patients with accidental ingestions, reliable histories, and mild predicted toxicity. It may delay the administration and decrease the effectiveness of activated charcoal, oral antidotes, and whole-bowel irrigation and is very rarely appropriate for patients treated at a health care facility. It is administered orally in a dose of 30 mL for adults, 15 mL for children, and 10 mL for small infants. Clear liquids should also be given. Ipecac irritates the stomach and stimulates the central chemoreceptor trigger zone. Vomiting usually occurs about 20 min after administration. The dose may be repeated if vomiting does not occur. In animal and human volunteer studies, ipecac decreases ingestant absorption by an average of 60% if given within 5 min of ingestant administration, 32% if given at 30 min, and 30% if given at 60 min. Side effects include lethargy in children (12%) and protracted vomiting (8 to 17%). Chronic ipecac use (by patients with anorexia nervosa or bulimia) may cause electrolyte and fluid abnormalities, cardiac toxicity, and myopathy. Except for aspiration, serious complications are rare. Gastric or esophageal tears and perforations and stroke have been reported. Ipecac is contraindicated in patients with recent gastrointestinal surgery, CNS depression, or seizures, and in those who have ingested corrosives or rapidly acting CNS poisons (camphor, cyanide, tricyclic antidepressants, propoxyphene, strychnine).

Whole-bowel irrigation is performed by administering a bowel-cleansing solution containing electrolytes and polyethylene glycol (Golytely, Colyte) orally or by gastric tube at a rate of up 0.5 L/h in children and 2.0 L/h in adults until rectal effluent is clear. The patient must be in a sitting position. Although data are limited, whole-bowel irrigation may be at least equally as effective as other decontamination procedures. It may be appropriate for those who have ingested foreign bodies, packets of illicit drugs, slow-release or enteric-coated medications, and agents that are poorly adsorbed by charcoal (e.g., heavy metals). It is contraindicated in patients with bowel obstruction,

ileus, hemodynamic instability, and compromised unprotected airways.

Cathartic salts (disodium phosphate, magnesium citrate and sulfate, sodium sulfate) or *saccharides* (mannitol, sorbitol) promote the rectal evacuation of gastrointestinal contents. The most effective cathartic is sorbitol in a dose of 1 to 2 g/kg of body weight. Alone, cathartics do not prevent ingestant absorption and should not be used as a method of gut decontamination. Their primary use is to prevent constipation following charcoal administration. Abdominal cramps, nausea, and occasional vomiting are side effects. Complications of repeated dosing include hypermagnesemia and excessive diarrhea. Cathartics are contraindicated in patients who have ingested corrosives and in those with preexisting diarrhea. Magnesium-containing cathartics should not be used in patients with renal failure.

Dilution (i.e., drinking 5 mL/kg of body weight of water or another clear liquid) should be accomplished as soon as possible after the ingestion of corrosives (acids, alkali). However, it may increase the dissolution rate (and hence absorption) of capsules, tablets, and other solid ingestants and should *not* be used in these circumstances.

Endoscopic or surgical removal of poisons may be useful in rare situations, such as ingestion of a potentially toxic foreign body that fails to transit the gastrointestinal tract, a potentially lethal amount of a heavy metal (arsenic, iron, mercury, thallium), or agents that have coalesced into gastric concretions or bezoars (barbiturates, gluthethimide, heavy metals, lithium, meprobamate, sustained-release preparations). Patients who become toxic from cocaine due to its leakage from multiple ingested drug packets require immediate surgical intervention.

Decontamination of Other Sites Immediate, copious flushing with water, saline, or another available clear, drinkable liquid is the initial treatment for topical exposures (exceptions include alkali metals, calcium oxide, phosphorus). Saline is preferred for eye irrigation. A triple wash (water, soap, water) may be best for dermal decontamination. Inhalational exposures should be treated initially with fresh air or oxygen. The removal of liquids from body cavities such as the vagina or rectum is best accomplished by irrigation. Solids (drug packets, pills) should be removed manually, preferably with visual guidance.

Enhancement of Poison Elimination Although the elimination of most poisons can be accelerated by therapeutic interventions, the pharmacokinetic efficacy (removal of drug at a rate greater than that accomplished by intrinsic elimination) and clinical benefit (in terms of a shortened duration of toxicity or improved outcome) of such interventions are often more theoretical than proven. Hence, the decision to use such measures should be based on the actual or predicted toxicity and the potential efficacy, cost, and risks of therapy.

Multiple-Dose Activated Charcoal Repetitive oral dosing with charcoal can enhance the elimination of previously absorbed substances by binding them within the gut as they are excreted in the bile, secreted by gastrointestinal cells, or passively diffuse into the gut lumen (reverse absorption or enterocapillary exsorption). Doses of 0.5 to 1 g/kg body weight every 2 to 4 h, adjusted downward to avoid regurgitation in patients with decreased gastrointestinal motility, are generally recommended. Experimentally, this

treatment enhances the elimination of nearly all substances tested. Pharmacokinetic efficacy approaches that of hemodialysis for some agents (e.g., phenobarbital, theophylline). Multiple-dose therapy is not effective in accelerating elimination of chlorpropamide, tobramycin, or agents that adsorb poorly to charcoal. Complications include intestinal obstruction, pseudoobstruction, and nonocclusive intestinal infarction in patients with decreased gut motility.

Forced Diuresis and Alteration of Urinary pH Diuresis and ion trapping via alteration of urine pH may prevent the renal reabsorption of poisons that undergo excretion by glomerular filtration and active tubular secretion. Since membranes are more permeable to nonionized molecules than to their ionized counterparts, acidic (low-pK_a) poisons are ionized and trapped in an alkaline urine, and basic poisons are ionized and trapped in an acid urine. Saline diuresis can enhance the renal excretion of alcohols, bromide, calcium, fluoride, lithium, meprobamate, potassium, and isoniazid. Alkaline diuresis (a urine pH^{3}7.5 and a urine output of 3 to 6 mL/kg body weight per hour) enhances the elimination of chlorphenoxyacetic acid herbicides, chlorpropamide, diflunisal, fluoride, methotrexate, phenobarbital, sulfonamides, and salicylates. Contraindications include congestive heart failure, renal failure, and cerebral edema. Acid-base, fluid, and electrolyte parameters should be monitored carefully. Acid diuresis enhances the renal elimination of amphetamines, chloroquine, cocaine, local anesthetics, phencyclidine, quinidine, quinine, strychnine, sympathomimetics, tricyclic antidepressants, and tocainide. Its use, however, has been largely abandoned because of potential complications and lack of clinical efficacy.

Extracorporeal Removal Peritoneal dialysis, hemodialysis, charcoal or resin hemoperfusion, hemofiltration, plasmapheresis, and exchange transfusion are capable of removing any toxin from the bloodstream. Agents most amenable to enhanced elimination by dialysis have low molecular mass (<500 Da), high water solubility, low protein binding, small volumes of distribution (<1 L/kg body weight), prolonged elimination (long half-life), and high dialysis clearance relative to total-body clearance. Molecular weight, water solubility, or protein binding do not limit the efficacy of the other forms of extracorporeal removal.

Dialysis should be considered in cases of severe poisoning due to barbiturates, bromide, chloral hydrate, ethanol, ethylene glycol, isopropyl alcohol, lithium, methanol, procainamide, theophylline, salicylates, and possibly heavy metals. Although hemoperfusion may be more effective in removing some of these poisons, it does not correct associated acid-base and electrolyte abnormalities. Hemoperfusion should be considered in cases of severe poisoning due to carbamazepine, chloramphenicol, disopyramide, and hypnotic-sedatives (barbiturates, ethchlorvynol, glutethimide, meprobamate, methaqualone), paraquat, phenytoin, procainamide, theophylline, and valproate. Both techniques require central venous access and systemic anticoagulation and often result in transient hypotension. Hemoperfusion may also cause hemolysis, hypocalcemia, and thrombocytopenia. Peritoneal dialysis and exchange transfusion are less effective but may be used when other procedures are either not available, contraindicated, or technically difficult (e.g., in infants). Exchange transfusion removes poisons affecting red blood cells (as in methemoglobinemia or arsine-induced hemolysis). The roles of hemofiltration and plasmapheresis are not yet defined.

Candidates for these treatments include patients with severe toxicity who deteriorate despite aggressive supportive therapy; those with potentially prolonged, irreversible, or fatal toxicity; those with dangerous blood levels of toxins; those who lack the capacity for self-detoxification because of liver or renal failure; and those with a serious underlying illness or complication that will adversely affect recovery.

Other Techniques The elimination of heavy metals can be enhanced by chelation, and the removal of carbon monoxide can be increased by hyperbaric oxygenation as discussed in sections on specific poisons.

Administration of Antidotes Antidotes counteract the effects of poisons by neutralizing them (e.g., antibody-antigen reactions, chelation, chemical binding) or by antagonizing their physiologic effects (e.g., activation of opposing nervous system activity, provision of competitive metabolic or receptor substrate). Poisons or conditions with specific antidotes include acetaminophen, anticholinergic agents, anticoagulants, benzodiazepines, beta blockers, calcium channel blockers, carbon monoxide, cardiac glycosides, cholinergic agents, cyanide, drug-induced dystonic reactions, ethylene glycol, fluoride, heavy metals, hydrogen sulfide, hypoglycemic agents, isoniazid, methemoglobinemia, narcotics, sympatomimetics, Vacor, and a variety of evenomations. Antidotes can significantly reduce morbidity and mortality, but most are potentially toxic. Since their safe use requires correct identification of a specific poisoning or syndrome, details of antidotal therapy are discussed with the conditions for which they are indicated.

Prevention of Reexposure Poisoning is a preventable illness. Unfortunately, some adults and children are poison-prone, and recurrences are common. Adults with accidental exposures should be instructed regarding the safe use of medications and chemicals (according to labeling instructions). Confused patients may need assistance with the administration of medications. Errors in dosing by health care providers may require educational efforts. Patients should be advised to avoid circumstances that result in chemical exposure or poisoning. Appropriate agencies and health departments should be notified in cases of environmental or workplace exposure. The best approach with young children and patients with intentional overdose is to limit access to poisons. In households where children live or visit, alcoholic beverages, medications, household products (automotive, cleaning, fuel, pet-care, toiletry products), nonedible plants, and vitamins should be kept out of reach or in locked or child-proof cabinets. Depressed or psychotic patients should receive psychiatric assessment, disposition, and follow-up. They should be given prescriptions for a limited supply of drugs and with a limited number of refills and be monitored for compliance and response to therapy.

SPECIFIC POISONS

The following discussion focuses on poisonings that are common, produce life-threatening toxicity, or require unique therapeutic interventions. Poisonings not covered here are described in the referenced texts. *Alcohol, cocaine, hallucinogens, and opioids are discussed in Chaps. 386 to 389, and heavy metal poisoning is discussed in Chap. 395.*

ACETAMINOPHEN

Acetaminophen is absorbed rapidly and has a volume of distribution of 1 L/kg body weight. Plasma concentrations range from 160 to 660 umol/L (5 to 20 ug/mL) following therapeutic doses. Most acetaminophen is metabolized by hepatic conjugation with sulfate and glucuronide to form nontoxic metabolites, with minor amounts being excreted unchanged or oxidized by hepatic cytochrome P450 enzymes (primarily CYPIIE1) to form a highly reactive, electrophilic, and potentially toxic intermediary metabolite n-acetyl-p-benzoquinoneimine (NAPQI). After therapeutic doses, NAPQI is rapidly detoxified by conjugation with glutathione and excreted as cysteine and mercapturic acid conjugates. Following an acute ingestion of ³140 mg/kg body weight, sulfate and glucuronide pathways become saturated, resulting in an increased fraction and amount of acetaminophen metabolized to NAPQI and eventual glutathione depletion. When this occurs, free NAPQI binds covalently to hepatocytes and causes their lysis (centrilobular necrosis). Less often, hepatotoxicity develops following the chronic ingestion of therapeutic or slightly greater amounts in conditions associated with decreased glutathione reserves (e.g., alcoholism, childhood, acute starvation, chronic malnutrition) and possibly in conditions with enhanced P450 enzyme activity (e.g., anticonvulsant and antitubercolosis drug use). The plasma half-life is usually 2 to 4 h but may be prolonged if hepatotoxicity develops.

Clinical Toxicity Early manifestations of poisoning are nonspecific and not predictive of subsequent hepatotoxicity. Within 2 to 4 h of acute overdose, nausea, vomiting, diaphoresis, and pallor may develop.CNSdepression is typically absent unless massive doses are ingested. Within 24 to 48 h, hepatotoxicity is evidenced by right upper quadrant tenderness and mild hepatomegaly. Renal function may also be impaired. Laboratory evidence of hepatic toxicity includes prolongation of the prothrombin time and elevation of serum bilirubin and transaminase activity (aspartate transaminase, alanine transaminase). Severe poisoning may cause hepatic failure. Greater than twofold prolongation of prothrombin time, a serum bilirubin level>68 umol/L (4 mg/dL), pH<7.30, serum creatinine>3.3, and a high-grade encephalopathy indicate a poor prognosis. In patients who recover, liver function returns to normal within 1 week, and liver histology returns to normal within 3 months. Chronic poisoning is usually similar, but alcoholics may present with a syndrome of severe combined hepatic and renal insufficiency with dehydration, jaundice, coagulopathy, hypoglycemia, and acute tubular necrosis.

Diagnostic Evaluation A serum acetaminophen level should be obtained between 4 and 24 h after ingestion. A level above the lower line on the Rumack-Matthew nomogram (Fig. 396-2) indicates possible hepatotoxicity and the need for antidote therapy.

TREATMENT

Activated charcoal is recommended for patients who present within 4 h of ingestion. (Charcoal does not interfere significantly with acetylcysteine therapy.) Antidotal therapy consists of oral N-acetylcysteine (NAC), diluted 3:1 with a nonalcoholic, nondairy beverage. It is given at a loading dose of 140 mg/kg body weight, followed by a maintenance dose of 70 mg/kg body weight every 4 h for 17 additional doses. Treatment is most effective if started within 8 to 10 h of an overdose and should be

administered before the serum level is known. If the level is subsequently shown to be nontoxic, therapy may be discontinued. Side effects of NAC include nausea, vomiting, and epigastric discomfort. The dose should be repeated if vomiting occurs within an hour of dosing. Antiemetics (metoclopramide, droperidol, odansetron) may be necessary. Liver and renal function should be monitored during therapy. Patients with severe hepatotoxicity should be considered for liver transplantation.

ACIDS AND ALKALI

Common alkaline products include ammonia, bleach (sodium hypochlorite), drain cleaners (sodium hydroxide), surface cleaners (phosphates), laundry and dishwasher detergents (phosphates, carbonates), disk batteries, denture cleaners (borates, phosphates, carbonates), and Clinitest tablets (sodium hydroxides). Acids are used in toilet bowl cleaners (hydrofluoric, phosphoric, and sulfuric acids), soldering fluxes (hydrochloric acid), antirust compounds (hydrofluoric and oxalic acids), automobile battery fluid (sulfuric acid), and stone cleaners (hydrofluoric and nitric acids). Other corrosives include hydrogen peroxide, hydrazine, and phenol.

Alkalis produce liquefactive necrosis with rapidly penetrating tissue injury and a higher risk of perforation of the esophagus and stomach than do acids. Acids produce coagulative necrosis. Both may burn the mouth, esophagus, stomach, and proximal small bowel. Liquids tend to produce superficial, often circumferential burns over a larger surface area, while solids and tablets cause localized but deeper burns. The severity of the burn relates to the contact time, the amount ingested, and the pH (especially if<2 or >12) of the ingested product.

Clinical Toxicity Burns of the mouth result in excess salivation, pain, dysphonia, and dysphagia and are manifested by erythema, edema, ulceration, and necrosis. Deep burns may destroy mucosal nerve endings and produce anesthesia. Lack of oral findings does not rule out esophageal or gastric injury. Esophageal symptoms and signs include drooling, painful swallowing, retrosternal pain, and neck tenderness. Vomiting of blood and mucus may occur. Esophageal perforation is suggested by increased severity of chest pain, often with respiratory distress. Epigastric pain, vomiting, and tenderness may occur with burns to the stomach. Aspiration of acids and alkalis may cause fulminant tracheitis and bronchial pneumonia. In severe cases, hypotension, shock, metabolic acidosis, liver and renal dysfunction, hemolysis, and disseminated intravascular coagulation may be seen. Deep burns, particularly if extensive or circumferential, may be followed by fibrosis with stricture formation and obstruction of the esophagus (alkalis) or of the gastric outlet (acids).

Diagnosis Endoscopy, best performed 12 to 24 h after ingestion, is used to document the site of injury and its severity and should be performed in symptomatic patients. Chest and abdominal x-rays and routine laboratory testing should be obtained to evaluate for aspiration, perforation, and organ dysfunction. Residual effects of the ingestion can be assessed by barium swallow.

TREATMENT

Treatment includes immediate dilution with milk or water. Administration of a weak acid

(carbonated beverage or citrus juice) or base (antacid) is also acceptable. Glucocorticoids and esophageal stents have traditionally been used for alkali burns to prevent esophageal stricture formation, but their efficacy is not proven. Animal studies suggest that glucocorticoids may be effective if begun immediately on presentation. If used, a dose of 1 to 2 mg of methylprednisolone per kilogram every 4 to 6 h for at least 2 weeks is suggested. Concomitant prophylactic broad-spectrum antibiotic use is also recommended. Glucocorticoids are not useful for acid burns. Antacids should be used for burns of the stomach. Esophageal stricture or gastric outlet obstruction may require subsequent dilatation and bouginage or surgical reconstruction.

ANTIARRHYTHMIC DRUGS

Class IA (disopyramide, moricizine, procainamide, and quinidine), IB (lidocaine, mexiletine, phenytoin, and tocainide), and IC (encainide, flecainide, propafenone) antiarrhythmics block myocardial cell membrane fast sodium channels and slow cardiac conduction, whereas class III agents (amiodarone, bretylium, ibutilide, and sotalol) block potassium currents and prolong refractoriness. These agents are rapidly absorbed (except for disopyramide and sustained-release formulations), have volumes of distribution ranging from 1 to 10 L/kg, have half-lives of 3 to 16 h, and are eliminated mainly by hepatic metabolism.

Clinical Toxicity The acute ingestion of more than twice the usual daily dose is potentially toxic. Effects generally begin within 1 h and peak within several hours. Toxicity may also develop during chronic therapeutic use. Manifestations include nausea, vomiting, and diarrhea, followed by lethargy, confusion, ataxia, bradycardia, hypotension, and cardiovascular collapse. Anticholinergic effects (blurred vision, dry mucosae) may be seen in disopyramide poisoning. Quinidine and class IB agents may cause agitation, dysphoria, and seizures. ECG findings include bradycardia with AV block, ventricular tachycardia, ventricular fibrillation (including the polymorphous form, torsade de pointes), and QT-interval prolongation. More specifically, class IA agents prolong the PR, QRS, and JT intervals, class IC agents prolong the QRS interval, and class III agents prolong the JT interval. Class IB agents have little or no effects on conduction intervals. Depressed myocardial contractility and arrhythmias may lead to decreased cardiac output and pulmonary edema. Hypoglycemia and mild hypokalemia may be seen with disopyramide and quinidine intoxication, respectively.

Diagnosis Comprehensive toxicology screening will detect most of these agents. Measurement of serum levels are used for monitoring therapy and for confirmation of overdose.

TREATMENT

Activated charcoal is the procedure of choice for gastrointestinal decontamination. Hypotension, bradyarrhythmias, and seizures are treated with standard measures. Patients with persistent hypotension may benefit from pulmonary arterial pressure measurement. Cardiac pacing, intraaortic balloon pump counterpulsation, and cardiopulmonary bypass may be necessary. Ventricular tachyarrhythmias that cause hemodynamic instability should be treated with lidocaine. Bretylium is probably also safe. Sodium bicarbonate (0.5 to 1 mmol/kg by intravenous bolus) may be effective for

tachyarrhythmias due to class IA or IC agents. Mild hypokalemia may be protective, and potassium levels as low as 3.0 mmol/L may be best treated by watchful waiting. Magnesium sulfate (4 g or 40 mL of a 10% solution given intravenously as an initial dose) and overdrive pacing (with isoproterenol or electricity) are used for torsade de pointes. Hemodialysis and hemoperfusion may enhance the elimination of disopyramide, the active procainamide metabolite *N*-acetylprocainamide, and possibly other agents.

ANTICHOLINERGIC AGENTS

Agents that can competitively block the binding of acetylcholine to CNS and parasympathetic postganglionic muscarinic neuroreceptors include antihistamines (H_1 blockers), belladonna alkaloids and related agents (atropine, glycopyrrolate, homatropine, hyoscine, ipratropium, scopolamine), drugs for Parkinson's disease (benztropine, biperiden, trihexyphenidyl), topical mydriatics (cyclopentolate, tropicamide), neuroleptics (clozapine, olanzepine, phenothiazines), skeletal muscle relaxants (cyclobenzaprine, orphenadrine), smooth-muscle relaxants (clidinium, dicyclomine, isometheptene, oxybutynin), tricyclic antidepressants, and some plants (e.g., *Datura stramonium*, or jimson weed) and mushrooms. Their absorption can be delayed following an overdose. Most are weak bases, exhibit variable binding to plasma proteins (18 to 98%), and have moderate volumes of distribution (2 to 6 L/kg). They are eliminated primarily by hepatic metabolism and have half-lives ranging from 2 to 24 h or more.

Clinical Toxicity Manifestations usually begin within an hour of acute overdosage and 1 to 3 days after beginning treatment in cases of chronic poisoning. Toxic doses are only slightly greater than therapeutic ones. CNS manifestations include agitation, ataxia, confusion, delirium, hallucinations, and movement disorders (choreoathetoid and picking movements). Lethargy, respiratory depression, and coma may occur. Peripheral nervous system findings include decreased or absent bowel sounds, dilated pupils, dry skin and mucosal surfaces, urinary retention, and increases in pulse rate, blood pressure, respiratory rate, and temperature. Neuromuscular hyperactivity may lead to rhabdomyolysis and hyperthermia. First-generation H_1 blockers (diphenhydramine and probably others) can sometimes cause tricyclic antidepressant-like cardiotoxicity and seizures. Because of class III antiarrhythmic activity, original nonsedating or second-generation antihistamines (astemizole, terfenadine) caused QT-interval prolongation with subsequent ventricular tachyarrhythmias, especially torsade de pointes, and were withdrawn from U.S. markets.

Diagnosis The diagnosis is supported by detecting these agents in the urine. It can be confirmed by demonstrating resolution of anticholinergic toxicity in response to physostigmine.

TREATMENT

Activated charcoal adsorbs these agents effectively and is the preferred method of gastrointestinal decontamination. Agitation may respond to benzodiazepines, and comatose patients may require intubation and mechanical ventilation. Cardiovascular toxicity and arrhythmias should be treated as described for antiarrhythmics and tricyclic

antidepressants. Physostigmine, an acetylcholinesterase inhibitor, reverses anticholinergic toxicity. It is indicated primarily for uncontrolled agitation and delirium. The dose is 1 to 2 mg given intravenously over 2 to 5 min; the dose can be repeated if there is an incomplete response or recurrent toxicity. If signs of cholinergic poisoning occur (see "Organophosphate and Carbamate Insecticides," below), they can be reversed by atropine in half the amount of physostigmine given. Physostigmine should not be given for seizures or for coma; its arousal effects are nonspecific and cannot be used for diagnostic purposes. Physostigmine is contraindicated in the presence of cardiac conduction defects or ventricular arrhythmias because it can cause asystole in such patients.

ANTICONVULSANTS

Carbamazepine, lamotrigine, phenytoin and other hydantoins, topiramate, and valproate act primarily to limit the spread of a seizure from its focus by inhibiting the passive influx of sodium through voltage-dependent sodium channels in neuronal membranes, an activity analogous to that of class I antiarrhythmics (see above). This action, and the resultant inhibition of the release of excitatory neurotransmitters (e.g., aspartate, glutamate), limits posttetanic potentiation of synaptic transmission. Like the barbiturates and benzodiazepines (see below), felbamate, gabapentin, and the investigational agents tiagabine and vigabatrin enhance synaptic transmission of the inhibitory neurotransmitterGABA. The succimides ethosuximide and methsuximide elevate the seizure threshold by reducing calcium conduction through T-type calcium channels. Valproate also inhibits GABA metabolism and calcium conductance. Valproate and its metabolites interfere with enzymes involved in fatty acid synthesis and oxidation, gluconeogenesis, and the urea cycle. Carbamazepine is structurally similar to the tricyclic antidepressants and can cause similar toxicity (see "Cyclic Antidepressant," below) in overdose.

Anticonvulsants are well absorbed after oral administration. Phenytoin is also available for intravenous use, both as phenytoin and the prodrug phosphenytoin. A prodrug formulation of valproate, divalproex, a molecule of which dissociates into two molecules of valproate, is also marketed. Gastrointestinal absorption is prolonged with regular and sustained-release formulations of carbamazepine, extended-release phenytoin, and enteric-coated divalproex, particularly following overdose. The volume of distribution is small for valproate (0.1 to 0.4 L/kg); moderate for phenytoin (0.5 to 0.8 L/kg); large for carbamazepine, felbamate, gabapentin, and lamotrigine (^{3}1 L/kg); and unknown for other agents. All are eliminated primarily by hepatic metabolism. Carbamazepine has an active (10,11-epoxide) metabolite. Half-lives, therapeutic doses, serum concentrations, adverse effects, and drug interactions are listed inTable 360-9. The half-life of phenytoin, valproate, and possibly carbamazepine and other agents is prolonged following overdose.

Clinical Toxicity Anticonvulsants primarily causeCNSdepression (Table 396-2). Cerebellar and vestibular function are affected first, with cerebral depression occurring later. Effects are the same and occur at similar blood levels, regardless of whether overdose is acute or chronic. Ataxia, blurred vision, diplopia, dizziness, nystagmus, slurred speech, tremors, and nausea and vomiting are common initial manifestations. Paradoxical excitation can occur, and membrane-active agents can sometimes cause

de novo seizures and exacerbation of epilepsy. Coma with respiratory depression usually occurs at serum carbamazepine concentrations >20 ug/mL, serum phenytoin levels >60 ug/mL, and serum valproate levels >180 ug/mL. Anticholinergic effects (see above) may be present in carbamazepine poisoning, and tricyclic antidepressant-like cardiotoxicity (see below) can occur at drug levels>30 ug/mL.

