CHAPTER
37

Alterations in Brain Function

Anatomically and functionally the brain is the most complex structure in the body. It controls our ability to think, our awareness of things around us, and our interactions with the outside world. Signals to and from various parts of the body are controlled by very specific areas within the brain. This renders the brain much more vulnerable to focal lesions than other organs in the body. For example, an isolated renal infarct would not be expected to have a significant effect on kidney function; whereas, an infarct of comparable size in specific areas of the brain could produce complete paralysis on one side of the body.[1]

BRAIN INJURY

The brain is protected from external forces by the rigid confines of the skull and the cushioning afforded by the cerebrospinal fluid (CSF). The metabolic stability required by its electrically active cells is maintained by a number of regulatory mechanisms, including the blood-brain barrier and autoregulatory mechanisms that ensure its blood supply. Nonetheless, the brain remains remarkably vulnerable to injury.

Mechanisms of Injury

Injury to brain tissue can result from a number of conditions, including trauma, tumors, stroke, and metabolic derangements. Brain damage resulting from these disorders involves several common pathways, including the effects of hypoxia and ischemia, cerebral edema, and injury caused by increased intracranial pressure. In many cases, the mechanisms of injury are interrelated.

Hypoxia and Ischemia

The brain relies on the ability of the cerebral circulation to deliver sufficient oxygen for its energy needs. Although the brain makes up only 2% of the body weight, it receives one sixth of the resting cardiac output and accounts for 20% of the oxygen consumption.[1,2] By definition, *hypoxia* denotes a deprivation of oxygen with maintained blood flow and ischemia, a situation of greatly reduced or interrupted blood flow. The cellular effects of hypoxia and ischemia are quite different, and the brain tends to have different sensitivities to the two conditions. Hypoxia interferes with the delivery of oxygen, and ischemia interferes with the delivery of oxygen and glucose as well as the removal of metabolic wastes.

Hypoxia usually is seen in conditions such as exposure to reduced atmospheric pressure, carbon monoxide poisoning, severe anemia, and failure to oxygenate the blood. Contrary to popular belief, hypoxia is fairly well tolerated, particularly in situations of chronic hypoxia. Neurons are capable of substantial anaerobic metabolism and are fairly tolerant of pure hypoxia; it commonly produces euphoria, listlessness, drowsiness, and impaired problem solving. Unconsciousness and convulsions may occur when hypoxia is sudden and severe. However, the effects of severe hypoxia (*i.e.*, anoxia) on brain function seldom are seen because the condition rapidly leads to cardiac arrest and ischemia.

Ischemia can be global or focal. Focal ischemia involves a single area of the brain, as in stroke. Collateral circulation may provide low levels of blood flow during focal ischemia. The residual perfusion may provide sufficient substrates to maintain a low level of metabolic activity, preserving neuronal integrity.

Global ischemia occurs when blood flow is inadequate to meet the metabolic needs of the entire brain. In contrast to persons with focal ischemia, those with global ischemia have no collateral circulation during the ischemic event.[1,3] The result is a spectrum of neurologic disorders. Unconsciousness occurs within seconds of severe global ischemia, such as that resulting from complete cessation of blood flow, as in cardiac arrest. If circulation is restored immediately, consciousness is regained quickly. However, if blood flow is not promptly restored, severe pathologic changes take place. Energy sources (*i.e.*, glucose and glycogen) are exhausted in 2 to 4 minutes, and cellular ATP stores are depleted in 4 to 5 minutes. Approximately 50% to 75% of the total energy requirement of neuronal tissue is spent on mechanisms for maintenance of ionic gradients across the cell membrane (*e.g.*, sodium-potassium pump), resulting in fluxes of sodium, potassium, and calcium ions[4] (Table 37-1). Excessive influx of sodium results in neuronal and interstitial edema. The influx of calcium initiates a cascade of events, including release of intracellular and nuclear enzymes that cause cell destruction.

Within the brain, certain regions and cell populations are more susceptible than others to hypoxic-ischemic injury.[1] For example, neurons are more susceptible to injury than are the glial cells. Among the neurons, the pyramidal cells of the hippocampus, the Purkinje cells of the cerebellum, and the neurons of the globus pallidus of the basal ganglia are particularly sensitive to generalized ischemic-hypoxic injury. The reason for this selectivity is uncertain but appears to be related at least to some extent on local levels and metabolism of certain excitatory neurotransmitters such as glutamate.

Excitatory Amino Acid Injury

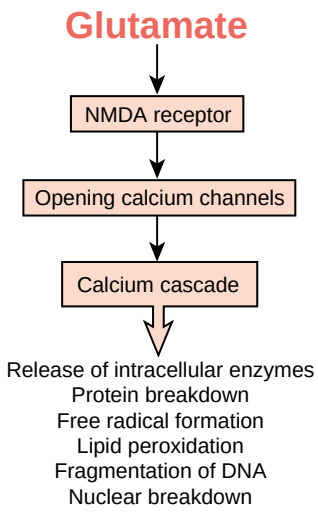
Glutamate is the principal excitatory neurotransmitter in the brain, and its interaction with specific receptors is responsible for many higher-order functions, including memory, cognition, movement, and sensation.[5] Normally, extracellular concentrations of glutamate are tightly regulated, with excess amounts removed and actively transported into astrocytes and neurons. During prolonged ischemia, these transport mechanisms become immobilized, causing extracellular glutamate to accumulate. In the case of cell injury and death, intracellular glutamate is released from the damaged cells.

Many of the actions of glutamate are coupled with receptor-operated ion channels. One type of glutamate receptor, called the *glutamate N-methyl-D-*aspartate (NMDA) receptor, has been implicated in causing central nervous system (CNS) injury. The uncontrolled opening of NMDA receptor-operated channels produces an increase in intracellular calcium and leads to a series of calcium-mediated processes called the *calcium cascade* (Fig. 37-1). Activation of the calcium cascade leads to the release of intracellular enzymes that cause protein breakdown,

TABLE 37-1 Pathophysiologic Consequences of Impaired Cerebral Perfusion

Consequences	Timing
Depletion of oxygen	10 sec
Depletion of glucose	2–4 min
Conversion to anaerobic metabolism	2–4 min
Exhaustion of cellular ATP	4–5 min
Consequences	
Efflux of potassium	
Influx of sodium	
Influx of calcium	

(Adapted from Richmond T.S. [1997]. Cerebral resuscitation after global brain ischemia: Linking research to practice. *AACN Clinical Issues* 8 [2], 173)



■ **FIGURE 37-1** ■ The role of the glutamate-NMDA receptor in brain cell injury.

free radical formation, lipid peroxidation, fragmentation of DNA, and nuclear breakdown. Drugs called *neuroprotectants* are being developed to interfere with the glutamate-NMDA pathway and thus reduce brain cell injury.

Cerebral Edema

Cerebral edema, or brain swelling, is an increase in tissue volume secondary to abnormal fluid accumulation. There are basically two types of brain edema: vasogenic or cytotoxic.[1]

Vasogenic Edema. Vasogenic edema results from an increase in the extracellular fluid that surrounds brain cells. It occurs with conditions such as tumors, prolonged ischemia, hemorrhage, brain injury, and infectious processes (*e.g.*, meningitis) that impair the function of the blood-brain barrier and allow water and plasma proteins to leave the capillary and move into the interstitium. Vasogenic edema occurs primarily in the white matter of the brain, possibly because the white matter is more compliant than the gray matter and offers less resistance to fluid accumulation. Vasogenic edema can be localized, as in the case of abscesses or neoplasms, or it may be more generalized. The functional manifestations of vasogenic edema include focal neurologic deficits, disturbances in consciousness, and severe intracranial hypertension.

Cytotoxic Edema. Cytotoxic edema involves the swelling of brain cells. It involves an increase in fluid in the intracellular space, chiefly the gray matter, although the white matter may be involved. Cytotoxic edema can result from hypo-osmotic states, such as water intoxication or severe ischemia, that impair the function of the sodium-potassium membrane pump. This causes rapid accumulation of sodium in the cell, followed by movement of water along the osmotic gradient. Depending on the nature of the insult, cellular edema can occur in the vascular endothelium or smooth muscle cells, astrocytes, the myelin-forming processes of oligodendrocytes, or neurons. Major changes in cerebral function, such as stupor and coma, occur with cytotoxic edema. The edema associated with ischemia may be severe enough to produce cerebral infarction with necrosis of brain tissue.

Increased Intracranial Volume and Pressure

Increased intracranial pressure (ICP) is a common pathway for brain injury from different types of insults and agents. Excessive ICP can obstruct cerebral blood flow, destroy brain cells, displace brain tissue as in herniation, and otherwise damage delicate brain structures.

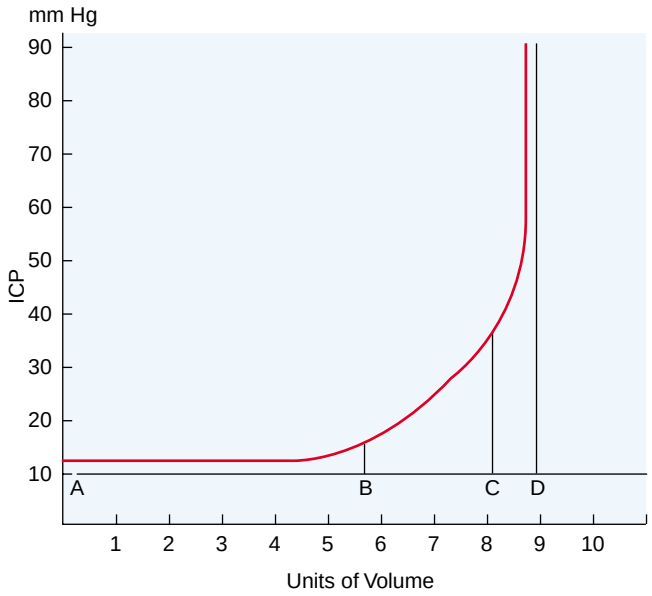
The cranial cavity contains blood (approximately 10%), brain tissue (approximately 80%), and CSF (approximately 10%) within the rigid confines of a nonexpandable skull.[6] Each of these three volumes contributes to the ICP, which normally is maintained within a range of 0 to 15 mm Hg when measured in the lateral ventricles. The volumes of each of these components can vary slightly without causing marked changes in ICP. This is because small increases in the volume of one component can be compensated for by a decrease in the volume of one or both of the other two components.[7] This association is called the *Monro-Kellie hypothesis*.

Abnormal variation in intracranial volume with subsequent changes in ICP can be caused by a volume change in any of the three intracranial components. For example, an increase in tissue volume can result from a brain tumor, brain edema, or bleeding into brain tissue. An increase in blood volume develops when there is vasodilatation of cerebral vessels or obstruction of venous outflow. Excess production, decreased absorption, or obstructed circulation of CSF affords the potential for an increase in the CSF component.

According to the modified Monro-Kellie hypothesis, reciprocal compensation occurs among the three intracranial compartments.[6] Of the three intracranial volumes, the tissue volume is relatively restricted in its ability to undergo change. Initial increases in ICP are buffered by a translocation of CSF to the spinal subarachnoid space and increased reabsorption of CSF. The compensatory ability of the blood compartment is limited by the small amount of blood that is in the cerebral circulation. The cerebral blood vessels contain less than 10% of the intracranial volume, most of which is contained in the low-pressure venous system. As the volume-buffering capacity of this compartment becomes exhausted, venous pressure increases and cerebral blood volume and ICP rise. In addition, cerebral blood flow is highly controlled by autoregulatory mechanisms, which affect its compensatory capacity. Conditions such as ischemia and elevated carbon dioxide (PCO_2) levels produce a compensatory vasodilation of the cerebral blood vessels.