Hypotension and arrhythmias (e.g., bradycardia, conduction disturbances, ventricular tachyarrhythmias) can occur during the rapid infusion of phenytoin. Although these effects have been attributed to its propylene glycol diluent, they have also been reported with rapid infusions of phosphenytoin, which does not contain this solvent. Cardiovascular toxicity after oral phenytoin overdose, however, is essentially nonexistent. Extravasation of phenytoin can result in local tissue necrosis due to the high pH of this formulation. Intravenous phenytoin may also cause the "purple glove syndrome" (limb edema, discoloration, and pain). This can occur hours after infusion and without signs of extravasation. A compartment syndrome with limb ischemia and muscle necrosis is a potential complication. Multiple metabolic abnormalities, including anion-gap metabolic acidosis, hyperosmolality, hypocalcemia, hypoglycemia, hypophosphatemia, hypernatremia, and hyperammonemia (with or without other evidence of hepatotoxicity), can occur in valproate poisoning. Three or more days may be required for resolution of toxicity in severe carbamazepine, phenytoin, and valproate poisoning.

Diagnosis The diagnosis of carbamazepine, phenytoin, and valproate poisoning can be confirmed by measuring serum drug concentrations. Serial drug levels should be obtained until a peak is observed following acute overdose. Quantitative serum levels of other agents are not generally available. Most anticonvulsants can be detected by comprehensive urine screening tests.

TREATMENT

Activated charcoal is the method of choice for gastrointestinal decontamination. Multiple-dose charcoal therapy can enhance the elimination of carbamazepine, phenytoin, valproate, and perhaps other agents. Airway protection and support of respiration with endotracheal intubation and mechanical ventilation, if necessary, are the mainstays of treatment. Seizures should be treated with benzodiazepines or barbiturates. Physostigmine (see "Anticholinergic Agents," above) should be considered for anticholinergic poisoning due to carbamazepine. The treatment of carbamazepine-induced hypotension, cardiac conduction disturbances, and ventricular tachyarrhythmias should include sodium bicarbonate (see "Antiarrhythmic Drugs," above). Phenytoin and phosphenytoin cardiotoxicity usually resolves promptly upon discontinuation of the infusion. Crystalloids and lidocaine can be given if necessary. Tissue injury secondary to phenytoin extravasation should be treated by standard wound care measures. Treatment of the purple glove syndrome includes elevation of the affected extremity. A vascular surgeon should evaluate this condition, if signs of ischemia are present. Occasionally,CNSdepression due to valproate will respond to naloxone (2 mg intravenously). Metabolic derangements should be corrected. Hemodialysis and hemoperfusion can enhance the elimination of valproate and its metabolites. Hemodialysis can also correct associated metabolic disturbances. Hemoperfusion only modestly increases carbamazepine elimination. These procedures

should be reserved for patients with persistently high drug levels (e.g., carbamazepine³40 ug/mL and valproate³1000 ug/mL) who do not respond to supportive care.

BARBITURATES

Barbiturates bind to the GABA receptor complex and prolong the opening of the chloride channels in response to GABA, thereby inhibiting excitable cells of the CNS and other tissues. They can be classified as long-acting (6 to 12 h; mephobarbital, barbital, phenobarbital, primidone), intermediate-acting (3 to 6 h; amobarbital, aprobarbital, butabarbital, butalbital), short-acting (1 to 3 h; hexobarbital, pentobarbital, and secobarbital), and ultrashort-acting (<30 min; methohexital, thiamylal, and thiopental).

Barbiturates are weak acids with pK_a values ranging from 7.2 to 8.5, volumes of distribution of 0.8 to 1.5 L/kg of body weight, and 45 to 70% protein binding in the plasma. With therapeutic doses, plasma concentrations generally peak in 1 to 4 h (earlier for short-acting agents than for long-acting ones). Most barbiturates are metabolized by the liver. Some are converted to active metabolites: mephobarbital to barbital, and primidone to phenobarbital and phenylethylmalonamide (PEMA). In contrast to short-acting agents, long-acting ones also undergo significant renal excretion: 95% for barbital, 25 to 33% for phenobarbital, 15 to 42% for primidone, and 95% for PEMA. Half-lives range from 1 h for ultrashort-acting agents to 6 d for long-acting ones.

Clinical Toxicity Barbiturates cause CNS depression (Table 396-2). Hypothermia, hypotension, pulmonary edema, and cardiac arrest may occur in severe cases. Pressure sores, bullous skin lesions, and rhabdomyolysis can develop with prolonged coma. Maximal toxicity usually occurs within 4 to 6 h but may be delayed to 10 h or more after overdosage with long-acting barbiturates.

Diagnosis Serum drug levels can confirm the diagnosis. Significant toxicity is usually apparent when serum concentrations of long-acting barbiturates exceed 170 umol/L (4 mg/dL) and those of short-acting barbiturates exceed 88 umol/L (2 mg/dL). Because of tolerance, the degree of CNS depression relative to dose and drug level is dependent on prior exposure to the drug.

TREATMENT

Activated charcoal effectively adsorbs barbiturates and is the method of choice for gastrointestinal decontamination. Hemodynamic and respiratory support and correction of temperature and electrolyte derangements may be necessary. Renal elimination of phenobarbital (and probably other long-acting agents) is enhanced by alkalinization of urine to a pH of 8 (by giving intravenous sodium bicarbonate) and by saline diuresis. Elimination can also be enhanced by repeated doses of activated charcoal. Since short-acting barbiturates are predominantly metabolized by the liver, diuresis is ineffective. Hemodialysis and hemoperfusion are effective in removing both long- and short-acting barbiturates, but their use should be reserved for patients with refractory hypotension.

BENZODIAZEPINES

Benzodiazepines potentiate the inhibitory effect of GABA on CNS neurons by binding to the GABA receptor complex and increasing the frequency of opening of chloride channels in response to GABA stimulation. They can be classified as long-acting (chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, prazepam, quazepam), short-acting (alprazolam, flunitrazepam, lorazepam, and oxazepam), and ultrashort-acting (estazolam, midazolam, temazepam, and triazolam). Benzodiazepines are readily absorbed, exhibit 85 to 99% protein binding in the plasma, are lipid soluble, and have an apparent volume of distribution of 0.3 to 2 L/kg body weight. They are weak acids with pK_a values ranging from 1.3 to 6.2 and are eliminated mainly by hepatic metabolism. Some have active metabolites. Half-lives range from 2 h for short-acting agents to 8 days for long-acting ones.

Clinical Toxicity CNS depressant effects (Table 396-2) begin within 30 min of acute overdose. Coma and respiratory depression are rare but can occur with ultrashort-acting agents and when benzodiazepines are combined with other CNS depressants. Paradoxical excitation may occur early in the course of poisoning.

Diagnosis The diagnosis is supported by identification of benzodiazepine metabolites in urine. Since immunoassays do not detect all benzodiazepines, a negative result does not exclude the diagnosis. A response to flumazenil confirms the diagnosis.

TREATMENT

Activated charcoal adsorbs benzodiazepines and is the method of choice for gastrointestinal decontamination. Respiratory support should be provided as necessary. Flumazenil, a competitive benzodiazepine receptor antagonist, can reverse CNS and respiratory depression and obviate the need for endotracheal intubation. Doses of 0.1 mg should be given intravenously at 1-min intervals until the desired effect is achieved or a cumulative dose of 3 mg has been given. Since flumazenil has a relatively short duration of action, patients must be monitored carefully for relapse. Should relapse occur, treatment can be repeated (at intervals of 20 min with a maximum dose of 3 mg/h). Flumazenil can cause seizures in patients who have coingested stimulants and tricyclic antidepressants or who are physically dependent on benzodiazepines as a result of chronic use. It should not be used in patients with ECG evidence of tricyclic antidepressant cardiotoxicity.

b-ADRENERGIC BLOCKING AGENTS

b-Adrenergic blocking agents act by competitively inhibiting b-adrenergic neurohumoral receptors. This activity defines them as class II antiarrhythmics. At therapeutic doses, some beta blockers act at both b_1 and b_2 receptors and are "nonselective" (carvedilol, labetalol, nadolol, pindolol, propranolol, timolol); some act predominantly on b_1 receptors and are "cardioselective" (acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol). Certain beta blockers have partial agonist or sympathomimetic activity (acebutolol, carteolol, pindolol, and possibly penbutolol), some have an a_1 blocking activity and the additional property of vasodilation (carvedilol, labetalol), and some have quinidine-like antiarrhythmic effects (acebutolol, metoprolol, pindolol, propranolol,

sotalol, and possibly betaxolol). Antiarrhythmic effects are due to a reduction of sodium and calcium influx during membrane depolarization (phase 0) as a consequence of decreased production of cyclic AMP by adenylate cyclase. Decreased cardiac contractility results from inhibition of calcium influx into cells and the release of calcium from sarcoplasmic reticulum.

Beta blockers are readily absorbed and exhibit variable protein binding (5 to 93%), water solubility, and volumes of distribution (0.23 to 10.0 L/kg body weight). Most beta blockers are eliminated predominantly by hepatic metabolism. Atenolol, nadolol, and sotalol are eliminated primarily by renal excretion, and esmolol is metabolized by erythrocyte esterases.

Clinical Toxicity Effects usually begin within 1/2 h following an overdose and peak within 2 h. Onset may be delayed with the ingestion of sustained-release preparations. Findings include nausea and vomiting followed by bradycardia, hypotension, andCNSdepression. However, agents with sympathomimetic activity can cause hypertension and tachycardia. CNS effects can include seizures and tend to be more pronounced with highly lipophilic agents (penbutolol, propranolol). The skin is often pale and cool. Bronchospasm and pulmonary edema are uncommon unless there is a history of asthma, chronic obstructive pulmonary disease, or congestive heart failure. Metabolic abnormalities include hyperkalemia and hypoglycemia (as a direct result of b-adrenergic receptor blockade) and metabolic acidosis (due to seizures, shock, or respiratory depression).ECGmanifestations include all degrees ofAVblock, bundle branch block, prolonged QRS duration, and asystole. Sotalol may cause QT-interval prolongation with ventricular tachycardia, ventricular fibrillation, and torsade de pointes occurring up to 20 h after overdose. Patients with mild poisoning usually recover within 6 to 12 h, whereas those with severe poisoning and ingestions of sustained-release preparations may be symptomatic for 24 to 48 h.

Diagnosis The diagnosis is primarily based on the clinical presentation. Urine toxicology screening may identify the presence of beta blockers, but blood levels are neither generally available nor helpful in guiding therapy.

TREATMENT

Activated charcoal adsorbs these agents effectively and is the preferred method of gastrointestinal decontamination. Gastric emptying procedures may produce vagal stimulation and exacerbate bradyarrhythmias. Bradycardia associated with hypotension will sometimes respond to atropine, isoproterenol, and vasopressors (amrinone, dopamine, dobutamine, epinephrine, and norepinephrine have been used with variable success, alone or in combination). With severe poisoning, these agents may be ineffective, and glucagon, calcium, cardiac pacing (external or internal), and intraaortic balloon pump support may be necessary. Glucagon, which stimulates adenylate cyclase by a nonadrenergic mechanism, is given at an initial dose of 5 to 10 mg. Patients who respond favorably can be treated with an infusion of 1 to 5 mg/h. Calcium and high-dose insulin can be given with glucose and potassium to reverse negative inotropic effects, as described for calcium channel blocker poisoning. Bronchospasm may be treated with an inhaled beta agonist, subcutaneous epinephrine, and intravenous aminophylline. Lidocaine, magnesium (as for antiarrhythmic poisoning), or overdrive pacing may be

used for sotalol-induced ventricular tachyarrhythmias. Extracorporeal elimination procedures are probably not of benefit, except possibly for atenolol, metoprolol, nadolol, and sotalol.

CALCIUM CHANNEL BLOCKERS

Bepridil, diltiazem, verapamil, and the dihydropyridine derivatives amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, and nisoldipine decrease the influx of calcium across slow (L-type) calcium channels in the membranes of myocardial and vascular smooth-muscle cells during phases 2 (plateau) and 4 (spontaneous depolarization) of the action potential. These actions define them as class IV antiarrhythmics. Bepridil also has class I antiarrhythmic activity. Electrophysiologic effects include decreased cardiac contractility, heart rate [sinoatrial (SA) node rate], andAV nodal conduction. At therapeutic doses, all calcium channel blockers cause vasodilation. Diltiazem and verapamil also have significant negative inotropic and chronotropic activity.

Calcium channel blockers are well absorbed and exhibit high (80 to 99%) plasma protein binding. Most have distribution volumes ranging from 1 to 8 L/kg body weight. They are eliminated mainly by hepatic metabolism, and the half-lives typically range from 1 to 24 h.

Clinical Toxicity Toxic effects begin within 2 h of ingestion of immediate-release preparations but may be delayed up to 18 h following overdoses of sustained-release preparations. Manifestations include nausea, vomiting, bradycardia, hypotension, andCNSdepression (Table 396-2). Hypotension caused by diltiazem and verapamil is usually due to myocardial depression (decreased cardiac output), whereas that caused by the dihydropyridine derivatives is usually due to low peripheral vascular resistance. Reflexive tachycardia is sometimes seen in dihydropyridine poisoning. Seizures can occur and are the result of direct membrane effects as well as cerebral hypoperfusion. Hypotension may precipitate mesenteric or myocardial ischemia or infarction, and depression of cardiac function may lead to pulmonary edema.ECGfindings include all degrees ofAVblock, prolonged QRS and QT intervals (mainly with verapamil), evidence of ischemia or infarction, and asystole. Metabolic acidosis (secondary to shock) and hyperglycemia (resulting from the inhibition of insulin release) may be present. Serum calcium levels, however, remain normal.

Diagnosis These agents can be detected by comprehensive urine screening tests. Serum levels are not generally available or helpful in guiding therapy.

TREATMENT

Activated charcoal is preferred for gastrointestinal decontamination. Symptomatic bradycardia should be treated with atropine, calcium, isoproterenol, glucagon, and electrical (external or internal) pacing. Restoring perfusion is particularly important in patients with organ ischemia. The initial dose of calcium is 10 mL of 10% calcium chloride or 30 mL of the 10% gluconate solution intravenously over 2 min. This dose may be repeated up to four times in patients with a partial, transient, or absent response. High serum calcium levels may be required for a therapeutic effect. A

continuous calcium infusion (0.2 mL/kg body weight per hour up to a maximum of 10 mL/h) may be appropriate when relapse occurs after an initial bolus. Although electrical pacing may be required, glucagon, in the same dose as for beta blocker poisoning, may also be effective. High-dose insulin (0.1-0.2 units/kg body weight of regular insulin as a bolus followed by 0.1-1 units/kg per hour) along with glucose (25-g bolus followed by 1 g/kg per hour of a 20% infusion) and potassium to maintain euglycemia and normokalemia should also be considered. This treatment enhances myocardial metabolism and improves myocardial contactility. It may be particularly effective in verapamil poisoning. Hypotension that persists despite resolution of bradycardia should initially be treated with fluids. Amrinone, dopamine, dobutamine, glucagon, and norepinephrine, alone or in combination, have also been used with success. Intraaortic balloon pump support should be used in patients with refractory shock. Patients with mild toxicity usually recover within a few hours, whereas those with severe toxicity or overdose with sustained-release preparations may remain symptomatic for 24 h or longer.

CARBON MONOXIDE

Carbon monoxide is produced in large amounts in industrial processes as well as by internal combustion engines, fossil-fueled home appliances (generators, heaters, stoves), and the incomplete combustion of nearly all natural materials and synthetic products. Methylene chloride, a solvent in paint removers, is metabolized to carbon monoxide.

Carbon monoxide is absorbed rapidly through the lungs and binds to hemoglobin (forming carboxyhemoglobin) with an affinity 210 times that of oxygen. Its binding reduces oxygen transport by hemoglobin and also decreases the release of oxygen in tissues (the oxygen dissociation curve shifts to the left). Carbon monoxide also binds to myoglobin, decreasing its oxygen-carrying capacity, and to mitochondrial cytochrome oxidase, inhibiting cellular respiration. The net effect is tissue hypoxia with anaerobic metabolism, lactic acidosis, lipid peroxidation, and free radical formation. Once carbon monoxide exposure is discontinued, dissociation of the hemoglobin-carbon monoxide complex occurs, and carbon monoxide is excreted through the lungs. At atmospheric pressure, the carboxyhemoglobin half-life is 4 to 6 h. It decreases to 40 to 80 min when breathing 100% oxygen and to 15 to 30 min with hyperbaric oxygen therapy. The apparent half-life after methylene chloride exposure is considerably longer.

Clinical Toxicity Manifestations of carbon monoxide poisoning include shortness of breath, dyspnea, tachypnea, headache, emotional lability, confusion, impaired judgment, clumsiness, and syncope. Nausea, vomiting, and diarrhea may also occur. Cerebral edema, coma, respiratory depression, and pulmonary edema may be seen in severe poisoning. Cardiovascular manifestations include ischemic chest pain, arrhythmias, heart failure, and hypotension. In comatose patients, blisters and bullae may develop over pressure points. Serum creatine kinase and lactate dehydrogenase levels may be elevated. Myoglobinuria secondary to muscle necrosis may result in renal failure. Visual field defects, blindness, and venous engorgement with papilledema or optic atrophy may be noted. Arterial blood gas analysis may reveal metabolic acidosis, a normal P_{O_2}, decreased oxygen saturation (when measured by CO-oximetry, but not when calculated from the P_{O_2} or measured by pulse oximetry), and a variable P_{CO_2}.

Oxygen saturation measured by pulse oximetry will be falsely elevated but less than normal. A cherry-red color of skin and mucous membranes is rare, and cyanosis is usual.

After brief exposure, carboxyhemoglobin fractions of 15 to 20% are associated with mild symptoms, 20 to 40% with moderate symptoms, and 40 to 50% with severe symptoms. Fractions>60% are often fatal. With prolonged exposure, toxicity occurs at lower fractions. Patients with loss of consciousness are at risk for developing neuropsychiatric sequelae 1 to 3 weeks after exposure. Manifestations vary from subtle personality changes and intellectual impairment to gross neurologic deficits such as blindness, deafness, incoordination, and parkinsonism.

Diagnosis An elevated carboxyhemoglobin fraction confirms exposure, but the result must be interpreted with respect to the time elapsed from exposure to sampling. If the carboxyhemoglobin fraction cannot be measured directly, the difference between the oxygen saturation calculated from the P_{O_2} and that measured by CO-oximetry can be used to estimate the carboxyhemoglobin fraction.

TREATMENT

In conscious patients, oxygen should be administered by a non-rebreather mask at 10 L/min until carboxyhemoglobin fraction is <10% and symptoms have resolved. Infants and pregnant women require treatment for several more hours, because fetal hemoglobin has a higher affinity for carbon monoxide than adult hemoglobin. Endotracheal intubation and mechanical ventilation with 100% oxygen are indicated in patients with coma, seizures, or cardiovascular instability. Arrhythmias and hypotension are treated by usual measures. Although hyperbaric oxygen therapy is often recommended for patients with coma, syncope, seizures, and cardiovascular instability, for those with less severe neurologic or cardiovascular dysfunction that does not resolve with oxygen and supportive measures, and for those who develop neurologic sequalae, recent data suggest that it is no more effective than prolonged high-flow normobaric oxygen in reversing acute toxicity and preventing sequelae.

CARDIAC GLYCOSIDES

Poisoning with digitalis and other cardiac glycosides occurs most often during therapeutic or suicidal use of digoxin. It can also occur when plants (foxglove, oleander, squill) or the skin (venom) of *Bufo* toads (Colorado River, Asian, Chinese, European) are ingested. Toad venom also contains hallucinogens and accounts for the practice of toad licking as a form of recreational drug abuse. At therapeutic doses, cardiac glycosides inhibit the enzyme Na_+, K_+-ATPase, leading to increased intracellular levels of Na_+ and Ca_{2+} and decreased intracellular K_+levels. Increased cytosolic Ca_{2+}enhances the excitation-contraction coupling of actin and myosin during systole and improves myocardial contractility. Electrophysiologic effects are due to indirect sympatholytic and vagotonic effects and to direct effects on cardiac muscle, pacemaker, and conduction cells (reduced action potential duration andAV node resting potential, prolongation of the refractory period).ECGmanifestations include prolongation of the PR interval, shortening of the QT interval, scooping and depression of the ST segment, and decreased T-wave amplitude. In toxic doses,SA node automaticity and AV nodal

conduction are decreased. Sympathetic tone; automaticity in muscle, AV nodal, and conduction cells; and afterdepolarizations are increased. ECG manifestations include bradydysrhythmias as well as triggered tachydysrhythmias. Hypokalemia potentiates the electrophysiologic effects of cardiac glycosides, increases their tissue binding, and decreases their renal excretion. Magnesium blocks calcium channels and modulates their sympathetic effects, whereas calcium and hypoxia enhance their activity.

Digoxin is absorbed and distributed slowly. Serum levels may not correlate with clinical effect for up to 8 h following a dose. Digoxin is 25 to 30% protein bound in the plasma, has a large volume of distribution of 5 to 6 L/kg body weight, and is eliminated primarily by renal excretion. The half-life ranges between 36 and 45 h, is prolonged in hepatic failure and in renal failure, and may be shortened in overdose. Therapeutic serum concentrations range from 0.6 to 2.5 nmol/L (0.5 to 2.0 ng/mL).

Clinical Toxicity Symptoms include vomiting, confusion, delirium, and occasionally hallucinations, blurred vision, photophobia, scotomata, and chromotopsia (disturbed color perception). Cardiac manifestations include sinus arrhythmia, sinus bradycardia, and all degrees of AV block. Premature ventricular contractions, bigeminy, ventricular tachycardia, and fibrillation also occur. The combination of a supraventricular tachyarrhythmia and AV block (e.g., paroxysmal atrial tachycardia with second-degree AV block, atrial fibrillation with third-degree AV block) or the presence of bidirectional ventricular tachycardia is highly suggestive of cardiac glycoside poisoning. Bradyarrhythmias and hypokalemia are common with chronic intoxication, whereas tachyarrhythmias and hyperkalemia are generally seen with acute poisoning. Similarly, serum digoxin levels may be minimally elevated or even therapeutic in chronic toxicity, whereas they are usually markedly elevated following acute overdose. Since chronic poisoning occurs almost exclusively in patients with underlying heart disease, the incidence, variety, and severity of dysrhythmias tend to be greater than with acute poisoning. In patients taking digoxin, poisoning should be suspected when a normal or fast heart rate becomes slow or the rhythm becomes regularly irregular.

Diagnosis The diagnosis is confirmed by measuring the serum digoxin level. Levels must be interpreted with respect to the time of the last dose. Digoxin assays may cross-react with nondigoxin glycosides and produce a false-positive result. Toxicology screening tests do not detect cardiac glycosides.

TREATMENT

Activated charcoal is preferred for gastrointestinal decontamination. Emesis and gastric intubation may cause vagal stimulation and precipitate or worsen conduction disturbances. Repeated doses of charcoal can enhance the elimination of digoxin. Potassium, magnesium, and calcium abnormalities and hypoxia should be corrected. Sinus bradycardia and second- and third-degree heart block resulting in hypotension can be treated with atropine, dopamine, epinephrine, and possible phenytoin (100 mg intravenously every 5 min up to 15 mg/kg) and isoproterenol. Magnesium sulfate (as for antiarrhythmic poisoning), phenytoin, lidocaine, bretylium, and amiodarone may be given for ventricular tachyarrhythmias. Antidotal therapy with digoxin-specific Fab-fragment antibodies should be administered for potentially life-threatening dysrhythmias. A serum potassium level ³5.5 meq/L following acute overdose is

associated with severe poisoning and is an indication for antibody therapy in the absence of dysrhythmias. Electrical pacing may be necessary as a temporizing measure. Prophylactic pacing is not recommended, as the pacing wire may increase ventricular irritability and precipitate tachydysrhythmias. If defibrillation is necessary, a low energy level (e.g., 50 W×s) should be used initially as the electrical shock may precipitate arrhythmias, which are more malignant and refractory to treatment. Digoxin-specific Fab-fragment antibodies are given intravenously over 15 to 30 min, unless cardiac arrest has occurred, in which case the solution is given as a bolus. Effects are usually apparent within an hour. The drug-antibody complex is excreted in the urine with a half-life of 16 to 20 h. In patients with renal failure, the drug-antibody complex is metabolized over a period of days to weeks. Although free digoxin levels decrease rapidly to zero following antibody administration, routine methods used to measure digoxin do not differentiate between bound and unbound drug, so that drug levels do not correlate with toxicity after antibody therapy.

Each vial (40 mg) of digoxin antibody fragments can neutralize 0.6 mg of digoxin. Formulas and tables for calculating the dose of antibody are available in the package insert. Unfortunately, toxicity may occur before distribution is complete or before levels are available. In addition, the amount of an acute overdose may be unknown, and calculated doses often exceed the effective dose (leading to costly overtreatment). The following empirical dosing guidelines are therefore offered. With chronic intoxication, the total-body drug load and serum drug levels only slightly exceed therapeutic amounts, patients may be dependent on inotropic effects, and a dose of 1 to 4 vials is usually effective. In acute poisoning, drug load is generally quite high, and 5 to 15 vials are usually required. Initial doses can be on the low side and repeated as necessary. Antibodies cross-react with other cardiac glycosides, but larger doses may be needed for toxicity not involving digoxin.

CYANIDE

Cyanide salts are used in photography, metallurgy, electroplating, metal cleaning, and ore refining. Hydrogen cyanide gas, which is used as a fumigant rodenticide and in chemical syntheses, is liberated when they are combined with acids. Cyanide is also produced during the decomposition and metabolism of nitroprusside. Organic cyanides (nitriles) are used in making rubber, in artificial nail removers, and as rodenticides. Cyanogenic glycosides are present in the seeds of the chokeberry, cherry, plum, peach, apricot, pear, bean, apple, and crabapple.