The impact of increases in blood, brain tissue, or CSF volumes on ICP varies among individuals and depends on the amount of increase that occurs, the effectiveness of compensatory mechanisms, and the compliance of brain tissue. Compliance represents the ratio of change in volume to the resulting change in pressure.[6] As depicted in Figure 37-2 even small changes in volume produce large changes in ICP once the compensatory mechanisms have been exceeded.

The cerebral perfusion pressure (CPP), which represents the difference between the mean arterial blood pressure (MABP) and the ICP, is the pressure perfusing the brain.[7] CPP is determined by the pressure gradient between the internal carotid artery and the subarachnoid veins. The MABP and ICP are monitored frequently in persons with brain conditions that increase ICP and impair brain perfusion. Normal CPP ranges from 70 to 100 mm Hg. Brain ischemia develops at levels



■ **FIGURE 37-2** ■ Pressure–volume curve. From point A to just before B, the ICP remains constant although there is an addition of volume (compliance is high). At point B, even though the ICP is within normal limits, compliance begins to change, as evidenced by the slight rise in ICP. From points B to C, the ICP rises with an increase in volume (low compliance). From points C to D, ICP rises significantly with each minute increase in volume (compliance is lost). (Hickey J.V. [2003]. *Neurological and neurosurgical nursing* [5th ed., p. 286]. Philadelphia: Lippincott Williams & Wilkins)

below 50 to 70 mm Hg.[6] When the ICP approaches or exceeds the MABP, tissue perfusion becomes inadequate, cellular hypoxia results, and if the elevated pressure is maintained, neuronal death may occur. The highly specialized cortical neurons are the most sensitive to oxygen deficit; a decrease in the level of consciousness is one of the earliest and most reliable signs of increased ICP.

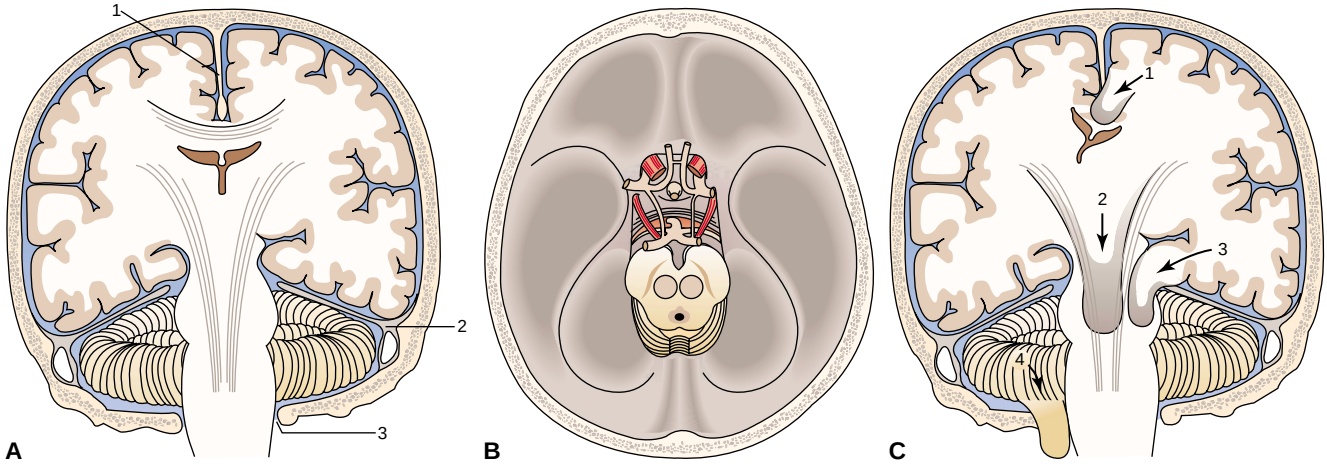
One of the late reflexes seen with a marked increase in ICP is the CNS ischemic response, which is triggered by ischemia of the vasomotor center in the brain stem. Neurons in the vasomotor center respond directly to ischemia by producing a marked increase in MABP, sometimes to levels as high as 270 mm Hg, accompanied by a widening of the pulse pressure and reflex slowing of the heart rate. These three signs, sometimes called the *Cushing reflex*, are important but late indicators of increased ICP.[2] The ischemic reflex represents a "last-ditch" effort by the nervous system to maintain the cerebral circulation.

Brain Herniation

The brain is protected by the nonexpandable skull and supporting septa, the falx cerebri and the tentorium cerebelli, that divide the intracranial cavity into *fossae* or compartments that normally protect against excessive movement. The falx cerebri is a sickle-shaped septum that separates the two hemispheres. The tentorium is a tentlike structure, higher in the center than at the sides of the skull, which separates the occipital lobes of the brain from the cerebellum and much of the brain stem (Fig. 37-3A). It creates the area above the tentorium, the supratentorial space, and the area below the tentorium, the infratentorial space. Extending posteriorly into the center of the tentorium is a large semicircular opening called the *incisura* or *tentorial notch*. The brain stem, blood vessels, and accompanying nerves pass through the incisura (see Fig. 37-3B).

Brain herniation is displacement of brain tissue under the falx cerebri or through the incisura of the tentorium cerebelli. It occurs when the presence of cerebral edema or a mass results in shifting or herniation of brain tissue from a compartment of higher pressure to one of lower pressure. The different types of herniation syndromes are based on the area of the brain that has herniated and the structure under which it has been pushed (see Fig. 37-3C). They commonly are divided into two broad categories, supratentorial and infratentorial, based on whether they are located above or below the tentorium.

There are three major patterns of supratentorial herniation: cingulate or across the falx cerebri, uncal or lateral, and trans-



■ **FIGURE 37-3** ■ Supporting septa of the brain and patterns of herniation. (**A**) The falx cerebri [1], tentorium cerebelli [2], foramen magnum [3]. (**B**) The location of the insicura or tentorial notch in relation to the cerebral arteries and oculomotor nerve. (**C**) Herniation of the cingulate gyrus under the falx cerebri [1], central or transtentorial herniation [2], herniation of the temporal lobe into the tentorial notch [3], and infratentorial herniation of the cerebellar tonsils [4]. (Courtesy of Carole Hilmer, C.M.I.)

tentorial or central.[6] *Cingulate herniation* involves displacement of the cingulate gyrus and hemisphere beneath the sharp edges of the falx cerebri to the opposite side of the brain. *Uncal herniation* occurs when a lateral mass pushes the brain tissue centrally and forces the medial aspect of the temporal lobe, which contains the uncus and hippocampal gyrus, under the edge of the tentorial incisura, into the posterior fossa. *Transtentorial* or *central herniation* involves the downward displacement of the cerebral hemispheres, basal ganglia, diencephalon, and midbrain through the tentorial incisura.

Each supratentorial herniation syndrome has distinguishing features in the early phases, but as the forced downward displacement on the pons and medulla continues, clinical signs become similar (see Table 37-2). Any of the supratentorial herniation syndromes can compress vascular and CSF flow, which can further complicate the neurologic manifestations of brain lesions. The progressive downward displacement from any of the supraventricular herniation syndromes can result in brain stem herniation, in which the medulla herniates into the foramen magnum. Death is immediate, caused by compression of cardiorespiratory centers in the medulla.

Infratentorial herniation results from increased pressure in the infratentorial compartment. Herniation may occur superiorly (upward) through the tentorial incisura or inferiorly (downward) through the foramen magnum. Upward displacement of brain tissue can cause blockage of the aqueduct of Sylvius and lead to hydrocephalus and coma. Downward displacement of the midbrain through the tentorial notch or of the cerebellar tonsils through the foramen magnum can interfere with medullary functioning and cause cardiac or respiratory arrest. In cases of pre-existing ICP, herniation may occur when the pressure is released from below, such as in a lumbar puncture.

Hydrocephalus

Enlargement of the CSF compartment occurs with hydrocephalus, which is defined as an abnormal increase in CSF volume in any part or all of the ventricular system (see Chapter 36, Fig. 36-25). There are two types of hydrocephalus: noncommunicating and communicating. *Hydrocephalus ex vacuo* refers to dilation of the ventricular system and a compensatory increase in CSF volume secondary to a loss of brain tissue. It is commonly associated with other evidence of brain atrophy.[1,8]

Noncommunicating or obstructive hydrocephalus occurs when obstruction in the ventricular system prevents the CSF from reaching the arachnoid villi. CSF flow can be obstructed by congenital malformations, tumors encroaching on the ventricular system, inflammation, or hemorrhage.[8]

Communicating hydrocephalus results from impaired reabsorption of CSF from the arachnoid villi into the venous system. Decreased absorption can result from a block in the CSF pathway to the arachnoid villi or a failure of the villi to transfer the CSF to the venous system. It can occur if too few villi are formed, if postinfective (meningitis) scarring occludes them, or if the villi become obstructed with fragments of blood or infectious debris. Normal-pressure hydrocephalus is an important type of communicating hydrocephalus seen in older adults. It is accompanied by ventricular enlargement with compression of cerebral tissue but normal CSF pressure.

Similar pathologic patterns occur with noncommunicating and communicating types of hydrocephalus. The cerebral hemispheres become enlarged, and the ventricular system is dilated behind the point of obstruction. The gyri on the surface of the brain tend to become less prominent as the sulci are compressed and the white matter is reduced in volume. The presence and extent of the increased ICP is determined by the amount of fluid accumulation and the type of hydrocephalus, the age at onset, and the rapidity and degree of pressure rise. Acute-onset hydrocephalus is usually marked by symptoms of increased ICP, including headache and vomiting, followed by edema of the optic disk (papilledema). If the obstruction is not relieved, mental deterioration eventually occurs. Slowly developing hydrocephalus is less likely to produce an increase in ICP, but it may produce deficits such as progressive dementia and gait changes.

Computed tomographic (CT) scans are used to diagnose all types of hydrocephalus. Treatment depends on the cause of the disorder. In noncommunicating hydrocephalus, shunting procedures are used to provide an alternative route for return of CSF to the circulation. Treatment for communicating hydrocephalus includes attempts to clear the arachnoid villi of exudate; if this is unsuccessful, surgical shunting may be required.[6]

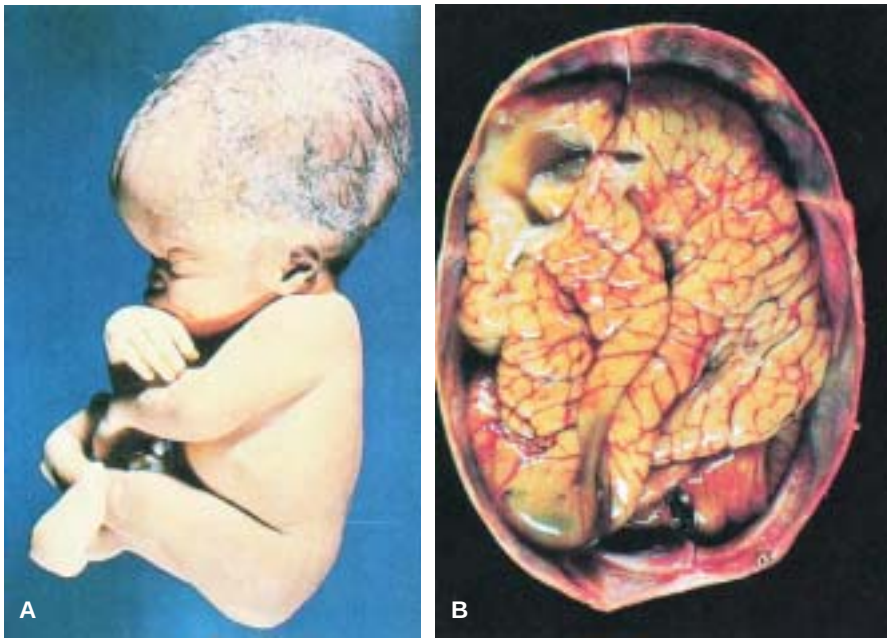
When hydrocephalus develops in utero or before the cranial sutures have fused in infancy, the ventricles expand beyond the point of obstruction, the cranial sutures separate, the head expands, and there is bulging of the fontanels (Fig. 37-4).[9] Because the skull is able to expand, signs of increased ICP usually are absent. Surgical placement of a shunt (*e.g.*, a ventriculoperitoneal shunt) that allows for diversion of excess CSF fluid is often used to prevent extreme enlargement of the head. The major complication of shunts is bacterial infection. Children with hydrocephalus are at risk for developmental disorders. Visual problems, including strabismus, visual field defects, and atrophy of the optic nerve, are common.[9]