Cyanide inhibits mitochondrial cytochrome oxidase, thereby blocking electron transport and preventing oxygen utilization and oxidative metabolism. Lactic acidosis occurs as a consequence of anaerobic metabolism. Cyanide is rapidly absorbed from the stomach, lungs, mucosal surfaces, and unbroken skin. Ingested salts react with gastric hydrochloric acid to form hydrocyanic acid, which is then absorbed. A dose of 200 mg of potassium or sodium cyanide, or 50 mg of hydrocyanic acid, is potentially lethal. Cyanide is 60% protein bound, concentrated in red cells, and has a volume of distribution of 1.5 L/kg body weight. Mitochondrial rhodanase mediates the transfer of sulfur from thiosulfate to the cyanide ion and converts it to less toxic thiocyanate, which is excreted in the urine. Cyanide poisoning during nitroprusside therapy can be prevented by the prophylactic administration of thiosulfate.

Clinical Toxicity Effects begin within seconds of inhalation and within 30 min of ingestion. Initial manifestations of cyanide poisoning include a burning sensation in the mouth and throat, agitation, anxiety, faintness, headache, nausea, vomiting, diaphoresis, dyspnea, tachycardia, and hypertension. A bitter almond odor may be detected on the breath. Later effects include coma, convulsions, opisthotonus, trismus, paralysis, respiratory depression, pulmonary edema, arrhythmias, bradycardia, and hypotension. A rough correlation exists between blood cyanide levels and symptoms: Levels<8 umol/L (0.02 mg/L) are associated with no symptoms; 20 to 40 umol/L (0.05 to 0.1 mg/dL) with flushing and tachycardia; 40 to 100 umol/L (0.1 to 0.25 mg/dL) with obtundation; 100 to 200 umol/L (0.25 to 0.3 mg/dL) with coma and respiratory depression; and levels >120 umol/L (0.3 mg/dL) with death. With significant poisoning, lactic acidosis is invariably present.ECGabnormalities include both tachyarrhythmias and bradyarrhythmias.

Diagnosis The diagnosis is based on the history and physical examination. Although measurement of the whole-blood cyanide level will confirm the diagnosis, cyanide assays are not routinely available and treatment decisions must be based on clinical findings. Lactate levels have been used as a surrogate marker.

TREATMENT

Management involves supportive therapy, gastrointestinal decontamination, high-dose oxygen, and antidotal therapy with amyl nitrite, sodium nitrite, and sodium thiosulfate (the Lilly cyanide antidote kit). Nitrites convert hemoglobin to methemoglobin, which has a higher affinity for cyanide than does cytochrome oxidase and thus promotes its dissociation from this enzyme. Thiosulfate reacts with cyanide, which is slowly released from cyanomethemoglobin, to form thiocyanate. Oxygen reverses the binding of cyanide to cytochrome oxidase sites and enhances the efficacy of sodium nitrite and sodium thiosulfate, in addition to acting as a substrate for metabolism.

Indications for antidotal therapy include altered mental status, abnormal vital signs, and metabolic acidosis. Amyl nitrite, administered for 30 s of each minute and using a fresh ampule every 3 min, is a first-aid measure and is omitted when intravenous sodium nitrite is available or the patient has been intubated. The ampule is broken between two pads of gauze and placed over the airway while the patient breathes spontaneously or is ventilated by a bag-mask unit. Sodium nitrite is administered as a 3% solution at a dose of 10 to 15 mL (300 to 450 mg) over 1 to 2 min. Sodium thiosulfate is also administered intravenously, as a 25% solution at a dose of 50 mL (12.5 g) given over 1 to 2 min. With recurrent or persistent symptoms, doses of sodium nitrite and sodium thiosulfate can be repeated. Hyperbaric oxygen therapy should be considered in patients who fail to respond to antidotal therapy. Hydroxycobalamin, a vitamin B_{12}precursor that also binds cyanide ion, is an alternative antidote that is not yet widely available.

CYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants (TCAs) such as amitriptyline, imipramine (and their respective active metabolites nortriptyline and desipramine), chlomipramine, doxepin, protriptyline,

and trimipramine and polycyclic agents such as amoxapine, bupropion, maprotiline, mirtazepine, and trazodone (and its metabolite nefazodone) act primarily by blocking the presynaptic reuptake monoamine neurotransmitters in the CNS, most importantly norepinephrine and serotonin, but also dopamine. They also have anticholinergic, a-adrenergic receptor blocking, and quinidine-like (class IA antiarrhythmic) effects as well as variable and selective blocking activity at histamine and monoamine receptors. Bupropion, nefazodone, and trazodone have serotonin agonist activity. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertaline, citalopram, and fluvoxamine can enhance the presynaptic release of serotonin and block its receptors in addition to inhibiting its reuptake. The nonselective serotonin reuptake inhibitors such as venlafaxine also inhibit norepinephrine reuptake.

Cyclic antidepressants are well absorbed. Peak serum levels usually occur within 2 to 6 h of ingestion but can sometimes occur later. These agents exhibit high (about 95%) protein binding in the plasma, have large volumes of distribution (20 to 45 L/kg body weight), and are eliminated mainly by hepatic metabolism, with half-lives of 24 h or more.

Clinical Toxicity Effects generally develop within 30 min of ingestion and peak within 6 h. Following low overdosage (about 10 mg/kg) of TCAs, anticholinergic effects predominate (see "Anticholinergic Agents," above). With larger doses, marked CNS depression (Table 396-2), cardiotoxicity, seizures, and hypotension occur. Ventricular tachyarrhythmias, atrioventricular and intraventricular conduction delays, terminal bradycardia, decreased cardiac output, and pulmonary edema may be seen. Death can occur within 6 h of ingestion from cardiovascular effects or much later from multiple organ failure or pulmonary complications. Terminal (last 40 ms) QRS right-axis deviation, an R wave greater than the S wave or >3 mm in lead aV_R, and prolongation of the QRS complex (>100 ms) of the ECG are sensitive indicators of TCA cardiotoxicity. Increasing duration of the QRS complex correlates with an increased risk of cardiac arrhythmias and seizures.

Although seizures can occur, CNS depression is typically mild with SSRIs and moderate with the polycyclic agents. Sinus tachycardia is common, but life-threatening cardiovascular effects are virtually nonexistent. An exception is trazodone, which can cause QT-interval prolongation and ventricular tachycardia. The serotonin syndrome (discussed separately) is also a potential complication of SSRI overdose.

Diagnosis The diagnosis is supported by the presence of these drugs in the urine on comprehensive screening tests. TCA serum levels are diagnostic and generally correlate with severity. Serum levels of active metabolites should be summed with that of the parent compound when estimating the serum concentration. Levels 1000 nmol/L (300 ng/mL) are therapeutic. Levels >3300 nmol/L (1000 ng/mL) are associated with severe poisoning.

TREATMENT

Activated charcoal is the preferred method of gastrointestinal decontamination. Repeated doses may enhance the elimination of some agents. Physostigmine (see "Anticholinergic Agents," above) can reverse anticholinergic effects due to

low-dose TCA poisoning and may be used if the ECG is normal and deterioration has been excluded by a suitable period of observation. For other toxicity, treatment includes support of respiration and volume expansion and norepinephrine or high-dose dopamine for hypotension. Seizures should be treated with benzodiazepines and barbiturates. Phenytoin is of uncertain benefit. Acidemia increases the likelihood of arrhythmias and should be corrected. Sodium bicarbonate should be given as a bolus following a seizure and as an infusion to maintain a serum pH of 7.45 to 7.50 in patients with QRS prolongation. Treatment of ventricular tachyarrhythmias is similar to that described for antiarrhythmic agents and should include sodium bicarbonate. Phenytoin is often recommended, but its efficacy is not established. b-Adrenergic blockers and class IA, IC, and III antiarrhythmics should be avoided. Cardiac pacing and invasive hemodynamic support may be necessary for severe cardiovascular depression.

ETHYLENE GLYCOL

Ethylene glycol is a colorless, odorless, sweet-tasting, water-soluble liquid used as a solvent for paints, plastics, and pharmaceuticals; in the manufacture of explosives, fire extinguishers, and foams; and as an ingredient in hydraulic fluids, windshield cleaners, radiator antifreeze, and de-icer solutions.

Ethylene glycol produces intoxication similar to that caused by ethanol but is more potent. Peak blood levels occur approximately 2 h after ingestion. The volume of distribution is 0.6 to 0.8 L/kg body weight. Ethylene glycol is oxidized by alcohol dehydrogenase to glycoaldehyde, which is metabolized successively to glycolic acid, glyoxylic acid, and oxalic acid. Pyridoxine and thiamine are cofactors in degradation pathways. As much as 20% is excreted unchanged in the urine. The half-life ranges from 3 to 8 h. Metabolites, primarily glycolic acid, cause CNS depression, metabolic acidosis with an increased anion gap, and interstitial and tubular damage to the kidney. Oxalic acid may precipitate as calcium oxalate in the brain, heart, kidney, lung, pancreas, and urine and cause hypocalcemia.

Ethanol and fomepizole bind to alcohol dehydrogenase with a higher affinity than ethylene glycol and hence block the production of toxic metabolites. Ethanol is metabolized by alcohol dehydrogenase, but fomepizole is not. Ethanol and fomepizole prolong the half-life of ethylene glycol to 15 to 20 h.

Clinical Toxicity As little as 120 mg/kg body weight or 0.1 mL/kg body weight (one swallow) of pure ethylene glycol can result in a potentially toxic serum concentration of 3 mmol/L (20 mg/dL). Effects begin about 30 min after ingestion and include nausea, vomiting, slurred speech, ataxia, nystagmus, and lethargy. A faint, sweet aromatic odor may be detected on the breath, and the serum osmolality may be elevated. Effects caused by metabolites begin 3 to 12 h after ingestion (longer if ethanol has also been ingested) and include tachypnea, agitation, confusion, lethargy, back pain, hypotension, coma, and seizures. In severe cases, ARDS, cyanosis, pulmonary edema, and cardiomegaly may be seen. Laboratory findings include metabolic acidosis, an increased anion gap (low bicarbonate and chloride), hypocalcemia, leukocytosis, increased BUN and creatinine, calcium oxalate crystalluria, and proteinuria. Acute tubular necrosis with oliguria or anuria typically becomes evident 12 to 24 h following ingestion. Renal failure is usually reversible but may last days to weeks.

Diagnostic Evaluation The diagnosis is established by measuring serum ethylene glycol and glycolate levels. The diagnosis is suggested by an elevated serum osmolality and ethanol-like effects soon after ingestion and by an increased anion-gap metabolic acidosis and crystalluria later on. If laboratory confirmation is not immediately available, the osmolal gap can also be used to estimate the serum ethylene glycol concentration (Table 396-3).

TREATMENT

Gastric aspiration is the decontamination procedure of choice. Activated charcoal should also be administered. Supportive measures include protection of the airway, ventilatory and circulatory support, and anticonvulsants for seizures. Metabolic acidosis will not resolve spontaneously and should be corrected with sodium bicarbonate; large doses may be required. Sodium bicarbonate should also be given to alkalinize the urine as this will enhance the excretion of acid metabolites. Fluids and diuretics can be used to treat oliguria but they do not increase the excretion of ethylene glycol. Hypocalcemia is treated with intravenous calcium salts. Supplemental pyridoxine (50 mg qid) and thiamine (100 mg qid) may be beneficial.

Indications for ethanol or fomepizole therapy include an ethylene glycol concentration>3 mmol/L (20 mg/dL); an elevated osmolal gap, an increased anion-gap metabolic acidosis, back pain, laboratory evidence of renal toxicity, or ethanol-like intoxication in a patient with a history of ethylene glycol ingestion and a low or undetectable ethanol level; an elevated osmolal gap not accounted for by the presence of ethanol, isopropyl alcohol, acetone, or propylene glycol in a patient with ethanol-like intoxication; and an increased anion-gap metabolic acidosis with a low lactate level not explained by alcoholic or diabetic ketoacidosis, uremia, or salicylate, formaldehyde, paraldehyde, or toluene exposure. A serum ethanol level of ³20 mmol/L (100 mg/dL) is required to inhibit the metabolism of ethylene glycol (higher levels may be needed with very high ethylene glycol concentrations). The loading dose of ethanol is 10 mL/kg of 10% ethanol intravenously or 1 mL/kg of 95% ethanol by mouth; the maintenance dose is 1.5 mL/kg per hour of 10% ethanol intravenously or 3 mL/kg per hour of 10% ethanol intravenously during hemodialysis. Maintaining a therapeutic concentration is often difficult; levels must be monitored frequently and the dose adjusted as necessary. Ethanol induces its own metabolism and progressively higher doses may be required as time passes. Fomepizole is diluted in 100 mL of intravenous fluid and administered over 30 min in a loading dose of 15 mg/kg followed by 10 mg/kg every 12 h for four doses and 15 mg/kg thereafter. Additional doses are required in patients undergoing dialysis. Although expensive (about $1000 U.S. per 1.5-g vial), fomepizole has a number of advantages over ethanol: it does not causeCNSdepression, hypoglycemia, or fluid, electrolyte, and serum osmolality derangements; it has a longer duration of action; and does not require monitoring of serum drug levels. Although seizures have occurred after fomepizole, their etiology is unclear, and side effects have generally been limited to headache, nausea, dizziness, rash, eosinophilia, and mild self-limited hepatotoxicity. Serum ethylene glycol concentrations should be monitored frequently. Ethanol or fomepizole should be continued until the ethylene glycol level falls below 1.5 mmol/L (10 mg/dL).

Hemodialysis enhances the elimination of ethylene glycol and its toxic metabolites so

that it is complete in about 3 h. Indications for hemodialysis include an ethylene glycol concentration>8 mmol/L (50 mg/dL) and metabolic acidosis not readily correctable with bicarbonate and antidotal therapy, lack of clinical improvement despite treatment, and laboratory evidence of renal toxicity (regardless of the ethylene glycol level). This therapy should be continued (repeated intermittently) until acidemia resolves and the ethylene glycol level is <3 mmol/L (20 mg/dL).

HYDROCARBONS

Aromatic hydrocarbons, such as xylene and toluene, halogenated hydrocarbons, such as carbon tetrachloride and trichloroethane, and petroleum distillate hydrocarbons, such as gasoline, lacquer thinner, mineral seal oil, kerosene, and lighter fluid, areCNSdepressants and gastrointestinal and respiratory tract irritants. They are absorbed rapidly following inhalation or pulmonary aspiration. Aromatic and halogenated hydrocarbons are also absorbed following ingestion and are toxic to the heart, liver, and kidneys. Aromatic hydrocarbons can cause bone marrow suppression and skeletal muscle damage. Petroleum distillate hydrocarbons are poorly absorbed following ingestion.

Clinical Toxicity Hydrocarbons produceCNSexcitation in low doses and depression in high doses. Rarely, coma and seizures occur. Psychosis, cerebral and cerebellar atrophy, encephalopathy, and peripheral neuropathy can result from chronic inhalation. Other effects include nausea, vomiting, abdominal pain, hepatitis, renal tubular acidosis, acute hepatic or renal failure, and rhabdomyolysis. Sudden death due to myocardial irritability and ventricular fibrillation may occur following hydrocarbon sniffing. After ingestion, hydrocarbons cause burning of the mouth and throat with subsequent nausea, vomiting, and diarrhea. Aspiration into the lungs may occur with ingestion or as a result of vomiting and cause pneumonia. Following aspiration, chest x-ray abnormalities include infiltrates, atelectasis, effusions, pneumothorax, and pneumatoceles. Renal tubular acidosis with decreased serum bicarbonate, calcium, phosphate, and potassium and increased serum chloride may result from chronic aromatic hydrocarbon inhalation.

Diagnosis The diagnosis is based on the clinical presentation. Assays for hydrocarbons are not routinely available.

TREATMENT

The ingestion of aromatic and halogenated hydrocarbons requires prompt gastric lavage. More than one episode of ipecac-induced emesis is contraindicated, and the role of activated charcoal is controversial. Since the ingestion of other types of hydrocarbons is unlikely to result in systemic toxicity and since the risk of aspiration during gastric decontamination is greater than the potential benefit, decontamination is contraindicated for these ingestions. Supportive therapy includes oxygen, respiratory support, and monitoring of liver, renal, and myocardial function. Metabolic abnormalities should be corrected, and patients with aspiration pneumonitis should be monitored for superimposed bacterial infection. Glucocorticoids are ineffective.

HYDROGEN SULFIDE

Hydrogen sulfide is a rapidly acting, malodorous ("rotten eggs"), colorless, irritating gas. It is encountered in the petroleum and mining industries, tanning of leather, vulcanization of rubber, the production of synthetic fabrics, metal refining, the production of heavy water for atomic reactors, and glue and felt manufacturing. It is also found in sewers, sulfur springs, and the holds of fishing vessels and as a byproduct of manure storage.

Sulfide anion inhibits electron transport in the cytochrome oxidase system, thereby inhibiting aerobic metabolism with resultant cellular anoxia and lactic acidosis. Hydrogen sulfide is rapidly detoxified by oxidation to sulfate products, which are excreted by the kidneys.

Clinical Toxicity Exposure to low concentrations of hydrogen sulfide results in rhinitis, conjunctivitis, and pharyngitis. Inhalation of large amounts causes headache, vertigo, nausea, vomiting, confusion, seizures, and coma. Hypoventilation, hypoxia, cyanosis, metabolic acidosis, pneumonia, and pulmonary edema can occur.

Diagnosis The diagnosis is based on the characteristic clinical features, including the characteristic odor, exposure setting, and rapidity of onset. Sulfide levels have been used to confirm the diagnosis but are not routinely available.

TREATMENT

Treatment includes prompt removal of the victim from the site of exposure, assisted ventilation, and 100% oxygen. Although controversial, amyl and sodium nitrite, in the same dose as for cyanide poisoning, should be considered for patients with coma or cardiac arrest who fail to respond to oxygen therapy. Nitrites promote the dissociation of sulfide ions from cytochrome oxidase by providing an alternative binding site (methemoglobin). They also enhance detoxification by acting as a catalyst for sulfide oxidation. Hyperbaric oxygen should be considered in patients who do not respond to the preceding measures.

IRON

Non-transferring-bound plasma iron catalyzes the formation of free radicals, which then cause mitochondrial injury, lipid peroxidation, increased capillary permeability, vasodilation, and intestinal, renal, hepatic, myocardial, and pulmonary toxicity. Ingestion of 20 mg/kg body weight of elemental iron typically produces gastrointestinal symptoms, and 60 mg/kg body weight may cause systemic toxicity. Ferrous sulfate, fumarate, gluconate, and succinate contains 20, 33, 12, and 35% elemental iron, respectively.

Ferrous iron is absorbed by duodenal and jejunal cells, oxidized to ferric iron, and bound to ferritin. It is then slowly released, binds to plasma transferrin (an iron-specific globulin) and other proteins, and is transported to tissues. Serum iron levels usually peak 4 to 6 h after overdosage (later for delayed-release formulations). Iron bound to transferrin is nontoxic.

Clinical Toxicity Initial manifestations include vomiting and diarrhea (often bloody).

X-rays may reveal iron tablets in the stomach or small bowel. Systemic effects include lethargy, hypotension, and metabolic acidosis. Seizures, coma, pulmonary edema, and vascular collapse may occur with severe poisoning. Jaundice, elevated hepatic enzyme levels, prolongation of prothrombin time, and hyperammonemia are indicative of liver injury. Proteinuria and cells in the urine indicate renal injury. In the recovering patient, gastric ulcerations and scars may cause outlet obstruction. Overgrowth of *Yersinia enterocolitica* with sepsis is a rare complication of iron overload.

Diagnosis The diagnosis is primarily based on clinical findings. A serum iron concentration>50 umol/L (300 ug/dL) is potentially toxic. A positive x-ray, fever>38.5°C, hyperglycemia >8.5 mmol/L (150 mg/dL), and leukocytosis (white blood cell count >15,000/uL) have also been associated with potential toxicity. Serious poisoning is generally associated with levels >80 umol/L (500 ug/dL). A positive urine deferoxamine provocative challenge test (see below) is also diagnostic.

TREATMENT

Gastric lavage and whole-bowel irrigation are the preferred methods of gastrointestinal decontamination. When iron tablets are visible on x-ray, serial films can be used to assess their success. Endoscopic removal and gastrostomy may be necessary when these procedures are ineffective (e.g., large ingestions, concretions). Complexation of ingested iron with orally administered activated charcoal, bicarbonate, phosphate, deferoxamine, or magnesium hydroxide has not been shown to reduce toxicity.

Intravenous sodium bicarbonate should be used to correct metabolic acidosis. Nearly all patients are volume depleted and should be given intravenous crystalloid. Coagulation abnormalities should be treated with vitamin K or blood products.

Parenteral deferoxamine should be given to patients with elevated serum iron levels or clinical manifestations of poisoning. If the iron level is mildly elevated or not immediately available or if the patient has mild clinical toxicity, an intravenous challenge dose of 15 mg/kg per hour can be given. Urine becomes a vin rose or rusty orange color in the presence of the iron-deferoxamine complex (ferrioxamine), indicating that free iron is present. Patients with a positive challenge test or significant clinical toxicity should be given intravenous deferoxamine at a rate of 10 to 15 mg/kg per hour. When iron levels exceed 180 umol/L (1000 ug/dL), larger deferoxamine doses (up to 30 mg/kg per hour) can be given initially. Once the patient is asymptomatic or improved, deferoxamine therapy should be discontinued. Rapid infusion of deferoxamine can cause hypotension. Pulmonary edema is a complication of prolonged, high-dose therapy, and renal failure can occur if it is administered to hypovolemic patients. Exchange transfusion or plasmapheresis should be reserved for patients with renal failure or who fail to respond to the preceding therapy.

ISONIAZID

Toxic doses of isoniazid decrease the synthesis of the inhibitoryCNSneurotransmitterGABA by interfering with the activation and supply of pyridoxal-5-phosphate, a cofactor for the enzyme glutamic acid decarboxylase, which converts glutamic acid to GABA. Isoniazid also causes pyridoxine depletion by

complexing with pyridoxine to form hydrazides that are then excreted, and it forms hydrazones that inhibit the production and activity of pyridoxal phosphate enzymes. The resultant decrease in GABA can cause seizures with increased lactate production by muscle. Since isoniazid also inhibits the metabolism of lactate to pyruvate, profound and intractable lactic acid acidosis may ensue.

Isoniazid is rapidly absorbed, with peak serum concentrations noted within 1 to 2 h. The volume of distribution is approximately 0.7 L/kg body weight. Serum protein binding is slight. Elimination is primarily by hepatic acetylation to acetylisoniazid followed by hydrolysis to isonicotinic acid. The rate of acetylation is genetically determined and characterized as either slow or fast with corresponding half-lives of 0.5 to 1.5 and 2 to 4 h.

Clinical Toxicity Nausea, vomiting, dizziness, slurred speech, lethargy, and confusion begin within 30 min of ingestion of doses greater than 20 mg/kg body weight. Severe poisoning results in coma, respiratory depression, generalized seizures, and lactic acid acidosis. Seizures may be protracted and relatively unresponsive to standard anticonvulsant therapy. Acidosis does not occur when seizures are prevented.

Diagnosis The diagnosis is primarily based on clinical findings. It can be confirmed by measuring isoniazid in blood, but isoniazid assays are not routinely available. Urine screening tests do not detect the drug.

TREATMENT

Activated charcoal adsorbs isoniazid quite well and is the preferred method of gastrointestinal decontamination. Ipecac-induced vomiting should be avoided because of the potential for rapid deterioration with coma and seizures. Seizures are sometimes responsive to benzodiazepines and barbiturates, but pyridoxine (vitamin B_6), which reverses isoniazid-induced enzyme inhibition, is often also necessary. Diazepam and pyridoxine are synergistic. Bicarbonate may be necessary to correct acidosis. Intravenous pyridoxine is given intravenously (over 5 min in patients with seizures and over 30 min in those without) in an amount equal to the ingested dose of isoniazid. When the ingested dose is not known, 5 g of pyridoxine should be administered. Seizures are usually promptly controlled, but the patient may not awake for several hours. The dose may be repeated if the response is partial or if symptoms recur. Saline diuresis enhances the excretion of isoniazid, and the drug is efficiently removed by hemodialysis. Because pyridoxine therapy is highly effective, these procedures are rarely necessary.

ISOPROPYL ALCOHOL AND ACETONE

Isopropyl alcohol is a component of rubbing alcohol, solvents, aftershave solutions, antifreeze, and window cleaners. Acetone is found in cleaners, solvents, and nail polish removers. Both are absorbed rapidly from the stomach and the lungs and distributed in body water with volumes of distribution of about 0.6 L/kg body weight. Isopropyl alcohol is metabolized to acetone in the liver by the enzyme alcohol dehydrogenase. Up to 20% is excreted unchanged in urine. Its half-life ranges from 3 to 6 h. Acetone is excreted by the kidneys and lungs with a half-life of 20 to 30 h. Isopropyl alcohol and acetone

are[CNS](#)depressants and have about twice the potency of ethanol.

Clinical Toxicity Effects begin within 30 min of ingestion and include vomiting, abdominal discomfort, and sometimes hematemesis as well as headache, dizziness, and ethanol-like intoxication. Obtundation, coma, respiratory depression, hypothermia, and hypotension may be seen with severe poisoning. Their characteristic odors may be detected on the breath or gastric contents. Both hypoglycemia and hyperglycemia can occur. Increased serum osmolality, mild ketoacidosis, and a falsely elevated serum creatinine with a normal[BUN](#) (due to the interference with creatinine assays by acetone) may be present.

Diagnosis Characteristic clinical and laboratory findings suggest the diagnosis. Direct measurement of serum levels will confirm it. Routine urine screening tests do not detect these agents. If laboratory confirmation is not readily available, the osmolal gap can be used to estimate the serum concentration ([Table 396-3](#)).

TREATMENT

Gastric aspiration is the preferred method of gastrointestinal decontamination. Activated charcoal is ineffective. Intravenous fluids and possibly bicarbonate should be given for dehydration, hypotension, and acidosis. Ventilatory support may be necessary. Hemodialysis is effective for removing isopropyl alcohol and acetone and should be considered in patients with high serum levels who do not respond to conservative therapy.