TABLE 37-2 Key Structures and Clinical Signs of Cingulate, Transtentorial, and Uncal Herniation

Herniation Syndrome	Key Structures Involved	Key Clinical Signs
Cingulate	Anterior cerebral artery	Leg weakness
Transtentorial	Reticular activating system	Altered level of consciousness
	Corticospinal tract	Decorticate posturing
		Rostral–caudal deterioration
Uncal	Cerebral peduncle	Hemiparesis
	Oculomotor nerve	Pupil dilatation
	Posterior cerebral artery	Visual field loss
	Cerebellar tonsil	
	Respiratory center	Respiratory arrest

Traumatic Head and Brain Injury

The term *head injury* is used to describe all structural damage to the head and has become synonymous with *brain injury*.[10,11] In the United States, head injury is the leading cause of death



■ **FIGURE 37-4** ■ Congenital hydrocephalus. (**A**) Hydrocephalus occurring before the fusion of the cranial sutures causes pronounced enlargement of the head. (**B**) Removal of the calvarium demonstrates an atrophic and collapsed cerebral cortex. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1454]. Philadelphia: Lippincott Williams & Wilkins)

among persons younger than 24 years. The main causes of head injury are road accidents, falls, and assaults, and the most common cause of fatal head injuries is road accidents involving vehicles and pedestrians.[12]

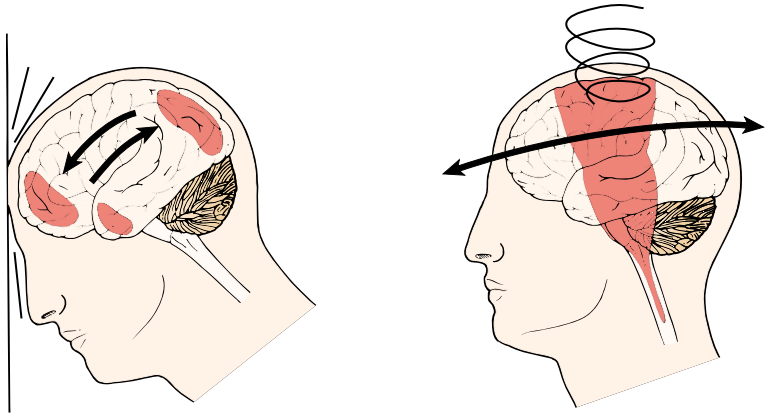
Skull Fractures

Although the skull affords protection for the tissues of the CNS, it also provides the potential for development of ischemic and traumatic brain injuries. This is because it cannot expand to accommodate the increase in volume that occurs when there is swelling or bleeding within its confines. The bony structures themselves can also cause injury to the nervous system. Fractures of the skull can compress sections of the nervous system, or they can splinter and cause penetrating wounds.

Skull fractures can be divided into three groups: simple, depressed, and basilar. A *simple* or *linear* skull fracture is a break in the continuity of bone. A *comminuted* skull fracture refers to a splintered or multiple fracture line. When bone fragments are embedded into the brain tissue, the fracture is said to be *depressed*. Radiologic examination usually is needed to confirm the presence and extent of a skull fracture.

Traumatic Brain Injury

The skull and CSF provide protection for the brain, but they also can contribute to brain trauma at the time of head injury. The two mechanisms responsible for brain injury are acceleration-deceleration and concurrent rotational movement (Fig. 37-5). Because the brain floats freely in the CSF, blunt force to the head can cause the brain to accelerate in the skull and then abruptly decelerate on hitting the inner confines of the skull. At the time of impact to the skull, there is always some acceleration/deceleration of the brain, whether the head is held in fixed or



■ **FIGURE 37-5** ■ Mechanisms of (**A**) brain acceleration-deceleration injury and (**B**) rotational injury.

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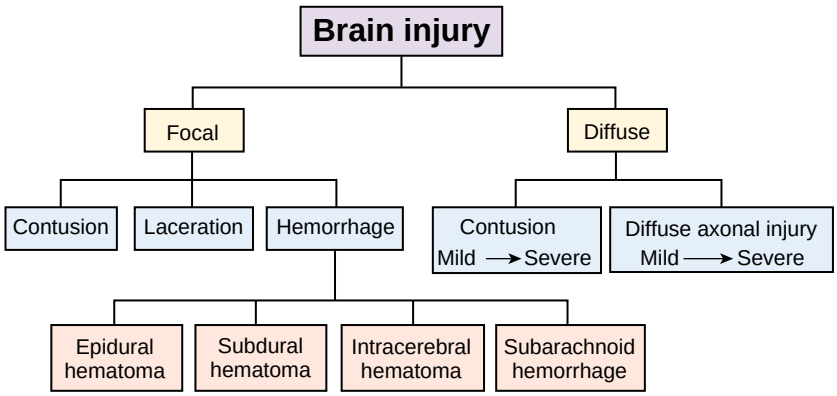


■ **FIGURE 37-6** ■ Focal and generalized brain injuries. (Hickey J.V. [1996]. *Neurological and neurosurgical nursing* [4th ed., p. 393]. Philadelphia: Lippincott-Raven).

free position. This results in what are called *coup-contrecoup* injuries.[6] The injury directly under the area of impact is called a *coup injury* and the injury sustained on the opposite pole of the brain, a *contrecoup injury*.

The effects of traumatic head injuries can be divided into two categories: primary or direct injuries, in which damage is caused by impact, and secondary injuries, in which damage results from the subsequent brain swelling, an intracranial hematoma, infection, or cerebral ischemia. Ischemia is considered to be the most common cause of secondary brain injury. It can cause the hypoxia and hypotension that occur during the resuscitation process or the impairment of regulatory mechanisms that maintain cerebral blood flow and oxygen supply.[13,14]

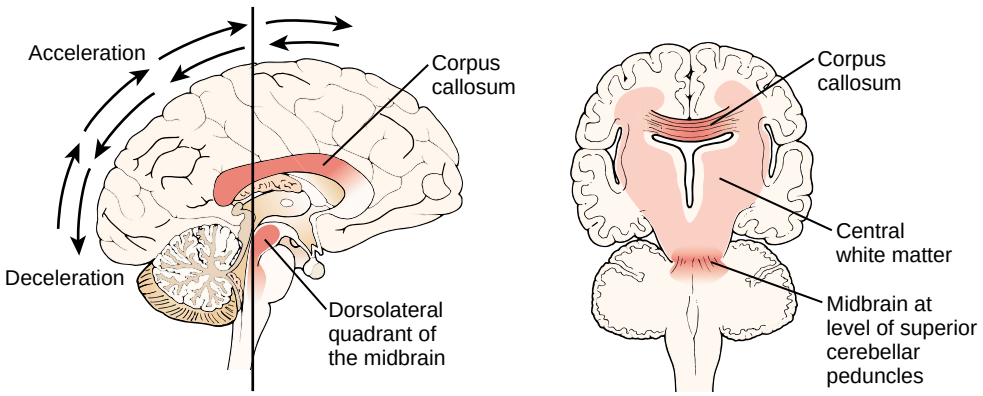
Even if there is no break in the skull, a blow to the head can cause severe and diffuse brain damage. Such closed injuries vary in severity and can be classified as focal or diffuse (Fig. 37-6). Diffuse injuries include concussion and diffuse axonal injury, and focal injuries, contusions, lacerations, and hemorrhage.

Concussion. The term *concussion* refers to a momentary interruption of brain function with or without loss of consciousness. In mild head injury, there may be momentary loss of consciousness without demonstrable neurologic symptoms or residual damage, except for possible residual amnesia. Microscopic changes usually can be detected in the neurons and supporting tissues within hours of injury. Although recovery usually takes place within 24 hours, mild symptoms, such as headache, irritability, insomnia, and poor concentration and memory, may persist for months. This is known as the *postconcussion syndrome*. Because these complaints are vague and subjective, they sometimes are regarded as being of psychological origin.

Diffuse Axonal Injury. Diffuse axonal injury is a primary injury with diffuse microscopic damage to axons in the cerebral hemisphere, corpus callosum, and brain stem. It is responsible for most cases of posttraumatic dementia and, in conjunction with hypoxic-ischemic injury, is the most common cause of persistent vegetative state. The lesions of diffuse axonal injury result from sudden deceleration and/or acceleration forces sufficient to stretch or, in extreme cases, tear nerve cell processes within the white matter of the brain (Fig. 37-7).

Contusion. A *contusion* is a bruise to the cortical surface of the brain caused by blunt head trauma.[1,7] Contusions may be single or multiple and occur at any place where the brain comes in contact with the skull; they often occur when the moving head strikes a fixed object (Fig. 37-8). They are most common in the frontal poles, orbital surfaces of the frontal lobes, temporal poles, occipital poles, and posterior cerebellum.[1]

Contusions are generally the result of anteroposterior displacement, when the moving head strikes a fixed object. As the



■ **FIGURE 37-7** ■ Diffuse axonal injury. Diffuse axonal injury results from acceleration-deceleration and shearing on the brain. Dependent upon the severity of injury, the areas of the brain most affected are the corpus callosum, the dorsolateral area of the midbrain, and the parasagittal white matter. Adapted from (Hickey J.V. [1996]. *Neurological and neurosurgical nursing* [4th ed., p. 386]. Philadelphia: Lippincott-Raven).

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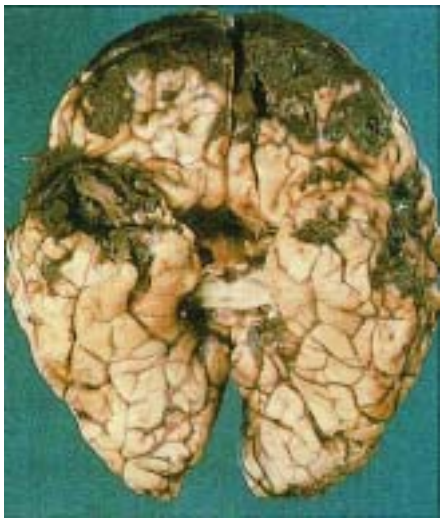
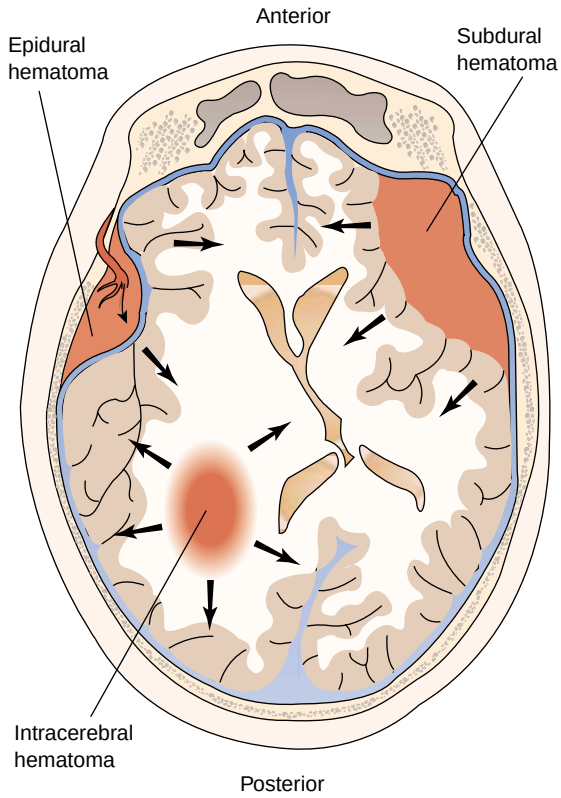


■ **FIGURE 37-8** ■ Recent cerebral contusion. Multiple areas of hemorrhage mark the poles of the frontal and temporal lobes. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1462]. Philadelphia: Lippincott Williams & Wilkins)



■ **FIGURE 37-9** ■ Location of epidural, subdural, and intracerebral hematomas.

brain strikes the rough surface of the cranial vault, brain tissue, blood vessels, nerve tracts, and other structures are bruised and torn. The extent of brain damage that occurs is dependent upon the force causing the injury. If the force is minimal, the contusion is limited to the apex of the gyri. Greater forces destroy larger expanses of the cortex, creating deeper lesions that extend into the white matter or lacerate the cortex and initiate cortical and subcortical hemorrhages. Cerebral contusions, particularly those accompanied by tearing of the superficial layers of the brain, are an important cause of traumatic subarachnoid hemorrhage.

Contusions cause permanent damage to brain tissue.[1,8] The bruised, necrotic tissue is phagocytized by macrophages, and scar tissue formed by astrocyte proliferation persists as a crater.

Hematomas. Hematomas result from vascular injury and bleeding. Depending on the anatomic position of the ruptured vessel, bleeding may involve the development of an epidural hematoma, the subdural hematoma, or an intracerebral hematoma (Fig. 37-9).

Epidural hematoma is one that develops between the inner table of the bones of the skull and the dura. It usually results from a tear in an artery, most often the middle meningeal, which is located under the thin temporal bone. Because bleeding is arterial in origin, rapid compression of the brain occurs from the expanding hematoma. Epidural hematoma is more common in a young person because the dura is not as firmly attached to the skull surface as it is in an older person. Typically, a person with an epidural hematoma presents with a history of head injury and a brief period of unconsciousness, followed by a lucid period in which consciousness is regained, followed by rapid progression to unconsciousness. The lucid interval does not always occur, but when it does, it is of great diagnostic value. With rapidly developing unconsciousness, there are focal symptoms related to the area of the brain involved. These symptoms can include ipsilateral (same side) pupil dilatation and contralateral (opposite side) hemiparesis. If the hematoma is not removed, the condition progresses, with increased ICP, tentorial herniation, and death. However, prognosis is excellent if the hematoma is removed before loss of consciousness occurs.

A *subdural hematoma* develops in the area between the dura and the arachnoid (subdural space) and usually is the result of a tear in the small bridging veins that connect veins on the surface of the cortex to dural sinuses. These veins are readily snapped in head injury when the brain moves suddenly in relation to the skull. A subdural hematoma develops more slowly than an epidural hematoma because the tear is in the venous, rather than the arterial, system.

Subdural hematomas are classified as acute, subacute, or chronic. Symptoms of an acute subdural hematoma are seen within 24 hours of the injury. Acute subdural hematomas progress rapidly and are associated with a high mortality rate because of the severe secondary injuries related to edema and uncontrolled rise in ICP. Subacute hematomas do not produce symptoms until 2 to 10 days after injury. There may be a period of improvement in the level of consciousness and neurologic symptoms, followed by deterioration if the hematoma is not removed.

The symptoms of chronic subdural hematomas may not arise until several weeks after the injury, so much later that the person may not remember having had a head injury. This is especially true of the older person with fragile vessels whose brain has shrunk away from the dura. Seepage of blood into the subdural space may occur slowly. Because the blood in the subdural space is not absorbed, fibroblastic activity begins,

■ **FIGURE 37-10** ■ Subdural hematoma. A chronic subdural hematoma is encapsulated by an outer membrane, evidenced as a narrow brown layer beneath the white dura. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1460]. Philadelphia: Lippincott Williams & Wilkins)

and the hematoma becomes encapsulated[8] (Fig. 37-10). Within this encapsulated area, the blood cells are slowly lysed, and a fluid with a high osmotic pressure is formed. This creates an osmotic gradient, with fluid from the surrounding subarachnoid space being pulled into the hematoma, causing the mass to increase in size and exert pressure on the surrounding intracranial contents. In some instances, the clinical picture is less defined, with the most prominent symptom being a decreasing level of consciousness indicated by drowsiness, confusion, and apathy. The person also may have headache.

Traumatic Intracerebral Hematomas. Traumatic intracerebral hematomas may be single or multiple. They can occur in any lobe of the brain but are most common in the frontal or temporal lobes. They may occur in association the severe motion that the brain undergoes during head injury, or a contusion can coalesce into a hematoma. Intracerebral hematomas occur more frequently in older persons and alcoholics whose brain vessels are more friable.

The signs and symptoms produced by an intracerebral hematoma depend on its size and location within the brain. Signs of increased ICP can be manifested if the hematoma is large and encroaching on vital structures. A hematoma in the temporal lobe can be dangerous because of the potential for lateral herniation.

Manifestations of Global Brain Injury

Global brain injury, whether caused by head trauma, stroke, or other pathologies, is manifested by alterations in sensory and motor function and by changes in the level of consciousness. In contrast to focal injury, which causes alterations in sensory function (Chapter 39) or motor function (Chapter 37), global injury tends to result in altered levels of consciousness. Severe injury that seriously compromises brain function may result in brain death.

The cerebral hemispheres are the most susceptible to damage, and the most common sign of brain dysfunction is altered level of consciousness and change in behavior. As the brain structures in the diencephalon, midbrain, pons, and medulla are affected, additional respiratory; pupillary and eye movement reflexes, and motor signs become evident (see Table 37-3). Hemodynamic and respiratory instability are the last signs to occur because their regulatory centers are located low in the medulla.

In progressive brain deterioration, the person's neurologic capabilities appear to deteriorate in stepwise fashion. Similarly, as neurologic function returns, there appears to be stepwise progress to higher levels of consciousness. Deterioration of brain function from supratentorial lesions tends to follow a rostral-to-caudal stepwise progression, which is observed as the brain initially compensates for injury and subsequently decompensates with loss of autoregulation and cerebral perfusion. Infratentorial (brain stem) lesions may lead to an early, sometimes abrupt disturbance in consciousness without any orderly rostrocaudal progression of neurologic signs.

Anatomic and Physiologic Basis of Consciousness

Consciousness is the state of awareness of self and the environment and of being able to become oriented to new stimuli.[6] It has traditionally been divided into two components: (1) arousal and wakefulness and (2) content and cognition. The content and cognition aspects of consciousness are determined by a functioning cerebral cortex. Arousal and wakefulness requires the concurrent functioning of both cerebral hemispheres and an intact reticular activating system (RAS) in the brain stem.

Reticular Activating System

The reticular formation is a diffuse, primitive system of interlacing nerve cells and fibers in the brain stem that receive input from multiple sensory pathways (Fig. 37-11). Anatomically, the reticular formation constitutes the central core of the brain

TABLE 37-3 Key Signs in Rostral-to-Caudal Progression of Brain Lesions

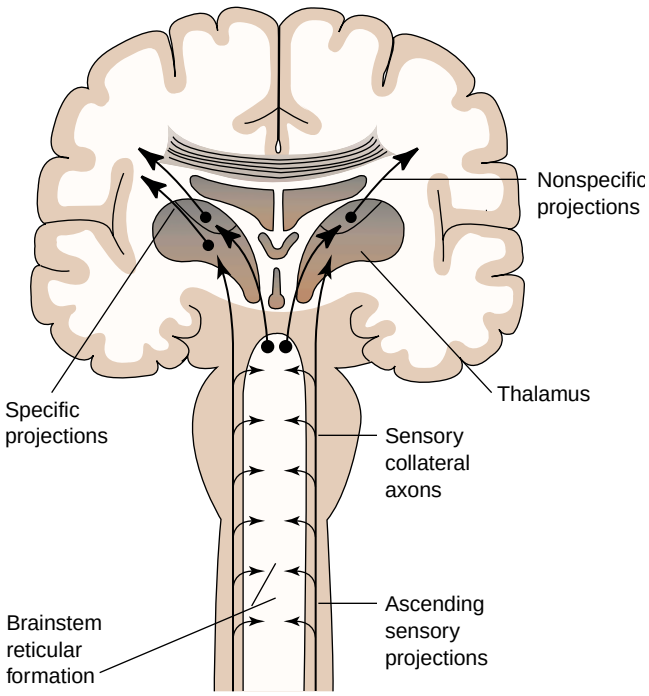
Level of Brain Injury	Key Clinical Signs
Diencephalon	Impaired consciousness (see Table 37-4); small, reactive pupils; intact oculocephalic reflex; decorticate posturing; Cheyne-Stokes respirations
Midbrain	Coma, fixed, midsize pupils; impaired oculocephalic reflex; neurogenic hyperventilation; decerebrate posturing
Pons	Coma, fixed, irregular pupils; dysconjugate gaze; impaired cold caloric stimulation; loss of corneal reflex; hemiparesis/quadriparesis; decerebrate posturing; apneustic respirations
Medulla	Coma, fixed pupils, flaccidity, loss of gag and cough reflexes, ataxic/apneic respirations

KEY CONCEPTS

BRAIN INJURY AND LEVELS OF CONSCIOUSNESS

- Consciousness is a global function that depends on a diffuse neural network that includes activity of the reticular activating system (RAS) and both cerebral hemispheres.
- Impaired consciousness implies diffuse brain injury to the RAS at any level (medulla through thalamus) or both cerebral hemispheres simultaneously.
- In contrast, local brain injury causes focal neurologic deficit but does not disrupt consciousness.

stem, extending from the medulla through the pons to the midbrain, which is continuous caudally with the spinal cord and rostrally with the subthalamus, the hypothalamus, and the thalamus.[15] Fibers from the RAS also project to the autonomic nervous system and motor systems. The hypothalamus plays a predominant role in maintaining homeostasis through integration of somatic, visceral, and endocrine functions. Inputs from the reticular formation, vestibulospinal projections, and other motor systems are integrated to provide a continuously adapting background of muscle tone and posture to facilitate voluntary motor actions. Reticular formation neurons that function in regulation of cardiovascular, respiratory, and other visceral functions are intermingled with those that maintain other reticular formation functions.



■ **FIGURE 37-11** ■ The brain stem reticular formation and reticular activating system. Ascending sensory tracts send axon collateral fibers to the reticular formation. These give rise to fibers synapsing in the nonspecific nuclei of the thalamus. From there the nonspecific thalamic projections influence widespread areas of the cerebral cortex and limbic system. (Rhoades R.A., Tanner G.A. [1996]. *Medical physiology*. Boston: Little, Brown)

Ascending fibers of the reticular formation, known as the *ascending RAS*, transmit activating information to all parts of the cerebral cortex. The flow of information in the ascending RAS activates the hypothalamic and limbic structures that regulate emotional and behavioral responses such as those that occur in response to pain and loud noises, and they exert facilitatory effects on cortical neurons. Without cortical activation, a person is less able to detect specific stimuli, and the level of consciousness is reduced. The pathways for the ascending RAS travel through the midbrain, and lesions of the midbrain can interrupt RAS activity, leading to altered levels of consciousness and coma.