LITHIUM

Lithium, an alkali metal like sodium and potassium, appears to act by substituting for endogenous cations, thereby intefering with cell membrane ion transport and excitability, adenylate cyclase activation, neurotransmitter (norepinephrine) release, and Na_+, K_+-ATPase activity. It is available as the carbonate salt in pill form and as the liquid citrate salt. These preparations contain 8 mmol (meq) of lithium per 300 mg and 5 mL, respectively.

Lithium is absorbed slowly, with peak serum levels occurring 2 to 4 h after ingestion (later with overdosage and with sustained-release preparations). Lithium is not bound to plasma proteins. It has an initial volume of distribution of 0.3 to 0.4 L/kg body weight and a final one of 0.7 to 1 L/kg. Therapeutic serum levels are 0.6 to 1.2 mmol/L. An increase in the postdistribution lithium level of 1 to 1.5 mmol/L for each mmol/kg ingested can be predicted following acute overdose. Levels obtained prior to complete distribution will be higher than those in tissue and not correlate with clinical effects. Elimination is primarily (95%) by renal excretion (glomerular filtration with significant reabsorption in the proximal tubule). Renal excretion is increased by diuresis and urinary alkalinization and decreased by hypovolemia and hyponatremia. The serum half-life ranges from 18 to 36 h and can be prolonged in patients with chronic intoxication.

Clinical Toxicity Effects begin 1 to 4 h after acute ingestion. Onset can be delayed following overdose of sustained-release preparations. It typically occurs insidiously during chronic therapy, often resulting from an intercurrent illness that causes

dehydration and decreased lithium elimination. Gastrointestinal effects include nausea, vomiting, and diarrhea; neuromuscular effects include weakness, confusion, ataxia, tremors, fasciculations, myoclonus, choreoathetosis, coma, and seizures; and cardiovascular effects include arrhythmias and hypotension. Hyperthermia can occur. Leukocytosis, hyperglycemia, albuminuria, glycosuria, nephrogenic diabetes insipidus, and a falsely elevated serum chloride level (due to interference by lithium with its assays) resulting in a low anion-gap may be present.ECGchanges include sinus tachycardia or bradycardia, flattened or inverted T waves,AVblock, and a prolonged QT interval. Prolonged or permanent encephalopathy and movement disorders can occur in patients with severe poisoning.

Diagnosis Since lithium is not detected by routine screening tests, a serum level must be requested specifically. Because of slow absorption and distribution, serial drug levels should be obtained following acute overdosage. In chronic poisoning, severe toxicity may occur at serum levels of 3 to 4 mmol/L. Following acute overdose, only mild effects may be present despite serum levels that rise to³8 mmol/L. As distribution occurs and levels fall, progressive toxicity may ensue.

TREATMENT

Gastric lavage and whole-bowel irrigation are the procedures of choice for gastrointestinal decontamination. Whole-bowel irrigation is preferred for sustained-release formulations because intact pills will not fit through a lavage tube. Endoscopy should be considered if a concretion is suspected (persistently high or rising drug levels 2 or more days following ingestion). Activated charcoal does not adsorb lithium. Experimentally, oral administration of the ion-exchange resin sodium polystyrene sulfonate (Kayexalate) can bind lithium, prevent its absorption, and enhance its elimination, but the clinical effectiveness of this therapy is unproven. Supportive therapy includes standard treatments for seizures, CNS depression, hypotension, and arrhythmias. Symptomatic patients should be given an intravenous saline bolus and infusion to correct dehydration, to achieve a normal urine output, and to replace fluid losses in those with diabetes insipidus. Although diuresis can enhance renal excretion of lithium, there is little evidence that this therapy is more effective than simply maintaining a normal urine output. Hemodialysis, however, is highly effective in enhancing lithium elimination. It is recommended for patients with coma, seizures, and severe, persistent or progressive confusion, CNS depression, or movement disorders; lesser toxicity in the presence of renal failure; and when the peak lithium level exceeds 8 mmol/L following acute overdose (because of the likelihood of severe postdistribution toxicity). Because of slow redistribution, drug levels typically rise following dialysis. Dialysis should be repeated until the postredistribution level is<1 mmol/L. Despite dialysis, clinical recovery may take days to weeks. There is no conclusive evidence that dialysis decreases the incidence of permanent sequelae.

METHANOL

Methanol is a component of shellacs, varnishes, paint removers, canned fuel (Sterno), windshield-washer solutions, and copy machine fluid. It is also used to denature ethanol and render it unfit for consumption. It is aCNSdepressant with a potency about half of that of ethanol. Methanol is initially metabolized by alcohol dehydrogenase to

formaldehyde, with subsequent oxidation to formic acid, and then to carbon dioxide and water. Formic acid is responsible for metabolic acidosis and retinal toxicity. Its detoxification utilizes tetrahydrofolate as a cofactor.

Methanol is readily absorbed, with peak serum levels occurring 1 to 2 h after ingestion. It is distributed throughout body water, with a volume of distribution of 0.7 L/kg body weight. Protein binding is negligible. Elimination occurs mainly by hepatic metabolism, with up to 10% excreted unchanged by the lungs and kidneys. Elimination follows first-order kinetics, with a half-life of 2 to 4 h at low serum levels (9 mmol/L or 30 mg/dL). At higher levels, it changes to zero-order kinetics, with an elimination rate of about 3 mmol/L per hour (10 mg/dL per hour) and an apparent half-life of up to 30 h. As with ethylene glycol, ethanol and fomepizole block the production of methanol metabolites, by competitively inhibiting alcohol dehydrogenase, and increase its elimination half-life to 30 to 60 h.

Clinical Toxicity As with ethylene glycol, as little as one swallow of pure methanol is potentially toxic. Effects begin within an hour of ingestion. Initial manifestations are caused by methanol itself and include nausea, vomiting (sometimes bloody), abdominal pain, headache, vertigo, and an ethanol-like intoxication. An increased osmolal gap may be present. Pancreatitis has been reported. Later effects are due to formic acid and include coma, seizures, an increased anion-gap metabolic acidosis, and retinal injury. Ophthalmologic manifestations occur 15 to 30 h after ingestion and include clouding and diminished vision, dancing and flashing spots, dilated or fixed pupils, hyperemia of optic disks, retinal edema, and blindness. These changes are potentially reversible with prompt institution of therapy. With severe poisoning, myocardial depression, bradycardia, and shock may occur.

Diagnosis The diagnosis is confirmed by measurement of serum methanol and formate levels. Early in the course, the diagnosis is suggested by ethanol-like intoxication and an elevated serum osmolality. Later, the diagnosis is suggested by an increased-anion-gap metabolic acidosis and visual complaints. If laboratory confirmation is not immediately available, the osmolal gap can also be used to estimate the serum methanol concentration (Table 396-3).

TREATMENT

Gastric aspiration is the treatment of choice for gastrointestinal decontamination. Supportive measures should include volume replacement, respiratory care, and treatment of seizures. Acidosis should be corrected with sodium bicarbonate; large amounts may be required. Sodium bicarbonate should also be given to alkalinize the urine as this will enhance the excretion of formic acid. Supplemental folate (50 mg qid) is recommended.

Indications for ethanol or fomepizole therapy include a methanol concentration>6 mmol/L (20 mg/dL); an elevated osmolal gap, an increased anion-gap metabolic acidosis, visual symptoms, or ethanol-like intoxication in a patient with a history of methanol ingestion and a low or undetectable ethanol level; an elevated osmolal gap not accounted for by the presence of ethanol, isopropyl alcohol, acetone, or propylene glycol in a patient with ethanol-like intoxication; and an increased anion-gap metabolic

acidosis with a low lactate level not explained by alcoholic or diabetic ketoacidosis or uremia or by salicylate, formaldehyde, paraldehyde, or toluene exposure. Doses and treatment considerations are the same as for ethylene glycol. Serum methanol concentrations should be monitored frequently. Ethanol or fomepizole should be continued until the methanol level falls below 3 mmol/L (10 mg/dL).

Hemodialysis enhances the elimination of methanol and formic acid. Indications for hemodialysis include methanol levels >15 mmol/L (50 mg/dL) and metabolic acidosis not readily correctable with bicarbonate and antidotal therapy, lack of clinical improvement despite treatment, or visual symptoms (regardless of the methanol level). This therapy should be continued or repeated intermittently until acidemia resolves and the methanol level is <6 mmol/L (20 mg/dL).

METHEMOGLOBINEMIA

Methemoglobinemia results from exposure to chemicals that oxidize the ferrous (Fe^{2+}) iron in hemoglobin to the ferric (Fe^{3+}) state. Concomitant oxidation of hemoglobin protein may cause its precipitation in erythrocytes and consequent hemolytic anemia, manifest as Heinz bodies and "bite cells," respectively, on peripheral blood smear. Oxidizing agents include aniline and its derivatives, aminophenols, aminophenones, chlorates, dapsone, local anesthetics (particularly benzocaine), nitrites, nitrates, naphthalene, nitrobenzene and related chemicals, oxides of nitrogen, phenazopyridine, primaquine and related antimalarials, and sulfonamides.

Methemoglobin (ferric hemoglobin) cannot carry oxygen and causes a functional anemia. It also shifts the oxygen-dissociation curve to the left, limiting the release of oxygen to tissues. Symptoms are due to hypoxia and anaerobic metabolism.

Various systems normally operate to keep methemoglobin at physiologic levels (1% of the total hemoglobin concentration). Oxidizing agents are inactivated by enzymes that utilize ascorbic acid and sulfhydryl agents such as glutathione. Methemoglobin is reduced to hemoglobin by NADH-methemoglobin reductase (responsible for 95% of baseline reducing capacity), NADPH-methemoglobin reductase, and the ascorbic acid and glutathione enzyme systems. When supplied with the cofactor methylene blue, the activity of NADPH-methemoglobin reductase is greatly increased. Because this enzyme is dependent on NADPH, individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency have profound impairment in the ability to reduce methemoglobin after oxidant exposure.

Clinical Toxicity Onset may be immediate or delayed depending on whether the parent compound or a metabolite is the oxidant. Cyanosis with a gray-brown hue that is unresponsive to oxygen occurs when the fraction of hemoglobin existing as methemoglobin exceeds 15% (about 15 g/L or 1.5 g/dL of absolute methemoglobin). Most patients are asymptomatic until the methemoglobin fraction is>20 to 30%, at which point fatigue, headache, tachycardia, dizziness, and weakness develop. At fractions>45%, dyspnea, bradycardia, hypoxia, metabolic (lactic) acidosis, seizures, coma, and cardiac arrhythmias may occur. Fractions>70% are rapidly fatal. Hemolytic anemia is typically delayed in onset and may cause hyperkalemia and renal failure.

Diagnosis The diagnosis is confirmed by measuring the methemoglobin level by CO-oximetry. If CO-oximetry is not available, the methemoglobin fraction can be estimated by the difference between the oxygen saturation calculated from the P_{O2} and that measured directly. Oxygen saturation measured by pulse oximetry will be subnormal but either falsely depressed or elevated with respect to the true value. Blood with high levels of methemoglobin is chocolate-colored when placed on filter paper and compared with normal blood. Urine toxicology testing may detect the oxidizing agent.

TREATMENT

Activated charcoal is the preferred method of gastrointestinal decontamination. Supplemental oxygen should be administered. Methylene blue is indicated for methemoglobin fractions >30% and at lower fractions in patients with anemia or cardiovascular disease, particularly if manifestations of hypoxia or organ ischemia are present. Methylene blue is given at a dose of 1 to 2 mg/kg body weight as a 1% solution over 5 min. If a clinical response is not observed within 1 h, the dose may be repeated. As long as the oxidizing agent is present, methemoglobin will continue to be generated, and additional doses may be necessary. Side effects of methylene blue include anxiety, dysuria, precordial pain, and blue or green discoloration of the urine. It is contraindicated in patients with G6PD deficiency in whom it may induce hemolysis. In doses >7 mg/kg of body weight, methylene blue itself can cause methemoglobinemia. Exchange transfusion and hyperbaric oxygen therapy may be of benefit in patients with very high methemoglobin fractions or severe clinical toxicity that is refractory to the above and those with G6PD deficiency. Erythrocyte transfusion may be necessary if hemolysis is severe. Hemodialysis may be useful for removing the offending agent.

MONOAMINE OXIDASE INHIBITORS

The antidepressants isocarboxazid, phenelzine, and tranylcypromine and the chemotherapeutic agent procarbazine irreversibly and nonselectively block monoamine oxidase (MAO) isoenzymes in the brain, gut, and liver, thus inhibiting the catabolism of endogenous MAO substrates such as epinephrine, dopamine, norepinephrine, and serotonin and exogenous ones such as ingested tyramine. Clorgyline and moclobemide selectively inhibit MAO-A, which preferentially deaminates serotonin, and pargyline and selegiline selectively inhibit MAO-B. Toxicity results from the accumulation and effects of MAO substrates. A tyramine reaction can occur when foods with high tyramine content such as aged cheese, aged, pickled, or smoked meat and fish, and red wine are ingested by individuals taking MAO inhibitors. Interactions with sympathomimetics can result in exaggerated sympathetic effects, and interactions with serotonergic agents can cause the serotonin syndrome (discussed subsequently).

MAO inhibitors are absorbed and appear to have relatively large volumes of distribution (>1 L/kg body weight). They are eliminated primarily by hepatic metabolism and have half-lives ranging from several hours to >24 h.

Clinical Toxicity Onset following overdose is typically delayed and insidious. Effects may not begin until 6 to 24 h after ingestion and progress slowly. Initial manifestations include dilated pupils, agitation, diaphoresis, tachycardia, hypertension, and tachypnea. Nausea and vomiting may also occur. Later, confusion, CNS depression, fasciculations,

twitching, tremor, muscle rigidity, rhabdomyolysis, hyperthermia, and lactic acidosis may be noted. Terminal bradycardia and cardiovascular collapse may ensue.

Tyramine and sympathomimetic reactions occur within 30 to 90 min of food or drug ingestion and resolve within a few hours. Manifestations are similar to overdose. Reflex bradycardia, seizures, and intracranial hemorrhage have also been described.

Diagnosis The diagnosis is based on the history and clinical presentation. Serum assays are not available, and urine screening tests do not usually detect these agents.

TREATMENT

Activated charcoal is the preferred method of gastrointestinal decontamination. Benzodiazepines should be given for neuromuscular hyperactivity. Therapeutic paralysis is recommended for refractory or progressive neuromuscular hyperactivity, particularly if concomitant rhabdomyolysis and hyperthermia are present. The treatment of hyperthermia should include external cooling measures. Replacement of insensible fluid losses is also important. Severe hypertension and tachycardia should be treated with labetalol or nitroprusside and esmolol. Hypotension should first be treated with intravenous fluids and then with pressors. Pressors should initially be given at lower than normal doses because of the possibility of an exaggerated response. In fact, before any drug is given, potential interaction with MAO inhibitors should be investigated. Because MAO inhibition may persist for up to 2 weeks after discontinuing therapy, drug and dietary precautions should be maintained during this period.

MUSCLE RELAXANTS AND MISCELLANEOUS SEDATIVE-HYPNOTICS

Muscle relaxants (baclofen, carisoprodol, chlorphenesin, chlorzoxazone, cyclobenzaprine, methocarbamol, and orphenadrine) and nonbarbiturate, nonbenzodiazepine sedative-hypnotics (buspirone, chloral hydrate, ethchlorvynol, glutethimide, meprobamate, methaqualone, methyprylon, zolpidem) including the street drugs g-butyrolactone (GBL) and its metabolite g-hydroxybutyrate (GHB) are primarily CNS depressants. Most interact with GABA receptor complexes, enhancing the effects of this inhibitory neurotransmitter. Some muscle relaxants also depress spinal synaptic reflexes. Cyclobenzaprine and orphenadrine have anticholinergic activity. Orphenadrine also has sodium channel blocking activity.

These agents are readily absorbed, with peak blood levels occurring 1 to 2 h after ingestion. They are eliminated primarily by hepatic metabolism. Baclofen, an exception, is largely excreted unchanged in the urine. Chloral hydrate is rapidly metabolized to trichloroethanol, an active compound with a much longer half-life than the parent drug. Carisoprodol is metabolized to meprobamate. Glutethimide also has an active metabolite. Half-lives are >20 h for cyclobenzaprine, ethchlorvynol, and methaqualone; 10 to 20 h for glutethimide, meprobamate, methyprylon, and orphenadrine; and <6 h for other agents.

Clinical Toxicity Effects begin within an hour of ingestion. All muscle relaxants cause CNS depression (Table 396-2). Nystagmus is usually present. Carisoprodol, chloral hydrate, chlorphenesin, chlorzoxazone, and methocarbamol also cause nausea

and vomiting. Cyclobenzaprine and orphenadrine cause anticholinergic toxicity, and orphenadrine can cause ventricular tachyarrhythmias, including torsades de pointes. Baclofen can produce hypothermia, excitability, delirium, myoclonus, seizures, cardiac conduction abnormalities, tachycardia, bradycardia, and hypotension. Intrathecal baclofen overdose can lead to precipitous and profound effects. Supraventricular and ventricular tachycardia can occur in chloral hydrate poisoning. GBL and GHB can cause paradoxical agitation, seizures, miosis, and bradycardia in addition to CNS depression. The effects of GBL and GHB typically last only a few hours; the duration of toxicity from other agents is substantially longer. Coma from ethchlorvynol and glutethimide, which are highly lipophilic, and from meprobamate, which can form concretions, can last for several days. With glutethimide, erratic absorption can result in cyclic coma.

Diagnosis The clinical diagnosis is supported by detecting the drugs on comprehensive urine screening. Quantitative measurements of serum levels are not routinely available.

TREATMENT

Activated charcoal is preferred for gastrointestinal decontamination. Repetitive doses may enhance their elimination. The treatment of anticholinergic poisoning is discussed in the section pertaining to these agents. Although arrhythmias due to orphenadrine have responded to physostigmine, they are more likely due to sodium channel blockade than to anticholinergic effects and should probably be treated as described above for class I antiarrhythmics. Cerebrospinal fluid drainage may enhance the elimination of intrathecal baclofen. CNS depression from zolpidem may respond to flumazenil (see "Benzodiazepines," above). Treatment is otherwise supportive. Extracorporeal hemodynamic support and enhanced elimination procedures should be considered for patients with cardiovascular depression unresponsive to standard therapy.

NEUROLEPTIC AGENTS

Clozapine, chlorprothixene, droperidol, haloperidol, loxapine, molindone, olanzapine, pimozide, quetiapine, risperidone, sertindole, thiothixene, trimethobenzamide, ziprasidone, and the phenothiazines (chlorpromazine, fluphenazine, perphenazine, prochlorperazine, promazine, promethazine, thiethylperazine, thioridazine and its metabolite mesoridazine, trifluoperazine, triflupromazine, trimeperazine) primarily act by blocking type 2 dopamine receptors in the CNS. They also have variable inhibitory activity at a-adrenergic, histaminergic, muscarinic, serotonergic, and other dopamine receptor subtypes. Some phenothiazines have a quinidine-like activity. Acute extrapyramidal effects (dystonia, akathisia, Parkinsonism) result from an imbalance of cholinergic and dopaminergic activity in the basal ganglia. These effects are idiosyncratic rather than dose-related and can be delayed in onset. The neuroleptic malignant syndrome (Chaps. 17 and 363) rarely, if ever, occurs following acute overdose.

Neuroleptic agents are well absorbed, exhibit 90 to 95% protein binding in plasma, have large apparent volumes of distribution (10 to 40 L/kg body weight), and are eliminated slowly by hepatic metabolism with half-lives of 10 to 40 h.

Clinical Toxicity Toxic effects begin within 30 to 60 min of ingestion and

includeCNSdepression (Table 396-2), respiratory depression, hypotension, pulmonary edema, and hypothermia. Pupils are often constricted, and the skin is usually warm and dry. Anticholinergic manifestations may be the predominant effect of low overdosage (see "Anticholinergic Agents," above). Cardiac effects include tachycardia, atrioventricular block, and atrial and ventricular arrhythmias. Torsade de pointes; prolonged PR, QRS, and QT intervals; and U- and T-wave abnormalities may be seen with pimozide, mesoridazine, respiridone, thioridazine ingestions and high-dose intravenous droperidol and haloperidol.

Acute dystonic reactions are characterized by sustained muscle contractions resulting in abnormal posturing of the eyes, face, tongue, jaw, neck, back, abdomen, and pelvis. Akathisia is the subjective sensation of motor restlessness, and Parkinsonism is manifest by akinesia and rigidity. Patients may be anxious but remain alert and oriented during these reactions.

Diagnosis The diagnosis is supported by detecting the presence of these agents on toxicologic screening of the urine. Quantitative measurement is not helpful.

TREATMENT

Activated charcoal is the preferred method of gastrointestinal decontamination. Supportive care includes airway protection and mechanical ventilation forCNS and respiratory depression, fluid resuscitation followed by pressors for hypotension, and anticonvulsants for seizures. Diuresis and dialysis are ineffective. Seizures should be treated with benzodiazepines, and hypotension should be managed with volume expanders and pressor agents. Physostigmine may be useful for anticholinergic toxicity (see "Anticholinergic Agents," above). Treatment of ventricular dysrhythmias is the same as described above for class I antiarrhythmics.

Acute extrapyramidal reactions usually respond rapidly to antimuscarinic therapy such as intravenous diphenhydramine (1 mg/kg body weight given over 2 min) or benztropine (1 to 2 mg). Doses may be repeated in 20 min if the response is incomplete. Treatment should be continued with an oral formulation for 2 to 3 days since these reactions can recur in the absence of additional exposure.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, naproxen, oxaprozin, piroxicam, phenylbutazone, sulindac, and tolmetin inhibit prostaglandin and thromboxane synthesis by blocking cyclooxygenase (COX) isoenzymes: COX-1, the constitutive form in the gastrointestinal tract, kidney, and platelets, and COX-2, an inducible form that becomes expressed in response to bacterial toxins and cytokines (tissue inflammation). They are absorbed rapidly, and blood concentrations peak 1 to 2 h after ingestion. They are highly protein bound (>90%) and have volumes of distribution of less than 1.0 L/kg body weight. They are primarily eliminated by hepatic metabolism. Half-lives range from 1 to 16 h except for phenylbutazone, which has a half-life of 2 to 4 days.

Clinical Toxicity Effects are usually mild and include nausea, vomiting, abdominal pain,

drowsiness, headache, glycosuria, hematuria, and proteinuria. Acute renal failure and hepatitis occur rarely. Diflunisal can cause hyperventilation, tachycardia, and sweating. Coma, respiratory depression, seizures, and cardiovascular collapse may occur with mefenamic acid and phenylbutazone. Ibuprofen can cause metabolic acidosis, coma, and seizures. Metabolic acidosis is relatively common in phenylbutazone poisoning and occurs rarely with naproxen. Seizures can also occur with ketoprofen and naproxen. Preliminary data indicates that selectiveCOX-2 inhibitors, such as celecobix and rofecobix, do not share the toxicity of these nonselective inhibitors.

Diagnosis Comprehensive toxicology screening will identify these drugs in the urine, but quantitative analysis is not useful.

TREATMENT

Activated charcoal is the preferred method of gastrointestinal decontamination. Repeated doses may enhance the elimination of indomethacin, phenylbutazone, and piroxicam. Renal excretion is not increased by diuresis, and protein binding limits the efficacy of hemodialysis. Hemoperfusion might be useful in patients with hepatic or renal failure and severe clinical toxicity. Treatment is otherwise supportive.

ORGANOPHOSPHATE AND CARBAMATE INSECTICIDES

Organophosphorus compounds such as the insecticides chlorpyrifos, phosphorothioic acid (Diazinon), dichlorvos, fenthion, malathion, and parathion and the chemical warfare "nerve gases" such as sarin irreversibly inhibit acetylcholinesterase and cause accumulation of acetylcholine at muscarinic and nicotinic synapses and in theCNS. Carbamates such as the insecticides aldicarb, propoxur (Baygon), carbaryl (Sevin), and bendiocarb (Ficam) and the therapeutic agents ambenonium, neostigmine, physostigmine, and pyridostigmine reversibly inhibit this enzyme. Agents that directly stimulate cholinergic receptors such as arecholine (from betel nuts), bethanechol, pilocarpine, and urecholine have the same effect.

Organophosphates are absorbed through the skin, lungs, and gastrointestinal tract; are distributed widely in tissues; and are slowly eliminated by hepatic metabolism. Oxidative metabolites of parathion and malathion (paraoxon, malaoxon) are the active forms of these agents. Carbamates are eliminated rapidly by serum and liver enzymes.

Clinical Toxicity The time from exposure to the onset of toxicity varies from minutes to hours but is usually between 30 min and 2 h. Muscarinic effects include nausea, vomiting, abdominal cramps, urinary and fecal incontinence, increased bronchial secretions, cough, wheezing, dyspnea, sweating, salivation, miosis, blurred vision, lacrimation, and urinary frequency and incontinence. In severe poisoning, bradycardia, conduction block, hypotension, and pulmonary edema may occur. Nicotinic signs include twitching, fasciculations, weakness, hypertension, tachycardia, and in severe cases paralysis and respiratory failure.CNSeffects include anxiety, restlessness, tremor, confusion, weakness, seizures, and coma. Toxicity due to carbamates is shorter in duration and usually less severe than that due to organophosphates. Most patients recover within 24 to 48 h, but fat-soluble organophosphates may cause effects for weeks to months. Death is most often due to pulmonary toxicity.

Diagnosis A reduction of cholinesterase activity in plasma and in red blood cells to<50% of normal confirms the diagnosis. A reduction in red blood cell cholinesterase activity is more specific; however, this test is less readily available, and some organophosphates inhibit only one type of cholinesterase. With carbamates, depression in plasma or red blood cell cholinesterase levels is transient because of the rapid reversibility of the inhibition. Since cholinesterase assays are not routinely or rapidly available, the initial diagnosis is clinical.