Any deficit in level of consciousness, from mild confusion to stupor or coma, indicates injury to either the RAS or to both cerebral hemispheres concurrently. For example, consciousness may decline because of severe systemic metabolic derangements that affect both hemispheres, or from head trauma causing shear injuries to white matter of both the RAS and the cerebral hemispheres. Brain injuries that affect a hemisphere unilaterally and also spare the RAS, such as cerebral infarction, usually do not cause impaired consciousness.

Levels of Consciousness

Levels of consciousness reflect an orientation to person, place, and time. A fully conscious person is totally aware of her or his surroundings.[6] Levels of consciousness exist on a continuum that includes consciousness, confusion, delirium, obtundation, stupor, and coma (Table 37-4).

The earliest signs of diminution in level of consciousness are inattention, mild confusion, disorientation, and blunted responsiveness. With further deterioration, the delirious person becomes markedly inattentive and variably lethargic or agitated. The person may progress to become obtunded and may respond only to vigorous or noxious stimuli, such as shaking.

Because of its simplicity of application, the Glasgow Coma Scale has gained almost universal acceptance as a method for assessing the level of consciousness in persons with brain injury[6,13,14] (Table 37-5). Numbered scores are given to responses of eye opening, verbal utterances, and motor responses. The total score is the sum of the best response in each category.

Other Manifestations of Deteriorating Brain Function

Additional elements in the initial neurological evaluation of a person with brain injury include checking for abnormalities in the size of the pupils and their reaction to light, weakness and asymmetry of motor function, and evidence of decortication or decerebration posturing.

Pupillary Reflexes and Eye Movements. Although the pupils may initially respond briskly to light, they become unreactive and dilated as brain function deteriorates. A bilateral loss of the pupillary light response is indicative of lesions of the brain stem. A unilateral loss of the pupillary light response may be caused by a lesion of the optic or oculomotor pathways. The oculocephalic reflex (doll's-head eye movement) can be used to determine if the brain stem centers for eye movement are intact (Fig. 37-12). If the oculocephalic reflex is inconclusive, and

TABLE 37-4 Descending Levels of Consciousness and Their Characteristics

Level of Consciousness	Characteristics
Confusion	Disturbance of consciousness characterized by impaired ability to think clearly, and to perceive, respond to, and remember current stimuli; also disorientation
Delirium	State of disturbed consciousness with motor restlessness, transient hallucinations, disorientation, and sometimes delusions
Obtundation	Disorder of decreased alertness with associated psychomotor retardation
Stupor	A state in which the person is not unconscious but exhibits little or no spontaneous activity
Coma	A state of being unarousable and unresponsive to external stimuli or internal needs; often determined by the Glasgow Coma Scale

(Data from Bates D. [1993]. The management of medical coma. *Journal of Neurology, Neurosurgery, and Psychiatry* 56, 590)

if there are no contraindications, the oculovestibular (*i.e.*, cold caloric test, in which cold water is instilled into the ear canal) may be used to elicit nystagmus (see Chapter 40).

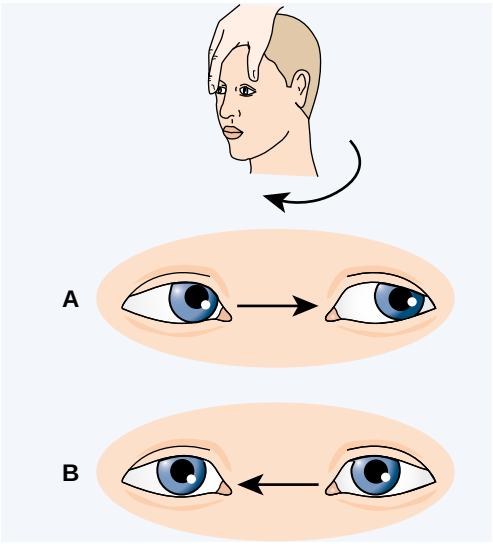
Decorticate and Decerebrate Posturing. With the early onset of unconsciousness there is some combative movement and purposeful movement in response to pain. As coma progresses, noxious stimuli can initiate rigidity and abnormal postures if the motor tracts are interrupted at specific levels. These abnormal postures are called *decortication* and *decerebration*. Decorticate (flexion) posturing is characterized by flexion of the arms, wrists, and fingers, with abduction of the upper extremities, internal rotation, and plantar flexion of the lower extremities (Fig. 37-13A). Decorticate posturing results from lesions of the cerebral hemisphere or internal capsule. Decerebrate (extensor) posturing results from increased muscle excitability (see Fig. 37-13B). It is characterized by rigidity of the arms with palms of the hands turned away from the body and with stiffly extended legs with plantar flexion of the feet. This response occurs when lesions of the diencephalon extend to involve the midbrain and upper brain stem. Both decerebrate and decorticate posturing are associated with poor prognosis.

Respiratory Responses. Early respiratory changes include yawning and sighing, with progression to Cheyne-Stokes breathing. With progression continuing to the midbrain, respirations change to neurogenic hyperventilation, in which the frequency of respirations may exceed 40 breaths per minute because of uninhibited stimulation of inspiratory and expiratory centers. With medullary involvement, respirations become ataxic (*i.e.*, totally uncoordinated and irregular). Apnea may occur because of a lack of responsiveness to carbon dioxide stimulation. Complete ventilatory assistance is often required at this point.

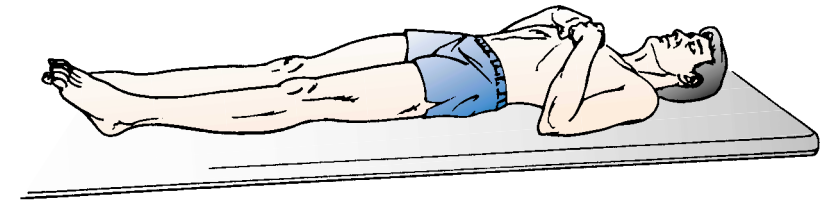
TABLE 37-5 The Glasgow Coma Scale

Test	Score*
Eye Opening (E)	
Spontaneous	4
To call	3
To pain	2
None	1
Motor Response (M)	
Obeys commands	6
Localizes pain	5
Normal flexion (withdrawal)	4
Abnormal flexion (decorticate)	3
Extension (decerebrate)	2
None (flaccid)	1
Verbal Response (V)	
Oriented	5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
None	1

*GCS Score = E + M + V. Best possible score = 15; worst possible score = 3.



■ **FIGURE 37-12** ■ The *doll's-head eye response* demonstrates the always-present vestibular static reflexes without forebrain interference or suppression. Severe damage to the forebrain or to the brain stem rostral to the pons often results in loss of rostral control of these static vestibular reflexes. If the person's head is moved from side to side or up and down, the eyes will move in conjugate gaze to the opposite side (**A**), much like those of a doll with counterweighted eyes. If the doll's-head phenomenon is observed, brain stem function at the level of the pons is considered intact (in a comatose person). In the unconscious person without intact brain stem function and vestibular static reflexes, the eyes stay in midposition (fixed) or turn in the same direction (**B**) as the head is turned.



A Flexor or decorticate posturing response

B Extensor or decerebrate posturing

■ **FIGURE 37-13** ■ Abnormal posturing. (**A**) Decorticate rigidity. In decorticate rigidity, the upper arms are held at the sides, with elbows, wrists, and fingers flexed. The legs are extended and internally rotated. The feet are plantar flexed. (**B**) Decerebrate rigidity. In decerebrate rigidity, the jaws are clenched and neck extended. The arms are adducted and stiffly extended at the elbows with the forearms pronated, wrists and fingers flexed. (From Fuller J., Schaller-Ayers J. [1994]. *Health assessment: A nursing approach* [2nd ed.]. Philadelphia: J.B. Lippincott)

Brain Death

Brain death is defined as the irreversible loss of function of the brain, including the brain stem.[16] Irreversibility implies that brain death cannot be reversed. Some conditions such as drug and metabolic intoxication can cause cessation of brain functions that is completely reversible, even when they produce clinical cessation of brain functions and EEG silence. This possibility needs to be excluded before declaring that a person is brain dead.

With advances in scientific knowledge and technology that have provided the means for artificially maintaining ventilatory and circulatory function, the definition of death has had to be continually re-examined. In 1995, the Quality of Standards Subcommittee of the American Academy of Neurology published the clinical parameters for determining brain death and procedures for testing persons older than 18 years.[17] According to these parameters, "brain death is the absence of clinical brain function when the proximate cause is known and demonstrably irreversible."[17] Clinical examination must disclose at least the absence of responsiveness, brain stem reflexes, and respiratory effort. Brain death is a clinical diagnosis, and a repeat evaluation at least 6 hours later is recommended.[17] Longer periods of observation of absent brain activity are required in cases of drug overdose (*e.g.*, barbiturates, other CNS depressants), drug toxicity (*e.g.*, neuromuscular blocking drugs, aminoglycoside antibiotics), neuromuscular diseases such as myasthenia gravis, hypothermia, and shock. Medical circumstances may require use of confirmatory tests.

Persistent Vegetative State

Advances in the care of brain-injured persons during the past several decades have resulted in survival of many persons who previously would have died. Unfortunately, some of these persons remain in what often is called a *persistent vegetative state*. The vegetative state is characterized by loss of all cognitive functions and the unawareness of self and surroundings. Reflex and vegetative functions remain.[18] Persons in the vegetative state must be fed and require full nursing care.

The criteria for diagnosis of vegetative state include the absence of awareness of self and environment and an inability to interact with others; the absence of sustained or reproducible voluntary behavioral responses; lack of language comprehension; sufficiently preserved hypothalamic and brain stem function to maintain life; bowel and bladder incontinence; and variably preserved cranial nerve (*e.g.*, pupillary, gag) and spinal cord reflexes.[19] The diagnosis of persistent vegetative state requires that the condition has continued for at least 1 month.

In summary, many of the agents that cause brain damage do so through common pathways, including hypoxia or ischemia, accumulation of excitatory neurotransmitters, increased ICP, and cerebral edema. Deprivation of oxygen (*i.e.*, hypoxia) or blood flow (*i.e.*, ischemia) can have deleterious effects on the brain structures. Ischemia can be focal, as in stroke, or global. Global ischemia occurs when blood flow is inadequate to meet the metabolic needs of the brain, as in cardiac arrest.

The term *head injury* is used to describe all structural damage to the head and has become synonymous with *brain injury*. The effects of traumatic head injuries can be divided into two categories: primary or secondary injuries. In secondary injuries, damage results from the subsequent brain swelling, intracranial hematomas, infection, cerebral hypoxia, and ischemia. Primary injuries result from direct impact. Even if there is no break in the skull, a blow to the head can cause severe and diffuse brain damage. Such closed injuries vary in severity and can be classified as focal or diffuse. Diffuse injuries include concussion and diffuse axonal injury. Focal injuries include contusion, laceration, and hemorrhage.

Brain injury is manifested by alterations in sensory and motor function and by changes in the level of consciousness. Consciousness is a state of awareness of self and environment. It exists on a normal continuum of wakefulness and sleep and a pathologic continuum of wakefulness and coma. In progressive brain injury, coma may follow a rostral-to-caudal progression with characteristic changes in levels of consciousness, respiratory activity, pupillary and oculovestibular reflexes, and muscle tone occurring as the diencephalon through the medulla are affected.

Brain death is defined as the irreversible loss of function of the brain, including that of the brain stem. Clinical examina-

tion must disclose at least the absence of responsiveness, brain stem reflexes, and respiratory effort. The vegetative state is characterized by loss of all cognitive functions and the unawareness of self and surroundings, while reflex and vegetative functions remain intact.

CEREBROVASCULAR DISEASE

Cerebrovascular disease encompasses a number of disorders involving vessels in the cerebral circulation. These disorders include stroke and transient ischemic attacks (TIAs), aneurysmal subarachnoid hemorrhage, and arteriovenous malformations.

Cerebral Circulation

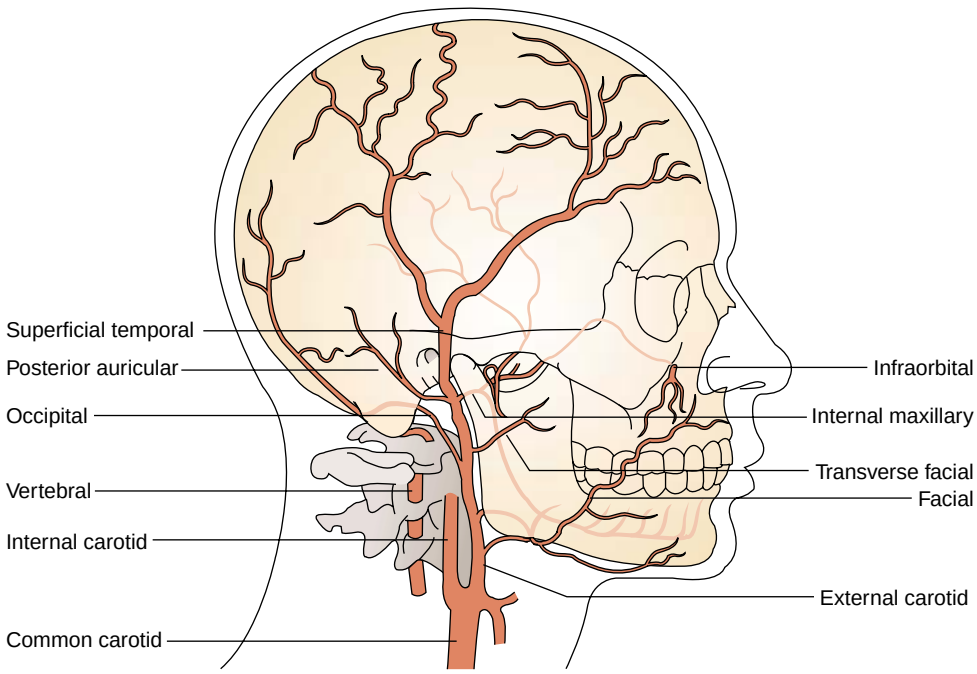
The blood flow to the brain is supplied by the two internal carotid arteries anteriorly and by the two vertebral arteries posteriorly (Fig. 37-14). The internal carotid artery, which provides the major blood supply to the brain, branches into several arteries: the ophthalmic artery, which supplies the eye and orbital structures; the posterior communicating artery, which forms part of the circle of Willis; and the anterior choroidal artery, which supplies the choroid plexus within the lateral ventricles of the brain. The internal carotid terminates by dividing into the anterior and middle cerebral arteries. The anterior cerebral arteries supply most of the medial and superior surfaces of the brain and the frontal lobe. The middle cerebral arteries supply the lateral surface of the brain, including the primary motor and sensory areas of the face and upper limbs, the optic radiations, and the speech area of the brain.

The two vertebral arteries unite to form the basilar artery. Branches of the basilar and vertebral arteries supply the medulla, pons, cerebellum, midbrain, and caudal part of the diencephalon. The basilar artery terminates by dividing into two posterior cerebral arteries that supply the remaining occipital and inferior regions of the temporal lobes and the thalamus. The posterior cerebral arteries also help to form the arterial circle of Willis, which connects the vertebral artery and the internal carotid arterial systems (Fig. 37-15). The union of these two systems provides alternate pathways for blood flow should one of the vessels become occluded.

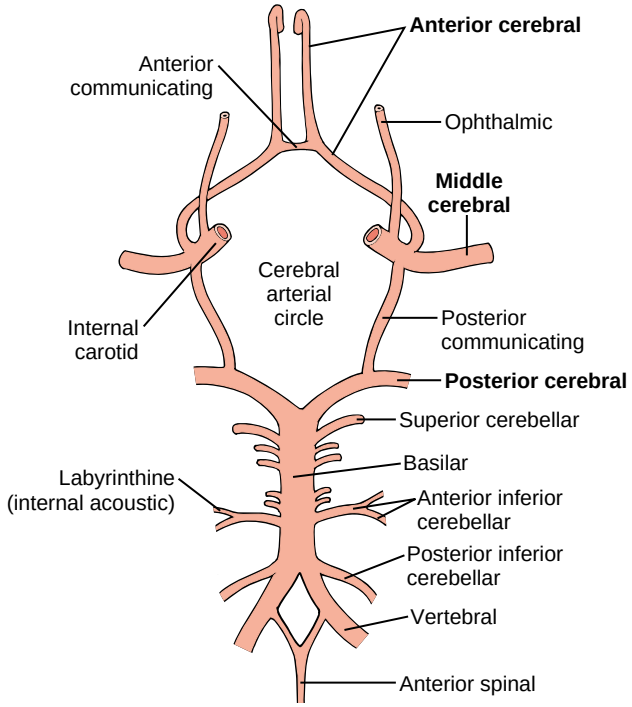
The cerebral blood is drained by two sets of veins that empty into the dural venous sinuses: the deep (great) cerebral venous system and the superficial venous system. The deep system is well protected, in contrast to the superficial cerebral veins that travel through the pia mater on the surface of the cerebral cortex. These vessels connect directly to the sagittal sinuses in the falx cerebri by way of bridging veins. They travel through the CSF-filled subarachnoid space and penetrate the arachnoid and then the dura to reach the dural venous sinuses. This system of sinuses returns blood to the heart primarily by way of the internal jugular veins. Alternate routes for venous flow also exist; for example, venous blood may exit through the emissary veins that pass through the skull and through veins that traverse various foramina to empty into extracranial veins.

Regulation of Cerebral Blood Flow

The blood flow to the brain is maintained at approximately 750 mL/minute or one sixth of the resting cardiac output.[2] The regulation of blood flow to the brain is controlled largely by autoregulatory mechanisms and by the sympathetic nervous system. The autoregulation of cerebral blood flow responds to the local metabolic needs of the brain tissue and is efficient within an MABP range of approximately 60 to 140 mm Hg.[2] If blood pressure falls below 60 mm Hg, cerebral blood flow becomes severely compromised, and if it rises above the upper limit of autoregulation, blood flow increases rapidly and overstretches the cerebral vessels. In persons with hypertension, this autoregulatory range shifts to a higher level.



■ **FIGURE 37-14** ■ Branches of the right external carotid artery. The internal carotid artery ascends to the base of the brain. The right vertebral artery is also shown as it ascends through the transverse foramina of the cervical vertebrae.



■ **FIGURE 37-15** ■ The cerebral arterial circle (circle of Willis).

Although total cerebral blood flow remains relatively stable throughout marked changes in cardiac output and arterial blood pressure, regional blood flow may change markedly in response to local changes in metabolism. At least three metabolic factors affect cerebral blood flow: carbon dioxide concentration, hydrogen ion concentration, and oxygen concentration. Increased carbon dioxide or increased hydrogen ion concentrations increase cerebral blood flow; decreased oxygen concentration also increases blood flow. Carbon dioxide, by way of the hydrogen ion concentration, provides a potent stimulus for control of cerebral blood flow—a doubling of the PCO_2 in the blood results in a doubling of cerebral blood flow. Other substances that alter the pH of the brain produce similar changes in cerebral blood flow. Because increased hydrogen ion concentration greatly depresses neural activity, the increase in blood flow is protective in that it washes the hydrogen ions and other acidic materials away from the brain tissue.[2]

In addition to the autoregulatory mechanisms that control blood flow in the deep cerebral vessels, the superficial and major cerebral blood vessels are innervated by the sympathetic nervous system. Under normal physiologic conditions, the sympathetic nervous system exerts little effect on superficial cerebral blood flow because local regulatory mechanisms are so powerful that they compensate almost entirely for the effects of sympathetic stimulation. However, when local mechanisms fail, sympathetic control of cerebral blood pressure becomes important.[2] For example, when the arterial pressure rises to very high levels during strenuous exercise or in other conditions, the sympathetic nervous system constricts the large and intermediate-size superficial blood vessels as a means of protecting the smaller, more easily damaged vessels. Sympathetic reflexes are believed to cause vasospasm in the intermediate and large arteries in some types of brain damage, such as that caused by rupture of a cerebral aneurysm.

Stroke (Brain Attack)

Stroke is an acute focal neurologic deficit from a vascular disorder that injures brain tissue. Stroke remains one of the leading causes of mortality and morbidity in the United States. Each year, 600,000 Americans are afflicted with stroke, and approximately 167,000 of these persons die, and many survivors of stroke are left with at least some degree of neurologic impairment.[20] The term *brain attack* has been promoted to highlight that time-dependent tissue damage occurs and to raise awareness of the need for rapid emergency treatment, similar to that with heart attack.

There are two main types of strokes: ischemic stroke and hemorrhagic stroke. Ischemic strokes are caused by an interruption of blood flow in a cerebral vessel and are the most common type of stroke, accounting for 70% to 80% of all strokes. The less common hemorrhagic strokes, which are caused by bleeding into brain tissue, are associated with a much higher fatality rate than are ischemic strokes.

Among the major risk factors for stroke are age, gender, race, heart disease, hypertension, high cholesterol levels, cigarette smoking, prior stroke, and diabetes mellitus.[20,21] Other risk factors include sickle cell disease, polycythemia, blood dyscrasias, excess alcohol use, cocaine and illicit drug use, obesity, and sedentary lifestyle. The incidence of stroke increases with age, with a 1% per year increased risk for persons 65 to 74 years of age; the incidence of stroke is approximately 19% greater in men than women; and African Americans have a 60% greater risk of death and disability from stroke than do whites.[20] Heart disease, particularly atrial fibrillation and other conditions that predispose to clot formation on the wall of the heart or valve leaflets or to paradoxical embolism through right-to-left shunting, predisposes to cardioembolic stroke. Polycythemia, sickle

KEY CONCEPTS

STROKE/BRAIN ATTACK

- Stroke is an acute focal neurologic deficit from an interruption of blood flow in a cerebral vessel (ischemic stroke, the most common type) due to thrombi or emboli or to bleeding into the brain tissue (hemorrhagic stroke).
- During the evolution of an ischemic stroke, there usually is a central core of dead or dying cells surrounded by an ischemic band of minimally perfused cells called a *penumbra*. Whether the cells of the penumbra continue to survive depends on the successful timely return of adequate circulation.
- The realization that there is a window of opportunity during which ischemic but viable brain tissue can be salvaged has led to the use of thrombolytic agents in the early treatment of ischemic stroke.

cell disease (during sickle cell crisis), and blood disorders predispose to clot formation in the cerebral vessels. Alcohol abuse can contribute to stroke in several ways: induction of cardiac arrhythmias and defects in ventricular wall motion that lead to cerebral embolism, induction of hypertension, enhancement of blood coagulation disorders, and reduction of cerebral blood flow.[22] Another cause of stroke is cocaine. Cocaine use causes both ischemic and hemorrhagic strokes by inducing vasospasm, enhanced platelet activity, and increased blood pressure, heart rate, body temperature, and metabolic rate. Cocaine stroke victims range in age from newborn (*i.e.*, from maternal cocaine use) to old age.[23]

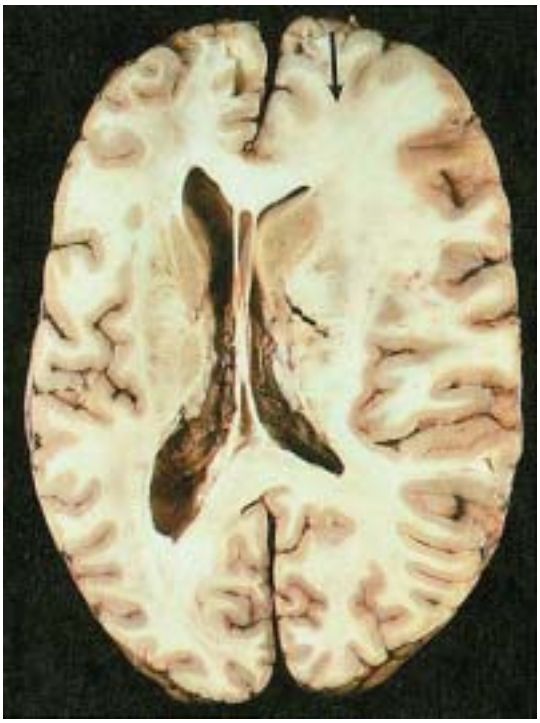
Elimination or control of risk factors for cerebrovascular disease (*e.g.*, use of tobacco, control of blood lipids and blood sugar, reduction of hypertension) offers the best opportunity to prevent cerebral ischemia from cerebral atherosclerosis. Early detection and treatment offer significant advantages over waiting until a serious event has occurred.