TREATMENT

Contaminated clothing should be removed, and the skin should be washed with soap and water. Gastrointestinal decontamination should include use of activated charcoal. Supportive measures include oxygen administration, ventilatory assistance, and treatment of seizures. Atropine, a muscarinic receptor antagonist, should be administered for muscarinic effects. A dose of 0.5 to 2 mg is given intravenously every 5 to 15 min until bronchial and other secretions have dried. Repeated doses or a constant infusion may be necessary for recurrent toxicity. Pralidoxime (2-PAM) reactivates cholinesterases and is indicated for nicotinic symptoms due to organophosphate poisoning. The use of pralidoxime in carbamate poisoning is controversial. It is usually unnecessary, but its use is safe, particularly if it is administered in conjunction with atropine. A dose of 1 to 2 g is given intravenously over 5 to 30 min (depending on severity). It can be repeated in 30 min if the response is incomplete. Rapid injection can cause tachycardia, laryngospasm, muscle rigidity, and weakness. Repeated doses (every 4 to 6 h) or a continuous infusion (500 mg/h) are indicated for recurrent effects. Neither atropine nor pralidoxime is particularly effective at reversingCNSeffects; seizures should be treated aggressively with benzodiazepines.

SALICYLATES

Aspirin (acetylsalicyclic acid) and salicylate salts have activity similar to that of other nonsteroidal anti-inflammatory drugs described above. Aspirin, but not other salicylates, also inhibits platelet aggregation. Toxic doses increase the sensitivity of respiratory centers in the brain to changes in oxygen and carbon dioxide concentrations. They also uncouple oxidative phosphorylation, increase the rate of metabolism (oxygen consumption, glucose utilization, and carbon dioxide and heat production), and inhibit the Krebs cycle and carbohydrate and lipid metabolism. Metabolic effects lead to respiratory center stimulation and respiratory alkalosis early in the course of poisoning and lactic and ketoacidosis in later stages. Salicylates can also inhibit the hepatic synthesis of clotting factors.

With therapeutic doses, peak serum levels of 0.7 to 1.4 mmol/L (10 to 20 mg/dL) occur 1 to 2 h after ingestion, 50 to 80% is bound to albumin, the volume of distribution is small (0.2 L/kg body weight), and the half-life is 2 to 3 h. Being a weak acid, the unbound portion in the serum exists mainly in an ionized state. Elimination occurs primarily by hepatic metabolism, with about 10% being excreted unchanged.

Although salicylates are absorbed rapidly, absorption may continue for 24 h or longer after an overdose. Acidosis increases the nonionized (diffusable) fraction, and unbound

salicylate promotes its tissue distribution (i.e., increases the volume of distribution). Saturation of metabolic pathways results in a prolonged half-life (20 to 36 h), and renal excretion becomes the most important route of elimination. Alkalinization of the urine enhances renal excretion by converting urinary salicylate to the ionized form, which cannot be reabsorbed.

Clinical Toxicity Initial manifestations occur 3 to 6 h after an overdose of³150 mg/kg and include vomiting, sweating, tachycardia, hyperpnea, fever, tinnitus, lethargy, confusion, respiratory alkalosis with compensatory bicarbonate excretion resulting in an alkaline urine (pH >6). Increases in the rate or depth of respirations may be subtle. Vomiting, diaphoresis, and hyperventilation may lead to dehydration and decreased renal function. As acid products of intermediary metabolism accumulate, increased anion-gap metabolic acidosis and ketosis develop, and their excretion results in the urine becoming acidic (pH<6). In moderate poisoning, both respiratory alkalosis and metabolic acidosis are present, usually with alkalemia and paradoxical aciduria, although the serum pH can be normal. Elevation of the hematocrit, white blood cell count, and platelet count; hypernatremia; hyperkalemia; hypoglycemia; and prolongation of the prothrombin time may be seen. Severe poisoning is manifest by coma, respiratory depression, seizures, cardiovascular collapse, and cerebral and pulmonary edema (both noncardiogenic and cardiogenic). At this stage, metabolic evaluation reveals acidemia (metabolic acidosis with respiratory alkalosis or acidosis) and aciduria.

Diagnosis The diagnosis should be suspected in anyone with an unexplained acid-base disorder. Salicylates are identified by a positive urine ferric chloride test (purple color), which is usually included in routine screening procedures, or quantitative serum analysis. Following acute overdose, a peak level of<2.2 mmol/L (30 mg/dL) is associated with little or no toxicity, one of 2.2 to 7 mmol/L (30 to 100 mg/dL) with mild to moderate effects, and one of >7 mmol/L (100 mg/dL) with severe poisoning. Because of delayed and prolonged absorption, serial levels should be obtained. In chronic poisoning, symptoms may occur at levels only slightly above the therapeutic range.

TREATMENT

Activated charcoal is the preferred method of gastrointestinal decontamination. Repeated doses may enhance elimination. Because of delayed absorption, decontamination may be helpful 12 to 24 h after ingestion. Gastric lavage and whole-bowel irrigation should be considered in patients with ingestions of>500 mg/kg, particularly when toxicity progresses and drug levels continue to rise following charcoal administration. Endoscopy may be useful for the diagnosis and removal of gastric bezoars. A bedside glucose level should be determined in patients with altered mental status. Intravenous saline should be given to replace fluid losses and to produce a brisk urine flow. The degree of dehydration is often underestimated; several liters or more may be necessary. Supplemental glucose and oxygen should also be given. Electrolyte and metabolic abnormalities should be corrected. Coagulopathy should be treated with intravenous vitamin K. Seizures and heart failure are treated with standard therapies. Saline diuresis and urinary alkalinization (to a pH of 8) enhance the elimination of salicylate and should be instituted in symptomatic patients and those with salicylate levels>2.2 mmol/L (30 mg/dL). Depending on severity, 50 to 150 mmol of bicarbonate (along with potassium) can be added to a liter of dextrose-containing saline solution

(such that the final sodium concentration is nearly isotonic) and administered at a rate of 2 to 6 mL/kg per hour. Electrolytes, calcium, acid-base status, urine pH, and fluid balance must be monitored carefully during such therapy. When acidemia is present, bicarbonate should also be given to correct the serum pH, increase the ionization of serum salicylate, and limit its tissue distribution. Diuresis is contraindicated when cerebral or pulmonary edema and renal failure are present. Salicylates are effectively removed by hemodialysis. Indications for hemodialysis include severe clinical toxicity, levels that approach or exceed 7 mmol/L (100 mg/dL) following acute overdose, and contraindications or failure to respond to other treatment modalities.

SEROTONIN SYNDROME

This syndrome is due to excessive CNS and peripheral serotonergic (5HT-1a and possibly 5HT-2) activity and results from the concomitant use of agents that promote the release of serotonin from presynaptic neurons (e.g., amphetamines, cocaine, codeine, methylenedioxy-methamphetamine or MDMA, reserpine, some MAO inhibitors), inhibit its reuptake (e.g., cyclic antidepressants, particularly the SSRIs, ergot derivatives, dextromethorphan, meperidine, pentazocine, sumatriptan and related agents, tramadol, some MAO inhibitors) or metabolism (e.g., cocaine, MAO inhibitors), or stimulate postsynaptic serotonin receptors (e.g., bromocryptine, bupropion, buspirone, levodopa, lithium, L-tryptophan, lysergic acid diethylamide or LSD, mescaline, trazodone). Less often, it results from the use or overdose of a single serotonergic agent or when one agent is taken soon after another has been discontinued (up to 2 weeks for some agents). Serotonergic effects also appear to have been responsible for pulmonary hypertension and valvulopathy associated with the anorexiants dexfenfluramine and fenfluramine (withdrawn from U.S. markets in 1997).

Clinical Toxicity Onset occurs as early as an hour after single or multiple drug overdose or the addition of another serotonergic agent to current therapy and as a long as several days after increasing the dose of one or more agents. Manifestations include altered mental status (agitation, confusion, delirium, mutism, coma, and seizures), neuromuscular hyperactivity (restlessness, incoordination, hyperreflexia, myoclonus, rigidity, and tremors), and autonomic dysfunction (abdominal pain, diarrhea, diaphoresis, fever, elevated and fluctuating blood pressure, flushed skin, mydriasis, tearing, salivation, shivering, and tachycardia). Complications include hyperthermia, lactic acidosis, rhabdomyolysis, kidney and liver failure, ARDS, and disseminated intravascular coagulation. Effects last from 6 to 48 h, depending on severity.

Diagnosis The diagnosis is based on clinical manifestations and the history of drug exposure. Toxicology testing is useful only for confirming an exposure or detecting an unsuspected one. In contrast to the neuroleptic malignant syndrome (Chap. 363), with which its shares many features, the serotonin syndrome becomes maximal and later resolves over a period of hours rather than days, and there is myclonus and hyperreflexia in contrast to "lead-pipe" rigidity.

TREATMENT

Gastrointestinal decontamination may be indicated for acute overdose. Supportive measures include hydration with intravenous fluids, airway protection and mechanical

ventilation, benzodiazepines (and paralytics, if necessary) for neuromuscular hyperactivity, and mechanical cooling measures for hyperthermia.

The administration of serotonin-receptor antagonists may hasten the resolution of this syndrome. Cyproheptadine (Periactin), an antihistamine with 5HT-1a and 5HT2 receptor blocking activity, and chlorpromazine (Thorazine), a nonspecific serotonin receptor antagonist, have been used with success. Cyproheptadine is given orally or by gastric tube in an initial dose of 4 to 8 mg and repeated as necessary every 2 to 4 h up to a maximum of 32 mg in 24 h. A response is usually noted in 1 to 2 h but may be absent in severe cases. Chlorpromazine has the advantage that it can be given parenterally (intramuscularly or by slow intravenous injection in doses of 50 to 100 mg). Since it can cause hypotension, its use should be preceded by adequate fluid hydration. The use of chlorpromazine for the neuroleptic malignant syndrome misdiagnosed as the serotonin syndrome, and conversely, the use of bromocriptine for the serotonin syndrome misdiagnosed as the neuroleptic malignant syndrome may result in worsening of symptoms. Other medications with variable success in treating the serotonin syndrome include propranolol, methysergide, and dantrolene.

SYMPATHOMIMETICS

Amphetamines (amphetamine itself, benzphetamine, dextroamphetamine, diethylpropion, methamphetamine, phendimetrazine, phentermine), cathinone (from khat, or the plant *Catha edulis*), ephedrine, mazindol, methylphenidate, and pemoline directly stimulate a- andb-adrenergic receptors. Some also induce the release of dopamine and norepinephrine. Phenylephrine, pseudoephedrine, and phenylpropanolamine primarily stimulate a receptors, whereas mephentermine and bronchodilators such as albuterol, bitoterol, isoetherine, etaproterenol, pirbuterol, and salmeterol primarily stimulateb receptors.

These agents are readily absorbed, with peak serum levels occurring 1 to 2 h after ingestion (sooner after nasal insufflation and with the "ice" or crystalline form of methamphetamine, which, like crack cocaine, can be smoked). They are weak bases with volumes of distribution of 2 to 6 L/kg body weight. Elimination occurs by a combination of hepatic metabolism and renal excretion of unchanged drug. Half-lives range from 2 to 34 h. Excretion is enhanced in an acid urine and slowed in an alkaline one.

Clinical Toxicity Effects are seen within 30 to 60 min after ingestion and include nausea, vomiting, abdominal cramps, and headache as well as manifestations of adrenergic andCNSstimulation (Table 396-2). Although hypertension and tachycardia occur with nonselective agents, hypertension with reflex bradycardia, and evenAVblock, may occur with agents that have predominantly alpha effects. Tachycardia with hypotension (as a result of vasodilation) can be seen with selectiveb agonists. Other findings may include combativeness, auditory and visual hallucinations, dilated pupils, dry mouth, pallor, and tachypnea. Complications include lactic acidosis, rhabdomyolysis, and intracranial hemorrhage. b-Adrenergic stimulation causes potassium to move into cells and may result in hypokalemia.

Diagnosis The diagnosis is supported by finding these agents in the urine by toxicology

screening. Quantitative measurement is not useful.

TREATMENT

Activated charcoal is the preferred method of gastrointestinal decontamination. Benzodiazepines or barbiturates should be used to control neuromuscular hyperactivity and to treat seizures. A nonselective adrenergic blocker such as labetalol or the selective a-adrenergic antagonist phentolamine (1 to 5 mg intravenously every 5 min until the desired response is achieved) with or without a cardioselective beta blocker such as esmolol are recommended for severe or symptomatic hypertension; propranolol or a cardioselective beta blocker is recommended for severe or symptomatic tachycardia. Lidocaine and propranolol are preferred for the treatment of ventricular tachyarrhythmias. Hyperthermia should be treated with external cooling measures along with sedation and, if necessary, paralyzing agents. Although theoretically effective for enhancing drug elimination, acid diuresis is not recommended due to lack of documented clinical efficacy and risks of side effects such as worsening of acidosis and potential triggering of myoglobinuric renal failure.

THEOPHYLLINE

Theophylline, caffeine, and other methylxanthines are phosphodiesterase inhibitors that reduce the degradation of intracellular cyclic AMP, thereby enhancing the actions of endogenous catecholamines and leading to b-adrenergic stimulation. Theophylline is absorbed rapidly from the stomach and upper small bowel. Following overdose, serum levels peak 1 to 2 h after ingestion of liquid preparations, 2 to 4 h after ingestion of tablets, and 6 to 24 h after ingestion of sustained-release preparations. Theophylline is approximately 60% bound to albumin and has a low volume of distribution (0.6 L/kg body weight). Therapeutic serum levels are 55 to 110 umol/L (10 to 20 mg/L). Elimination occurs primarily by hepatic metabolism, which is saturable at levels in the high therapeutic range. The serum half-life, normally 4 to 6 h, is therefore prolonged in overdoses. Elimination is also decreased with impaired liver function, congestive heart failure, viral infections, and concomitantly administered drugs such as cimetidine, erythromycin, fluoroquinolones, and tetracycline.

Clinical Toxicity Effects begin 30 min to 2 h following overdose and include nausea, vomiting, psychomotor excitation, pallor, diaphoresis, tachypnea, tachycardia, and muscle tremors. Severe poisoning is characterized by coma, seizures, respiratory depression, cardiac arrhythmias, hypotension, and rhabdomyolysis. Seizures can be focal and are often protracted, repetitive, and resistant to therapy. Both atrial and ventricular tachyarrhythmias, including ventricular fibrillation, can occur. Hypotension develops only after acute overdose. Ketosis, metabolic acidosis, hyperamylasemia, hyperglycemia, hypokalemia, hypocalcemia, and hypophosphatemia may also be seen in acute poisoning.

Diagnosis The diagnosis is confirmed by measuring a serum drug level. Theophylline is not readily detected by routine urine screening. Wtih chronic exposure, arrhythmias and seizures occur at lower serum levels (200 to 300 umol/L, or 40 to 60 mg/L) than the levels seen after acute overdose (400 to 500 umol/L, 80 to 100 mg/L). Because of prolonged and delayed absorption after overdosage, particularly with sustained-release

preparations, levels should be measured serially to determine the peak concentration.

TREATMENT

Activated charcoal is the preferred method of gastrointestinal decontamination. With sustained-release forms, whole-bowel irrigation should also be considered. Antiemetics are often required for vomiting. Seizures and neuromuscular hyperactivity should be treated with benzodiazepines and barbiturates and pharmacologic paralysis in refractory cases; phenytoin is ineffective. Intravenous propranolol is preferred for the treatment of tachyarrhythmias. It can also reverse hypotension, which results from b_2-adrenergic stimulation. Although b_2 receptor blockade can potentially cause bronchospasm in those with reactive or obstructive airway disease, this has not been reported when propranolol has been used in this setting. The selective beta$_1$ blocker esmolol can also be used for supraventricular tachycardias, and ventricular tachycardias can be treated with lidocaine or other antiarrhythmics. Volume expansion and an a agonist such as norepinephrine can be given for hypotension. Repeated doses of charcoal shorten the serum half-life of theophylline by approximately 50% and are recommended for all patients. Hemodialysis and hemoperfusion are effective in removing theophylline and are indicated for patients with severe clinical toxicity or a serum drug level equal to or greater than that associated with such toxicity.

(Bibliography omitted in Palm version)

397. DISORDERS CAUSED BY REPTILE BITES AND MARINE ANIMAL EXPOSURES - *Robert L. Norris, Paul S. Auerbach*

Few topics in medicine are as controversial or as influenced by tradition as the management of bites and stings from venomous creatures. Because the incidence of serious bites and stings is relatively low in developed nations, there remains a paucity of relevant clinical research and literature, and therapeutic decision-making is often based on anecdotal information. Furthermore, the responses of different species to various toxins make it difficult to extrapolate data from animal studies to clinical application. This chapter outlines general principles for the evaluation and management of victims of venom poisoning or intoxication by certain reptiles and marine creatures and presents a clinical approach to these emergencies.

VENOMOUS SNAKEBITE

EPIDEMIOLOGY

The venomous snakes of the world are grouped into the families Viperidae (subfamily Viperinae: the Old World vipers; subfamily Crotalinae: the New World and Asian pit vipers), Elapidae (including the cobras, coral snakes, and all Australian venomous snakes), Hydrophiidae (the sea snakes), Atractaspididae (the burrowing asps), and Colubridae (a large group of which only a few species are dangerously toxic to humans). The highest bite rates occur in temperate and tropical regions where people subsist by manual agriculture. Global estimates suggest that 30,000 to 40,000 persons die each year from venomous snakebite, but this range is likely an underestimate because of incomplete reporting.

SNAKE ANATOMY/IDENTIFICATION

The typical snake-venom apparatus consists of bilateral venom glands -- one on each side of the head, below and behind the eye -- connected by ducts to hollow, anterior maxillary teeth. In viperids (vipers and pit vipers), these teeth are long, mobile fangs that retract against the roof of the mouth when the animal is at rest. In elapids and sea snakes, the fangs are less enlarged and are fixed in an erect position. Venomous snakes can bite without injecting venom. Approximately 20% of pit viper bites and an even higher percentage of bites inflicted by some other snake families (e.g., up to 75% for sea snakes) are "dry."

Differentiation of venomous from nonvenomous snake species can be difficult. Viperids are characterized by somewhat triangular heads (a feature shared with many harmless snakes); elliptical pupils (also seen in some nonvenomous snakes, such as boas and pythons); enlarged maxillary fangs; subcaudal scalation that involves a single scale running the full width of the ventral surface of the tail for several rows just distal to the anal plate (as opposed to two scales in each subcaudal row for most nonvenomous snakes); and, in the case of pit vipers, the heat-sensing pits (foveal organs located slightly inferior and anterior to the eyes on each side) for which they are named. Color pattern is notoriously misleading in identifying most venomous snakes except for the coral snakes, whose other body characteristics are similar to those of harmless colubrids. The American coral snakes can be identified by red, yellow (or white), and

black bands completely encircling the body; a few species have red and black bands only. North of Mexico City, the immediate contiguity of red and yellow bands is fairly reliable for distinguishing a coral snake from its many harmless mimics. Further south, differentiation by color pattern is more problematic.

In many areas of the world, enzyme-linked immunoassay (ELISA) kits are available to aid in determining the specific snake species involved in a bite. These kits identify venom in the victim's blood, urine, or wound aspirate. No such kit is commercially available in the United States, however.

VENOMS AND CLINICAL MANIFESTATIONS

Snake venoms are complex mixtures of enzymes, low-molecular-weight polypeptides, glycoproteins, and metal ions. Among the deleterious components are hemorrhagins that promote vascular leaking and cause both local and systemic bleeding. Various proteolytic enzymes cause local tissue necrosis, affect the coagulation pathway at various steps, and impair organ function. Myocardial depressant factors reduce cardiac output, and neurotoxins act either pre- or postsynaptically to inhibit peripheral nerve impulses. Most snake venoms have multisystem effects in their victims.

TREATMENT

Field Management Initial (prehospital) measures should focus on rapidly delivering the victim to definitive medical care while keeping him/her as inactive as possible to limit systemic spread of venom. Any other measures employed should at least do no further harm to the victim.

After viperid bites, local mechanical suction applied to the site within 3 to 5 min may remove a small percentage of deposited venom. A useful device is the Extractor (Sawyer Products, Safety Harbor, FL), which delivers one atmosphere of negative pressure to the wound. Suction should be continued for at least 30 min. Mouth suction should be avoided as it inoculates the wound with oral flora and theoretically can also result in the absorption of venom by the rescuer through lesions of the upper digestive tract. If the victim is >60 min from medical care, a proximal lympho-occlusive constriction band may limit the spread of venom when applied within 30 min. To avoid worsening tissue damage, however, the band should not interrupt arterial blood flow. The bitten extremity should be splinted if possible and kept at approximately heart level. Measures to be avoided include incising or cooling the bite site, giving the victim an alcoholic beverage, or applying electric shocks.

For elapid or sea snake bites, the Australian pressure-immobilization technique, in which the entire bitten extremity is wrapped with an elastic or crepe bandage and then splinted, is highly effective. The bandage is applied with the same snugness used for a sprained ankle. This technique greatly restricts absorption and circulation of venom. The utility of this method in viperid poisoning requires further research, as it theoretically could compound local tissue damage by restricting venom to the local tissues.

Hospital Management In the hospital, the victim should be closely monitored (vital signs, cardiac rhythm, and oxygen saturation) while a history is quickly obtained and a

brief but thorough physical examination is performed. The level of erythema and/or swelling in a bitten extremity should be marked and limb circumferences measured in several locations every 15 min until swelling has stabilized. Large-bore intravenous access in unaffected extremities should be established. Early hypotension is due to pooling of blood in the pulmonary and splanchnic vascular beds. Hours later, hemolysis and loss of intravascular volume into soft tissues may play important roles. Fluid resuscitation with normal saline or Ringer's lactate should be initiated for clinical shock. If the blood pressure response is inadequate after administration of 20 to 40 mL/kg of body weight, then a trial of 5% albumin (10 to 20 mL/kg) is in order. If tissue perfusion fails to respond to volume resuscitation and antivenom infusion (see below), vasopressors (e.g., dopamine) should be administered. Invasive hemodynamic monitoring (central venous and/or pulmonary arterial pressures) can be helpful in such cases, although obtaining access is riskier if coagulopathy is present.

Blood should be drawn for laboratory evaluation as soon as possible. Blood typing and cross-matching procedures can be affected over time by circulating venom. Also important are a complete blood count to evaluate the degree of hemorrhage or hemolysis, studies of renal and hepatic function, coagulation studies to identify signs of consumptive coagulopathy, and testing of urine for blood or myoglobin. In severe cases or in the face of significant comorbidity, arterial blood gas studies, electrocardiography, and chest radiography are indicated.

Attempts to locate a source of appropriate antivenom should begin early in all cases of known venomous snakebite, regardless of symptoms. In the event that signs and symptoms progress rapidly, any delay in the administration of antivenom is dangerous. Antivenoms rarely offer cross-protection against snake species other than those used in their production unless the species are closely related. An example of good cross-protection is that of Australian tiger snake (*Notechis scutatus*) antivenom for sea snake bites (see below). The package insert accompanying a particular antivenom should be consulted for information regarding the spectrum of coverage. In the United States, assistance in finding antivenom can be obtained 24 hours a day from the University of Arizona Poison and Drug Information Center (telephone: 520-626-6016).

Rapidly progressive or severe local findings (soft tissue swelling, ecchymosis, petechiae, etc.) or manifestations of systemic toxicity (signs and symptoms or laboratory abnormalities) are indications for the administration of intravenous antivenom. The package insert outlines techniques for reconstitution of antivenom (when necessary), skin-testing procedures (for potential allergy), and appropriate starting doses. Most commercial antivenoms are of equine origin and carry a risk of anaphylactic, anaphylactoid, and delayed-hypersensitivity reactions. Skin testing does not reliably predict which patients will have an allergic reaction to equine antivenom; false-negative and false-positive results are common. Before antivenom infusion, the patient should receive appropriate loading doses of intravenous antihistamines (e.g., diphenhydramine, 1 mg/kg to a maximum of 100 mg; and cimetidine, 5 to 10 mg/kg to a maximum of 300 mg) in an effort to limit acute reactions. Modest expansion of the patient's intravascular volume with crystalloids may also be beneficial in this regard. Epinephrine should be immediately available, and the antivenom dose to be administered should be diluted (e.g., in 1000 mL of normal saline for adults or in 20 mL/kg for children). This volume can be decreased if necessary (e.g., if the victim has a history of congestive heart

failure). The antivenom should be started slowly, with the physician at the bedside to intervene in the event of an acute reaction. The rate of infusion can be increased gradually in the absence of allergic phenomena until the total starting dose has been administered (over a total period of 1 to 4 h). Further antivenom may be necessary if the patient's clinical condition worsens. Laboratory values should be rechecked hourly, particularly if abnormal, until stability is apparent.

The management of a life-threatening envenomation in a victim with an apparent allergy to antivenom requires significant expertise. Consultation with a poison specialist, an intensive care specialist, and/or an allergist is recommended. Often antivenom can still be administered in these situations under closely controlled conditions and with intensive premedication (e.g., with epinephrine, antihistamines, and steroids).

Care of the bite wound should include application of a dry sterile dressing and splinting of the extremity with padding between the digits. Once the administration of an indicated antivenom has been initiated, the extremity should be elevated above heart level to relieve edema. Tetanus immunization should be updated as appropriate. The use of prophylactic antibiotics is controversial, as the incidence of secondary infection following venomous snakebite appears to be low. Many authorities, however, prescribe a broad-spectrum antibiotic (such as ampicillin or a cephalosporin) for the first few days.

If swelling in the bitten extremity raises concern that subfascial muscle edema may be impeding tissue perfusion (muscle-compartment syndrome), intracompartmental pressures should be checked by any minimally invasive technique (e.g., the wick catheter). If pressures are elevated and remain so despite antivenom administration, prompt surgical consultation for possible fasciotomy should be obtained. This complication, fortunately, is rare after snakebites.

Whether or not antivenom is given, any patient with signs of venom poisoning should be observed in the hospital for at least 24 h. A patient with an apparently "dry" bite should be watched for at least 6 to 8 h before discharge, as significant toxicity occasionally develops after a delay of several hours. The onset of systemic symptoms is commonly delayed for a number of hours after bites by several of the elapids (including the coral snakes) and sea snakes. Patients bitten by these reptiles should be observed in the hospital for 24 h.