Ischemic Stroke

Ischemic strokes are caused by local interruption of blood flow caused by thrombosis or emboli. A common classification system identifies five stroke subtypes and their frequency: 20% large artery atherosclerotic disease (both thrombosis and plaque emboli); 25% small vessel or penetrating artery disease (*lacunar stroke*); 20% cardiogenic embolism; 30% cryptogenic stroke (undetermined cause); and 5% other, unusual causes[24] (*i.e.*, migraine, dissection, coagulopathy).

During the evolution of an ischemic stroke, there usually is a central core of dead or infarcted tissue, surrounded by an ischemic band or area of minimally perfused tissue called the *penumbra* (*i.e.*, halo). Brain cells of the penumbra receive marginal blood flow, and their metabolic activities are impaired; although the area undergoes an "electrical failure," the structural integrity of the brain cells is maintained.[25] Whether the cells of the penumbra continue to survive depends on the successful timely return of adequate circulation, the volume of toxic products released by the neighboring dying cells, the degree of cerebral edema, and alterations in local blood flow. If the toxic products result in additional death of cells in the penumbra, the core of infarcted tissue enlarges, and the volume of surrounding ischemic tissue increases (Fig. 37-16).

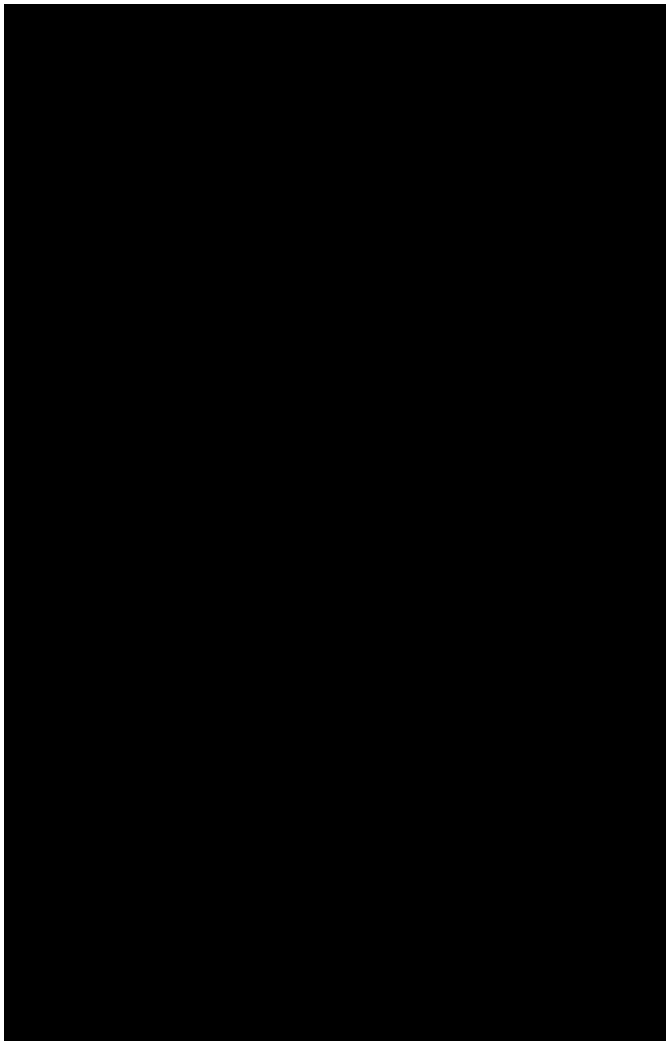
Large Vessel (Thrombotic) Stroke. Cerebral atherosclerosis is the most common cause of ischemic strokes. In the cerebral circulation, atherosclerotic plaques are found most commonly at arterial bifurcations. Common sites of plaque formation include larger vessels of the brain, notably the origins of the internal carotid and vertebral arteries, and junctions of the basilar and vertebral arteries (Fig. 37-17). Cerebral infarction can result from an acute local thrombosis and occlusion at the site of chronic atherosclerosis, with or without embolization of the plaque material distally, or from critical perfusion failure distal to a stenosis. These infarcts often affect the cortex, causing aphasia or neglect, visual field defects, or the retina. In most cases of stroke, a single cerebral artery and its territories are affected. Usually, thrombotic strokes are seen in older persons and frequently are accompanied by evidence of atherosclerotic heart or peripheral arterial disease. The thrombotic stroke is not associated with activity and may occur in a person at rest.



■ **FIGURE 37-16** ■ Recent cerebral infarct. A horizontal section of the brain shows expansion and softening in the distribution of the right middle cerebral artery. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1472]. Philadelphia: Lippincott Williams & Wilkins)

Small Vessel Stroke (Lacunar Infarct). Lacunar infarcts are small (1.5 to 2.0 cm) to very small (3 to 4 mm) infarcts located in the deeper, noncortical parts of the brain or in the brain stem. They are found in the territory of single deep penetrating arteries supplying the internal capsule, basal ganglia, or brain stem. They result from occlusion of the smaller branches of large cerebral arteries, commonly the middle cerebral and posterior cerebral arteries and less commonly the anterior cerebral, vertebral, or basilar arteries. In the process of healing, lacunar infarcts leave behind small cavities, or lacunae (lakes). Six basic causes of lacunar infarcts have been proposed: embolism, hypertension, small vessel occlusive disease, hematologic abnormalities, small intracerebral hemorrhages, and vasospasm. Because of their size and location, lacunar infarcts usually do not cause cortical deficits such as aphasia or apraxia. Instead, they produce classic recognizable "lacunar syndromes," such as pure motor hemiplegia, pure sensory hemiplegia, and dysarthria with the clumsy hand syndrome. Because CT scans are not sensitive enough to detect these tiny infarcts, diagnosis used to depend on clinical features alone. The use of magnetic resonance imaging (MRI) has allowed frequent visualization of small vessel infarcts and is obligatory to confirm such a lesion.

Cardiogenic Embolic Stroke. An embolic stroke is caused by a moving blood clot that travels from its origin to the brain. Various cardiac conditions predispose to formation of emboli that produce embolic stroke, including rheumatic heart disease, atrial fibrillation, recent myocardial infarction, ventricular aneurysm, mobile aortic arch atheroma, and bacterial endocarditis. Although most cerebral emboli originate from a



thrombus in the left heart, they also may originate in an atherosclerotic plaque in the carotid arteries.

Embolic strokes usually affect the larger proximal cerebral vessels, often lodging at bifurcations. The most common site is the middle cerebral artery, probably because it offers the path of least resistance, reflecting the large territory of this vessel and its position as the terminus of the carotid artery. Embolic stroke usually has a sudden onset with immediate maximum deficit.

Hemorrhagic Stroke

The most frequently fatal stroke is a spontaneous hemorrhage into the brain substance.[26] With rupture of a blood vessel, hemorrhage into the brain tissue occurs, resulting in edema, compression of the brain contents, or spasm of the adjacent blood vessels. The most common predisposing factors are advancing age and hypertension. Other causes of hemorrhage are aneurysm, trauma, erosion of the vessels by tumors, arteriovenous malformations, coagulopathies, vasculitis, and drugs.

A cerebral hemorrhage occurs suddenly, usually when the person is active. Vomiting commonly occurs at the onset, and headache sometimes occurs. Focal symptoms depend on which vessel is involved. In the most common situation, hemorrhage into the basal ganglia results in contralateral hemiplegia, with initial flaccidity progressing to spasticity. The hemorrhage and resultant edema exert great pressure on the brain substance, and the clinical course progresses rapidly to coma and frequently to death.

Transient Ischemic Attacks

A transient ischemic attack (TIA) is characterized by a focal ischemic cerebral neurologic deficit that lasts less than 24 hours (usually less than 1 to 2 hours). A TIA or "ministroke" is equivalent to "brain angina" and reflects a temporary disturbance in focal cerebral blood flow, which reverses before infarction occurs, analogous to angina in relation to heart attack. The causes of TIAs are the same as those of ischemic stroke and include atherosclerotic disease of cerebral vessels and emboli.

TIAs are important because they may provide warning of impending stroke. In fact, the risk of stroke after a TIA is similar to the risk after a first stroke and is maximal immediately after the event: 4% to 8% risk of stroke within 1 month, 12% to 13% risk during the first year, and 24% to 29% risk during the next 5 years.[27] Diagnosis of TIA before a stroke may permit surgical or medical intervention that prevents an eventual stroke and the associated neurologic deficits.[26]

Acute Manifestations of Stroke

The specific manifestations of stroke or TIA are determined by the cerebral artery that is affected, by the area of brain tissue that is supplied by that vessel, and by the adequacy of the collateral circulation. Symptoms of stroke/TIA always are sudden in onset and focal and are usually one-sided. The most common symptom is unilateral weakness of the face and arm or less commonly of the leg. Other frequent stroke symptoms are unilateral numbness, vision loss in one eye or to one side (hemianopia), language disturbance (aphasia) or slurred speech (dysarthria), and sudden loss of balance or ataxia. In the event of TIA, symptoms rapidly resolve spontaneously, although the underlying mechanisms are the same as for stroke. The specific stroke signs depend on the specific vascular territory compromised (Table 37-6). Discrete subsets of these vascular syndromes usually occur, depending on which branches of the involved artery are blocked.

Diagnosis and Treatment

Diagnosis. Accurate diagnosis of stroke is based on a complete history and thorough physical and neurologic examination. A careful history, including documentation of previous TIAs, the time of onset and pattern and rapidity of system progression, the specific focal symptoms (to determine the likely vascular territory), and the existence of any coexisting diseases, can help to determine the type of stroke that is involved. The diagnostic evaluation should aim to determine the presence of hemorrhage or ischemia, identify the stroke or TIA mechanism (large vessel or small vessel atherothrombotic, cardioembolic, other or cryptogenic, hemorrhagic), characterize the severity of clinical deficits, and unmask the presence of risk factors.