Significant work is being done in several regions of the world to produce safer, more effective antivenoms. Much of this work involves production of ovine-based antivenoms that are further purified and enzymatically cleaved to yield functional F(ab) fragments of the immunoglobulin molecules. These antivenoms are currently in clinical use in many countries, and trials of one product are under way in the United States.

MORBIDITY AND MORTALITY

The overall mortality rates for venomous snakebite are low in areas of the world with rapid access to medical care and appropriate antivenom. In the United States, for example, the mortality rate is <1% for victims who receive antivenom. Eastern and western diamondback rattlesnakes (*Crotalus adamanteus* and *C. atrox*, respectively) are responsible for most snakebite deaths in the United States. Snakes responsible for

large numbers of deaths in other regions of the world include the cobras (*Naja* spp.) of Asia and Africa, the carpet and saw-scaled vipers (*Echis* spp.) of the Middle East and Africa, Russell's viper (*Daboia russelli*) of the Middle East and Asia, the large African vipers (*Bitis* spp.), and the lancehead pit vipers (*Bothrops* spp.) of Central and South America.

The incidence of morbidity in terms of permanent functional loss in a bitten extremity is difficult to estimate but is probably substantial. Such loss may be due to muscle, nerve, or vascular injury or to scar contracture. In the United States, such loss due to snakebite tends to be much more common and severe after rattlesnake bites than after bites by copperheads or water moccasins.

LIZARD BITES

Bites from the two species of venomous lizards (the gila monster, *Heloderma suspectum*, of the southwestern United States and the Mexican beaded lizard, *H. horridum*) are infrequent and usually follow attempts to capture or handle these creatures. The wounds are characterized by soft tissue trauma with surrounding local edema and occasionally local cyanosis and ecchymosis. Broken teeth may be embedded in the wounds. The venom contains proteases and phospholipases. Systemic effects may include hypotension, weakness, dizziness, and diaphoresis.

Prehospital care measures for these bites should follow the guidelines listed above for viperid bites. If the biting lizard is still attached to the victim, its jaws may need to be manually pried apart for removal.

The sparseness of data on the pathophysiologic effects of helodermatid venom precludes specific recommendations regarding laboratory evaluation, but routine studies (complete blood count, coagulation studies, electrolyte analysis, blood typing and cross-matching, urinalysis, and electrocardiography) are prudent in anything other than a trivial bite. Wounds should be cleansed thoroughly and irrigated when possible. Tetanus immunization should be updated as indicated. Soft tissue radiography of the bite site and sterile probing under local anesthesia may identify retained teeth. The extremity should be splinted and elevated, but antibiotic treatment is not usually required. Systemic care is supportive (e.g., crystalloid infusion for hypotension). No commercial antivenom exists. Pain due to local venom effects and mechanical trauma can be treated with opiates and regional nerve blocks. The mortality rate is extremely low.

MARINE ENVENOMATIONS

Management of venom poisoning by marine creatures is similar to that of venomous snakebite in that much of the treatment administered is supportive in nature. A few specific marine antivenoms can be used when appropriate.

INVERTEBRATES

Hydroids, fire coral, jellyfish, Portuguese man-of-war, and *sea anemones* possess specialized stinging cells called nematocysts. The venoms from these organisms are

mixtures of proteins, carbohydrates, and other components. The clinical syndrome following envenomation by any of these species is similar but of variable severity. Victims usually report immediate prickling or burning, pruritus, paresthesia, and painful throbbing with radiation. A legion of neurologic, cardiovascular, respiratory, rheumatologic, gastrointestinal, renal, and ocular symptoms have been described. Victims in unstable condition with hypotension or respiratory distress should be treated supportively. During stabilization, the skin should be immediately decontaminated with a forceful jet of vinegar (5% acetic acid) or rubbing alcohol (40 to 70% isopropyl alcohol), which inactivates nematocysts. For the venomous *box-jellyfish* (*Chironex fleckeri*;Plate IID-53), vinegar should be used. Perfume, aftershave lotion, and high-proof ethanol are less efficacious and may be detrimental. Shaving the skin helps remove remaining nematocysts. Freshwater irrigation and rubbing lead to further stinging by adherent nematocysts and should be avoided. After decontamination, application of anesthetic ointments (lidocaine, benzocaine), antihistamine creams (diphenhydramine), or steroid lotions (hydrocortisone) may be helpful. Persistent pain following decontamination may be treated with morphine or meperidine. Muscle spasms may respond to 10% calcium gluconate (5 to 10 mL) or diazepam (2 to 5 mg, titrated upwards as necessary) given intravenously. An antivenom is available from Commonwealth Serum Laboratories (see section on antivenom sources, below) for stings from the box-jellyfish found in Australian waters.

Touching a *sea sponge* may result in dermatitis. If contact occurs, the skin should be gently dried and adhesive tape used to remove embedded spicules. Vinegar should be applied immediately and then for 10 to 30 min three or four times a day. Rubbing alcohol may be used if vinegar is unavailable. After spicule removal and skin decontamination, a steroid or antihistamine cream may be applied to the skin. Severe vesiculation should be treated with a 2-week course of systemic glucocorticoids.

Annelid worms (bristleworms) possess rows of soft, cactus-like spines capable of inflicting painful stings. Contact results in symptoms similar to those of nematocyst envenomation. Without treatment, pain usually subsides over several hours, but inflammation may persist for up to a week. Victims should resist the urge to scratch, since scratching may fracture retrievable spines. Visible bristles should be removed with forceps and adhesive tape, a commercial facial peel, or a thin layer of rubber cement. Use of vinegar, rubbing alcohol, or dilute ammonia or a brief application of unseasoned meat tenderizer (papain) may provide additional relief. Local inflammation should be treated with topical or systemic glucocorticoids.

Sea urchins possess either hollow, venom-filled, calcified spines or triple-jawed, globiferous pedicellariae with venom glands. Their venom contains several toxic components, including steroid glycosides, hemolysins, proteases, serotonin, and cholinergic substances. Contact with either venom apparatus produces immediate and intensely painful stings. The affected part should be immersed immediately in hot water (see below). Accessible embedded spines should be removed but may break off and remain lodged in the victim. Residual dye from the surface of a spine remaining after the spine's removal may mimic a retained spine but is otherwise of no consequence. Soft tissue radiography or magnetic resonance imaging can confirm the presence of retained spines; this finding may warrant referral for attempted surgical removal if the spines are located near vital structures (e.g., joints, neurovascular bundles). Retained spines may

cause the formation of granulomas that are amenable to excision or to intralesional injection with triamcinolone hexacetonide (5 mg/mL).

Cone shells are predatory, carnivorous mollusks. The most dangerous of these creatures are found in the Indian and Pacific oceans. A neurotoxic venom comprising multiple peptides is delivered through harpoon-like darts propelled from an extensible proboscis. Clinically, the sting is like that of a bee. The victim may report wound, perioral, and generalized paresthesias. Bulbar dysfunction and systemic muscular paralysis indicate severe envenomation. The sting of the geographer cone (*Conus geographus*) can cause cerebral edema, coma, and death due to respiratory or cardiac failure. Immediately after envenomation, a circumferential pressure-immobilization dressing 15 cm wide should be applied over a gauze pad measuring approximately 7 ´ 7´ 2 cm that has been placed directly over the sting. The dressing should be applied at venous-lymphatic pressure with the preservation of distal arterial pulses. Once the victim has been transported to the nearest medical facility, the bandage can be released. Provision should be made for cardiovascular and respiratory support.

Serious envenomations and deaths have followed bites of the *Australian blue-ringed octopuses* (*Octopus maculosus* and *O. lunulata*). Although these animals rarely exceed 20 cm in length, their venom contains a potent neurotoxin (maculotoxin) that inhibits peripheral nerve transmission by blocking sodium conductance. Within several minutes of a serious envenomation, oral and facial numbness develops and rapidly progresses to total flaccid paralysis, including failure of respiratory muscles. If respirations are assisted, the victim may remain awake although completely paralyzed. Since there is no antidote, treatment is supportive. Immediately after envenomation, attempts should be made to limit the dispersion of venom by application of a pressure-immobilization or venous-lymphatic pressure dressing. Hot-water immersion and cryotherapy are ineffective. Artificial respiration should be provided. Even with serious envenomations, significant recovery often takes place within 4 to 10 h. Sequelae are uncommon unless related to hypoxia.

VERTEBRATES

A number of marine vertebrates, including stingrays, scorpionfish, catfish, surgeonfish, and weeverfish, can envenom humans. The management of most of these stings is similar.

A *stingray* injury is both an envenomation and a traumatic wound. The venom, which contains serotonin, 5¢-nucleotidase, and phosphodiesterase, causes immediate and intense pain that may last up to 48 h. Systemic effects include weakness, diaphoresis, nausea, vomiting, diarrhea, dysrhythmias, syncope, hypotension, muscle cramps, fasciculations, paralysis, and (in rare cases) death.

The designation *scorpionfish* encompasses members of the family Scorpaenidae and includes not only scorpionfish but also lionfish and stonefish. A complex venom with neuromuscular toxicity is delivered through 12 or 13 dorsal, two pelvic, and three anal spines. Pectoral spines do not contain venom. The severity of envenomation depends on the species of fish, the number of stings, and the amount of venom released. In general, the sting of a stonefish is regarded as the most serious (severe to

life-threatening); that of the scorpionfish is of intermediate seriousness; and that of the lionfish is the least serious. Like that of a stingray, the sting of a scorpionfish is immediately and intensely painful. Pain from a stonefish envenomation may last for days. The systemic manifestations are similar to those of stingray envenomations but may be more pronounced, particularly in the case of a stonefish sting. The rare deaths following stonefish envenomation usually occur within 6 to 8 h.

Two species of marine *catfish*, *Plotosus lineatus* (the oriental catfish) and *Galeichthys felis* (the common sea catfish), as well as several species of freshwater catfish are capable of stinging humans. Venom is delivered through a single dorsal spine and two pectoral spines. Clinically, a catfish sting is comparable to that of a stingray, although marine catfish envenomations are generally more severe than those of their freshwater counterparts. *Surgeonfish* (doctorfish, tang), *weeverfish*, and *horned venomous sharks* have also been implicated in human envenomations.

The stings of all these marine vertebrates are treated in a similar fashion. Except for stonefish and serious scorpionfish envenomations (see below), no antivenom is available. The affected part should be immersed immediately in nonscalding hot water (113°F/45°C) for 30 to 90 min or until there is significant relief of pain. This measure also helps inactivate the heat-labile components of the venoms. Recurrent pain may respond to repeated hot-water treatment. Cryotherapy is contraindicated. Opiates will help alleviate the pain, as will local wound infiltration or regional nerve block with 1% lidocaine, 0.5% bupivacaine, and sodium bicarbonate mixed in a 5:5:1 ratio. After soaking and anesthetic administration, the wound must be explored and debrided. Radiography may be helpful in the identification and location of foreign bodies. After exploration and debridement, the wound should be vigorously irrigated with warm sterile water, saline, or 1% povidone-iodine in solution. Bleeding can usually be controlled by sustained local pressure for 10 to 15 min. In general, wounds should be left open to heal by secondary intention or be treated by delayed primary closure. Tetanus immunization should be updated. Antibiotic treatment should be considered for serious wounds and for envenomation in immunocompromised hosts. The initial antibiotics should cover *Staphylococcus* and *Streptococcus* spp. If the victim is immunocompromised or an infection develops, antibiotic coverage should be broadened to include *Vibrio* spp.

Approach to the Patient

It is not uncommon for a physician to encounter a patient who has been envenomed by a marine creature that cannot be positively identified at the scene of the envenomation. Therefore, it is useful to be familiar with the local marine fauna and to recognize patterns of injury.

A large puncture wound or jagged laceration, particularly on the lower extremity, that is more painful than one would expect from the size and configuration of the wound is likely a stingray envenomation. Smaller punctures, as described above, represent the activity of a sea urchin or starfish. Stony corals cause rough abrasions and, in rare instances, lacerations or puncture wounds.

Coelenterate (marine invertebrate) stings sometimes create diagnostic skin patterns. A diffuse urticarial rash on exposed skin is often indicative of exposure to fragmented

hydroids or larval anemones. A linear, whiplike print pattern appears where a jellyfish tentacle has contacted the skin. In the case of the dreaded box-jellyfish ([Plate IID-53](#)), a frosted cross-hatched appearance followed by dark purple coloration within a few hours of the sting heralds skin necrosis. An encounter with fire coral causes immediate pain and a red, swollen skin irritation in the pattern of contact, similar to but more severe than the imprint left by exposure to an intact feather hydroid. Seabather's eruption, caused by thimble jellyfishes and larval anemones, may cause a diffuse rash that consists of clusters of erythematous macules or raised papules, accompanied by intense itching. Toxic sponges (exposure to which usually occurs during handling) create a burning and painful red rash on exposed skin, which may blister and later desquamate. Virtually all marine stingers invoke the sequelae of inflammation, so that local erythema, swelling, and adenopathy are fairly nonspecific.

SOURCES OF ANTIVENOMS AND OTHER ASSISTANCE

An antivenom for stonefish (and severe scorpionfish) envenomation, made in Australia by the Commonwealth Serum Laboratories (CSL; 45 Poplar Road, Parkville, Victoria, Australia 3052; 61-3-389-1911; fax: 61-3-389-1434), is available in the United States through the pharmacies of Sharp Cabrillo Hospital Emergency Department, San Diego, CA, at (619) 221-3429, and Community Hospital of Monterey Peninsula (CHOMP) Emergency Department, Monterey, CA, at (408) 625-4900.

Polyvalent sea snake antivenom is available from CSL or CHOMP. If sea snake antivenom is unavailable, tiger snake (*N. scutatus*) antivenom should be used.

Divers Alert Network, a nonprofit organization designed to assist in the care of injured divers, may also help with the treatment of marine injuries. The network can be reached 24 h a day at (919) 684-8111 or on the Internet athttp://www.dan.ycg.org.

MARINE POISONINGS

CIGUATERA

Ciguatera poisoning is the most common nonbacterial food poisoning associated with fish in the United States. The poisoning involves almost exclusively tropical and semitropical marine coral reef fish. Of reported cases, 75% (except in Hawaii) involve the barracuda, snapper, jack, or grouper. The ciguatera syndrome is associated with at least five toxins, all of which are unaffected by freeze-drying, heat, cold, and gastric acid and none of which affects the odor, color, or taste of fish.

The onset of symptoms may come within 15 to 30 min of ingestion and typically takes place within 1 to 3 h. Symptoms then increase in severity over the ensuing 4 to 6 h. Most victims develop symptoms within 12 h of ingestion, and virtually all are afflicted within 24 h. The more than 150 symptoms reported include abdominal pain, nausea, vomiting, diarrhea, chills, paresthesias, pruritus, tongue and throat numbness or burning, sensation of "carbonation" during swallowing, odontalgia or dental dysesthesias, dysphagia, dysuria, dyspnea, weakness, fatigue, tremor, fasciculations, athetosis, meningismus, aphonia, ataxia, vertigo, pain and weakness in the lower extremities, visual blurring, transient blindness, hyporeflexia, seizures, nasal congestion

and dryness, conjunctivitis, maculopapular rash, skin vesiculations, dermatographism, sialorrhea, diaphoresis, headache, arthralgias, myalgias, insomnia, bradycardia, hypotension, central respiratory failure, and coma. Death is rare.

Diarrhea, vomiting, and abdominal pain usually develop 3 to 6 h after ingestion of a ciguatoxic fish. Symptoms may persist for 48 h and then generally resolve (even without treatment). A pathognomonic symptom is the reversal of hot and cold tactile perception, which develops in some persons after 3 to 5 days and may last for months. Tachycardia and hypertension have been described, in some cases after potentially severe transient bradycardia and hypotension. More severe reactions tend to occur in persons previously stricken with the disease. Persons who have ingested parrotfish (scaritoxin) may suffer from classic ciguatera poisoning as well as a "second-phase" syndrome (after 5 to 10 days' delay) of disequilibrium with locomotor ataxia, dysmetria, and resting or kinetic tremor. This affliction may persist for 2 to 6 weeks.

The differential diagnosis of ciguatera includes paralytic shellfish poisoning, eosinophilic meningitis, type E botulism, organophosphate insecticide poisoning, tetrodotoxin poisoning, and psychogenic hyperventilation. At present, the diagnosis of ciguatera poisoning is made on clinical grounds because no routinely used laboratory test detects ciguatoxin in human blood. A ciguatoxin enzyme immunoassay or radioimmunoassay may be used to test small portions of the suspected fish.

Therapy is supportive and based on symptoms. Although not of proven efficacy, gastric lavage or syrup of ipecac-induced emesis followed by the administration of a slurry of activated charcoal (100 g) in sorbitol may be of limited value if performed within 3 h after ingestion. Nausea and vomiting may be controlled with an antiemetic, such as prochlorperazine (2.5 to 5 mg intravenously). Hypotension may require the administration of intravenous crystalloid and, in rare cases, a pressor drug. Bradyarrhythmias that lead to cardiac insufficiency and hypotension generally respond well to atropine (0.5 mg intravenously, up to 2 mg). Cool showers or the administration of hydroxyzine (25 mg orally every 6 to 8 h) may relieve pruritus. Amitriptyline (25 mg orally twice a day) reportedly ameliorates pruritus and dysesthesias. In three cases unresponsive to amitriptyline, tocainide appeared to be efficacious. Intravenous infusion of mannitol may be beneficial in moderate or severe cases, particularly for the relief of distressing neurologic or cardiovascular symptoms. The infusion is rendered initially as 1 g/kg per day over 45 to 60 min during the acute phase (days 1 to 5). The mechanism of the benefit against ciguatera intoxication is hyperosmotic water-drawing action, which reverses ciguatoxin-induced Schwann cell edema. Mannitol may also act in some fashion as a "hydroxyl scavenger."

During recovery from ciguatera poisoning, the victim should exclude the following from the diet: fish (fresh or preserved), fish sauces, shellfish, shellfish sauces, alcoholic beverages, and nuts and nut oils. Consumption of fish in ciguatera-endemic regions should be avoided. All oversized fish of any predacious reef species should be suspected of harboring ciguatoxin. Neither moray eels nor the viscera of tropical marine fish should ever be eaten.

PARALYTIC SHELLFISH POISONING

Paralytic shellfish poisoning (PSP) is induced by the ingestion of any of a variety of feral or aquacultured filter-feeding organisms, including clams, oysters, scallops, mussels, chitons, limpets, starfish, and sand crabs. The origin of their toxicity is the chemical toxin they accumulate and concentrate by feeding on various planktonic dinoflagellates and protozoan organisms. The unicellular phytoplanktonic organisms form the foundation of the food chain, and in warm summer months these organisms "bloom" in nutrient-rich coastal temperate and semitropical waters. A number of dinoflagellates produce a variety of toxins. These planktonic species can release massive amounts of toxic metabolites into the water and cause enormous mortality in bird and marine populations. The paralytic shellfish toxins are water-soluble as well as heat- and acid-stable; they cannot be destroyed by ordinary cooking. The best-characterized and most frequently identified paralytic shellfish toxin is saxitoxin, which takes its name from the Alaska butter clam *Saxidomus giganteus*. A toxin concentration of >75 ug/100 g of foodstuff is considered hazardous to humans. In the 1972 New England "red tide," the concentration of saxitoxin in blue mussels exceeded 9000 ug/100 g of foodstuff. Saxitoxin appears to block sodium conductance, inhibiting neuromuscular transmission at the axonal and muscle membrane levels.

Within minutes to a few hours after ingestion of contaminated shellfish, there is the onset of intraoral and perioral paresthesias, notably of the lips, tongue, and gums, that progress rapidly to involve the neck and distal extremities. The tingling or burning sensation later changes to numbness. Other symptoms rapidly develop and include lightheadedness, disequilibrium, incoordination, weakness, hyperreflexia, incoherence, dysarthria, sialorrhea, dysphagia, thirst, diarrhea, abdominal pain, nausea, vomiting, nystagmus, dysmetria, headache, diaphoresis, loss of vision, chest pain, and tachycardia. Flaccid paralysis and respiratory insufficiency may follow 2 to 12 h after ingestion. In the absence of hypoxia, the victim often remains alert but paralyzed.

Treatment is supportive and based on symptoms. If the victim comes to medical attention within the first few hours after poison ingestion, the stomach should be emptied by gastric lavage and then irrigated with 2 L (in 200-mL aliquots) of a solution of 2% sodium bicarbonate. The administration of activated charcoal (50 to 100 g) and a cathartic (sorbitol, 20 to 50 g) makes empirical sense but has not been proved effective. Some authors advise against administration of magnesium-based solutions, such as certain cathartics, cautioning that hypermagnesemia may contribute to suppression of nerve conduction.

The most serious problem is respiratory paralysis. The victim should be closely observed in a hospital for at least 24 h for respiratory distress. With prompt recognition of ventilatory failure, endotracheal intubation and assisted ventilation prevent anoxic myocardial and brain injury.

DOMOIC ACID INTOXICATION

In late 1987 in eastern Canada, an outbreak of gastrointestinal and neurologic symptoms (amnestic shellfish poisoning) occurred after consumption of mussels found to be contaminated with domoic acid. A heat-stable neuroexcitatory amino acid whose biochemical analogs are kainic acid and glutamic acid, domoic acid binds to the kainate type of glutamate receptor with three times the affinity of kainic acid and is 20 times as

powerful a toxin. Mussels can be tested for domoic acid by mouse bioassay and high-performance liquid chromatography. The regulatory limit for domoic acid in shellfish is 20 parts per million.

The abnormalities noted within 24 h of ingesting contaminated mussels *(Mytilus edulis)* include arousal, confusion, disorientation, and memory loss. The median time of onset is 5.5 h. Other prominent symptoms include severe headache, nausea, vomiting, diarrhea, abdominal cramps, hiccoughs, arrhythmias, hypotension, seizures, ophthalmoplegia, hemiparesis, mutism, grimacing, agitation, emotional lability, coma, copious bronchial secretions, and pulmonary edema. Histologic study of brain tissue taken at autopsy has shown neuronal necrosis or cell loss and astrocytosis, most prominently in the hippocampus and the amygdaloid nucleus -- findings similar to those in animals poisoned with kainic acid. Several months after the primary intoxication, victims still demonstrate chronic residual memory deficits and motor neuronopathy or axonopathy. Nonneurologic illness does not persist.

Therapy is supportive and based on symptoms. Since kainic acid neuropathology seems to be nearly entirely seizure mediated, an emphasis should be placed on anticonvulsive therapy, for which diazepam appears to be as effective as any other drug.

SCOMBROID

Scombroid (mackerel-like) fish include the albacore, bluefin, and yellowfin tuna; mackerel; saury; needlefish; wahoo; skipjack; and bonito. Nonscombroid fish that produce scombroid poisoning include the dolphinfish (mahimahi, *Coryphaena*), kahawai, sardine, black marlin, pilchard, anchovy, herring, amberjack, and Australian ocean salmon. In the northeastern and mid-Atlantic United States, bluefish has been linked to scombroid poisoning. Because greater numbers of nonscombroid fish are being recognized as scombrotoxic, the syndrome may more appropriately be called *pseudoallergic fish poisoning*.

Under conditions of inadequate preservation or refrigeration, the musculature of these dark- or red-fleshed fish undergoes bacterial decomposition, which includes the decarboxylation of the amino acid L-histidine to histamine, histamine phosphate, and histamine hydrochloride. Histamine levels of >20 to 50 mg/100 g are noted in toxic fish, with levels in excess of 400 mg/100 g on occasion. The toxin is heat stable and is not destroyed by domestic or commercial cooking. Affected fish typically have a sharply metallic or peppery taste; however, they may be normal in appearance, color, and flavor.

Symptoms occur within 15 to 90 min of ingestion and include flushing (sharply demarcated; exacerbated by ultraviolet exposure; particularly pronounced on the face, neck, or upper trunk), a sensation of warmth without elevated core temperature, conjunctival hyperemia, pruritus, urticaria, angioneurotic edema, bronchospasm, nausea, vomiting, diarrhea, epigastric pain, abdominal cramps, dysphagia, headache, thirst, pharyngitis, burning of the gingiva, palpitations, tachycardia, dizziness, and hypotension. Without treatment, the symptoms generally resolve within 8 to 12 h. The reaction may be more severe in a person who is concurrently ingesting isoniazid

because of blockade of gastrointestinal tract histaminase.

Therapy is directed at reversing the histamine effect with antihistamines, either H-1 or H-2. If bronchospasm is severe, an inhaled bronchodilator -- or in rare, extremely severe circumstances, injected epinephrine -- may be used. Glucocorticoids are of no proven benefit. Protracted nausea and vomiting, which may empty the stomach of toxin, may be controlled with a specific antiemetic, such as prochlorperazine. The persistent headache of scombroid poisoning may respond to cimetidine or a similar antihistamine if standard analgesics are not effective.

PFIESTERIA

In the summer of 1997, reports of adverse reactions after casual exposure to Maryland waters infested with the fish-eating dinoflagellate *Pfiesteria* prompted the Centers for Disease Control and Prevention (CDC) to undertake multistate surveillance and to establish a case definition. As defined by the CDC, the human disease syndrome associated with *Pfiesteria* is characterized by either of two groups of signs and symptoms: (1) memory loss, confusion, or acute skin burning on direct contact with infested water; or (2) at least three of the following: headache, rash (flat red sores), eye irritation, upper respiratory irritation, muscle cramps, and gastrointestinal symptoms. Since the initial reports from Maryland, many such cases have followed both casual exposure to infested water and laboratory work with *Pfiesteria* (which is currently conducted in biohazard III facilities).

Research on *Pfiesteria* has been complicated by a variety of factors, including the lack of a test for detection of its toxins, which have yet to be purified, and the organism's complex life cycle, which includes at least two dozen stages. In nature, the proximity of a school of fish elicits *Pfiesteria's* transformation into a flagellated zoospore that releases at least two toxins: a water-soluble, neuroactive toxin that kills fish within minutes, and a fat-soluble toxin that causes epidermal delamination. Polluted environments appear to favor *Pfiesteria*.

For the treatment of *Pfiesteria*-associated syndromes, one teaspoon of milk of magnesia followed by one scoop of cholestyramine in 8 ounces of water and 70% sorbitol solution is administered daily for 2 weeks.

(Bibliography omitted in Palm version)

398. ECTOPARASITE INFESTATIONS, ARTHROPOD BITES AND STINGS - *James H. Maguire, Andrew Spielman*

Ectoparasites are arthropods or helminths that *infest* the skin of other animals from which they derive sustenance. They may penetrate beneath the surface of the host or attach superficially by their mouthparts. These organisms damage their hosts by inflicting direct injury, by eliciting a hypersensitivity reaction, or by inoculating toxins or pathogens. The main medically important ectoparasites are arachnids (including mites and ticks), insects (including lice, fleas, and flies), pentastomes (tongue worms), and leeches. Arthropods may also harm humans through brief encounters in which they take a blood meal or attempt to defend themselves by biting, stinging, or inoculating venoms. Various arachnids (spiders, scorpions), insects (including bees, hornets, wasps, ants, flies, bugs, caterpillars, and beetles), millipedes, and centipedes produce ill effects in this manner, as do certain ectoparasites of animals, including ticks, biting mites, and fleas (discussed in this chapter as biting arthropods). More people in the United States die each year as a consequence of arthropod stings than from poisonous snake bites.

ECTOPARASITE INFESTATIONS

SCABIES

The human itch mite, *Sarcoptes scabiei* (Fig. 398-CD1), which infests some 300 million persons each year, is one of the most common causes of itching dermatoses throughout the world. Gravid female mites measuring 0.3 to 0.4 mm in length burrow superficially beneath the stratum corneum for a month, depositing two or three eggs a day. Nymphs that hatch from these eggs mature in about 2 weeks through a series of molts and then emerge as adults to the surface of the skin, where they mate and subsequently reinvade the skin of the same or another host. Transfer of newly fertilized female mites from person to person occurs by intimate personal contact and is facilitated by crowding, uncleanliness, and multiple sexual partners. Medical practitioners are at particular risk of infestation. Transmission via sharing of contaminated bedding or clothing is infrequent because these mites cannot survive much more than a day without host contact. In the United States, scabies may account for 2 to 5% of visits to dermatologists; involved particularly often are children, immigrants from developing countries, and close household contacts. Outbreaks occur in nursing homes, mental institutions, and hospitals.

The itching and rash associated with scabies derive from a sensitization reaction directed against the excreta that the mite deposits in its burrow (Plate IID-52). For this reason, an initial infestation remains asymptomatic for 4 to 6 weeks, and a reinfestation produces a hypersensitivity reaction without delay. Scratching generally destroys the burrowing mite, but symptoms remain even in its absence. Burrows become surrounded by infiltrates of eosinophils, lymphocytes, and histiocytes, and a generalized hypersensitivity rash later develops in remote sites. By destroying these pathogens, immunity and associated scratching limit most infestations to fewer than 15 mites per person. Hyperinfestation with thousands or millions of mites, a condition known as *crusted scabies* or *Norwegian scabies*, may result from glucocorticoid use, immunodeficiency diseases (including AIDS and infection with human T-lymphotropic virus type I), and neurologic and psychiatric illnesses that interfere with itching and

scratching.

Patients with scabies report intense itching that worsens at night and after a hot shower. Typical burrows may be difficult to find because they are few in number and may be obscured by excoriations. Burrows appear as dark wavy lines in the epidermis, measure 3 to 15 mm, and end in a small pearly bleb that contains the female mite. Such lesions generally develop on the volar wrists, between the fingers, on the elbows, and on the penis. Small papules and vesicles, often accompanied by eczematous plaques, pustules, or nodules, are symmetrically distributed in these sites (Fig. 398-CD2) and in skin folds under the breasts and around the navel, axillae, belt line, buttocks, upper thighs, and scrotum. Except in infants, the face, scalp, neck, palms, and soles are spared. Burrows and other typical lesions may be sparse in persons who wash frequently, and topical glucocorticoid treatment and bacterial superinfection may alter the appearance of the rash. Atypical presentations of scabies include bullous lesions, which resemble those of bullous pemphigoid, and vesicular lesions, which resemble those of dermatitis herpetiformis. Superinfection with nephritogenic strains of streptococci has led to acute glomerulonephritis. Crusted scabies resembles psoriasis in its typical widespread erythema, thick keratotic crusts, scaling, and dystrophic nails. Characteristic burrows are not seen in crusted scabies, and patients usually do not itch, although their infestations are highly contagious and have been responsible for outbreaks of classic scabies in hospitals. Bacteremia occurs frequently in AIDS patients with crusted scabies and prominent fissures. Persons with massive infestations occasionally present with diffuse pruritus and generalized papules or with minimal or no cutaneous signs.

A diagnosis of scabies should be considered in patients with pruritus and symmetric polymorphic skin lesions in characteristic locations, particularly if there is a history of household contact with a case. Burrows should be sought and unroofed with a sterile needle or scalpel blade, and the scrapings should be examined microscopically for the mite, its eggs, and its fecal pellets. A drop of mineral oil facilitates removal of the sample. Biopsies or scrapings of papulovesicular lesions may also be diagnostic. In the absence of identifiable mites or mite products, the diagnosis is based on clinical presentation and history. The possibility of other sexually transmitted diseases should be excluded in adults with scabies.

TREATMENT

For the treatment of scabies, 5% permethrin cream is less toxic than the once commonly used 1% lindane preparations and is effective against lindane-tolerant infestations. Both scabicides are applied thinly but thoroughly behind the ears and from the neck down after bathing and are removed 8 h later with soap and water. Lindane is absorbed through the skin, and its overuse has led to seizures and aplastic anemia. It should not be applied to pregnant women or infants. Alternatives include topical crotamiton cream, benzyl benzoate, and sulfur ointments. Successful treatment of crusted scabies requires the application first of a keratolytic agent such as 6% salicylic acid (to improve the penetration of scabicides) and then of scabicides to the scalp, face, and ears (with care to avoid the eyes). Repeated treatments or the sequential use of several agents may be necessary. A single oral dose of ivermectin (200 ug/kg) effectively treats scabies in otherwise healthy persons. Patients with crusted scabies

may require two or more doses of ivermectin. Although ivermectin may become the agent of choice for treating crusted scabies, it has not yet received approval by the U.S. Food and Drug Administration (FDA) for any form of scabies. Its use should be reserved for persons who fail to respond to topical scabicides, the elderly, persons with generalized eczema, and other persons who may not tolerate topical therapy.

Although effectively treated scabies infestations become noninfectious within a day, itching and rash due to hypersensitivity frequently persist for weeks or months. Unnecessary re-treatment of the affected patients may provoke contact dermatitis. Antihistamines, salicylates, and calamine lotion relieve itching during treatment, and topical glucocorticoids are useful for the pruritus that lingers after effective treatment. An oral antibiotic may be necessary for bacterial superinfections that fail to resolve with antiscabietic therapy. Relapses of scabies may be due to infestations of the scalp when topical therapy is applied only from the neck down. To prevent reinfestations, bedding and clothing should be washed in hot water, and close contacts, even if asymptomatic, should be treated simultaneously.

OTHER MITE INFESTATIONS

Species of *Demodex*, the follicle mite, live in hair follicles and sebaceous glands of the face and ears. The wormlike mites measure up to 0.4 mm in length and, if carefully sought, can be found on almost all persons. They appear not to cause disease, although their density is high in persons with rosacea. House dust mites of the genus *Dermatophagoides* infest houses throughout the world, living on furniture and rugs and feeding on shed human dander. Exposure to their allergens causes asthma, rhinitis, conjunctivitis, and eczema in persons with house dust allergies. Management includes immunotherapy with mite extracts and environmental interventions such as frequent vacuuming and removal of rugs from bedrooms to reduce mite density.

PEDICULOSIS (LOUSE INFESTATIONS)

All three species of human louse feed at least once a day on human blood. *Pediculus humanus* var. *capitis* (Fig. 398-CD3) infests the head (Fig. 398-CD4), *P. humanus* var. *corporis* the clothing (Fig. 398-CD5), and *Phthirus pubis* (Fig. 398-CD6) mainly the hair of the pubis (Fig. 398-CD7). Females cement their eggs (nits) firmly to hair or clothing. The saliva of lice produces an intensely irritating maculopapular or urticarial rash in sensitized persons.

Head lice, which infest an estimated 6 to 12 million people in the United States, are transmitted directly from person to person and occasionally by shared headgear and grooming implements. The prevalence is highest among school-aged girls who wear long hair; in the United States, black children are less frequently infested than other children. Excoriations of pruritic lesions on the scalp, neck, and shoulders lead to oozing, crusting, matting of hair, bacterial infections, and regional lymphadenopathy. Adult lice are frequently seen crawling in the hair with a velocity that approaches 25 mm/min.

Body lice remain in clothing except when feeding and cannot survive more than a few hours away from the human host. It follows, therefore, that *P. humanus* var. *corporis*

mainly infests disaster victims or indigent persons who do not change their clothes. Transmission by direct contact or by sharing of clothing and beds is enhanced under crowded conditions. The fact that the body louse leaves febrile persons or corpses as they become cold facilitates the transmission of typhus, louse-borne relapsing fever, and trench fever (Chap. 177). Trench fever and endocarditis due to *Bartonella quintana* have emerged as diseases of homeless persons living in large cities of the United States and Europe. Pruritic lesions are particularly common around the neckline. Chronic infestations result in the postinflammatory hyperpigmentation and thickening of skin known as *vagabonds' disease*.

The cosmopolitan crab or pubic louse is transmitted mainly by sexual contact but can infest eyelashes, axillary hair, and hair in other sites as well as pubic hair. Children with pubic lice generally acquire their infestations from parents rather than via sexual transmission. Polymerase chain reaction (PCR) analysis of the blood meal of lice permits identification of host DNA in cases of child abuse or rape. Intensely pruritic lesions and 2- to 3-mm blue macules (maculae ceruleae) develop at the site of bites. Blepharitis commonly accompanies infestations of the eyelashes.

A suspected diagnosis of pediculosis is confirmed by the finding of nits or adult lice on hairs or in clothing. The dorsoventrally flattened adult lice measure 2 to 4 mm in length and have three pairs of legs ending in claws that enable them to grasp hair shafts or clothing. Oval nits measure 0.8 mm in length and are opaque white or cream-colored (body and head lice) or dark brown (pubic lice).

TREATMENT

The preferred treatment is a 10-min application of 1% permethrin creme rinse, which kills both lice and eggs and is available without prescription. An alternative, 0.5% malathion, requires a prescription and must be left in place for 8 to 12 h. Other agents, such as the more toxic 1% lindane and pyrethrins with piperonyl butoxide, are not ovicidal and require a second application 1 week after the first to kill hatching nymphs. Dead or hatched nits, which remain attached to hair sheaths and become translucent or opalescent, may falsely suggest an active infection. Resistance of head lice to permethrin, malathion, and lindane has been reported. When a properly applied treatment fails, a higher concentration (5%) of permethrin may be tried or the class of pediculicide changed (e.g., by switching from permethrin to malathion). Ivermectin may be useful in cases of resistance to both malathion and permethrin but has not been approved for this purpose by theFDA.

After louse infestations have been treated with insecticide, the hair should be combed with a fine-toothed nit comb to remove nits. Combs and brushes should be disinfected in hot water at 65°C for 5 min or soaked in insecticide for 1 h. Body lice can be eliminated by bathing and application of topical pediculicides from head to foot. Clothes and bedding are deloused by heat sterilization in a dryer at 65°C for 30 min or by fumigation. Infestations with pubic lice are treated with topical pediculicides except for eyelid infestations (*phthiriasis palpebrum*), which respond to a coating of petroleum applied for 3 to 4 days or 1% yellow oxide of mercury ointment applied four times daily for 2 weeks.

TUNGIASIS

Tunga penetrans, like other fleas, is a wingless, laterally flattened insect measuring 2 to 4 mm in length that feeds on blood. Also known as the chigoe flea, sand flea, or jigger, it occurs in tropical regions of Africa and the Americas. Adults live in sandy soil and burrow under the skin between toes, under nails, or on the soles of bare feet. The fleas engorge on blood and grow from pinpoint to pea size over a 2-week period. The lesions resemble a white pustule with a central black depression and may be pruritic or painful. Occasional complications include tetanus, bacterial infections, and autoamputation of toes. Tungiasis is treated by removal of the intact flea with a sterile needle or scalpel, tetanus vaccination, and topical antibiotics.

MYIASIS

Myiasis refers to infestations by maggots, mainly due to the larvae of metallic-colored screw-worm flies or botflies. Maggots invade living or necrotic tissue or body cavities and produce different clinical syndromes depending on the species of fly.

Furuncular Myiasis (Fig. 398-CD8) In forested parts of Central and South America, larvae of *Dermatobia hominis* (the human botfly) produce boil-like subcutaneous nodules 2 to 3 cm in diameter. The adult female captures a mosquito or other bloodsucking insect and deposits her eggs beneath its abdomen. When the carrier insect attacks a human or bovine host several days later, the warmth and moisture of the host's surface stimulate the larvae to hatch and penetrate the skin. After 6 to 12 weeks, the larvae mature and drop to the ground, where they pupate. The African tumbu fly, *Cordylobia anthropophaga*, produces similar lesions. Dozens of eggs are deposited on sand or drying laundry that is contaminated with urine or sweat. Larvae hatch on contact with the body, penetrate the skin, and produce boils from which they emerge 8 or 9 days later. A diagnosis of furuncular myiasis is suggested by uncomfortable lesions with a central breathing pore that emits bubbles when submerged in water. There is often a sensation of movement under the skin that may lead to severe emotional distress. Tumbu fly larvae can be removed by manual expression after the air pore is coated with petroleum to suffocate the larvae and induce them to emerge. Removal of *Dermatobia* larvae is facilitated by injection of a local anesthetic into the surrounding tissue, but surgical excision is often necessary because up-pointing spines hold the larva firmly in place.

Creeping Dermal Myiasis Maggots of the horse botfly, *Gasterophilus intestinalis*, do not mature after penetrating human skin but migrate for weeks in the epidermis. The resulting pruritic and serpiginous eruption resembles cutaneous larva migrans caused by *Ancylostoma braziliense*. Horseback riders become infested when eggs deposited on the flank of the horse hatch against their bare legs. The black spines of the larvae can be identified after mineral oil is smeared over the lesion. Larva are removed with a needle. The larvae of the cattle botfly (*Hypoderma* species) invade more deeply and produce boil-like swellings.

Wound (Fig. 398-CD9) and Body Cavity Myiasis Certain flies are attracted to blood and pus, and their newly hatched larvae enter wounds or diseased skin. Larvae of species such as *Phaenicia sericata*, the green-bottle fly, remain superficial and confined to necrotic tissue and were used in the past to debride purulent wounds. Other species,

including the screw-worms (*Chrysomyia bezziana* in Asia and Africa and *Cochliomyia hominivorax* in Latin America) and the flesh fly (*Wohlfahrtia vigil* in northern North America), invade more deeply into viable tissue and produce large suppurating lesions. Larvae that infest wounds also may infest body cavities such as the mouth, nose, ears, sinuses, anus, vagina, and lower urinary tract, particularly in unconscious or otherwise debilitated patients. The consequences range from harmless colonization to destruction of the nose, meningitis, and deafness. Treatment involves removal of maggots and debridement of tissue.

Other Forms of Myiasis The maggots responsible for furuncular and wound myiasis may also cause ophthalmomyiasis. Sequelae include nodules in the eyelid, retinal detachment, and destruction of the globe. In addition, the adult sheep botfly, *Oestrus ovis*, may deposit larvae in the eyes of persons tending sheep and goats, and the larvae may produce a conjunctival infestation and acute conjunctivitis. True intestinal myiasis occurs when eggs or larvae of the drone fly (*Eristalis tenax*) are ingested with contaminated food, mature in the gut, and cause enteritis. Most instances in which maggots are found in human feces are the result of larviposition by flesh flies on recently passed stools.

PENTASTOMIASIS

Pentastomids, or tongue worms, are parasites with characteristics of both helminths and arthropods and are classified in a separate phylum. The wormlike adults inhabit the respiratory passages of reptiles and carnivorous mammals. Human infestation with *Linguatula serrata* is common in the Middle East and occurs in the Sudan following ingestion of encysted larval stages in raw liver or lymph nodes of sheep and goats, the intermediate hosts. The larvae migrate to the nasopharynx and produce an acute self-limiting syndrome known as *halzoun* (*Marrara* in the Sudan), which is characterized by pain and itching of the throat and ears, coughing, hoarseness, dysphagia, and dyspnea. Severe edema may cause obstruction and necessitate tracheostomy, and ocular invasion has been described. Diagnostic larvae measuring 5 to 10 mm in length are found in the copious nasal discharge or vomitus. Human beings become infected with *Armillifer armillatus* by ingesting eggs in contaminated food or drink or after handling the definitive host, the African python. Larvae encyst in various organs but rarely cause symptoms unless they compress vital structures or perforate an organ during migration. Cysts occasionally require surgical removal as they enlarge during molting, but they are usually encountered as an incidental finding at autopsy. There are reports of the cutaneous larva migrans syndrome due to other pentastomes (*Reighardia* and *Sebekia* species) in Southeast Asia and Central America.

LEECH INFESTATIONS

Medically important leeches are annelid worms that attach to their hosts with chitinous cutting jaws and draw blood with muscular suckers. The medicinal leech, *Hirudo medicinalis*, is still used occasionally to reduce venous congestion in surgical flaps or replanted body parts. This practice has been complicated by wound infections, myonecrosis, and sepsis due to *Aeromonas hydrophila*, which colonizes the gullets of commercially available leeches.

Ubiquitous aquatic leeches that parasitize fish, frogs, and turtles readily attach to the skin of human beings and avidly suck blood. More notorious are the land leeches (*Haemadipsa*) that live in moist vegetation of tropical rain forests. Attachment is usually painless. Hirudinin, a powerful anticoagulant secreted by the leech, causes continued bleeding after the leech has detached. Healing of the wound is slow, and bacterial infections are not uncommon. Several species of aquatic leeches in Africa, Asia, and southern Europe can enter through the mouth, nose, and genitourinary tract and attach to mucosal surfaces at sites as deep as the esophagus and trachea. Bleeding may be intense. Externally attached leeches are removed by steady gentle traction. Removal is hastened by application of alcohol, salt, vinegar, or a flame to the leech. Internally attached leeches may detach on exposure to gargled saline or may be removed by forceps.

DELUSIONAL INFESTATIONS

The groundless conviction that one is infested with arthropods or other parasites is an extremely difficult disorder to treat and unfortunately is not rare. Patients report infestations of their skin, clothing, or homes and describe sensations of something moving in or on their skin. Excoriations often accompany complaints of pruritus or insect bites. Patients bring in as evidence of infestation specimens that are identified microscopically as plant-feeding or peridomestic arthropods, pieces of skin, vegetable matter, or inanimate objects. In suspected cases, it is imperative to rule out true infestations and neuropathies, environmental irritants such as fragments of fiberglass, and other causes of tingling or prickling sensations. Pharmacotherapy with pimozide, which blocks dopamine receptors, has been more helpful than psychotherapy in treating this disorder.

ARTHROPOD BITES AND STINGS

SPIDER BITES

Of the>30,000 recognized species of spider, only about 100 defend themselves aggressively and have fangs sufficiently long to penetrate human skin. The venom that spiders use to immobilize and digest their prey can cause necrosis of skin and systemic toxicity. While the bites of most spiders are painful but not harmful, envenomations of the brown or fiddle spiders (*Loxosceles* species), widow spiders (*Latrodectus* species), and other species may be life-threatening. Identification of the offending spider should be attempted, since specific treatments exist for bites of widow and brown recluse spiders and since injuries attributed to spiders are frequently due to other causes.

Recluse Spider Bites and Necrotic Arachnidism Severe necrosis of skin and subcutaneous tissue follows envenomation by *Loxosceles reclusa*, the brown recluse spider, and by at least four other species of *Loxosceles* in the southern and midwestern United States. Other spiders that produce necrotic ulceration include the hobo spider (*Tegenaria agrestis*) in the Pacific Northwest, the sac spiders (*Chiracanthium* species) throughout the United States and abroad, the South American brown spider *Loxosceles laeta* in Central and South America, and other *Loxosceles* species in Africa and the Middle East. All these spiders measure 7 to 15 mm in body length and 2 to 4 cm in leg span. Recluse spiders are brown and have a dark violin-shaped spot on their dorsal

surface; hobo spiders are brown with gray markings; and sac spiders may be pale yellow, green, or brown.

These spiders are not aggressive toward human beings and bite only if threatened or pressed against the skin. They hide under rocks and logs or in caves and animal burrows, and they emerge at night to hunt other spiders and insects. They invade homes, particularly in the fall, and seek dark and undisturbed hiding spots in closets, in folds of clothing, or under furniture and rubbish in storage rooms, garages, and attics. Bites often occur while the victim is dressing and are sustained primarily to the arms, neck, and lower abdomen.

The clear viscous venoms of these spiders contain an esterase, alkaline phosphatase, protease, and other enzymes that produce tissue necrosis and hemolysis. Sphingomyelinase B, the most important dermonecrotic factor, binds cell membranes and promotes chemotaxis of neutrophils, leading to vascular thrombosis and an Arthus-like reaction. Initially, the bite is painless or produces a stinging sensation. Within the next few hours, the site becomes painful and pruritic, with central induration surrounded by a pale zone of ischemia and a zone of erythema. In most cases, the lesion resolves without treatment over 2 to 3 days. In severe cases, the erythema spreads, and the center of the lesion becomes hemorrhagic and necrotic with an overlying bulla. A black eschar forms and sloughs several weeks later, leaving an ulcer that may be ³25 cm in diameter and eventually a depressed scar. Healing usually takes place within 3 to 6 months but may take as long as 3 years if adipose tissue is involved. Local complications include injury to nerves and secondary infection. Fever, chills, weakness, headache, nausea, vomiting, myalgia, arthralgia, maculopapular rash, and leukocytosis may develop within 72 h of the bite. In rare instances, acute complications such as hemolytic anemia, hemoglobinuria, and renal failure are fatal.

TREATMENT

Initial management includes local cleansing, application of sterile dressings and cold compresses, and elevation and loose immobilization of the affected limb. Analgesics, antihistamines, antibiotics, and tetanus prophylaxis should be administered if indicated. Within the first 48 to 72 h, the administration of dapsone, a leukocyte inhibitor, may halt the progression of lesions that are becoming necrotic. Dapsone is given in oral doses of 50 to 100 mg twice daily after glucose-6-phosphate dehydrogenase deficiency has been ruled out. The efficacy of locally or systemically administered glucocorticoids has not been demonstrated, and a potentially useful *Loxosceles*-specific antivenin has not been approved for use in the United States. Debridement and later skin grafting may be necessary after signs of acute inflammation have subsided, but immediate surgical excision of the wound is detrimental. Patients should be monitored closely for signs of hemolysis, renal failure, and other systemic complications.

Widow Spider Bites The bite of the female widow spider is notorious for the effect of its potent neurotoxin. *Latrodectus mactans*, the black widow, has been found in every state of the United States except Alaska and is most abundant in the southeast. It measures up to 1 cm in body length and 5 cm in leg span, is shiny black, and has a red hourglass marking on the ventral abdomen. Other dangerous North American *Latrodectus* species include *L. geometricus* (the brown widow), *L. bishopi* (the red widow), *L. variolus*, and *L.*

hesperus, and there are related species in other temperate and subtropical parts of the world.

Widow spiders spin their webs under stones, logs, plants, or rock piles or in dark spaces in barns, garages, and outhouses. Bites are most common in the summer and early autumn and occur when the web is disturbed or when the spider is trapped or provoked. The buttocks or genitals are sites of bites incurred by humans while sitting in an outdoor privy.

The initial bite goes unnoticed or is perceived as a sharp pinprick. Two small red marks, mild erythema, and edema develop at the fang entrance site. The oily yellow venom that is injected does not produce local necrosis, and some persons experience no other symptoms. However, a-latrotoxin, the most active component of the venom, binds irreversibly to nerves and causes release and eventual depletion of acetylcholine, norepinephrine, and other neurotransmitters from presynaptic terminals. Within 30 to 60 min, painful cramps spread from the bite site to large muscles of the extremities and the trunk. Extreme rigidity of the abdominal muscles and excruciating pain may suggest peritonitis, but the abdomen is not tender on palpation. Other features include salivation, diaphoresis, vomiting, hypertension, tachycardia, labored breathing, anxiety, headache, weakness, fasciculations, paresthesia, hyperreflexia, urinary retention, uterine contractions, and premature labor. Rhabdomyolysis and renal failure have been reported, and respiratory arrest, cerebral hemorrhage, or cardiac failure may end fatally, especially in very young, elderly, or debilitated persons. The pain begins to subside during the first 12 h but may recur during several days or weeks before resolving spontaneously.

TREATMENT

Treatment consists of local cleansing, application of ice packs, and tetanus prophylaxis. Hypertension that does not respond to analgesics and antispasmodics, such as benzodiazepines or methocarbamol, requires specific antihypertensive medication. Intravenous administration of one or two vials of a widely available equine antivenin rapidly relieves pain and can be life-saving. Because of the risk of anaphylaxis and serum sickness, antivenin should be reserved for severe cases involving respiratory arrest, uncontrollable hypertension, seizures, or pregnancy.

Envenomations by Tarantulas and Other Spiders Tarantulas are long-lived, hairy spiders of which 30 species are found in the United States, primarily in the southwest. The tarantulas that have become popular household pets are usually imported species with bright colors and a leg span of up to 25 cm. Tarantulas bite only when threatened and cause no more harm than a bee sting, but the venom occasionally provokes deep pain and swelling. Several species are covered with urticating hairs that are launched in the thousands when a threatened spider rubs its hind legs across the dorsal abdomen. These hairs penetrate human skin and produce pruritic papules that last for weeks. Failure to wear gloves or to wash the hands after handling the Chilean Rose tarantula, the most popular pet spider, has resulted in transfer of hairs to the eye and devastating ocular inflammation. Treatment of bites includes local washing and elevation of the bitten area, tetanus prophylaxis, and analgesic administration. Antihistamines and topical or systemic glucocorticoids are given for exposure to urticating hairs.

Atrax robustus, the Sydney funnel-web spider of Australia, and *Phoneutria* species, the South American banana spiders, are among the most dangerous spiders in the world because of their aggressive behavior and potent neurotoxins. Envenomation by *A. robustus* causes a rapidly progressive neuromotor syndrome that can be fatal within 2 h. The bite of the banana spiders causes severe local pain followed by profound systemic symptoms and respiratory paralysis that can lead to death within 2 to 6 h. Specific antivenins for envenomation by each of these spiders are available. *Lycosa* species (wolf spiders) are found throughout the world and may produce painful bites and transient local inflammation.

SCORPION STINGS

Scorpions are crablike arachnids that feed on ground-dwelling arthropods and small lizards, which they grasp with a pair of frontal pinchers and paralyze by injecting venom from a stinger on the tip of the tail. Painful but relatively harmless scorpion stings need to be distinguished from the potentially lethal envenomations that are produced by about 30 of the approximately 1000 known species and cause more than 5000 deaths worldwide each year. Scorpions feed at night and remain hidden during the day in crevices or burrows or under wood, loose bark, or rocks on the ground. They seek cool spots under buildings and often enter houses, where they get into shoes, clothing, or bedding or enter bathtubs and sinks in search of water. Scorpions sting human beings only when disturbed.

Scorpions of the United States Of the 40 or so scorpion species in the United States, only the bark scorpion (*Centruroides sculpturatus* or *C. exilicauda*) produces a venom that can be lethal. Stings of the other species, such as the common striped scorpion *C. vittatus* and the large *Hadrurus arizonensis*, cause immediate sharp local pain followed by edema, ecchymosis, and a burning sensation. Symptoms typically resolve within a few hours, and skin does not slough. Allergic reactions to the venom sometimes develop.

The deadly *C. sculpturatus* of the southwestern United States and northern Mexico measures about 7 cm in length and is yellow-brown in color. Its venom contains neurotoxins that cause sodium channels to remain open and neurons to fire repetitively. In contrast to the stings of nonlethal species, *C. sculpturatus* envenomations are usually associated with little swelling, but prominent pain, paresthesia, and hyperesthesia can be accentuated by tapping on the affected area (the tap test). These symptoms soon spread to other locations; dysfunction of cranial nerves and hyperexcitability of skeletal muscles develop within hours. Patients present with restlessness, blurred vision, abnormal eye movements, profuse salivation, lacrimation, rhinorrhea, slurred speech, difficulty in handling secretions, diaphoresis, nausea, and vomiting. Muscle twitching, jerking, and shaking may be mistaken for a seizure. Complications include tachycardia, arrhythmias, hypertension, hyperthermia, rhabdomyolysis, and acidosis. Symptoms progress to maximal severity in about 5 h and subside within a day or two, although pain and paresthesia can last for weeks. Fatal respiratory arrest is most common among young children and the elderly.

Other Dangerous Scorpions Envenomations by *Leiurus quinquestriatus* in the Middle

East and North Africa, by *Mesobuthus tamulus* in India, by *Androctonus* species along the Mediterranean littoral and in North Africa and the Middle East, and by *Tityus serrulatus* in Brazil cause massive release of endogenous catecholamines with hypertensive crises, arrhythmias, pulmonary edema, and myocardial damage. Acute pancreatitis occurs with stings of *Tityus trinitatis* in Trinidad, and central nervous toxicity complicates stings of *Parabuthus* and *Buthotus* scorpions of South Africa. Tissue necrosis and hemolysis may follow stings of the Iranian *Hemiscorpius lepturus*.

TREATMENT

Identification of the offending scorpion aids in planning therapy. Stings of nonlethal species require at most ice packs, analgesics, or antihistamines. Because most victims of dangerous envenomations (such as those produced by *C. sculpturatus*) experience only local discomfort, they can be managed at home with instructions to return to the emergency department if signs of cranial-nerve or neuromuscular dysfunction develop. Aggressive supportive care and judicious use of antivenin can reduce or eliminate mortality from more severe envenomations. Keeping the patient calm and applying pressure dressings and cold packs to the sting site decrease the absorption of venom. A continuous intravenous infusion of midazolam controls the agitation, flailing, and involuntary muscle movements produced by scorpion stings. Close monitoring during treatment with this drug and other sedatives or narcotics is necessary for persons with neuromuscular symptoms because of the risk of respiratory arrest. Hypertension and pulmonary edema respond to nifedipine, nitroprusside, hydralazine, or prazosin, and bradyarrhythmias can be controlled with atropine.

Commercially prepared antivenins are available in several countries for some of the most dangerous species. A caprine *C. sculpturatus* antivenin (not yet FDA approved) is available as an investigational drug from the Arizona State University for use only in Arizona. Because of the risk of anaphylaxis or serum sickness following administration of goat serum, use of the antivenin is controversial. Intravenous administration of antivenin rapidly reverses cranial-nerve dysfunction and muscular symptoms but does not affect pain and paresthesia. The benefit of scorpion antivenin has not been established in controlled trials.

Prevention In scorpion-infested areas, shoes, clothing, bedding, and towels should be shaken and inspected before being used. Removal of wood, stones, and debris from yards and campsites eliminates hiding places for scorpions, and household spraying of insecticides can deplete their source of food.

CHIGGERS AND OTHER BITING MITES

Chiggers are the larvae of trombiculid (harvest) mites that normally feed on mice in grassy or brush-covered sites in the tropics and subtropics and (less frequently) in temperate areas during warm months. They wait for hosts on low vegetation and attach themselves to passing animals or to people. The larva then pierces the skin of its host and deposits a tubelike structure in the dermis through which it imbibes lymph and tissue juices. This highly antigenic "stylostome" serves as the focus of an exceptionally pruritic papular, papulovesicular, or papulourticarial lesion that may be 2 cm in diameter and that develops within hours of attachment in persons previously sensitized to mite

antigen. Feeding mites appear as tiny red vesicles in hair follicles. Scratching invariably destroys the body of a mite attached to a person. These lesions generally vesiculate and develop a hemorrhagic base. Itching and burning last for weeks. The rash is most common on the ankles or near tight-fitting clothes that obstruct the mites' movements. Chiggers are the vectors of scrub typhus in tropical and subtropical parts of Asia. Repellents are useful for preventing chigger bites.

Certain mesostigmatid mites that infest the nests of mice or birds feed on human beings when their usual hosts have been displaced. For example, intense episodes of itching dermatitis in humans may follow the removal of trash from a human residence or the departure of pigeons that have been nesting on a window air-conditioner. Other mites that infest grain, straw, cheese, or other animal products occasionally produce similar episodes. Persons who have close contact with dogs -- and, to a lesser extent, cats -- may develop a self-limited pruritic papulovesicular rash from bites of cheyletiellid mites that cause a mangelike condition in these animals. Mouse mites are the vectors of rickettsialpox in cities of the northeastern United States. Fowl and chicken mites transmit the viruses of St. Louis encephalitis and western equine encephalitis. Although sanitary measures effectively prevent rickettsialpox, removal of accumulated refuse may result in a transient period of elevated risk.

Diagnosis of mite-induced dermatitides (including those caused by chiggers) relies heavily on a history of exposure to the source of the mite, since the tiny mite may escape notice or may already have fallen off or been scratched off the lesions. Antihistamines or topical steroids effectively reduce mite-induced pruritus.

HYMENOPTERA STINGS

Insects that sting to defend their colonies or subdue their prey belong to the order Hymenoptera, which includes apids (bees and bumblebees), vespids (wasps, hornets, and yellow jackets), and ants. Their venoms contain a wide array of amines, peptides, and enzymes that are responsible for local and systemic reactions. Although the toxic effect of multiple stings can be fatal, nearly all of the 50 or more deaths due to hymenopteran stings in the United States each year are the result of allergic reactions.

Bee and Wasp Stings Bees lose their venom apparatus in the act of stinging and subsequently die, while vespids can sting numerous times in succession. The familiar honeybees (*Apis mellifera*) and bumblebees (*Bombus* and other genera) attack when a colony is disturbed, but the extremely aggressive Africanized honeybees respond to minimal intrusions rapidly and in large numbers. Since their introduction into Brazil in 1957, these "killer bees" have spread through South and Central America to the southern and western United States.

The common vespids in the United States include the yellow jacket, notable for the yellow and black bands on its abdomen; the bald-faced hornet, with a black body and a white face; the brown hornet, measuring 2.5 to 3.5 cm in length; and the paper wasps, which have variously colored elongate bodies. Vespids sting in defense of their nests, which they often build near human dwellings and suspend from eaves or shubbery, plaster onto walls, or burrow into wood or soil. Yellow jackets feed on sugary substances and decaying meat and are annoyingly abundant at recreation sites and

around garbage, particularly in the late summer and fall.

Venom is produced in glands at the posterior end of the abdomen and is expelled rapidly by contraction of muscles of the venom sac, which has a capacity of up to 0.1 mL in large insects. The venoms of different species of hymenopterans are biochemically and immunologically distinct. Direct toxic effects are mediated by mixtures of low-molecular-weight compounds such as serotonin, histamine, and acetylcholine and several kinins. Polypeptide toxins in honeybee venom include mellitin, which damages cell membranes; mast cell-degranulating protein, which causes histamine release; apamin, a neurotoxin; and adolapin, which has anti-inflammatory action. Enzymes in venom include hyaluronidase, which allows the spread of other venom components, and phospholipases, which may be among the major venom allergens. There appears to be little cross-sensitization between honeybee and wasp venoms.

Uncomplicated stings cause immediate pain, a wheal-and-flare reaction, and local edema and swelling that subside in a few hours. Stings from accidentally swallowed insects may induce life-threatening edema of the upper airways. Multiple stings can lead to vomiting, diarrhea, generalized edema, dyspnea, hypotension, and collapse. Rhabdomyolysis and intravascular hemolysis may cause renal failure. Death from the direct effects of venom has followed 300 to 500 honeybee stings.

Large local reactions that spread³10 cm around the sting site over 24 to 48 h are not uncommon. These reactions may resemble cellulitis but are caused by hypersensitivity rather than secondary infection. Such reactions tend to recur on subsequent exposure but are seldom accompanied by anaphylaxis and are not prevented by venom immunotherapy.

An estimated 0.4 to 4.0% of the U.S. population exhibits clinical immediate-type hypersensitivity to insect stings, and 15% may have asymptomatic sensitization manifested by positive skin tests. Persons who experience severe allergic reactions are likely to have similar reactions after subsequent stings; occasionally, adults who have had mild reactions later experience serious reactions. Mild anaphylactic reactions from insect stings, as from other causes, consist of nausea, abdominal cramping, generalized urticaria, flushing, and angioedema. Serious reactions, including upper airway edema, bronchospasm, hypotension, and shock, may be rapidly fatal. Severe reactions usually begin within 10 min of the sting and only rarely develop after 5 h. Unusual complications, including serum sickness, vasculitis, neuritis, and encephalitis, develop several days or weeks after a sting.

TREATMENT

Stingers embedded in the skin should be scraped or brushed off with a blade or a fingernail but not removed with forceps, which may squeeze more venom out of the venom sac. The site should be cleansed and disinfected and ice packs used to slow the spread of venom. Elevation of the affected site and administration of analgesics, oral antihistamines, and topical calamine lotion relieve symptoms; application of meat tenderizer containing papain is of no proven value. Large local reactions may require a short course of oral therapy with glucocorticoids. Patients with numerous stings should be monitored for 24 h for evidence of renal failure or coagulopathy.

Anaphylaxis is treated with subcutaneous injection of 0.3 to 0.5 mL of epinephrine hydrochloride in a 1:1000 dilution; treatment is repeated every 20 to 30 min if necessary. Intravenous epinephrine (2 to 5 mL of a 1:10,000 solution administered by slow push) is indicated for profound shock. A tourniquet may slow the spread of venom. Parenteral antihistamines, fluid resuscitation, bronchodilators, oxygen, intubation, and vasopressors may be required. Patients should be observed for 24 h for recurrent anaphylaxis.

Prevention Persons with a history of allergy to insect stings should carry a sting kit with a preloaded syringe containing epinephrine for self-administration in case of a sting. These patients should seek medical attention immediately after using the kit. To avoid stings when outdoors, individuals can wear shoes and protective clothing and avoid attracting insects with sweet foods, bright-colored clothes, perfumes, or cosmetics.

Venom Immunotherapy Repeated injections of purified venom produce a blocking IgG antibody response to venom and reduce the incidence of recurrent anaphylaxis from between 50 and 60% to <5%. Honeybee, wasp, yellow jacket, and mixed vespid venoms are commercially available for desensitization and for skin testing. Adults with a history of anaphylaxis should undergo desensitization. Results of skin tests and venom-specific radioallergosorbent tests aid in the selection of patients for immunotherapy and guide the design of such treatment. The risk of a systemic reaction to a sting is ~5 to 10% after discontinuation of a ³5-year course of immunotherapy.

Stings of Fire Ants and Other Ants All ants that are large enough can bite human beings, and some can secrete repugnant substances when handled. Stinging fire ants are an important medical problem in the United States. The imported fire ants *Solenopsis richteri* and *S. invicta* were introduced from South America into Alabama in 1918 and now infest urban and rural areas of southern states from Texas to North Carolina, with colonies in California, New Mexico, Arizona, and Virginia. They excavate open fields and yards to build tall mounds that can harbor 200,000 worker ants. Slight disturbances of the mounds have provoked massive outpourings of ants and as many as 10,000 stings on a single person. Each year fire ants sting up to 60% of the inhabitants of some cities. Waterborne ants bite on contact during times of flooding. The elderly and immobile persons are at high risk for attacks when fire ants invade dwellings.

Red-brown or brown-black fire ants attach to human skin with powerful mandibles and rotate their bodies around their heads while repeatedly injecting venom with posteriorly situated stingers. The alkaloid venom consists of cytotoxic and hemolytic piperidines and several proteins with enzymatic activity. The initial wheal-and-flare reaction, burning, and itching resolve in about 30 min, and a sterile pustule develops within 24 h. The pustule ulcerates over the next 48 h and then heals a week or 10 days later unless it becomes secondarily infected. Large areas of erythema and edema lasting several days are not uncommon and in extreme cases may compress nerves and blood vessels. Anaphylaxis occurs in ~1 to 2% of persons, and seizures and mononeuritis have been reported. Stings are treated with ice packs, topical glucocorticoids, and oral antihistamines. Covering pustules with bandages and antibiotic ointment may prevent bacterial infection. Epinephrine and supportive measures are indicated for anaphylactic

reactions. Whole-body extracts are available for skin testing and immunotherapy, which appears to lower the rate of anaphylactic reactions.

The western United States is home to harvester ants (*Pogonomyrmex* species) as well as to less aggressive fire ants not yet displaced by the introduced species. The painful local reaction following harvester ant stings often extends to lymph nodes and may be accompanied by anaphylaxis. Large Australian bulldog ants and the aggressive South American *Paranopera* ants deliver extremely painful stings and may cause systemic symptoms. Velvet ants that inhabit sandy beaches in the United States and sting the bare feet of bathers are actually wingless female wasps of the genus *Dasymutilla*.

TICK BITES AND TICK PARALYSIS

In the United States, hard ticks (Ixodidae) have increased in abundance since the mid-1900s to become the most common carriers of vector-borne diseases. Deer ticks of the genus *Ixodes* transmit the pathogens of Lyme disease, babesiosis, and human granulocytic ehrlichiosis. Other ticks, such as *Dermacentor variabilis* (the dog tick), *D. andersoni* (the wood tick), and *Amblyomma americanum* (the Lone Star tick), are vectors of tularemia, Rocky Mountain spotted fever, Colorado tick fever, and human monocytic ehrlichiosis. Outside the United States, hard ticks transmit pathogenic rickettsiae and arboviruses as well. Soft ticks (Argasidae) of the genus *Ornithodoros* transmit tick-borne relapsing fever (Chap. 175). Except in parts of Africa, soft ticks rarely attack human beings, and relapsing fever occurs only sporadically in the United States. Hard ticks differ from soft ticks by virtue of a dorsal scutum or plate and their preference for wooded, brushy, or weedy habitats. Soft ticks, which are nonscutate and leathery, are generally found in animal burrows and bird nests.

Ticks attach and feed painlessly; blood is their only food. Their secretions, however, produce local reactions, a febrile illness, or paralysis. Soft ticks attach for<1 h and produce erythematous macular lesions up to 2 to 3 cm in diameter. Some species in Africa, the western United States, and Mexico produce painful hemorrhagic lesions. At the site of hard-tick bites, small areas of induration with surrounding erythema and occasionally necrotic ulcers develop. Chronic nodules, or "tick granulomas," reach several centimeters in diameter and may require surgical excision. Tick-induced fever, associated with headache, nausea, and malaise, usually resolves within 24 to 36 h after the tick is removed. Tick paralysis is an ascending flaccid paralysis believed to be caused by a toxin in tick saliva that causes neuromuscular block and decreased nerve conduction. Throughout the world, this rare complication has followed the bites of more than 40 kinds of tick -- most commonly, dog and wood ticks in the United States. Children, especially girls with long hair, are most often affected. Weakness begins in the lower extremities 5 to 6 days after the tick's attachment and ascends symmetrically over several days to result in complete paralysis of the extremities and cranial nerves. Deep tendon reflexes are diminished or lacking altogether, but sensory examination and findings on lumbar puncture are typically normal. Removal of the tick results in improvement within a few hours and usually in complete recovery after several days. Failure to remove the tick may lead to dysarthria, dysphagia, and ultimately death from aspiration or respiratory paralysis. Diagnosis depends on finding the tick, which often is hidden beneath hair and which, when engorged, may resemble a pedunculated nevus.

An antiserum to the saliva of *Ixodes holocyclus*, the usual cause of tick paralysis in Australia, effectively reverses paralysis caused by these ticks. Ticks should be removed by firm traction with a forceps placed near their point of attachment. The site of attachment should be disinfected (e.g., with tincture of iodine). Mouthparts remaining in the skin may cause persistent irritation or lead to secondary infection. Removal of ticks during the first 48 h of attachment nearly always prevents transmission of the agents of Lyme disease, babesiosis, and erhlichiosis. Gentle handling to avoid rupture of ticks and use of gloves may avert accidental contamination with tick fluids containing pathogens. Protective measures against ticks include avoidance of brushy vegetation, removal of ticks from pet dogs and cats, use of protective clothing sprayed with 0.5% permethrin, and application of a repellent containing *N*,*N*-diethyl-*m*-toluamide (DEET). The cuffs of trousers should be tucked inside the socks.

OTHER ARTHROPOD BITES AND ENVENOMATIONS

Dipteran (Fly and Mosquito) Bites In the process of feeding on vertebrate blood, adults of certain fly species inflict painful bites, produce local allergic reactions, or transmit infectious diseases. Unlike insect stings, insect bites rarely cause anaphylaxis. Mosquitoes are ubiquitous pests and are the vectors of malaria, filariasis, yellow fever, dengue, and viral encephalitides. Female mosquitoes require a blood meal to produce eggs and an environment of standing water in which to deposit them. Their bite typically produces a wheal and later a pruritic papule. In the United States, a similar reaction follows the bite of tiny but aggressive midges known as "no-see-ums," which attack in swarms during warm months, or of other *Culicoides* species that transmit "nonpathogenic" filariae in tropical climates. Nodular lesions at the site of midge bites may last for months. The bite of the small humpbacked blackfly of the genus *Simulium* leaves a large bleeding puncture and painful and pruritic sores that are slow to heal; regional lymphadenopathy, fever, or anaphylaxis occasionally ensues. Blackflies are common summertime nuisances in the United States and Canada and are vectors of onchocerciasis in Africa and Latin America. The widely distributed tabanids, including deerflies (*Chrysops* species) and horseflies (*Tabanus* species), are stout flies measuring 10 to 25 mm in length that attack during the day and produce large and painful bleeding punctures. Deerflies transmit loiasis in African equatorial rain forests and tularemia in the United States and elsewhere. Tsetse flies of the genus *Glossina* transmit African trypanosomiasis in sub-Saharan Africa. Tiny phlebotomine sandflies are the vectors of leishmaniasis, bartonellosis (Carrion's disease), sandfly fever, and other arboviral infections in warm climates. *Stomoxys calcitrans*, the stable fly, which resembles a large housefly, is a fierce biter of human beings and domestic animals and a major pest in seacoast areas. Houseflies do not bite.

TREATMENT

Treatment of fly bites is symptom-based. Topical application of antipruritic agents, glucocorticoids, or antiseptic lotions may relieve the itching and pain. Allergic reactions may require oral antihistamines. Antibiotics may be necessary for large bite wounds that become secondarily infected. Personal protection measures against biting flies include avoidance of infested areas, application of a DEET-containing repellent to exposed skin, and use of protective clothing and bed nets treated with permethrin. Higher concentrations of DEET provide longer-lasting protection, and 10 to 35% DEET

provides adequate protection under most conditions. Repellents used on children should contain£10% DEET to avoid absorption of toxic levels that provoke encephalopathy and seizures. Permethrin applied to clothing maintains its potency for at least 2 weeks, even with laundering. It should not be applied to the skin.

Flea Bites Common human-biting fleas include the dog and cat fleas (*Ctenocephalides* species) and the rat flea (*Xenopsylla cheopis*), which inhabit the nests and resting sites of their hosts. Larval fleas feed on pellets of dried host blood that the adult fleas eject from their rectums while feeding. The high-jumping adults attack human beings or other available warm-bodied animals when the usual host abandons or is driven from its nest. The human flea (*Pulex irritans*) infests human bedding and furniture but mainly in relatively humid buildings that lack central heating. Sensitized persons develop erythematous pruritic papules, urticaria, and occasionally vesicles and bacterial superinfection at the site of the bite. Treatment consists of antihistamines and antipruritics.

Fleas transmit plague, murine typhus, a typhus-like illness due to *Rickettsia felis*, the rat and dog tapeworms, and *B. henselae*. Flea infestations are eliminated by frequent cleaning of the nesting sites and bedding of the host or judicious dusting or spraying of insecticides such as pyrethrin, DDT, or malathion.

Hemipteran (True Bug) Bites Several true bugs of the family Reduviidae inflict bites that produce allergic reactions and are sometimes painful. The cosmopolitan bedbug (*Cimex* species) hides in mattresses, behind bedboards, and under loose wallpaper during the day and takes its blood meal at night. The bite is painless, but sensitized persons develop erythema, itching, and wheals around a central hemorrhagic punctum. The cone-nose bugs, so called because of their elongated heads, include the assassin and wheel bugs, which feed on other insects and bite human beings only in self-defense, and the kissing bugs, which routinely feed on vertebrate blood. Assassin and wheel bugs inhabit many parts of the world, including the southwestern and southern United States, where they are notorious for their painful bites. The bites of the nocturnally feeding kissing bugs are painless and occur commonly in groups on the face and other exposed parts of the body. Reactions to such bites depend on prior sensitization and include tender and pruritic papules, vesicular or bullous lesions, giant urticaria, fever, lymphadenopathy, and anaphylaxis. *Triatoma infestans* and other species of kissing bug are the vectors of *Trypanosoma cruzi* in South and Central America and Mexico, but transmission of *T. cruzi* to human beings by species indigenous to the United States is exceedingly rare. Bug bites are treated with topical antipruritics or oral antihistamines. Persons with anaphylactic reactions to reduviid bites should keep an epinephrine kit available.

Centipede Bites and Millipede Dermatitis The fangs of centipedes of the genus *Scolopendra* can penetrate human skin and deliver a venom that produces intense burning pain, swelling, erythema, and lymphangitis. Dizziness, nausea, and anxiety are occasionally described, and rhabdomyolysis and renal failure have been reported. Treatment includes washing of the site, application of cold dressings, oral analgesic administration or local lidocaine infiltration, and tetanus prophylaxis. Species of *Scolopendra*, measuring up to 25 cm, occur widely in the southern United States and other areas with warm climates worldwide. The smaller house centipede *Scutigera*

coleopatrata, which is common throughout the United States, is harmless.

Millipedes, unlike centipedes, do not bite but rather secrete and in some cases eject defensive fluids that burn and discolor human skin. Affected skin turns brown overnight and may blister and exfoliate. Secretions in the eye cause intense pain and inflammation that may lead to corneal ulceration and blindness. Management includes irrigation with copious amounts of water or saline, use of analgesics, and local care of denuded skin. Millipedes are found throughout the world in leaf litter and under rocks.

Caterpillar Stings and Dermatitis The surface of caterpillars of several moth species is covered with hairs or spines that produce mechanical irritation and may contain or be coated with venom. Contact with these caterpillars causes an immediate burning sensation followed by local swelling and erythema and occasionally by regional lymphadenopathy, nausea, vomiting, and headache; shock, seizures, and coagulopathy are rare complications. In the United States, stings are most often caused by io moth larvae and puss as well as saddleback and brown-tail moth caterpillars as they cling to leaves and branches. Contact with even detached hairs of other caterpillars, such as gypsy moth larvae (*Lymantria dispar*) in the northeastern United States, can produce a pruritic urticarial or papular rash hours later. Spines may be deposited on tree trunks and drying laundry or may be airborne and cause irritation of the eyes and upper airways. Treatment of caterpillar stings consists of repeated application of adhesive or cellophane tape to remove the hairs, which can then be identified microscopically. Local ice packs, topical steroids, and oral antihistamines relieve symptoms.

Beetle Vesication When disturbed, blister beetles extrude cantharidin, a low-molecular-weight toxin that produces thin-walled blisters measuring up to 5 cm in diameter 2 to 5 h after contact with the beetle. The blisters are not painful or pruritic unless broken, and they resolve without treatment in a week to 10 days. Nephritis may follow unusually heavy cantharidin exposure. In the southern United States, blister beetles of several *Epicauta* species are abundant in the summer months. Contact occurs when people sit on the ground, work in the garden, or deliberately handle the beetles. In other countries, different species of beetle produce different vesicants. No treatment is necessary, although ruptured blisters should be kept clean and bandaged until healing is complete.

(Bibliography omitted in Palm version)