Imaging studies document the brain infarction and the anatomy and pathology of the related blood vessels. CT scans and MRI have become essential tools in diagnosing stroke, differentiating cerebral hemorrhage from ischemia, and excluding intracranial lesions that mimic stroke clinically. CT scans are a necessary screening tool in the acute setting for rapid identification of hemorrhage but are insensitive to ischemia within 24 hours and to any brain stem or small infarcts. MRI is supe-

TABLE 37-6 Signs and Symptoms of Stroke by Involved Cerebral Artery

Cerebral Artery	Brain Area Involved	Signs and Symptoms*
Anterior cerebral	Infarction of the medial aspect of one frontal lobe if lesion is distal to communicating artery; bilateral frontal infarction if flow in other anterior cerebral artery is inadequate	Paralysis of contralateral foot or leg; impaired gait; paresis of contralateral arm; contralateral sensory loss over toes, foot, and leg; problems making decisions or performing acts voluntarily; lack of spontaneity, easily distracted; slowness of thought; aphasia depends on the hemisphere involved; urinary incontinence; cognitive and affective disorders
Middle cerebral	Massive infarction of most of lateral hemisphere and deeper structures of the frontal, parietal, and temporal lobes; internal capsule; basal ganglia	Contralateral hemiplegia (face and arm); contralateral sensory impairment; aphasia; homonymous hemianopia; altered consciousness (confusion to coma); inability to turn eyes toward paralyzed side; denial of paralyzed side or limb (hemiattention); possible acalculia, alexia, finger agnosia, and left–right confusion; vasomotor paresis and instability
Posterior cerebral	Occipital lobe; anterior and medial portion of temporal lobe	Homonymous hemianopia and other visual defects such as color blindness, loss of central vision, and visual hallucinations; memory deficits, perseveration (repeated performance of same verbal or motor response)
	Thalamus involvement	Loss of all sensory modalities; spontaneous pain; intentional tremor; mild hemiparesis; aphasia
	Cerebral peduncle involvement	Oculomotor nerve palsy with contralateral hemiplegia
Basilar and vertebral	Cerebellum and brain stem	Visual disturbance such as diplopia, dystaxia, vertigo, dysphagia, dysphonia

*Depend on hemisphere involved and adequacy of collaterals.

rior for imaging ischemic lesions in all territories. Arteriography can demonstrate the site of the vascular abnormality and afford visualization of most intracranial vascular areas. The introduction of several Doppler ultrasonographic techniques has facilitated the noninvasive evaluation of the cerebral circulation, especially for detection of carotid stenosis.

Treatment. The treatment of acute ischemic stroke has changed markedly since the early 1990s, with an emphasis on salvaging brain tissue and minimizing long-term disability. The realization that there is a window of opportunity during which ischemic but viable brain tissue can be salvaged has led to the use of thrombolytic (clot disrupting) agents in the early treatment of ischemic stroke.[24] Although the results of emergent treatment of hemorrhagic stroke have been less dramatic, continued efforts to reduce disability have been promising.

A subcommittee of the Stroke Council of the American Heart Association has developed guidelines for the use of thrombolytic therapy for acute stroke.[28,29] The major risk of treatment with thrombolytic agents is intracranial hemorrhage of the infarcted brain. A number of conditions, including use of oral anticoagulant medications, a history of gastrointestinal bleeding, recent myocardial infarction, previous stroke or head injury within 3 months, surgery within the past 14 days, and a blood pressure greater than 200/120 mm Hg, are considered contraindications to thrombolytic therapy.[29]

The successful treatment of stroke depends on education of the public, paramedics, and health care professionals in emergency care facilities about the need for early diagnosis and treatment. As with heart attack, the message should be "do not wait to decide if the symptoms subside but seek immediate treatment." Effective medical and surgical procedures may preserve brain function and prevent disability. During the acute phase, proper positioning and range-of-motion exercises are essential. Early rehabilitation efforts include all members of the rehabilitation team—physician, nurse, speech therapist, physical therapist, and occupational therapist—and the family.

Stroke and cerebrovascular disorders often cause long-term disabilities, including motor and sensory deficits, language and speech problems, and a condition called the *hemineglect syndrome* (denial of one half of the body and environment on that side of the body). Longer-term treatment is aimed at preventing complications and recurrent stroke and promoting the fullest possible recovery of function.

Aneurysmal Subarachnoid Hemorrhage

An aneurysm is a bulge at the site of a localized weakness in the muscular wall of an arterial vessel. Most cerebral aneurysms are small saccular aneurysms called *berry aneurysms* (Fig. 37-18). They usually occur in the anterior circulation and are found at bifurcations and other junctions of vessels such as those in the circle of Willis (Fig. 37-19). They are thought to arise from a congenital defect in the media of the involved vessels, particularly at bifurcations. Persons with heritable connective tissue disorders such as autosomal dominant polycystic kidney disease, Ehlers-Danlos syndrome, neurofibromatosis type I, and Marfan's syndrome are at particular risk.[1] Other causes of cerebral aneurysms are atherosclerosis, hypertension, and bacterial infections.

Rupture of a cerebral aneurysm results in subarachnoid hemorrhage.[30,31] The probability of rupture increases with the size of the aneurysm; aneurysms larger than 10 mm in diameter have a 50% chance of bleeding per year.[1] Rupture often occurs with acute increases in ICP. Of the various environmental factors that may predispose to aneurysmal subarachnoid hemorrhage, cigarette smoking and hypertension appear to constitute

■ **FIGURE 37-18** ■ Berry aneurysm. A thin-walled aneurysm protrudes from the arterial bifurcation in the circle of Willis. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1466]. Philadelphia: Lippincott Williams & Wilkins)

the greatest threat. The mortality and morbidity rates associated with aneurysmal subarachnoid hemorrhage are high.

The signs and symptoms of cerebral aneurysms can be divided into two phases: those presenting before rupture and bleeding and those presenting after rupture and bleeding. Most small aneurysms are asymptomatic; intact aneurysms frequently are found at autopsy as an incidental finding.[1] Large aneurysms may cause chronic headache, neurologic deficits, or both. Approximately 50% of persons with subarachnoid hemorrhage have a history of atypical headaches occurring days to weeks before the onset of hemorrhage, suggesting the presence of a small leak.[30,31] These headaches are characterized by sudden onset and often are accompanied by nausea, vomiting, and dizziness. Persons with these symptoms may be mistakenly diagnosed as having tension or migraine headaches.

The onset of subarachnoid aneurysmal rupture often is heralded by a sudden and severe headache, described as "the worst headache of my life." If the bleeding is severe, the headache may be accompanied by collapse and loss of consciousness. Vomiting may accompany the presenting symptoms. Other manifestations include signs of meningeal irritation such as nuchal rigidity (neck stiffness) and photophobia (light intolerance); cranial nerve deficits, especially cranial nerve II, and sometimes III and IV (diplopia and blurred vision); stroke syndrome (motor and sensory deficits); cerebral edema and increased ICP; and pituitary dysfunction (diabetes insipidus and hyponatremia).

The complications of aneurysmal rupture include rebleeding, vasospasm with cerebral ischemia, hydrocephalus, hypothalamic dysfunction, and seizure activity. Rebleeding and vasospasm are the most severe and most difficult to treat. Rebleeding, which has its highest incidence on the first day after the initial rupture, results in further and usually catastrophic neurologic deficits.

Vasospasm is a dreaded complication of aneurysmal rupture. The condition is difficult to treat and is associated with a high incidence of morbidity and mortality. Although the description of aneurysm-associated vasospasm is relatively uniform, its proposed mechanisms are a matter of controversy. Usually, the condition develops within 3 to 10 days (peak, 7 days) after aneurysm rupture and involves a focal narrowing of the cerebral artery or arteries that can be visualized on arteriography. The neurologic status gradually deteriorates as blood supply to the brain in the region of the spasm is decreased; this usually can be differentiated from the rapid deterioration seen in rebleeding.

Another complication of aneurysm rupture is the development of hydrocephalus. It is caused by plugging of the arachnoid villi with products from lysis of blood in the subarachnoid space.

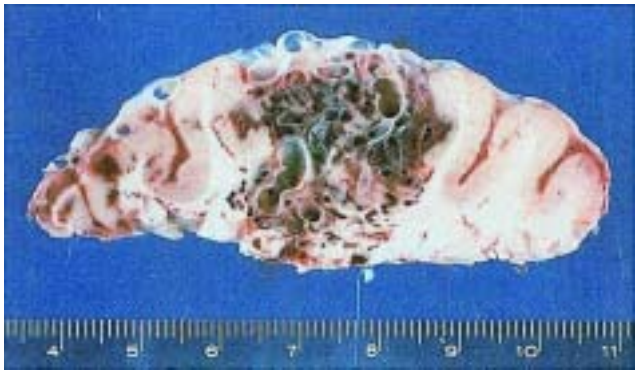
The diagnosis of subarachnoid hemorrhage and intracranial aneurysms is made by clinical presentation, CT scan, lumbar puncture, and angiography. Lumbar puncture may be used to detect blood in the CSF, but the procedure carries with it the risk of rebleeding and brain herniation.

The course of treatment after aneurysm rupture depends on the extent of neurologic deficit. Persons with less severe deficits, with or without headache and no neurologic deficits, may undergo cerebral arteriography and early surgery, usually within 24 to 72 hours. A procedure involving craniotomy and clipping often is used. In this procedure, a specially designed silver clip is inserted and tightened around the neck of the aneurysm. This procedure offers protection from rebleeding and may permit removal of the hematoma. Some persons with subarachnoid hemorrhage are managed medically for 10 days or more in an attempt to improve their clinical status before surgery. The use of endovascular techniques such as balloon embolization and platinum coil electrothrombosis is evolving.

Arteriovenous Malformations

Arteriovenous malformations are a complex tangle of abnormal arteries and veins linked by one or more fistulas (Fig. 37-20).[32] These vascular networks lack a capillary bed, and the small arteries have a deficient muscularis layer. Arteriovenous malformations are thought to arise from failure in development of the capillary network in the embryonic brain. As the child's brain grows, the malformation acquires additional arterial contributions that enlarge to form a tangled collection of thin-walled vessels that shunt blood directly from the arterial to the venous circulation. Arteriovenous malformations typically present before 40 years of age and affect men and

■ **FIGURE 37-19** ■ Common sites of berry aneurysms.



■ **FIGURE 37-20** ■ Arteriovenous malformation. Abnormal blood vessels replace the cortical gray matter and extend deeply into the underlying white matter. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1466]. Philadelphia: Lippincott Williams & Wilkins)

women equally. Rupture of vessels in the malformation accounts for approximately 2% of all strokes.[32]

The hemodynamic effects of arteriovenous malformations are twofold. First, blood is shunted from the high-pressure arterial system to the low-pressure venous system without the buffering advantage of the capillary network. The draining venous channels are exposed to high levels of pressure, predisposing them to rupture and hemorrhage. Second, impaired perfusion affects the cerebral tissue adjacent to the arteriovenous malformation. The elevated arterial and venous pressures and lack of a capillary circulation impair cerebral perfusion by producing a high-flow situation that diverts blood away from the surrounding tissue. Clinically, this is evidenced by slowly progressive neurologic deficits.

The major clinical manifestations of arteriovenous malformations are hemorrhage, seizures, headache, and progressive neurologic deficits. Headaches often are severe, and persons with the disorder may describe them as being throbbing and synchronous with their heart beat. Other, less common symptoms include visual symptoms (*i.e.*, diplopia and hemianopia), hemiparesis, mental deterioration, and speech deficits. Learning disorders have been documented in 66% of adults with arteriovenous malformations.[32]

Definitive diagnosis often is obtained through cerebral angiography. Treatment methods include surgical excision, endovascular occlusion, and radiation therapy. Because of the nature of the malformation, each of these methods is accompanied by some risk of complications.

In summary, a stroke, or "brain attack," is an acute focal neurologic deficit caused by a vascular disorder that injures brain tissue. It is the third leading cause of death in the United States and a major cause of disability. There are two main types of stroke: ischemic and hemorrhagic. Ischemic stroke, which is the most common type, is caused by cerebrovascular obstruction by a thrombus or emboli. Hemorrhagic stroke, which is associated with greater morbidity and mortality, is caused by the rupture of a blood vessel and bleeding into the brain. The acute manifestations of stroke depend on the location of the blood vessel that is involved and can include motor, sensory, language, speech, and cognitive disorders. Early diagnosis and treatment with thrombolytic agents has improved the outlook for many persons with ischemic stroke.

A subarachnoid hemorrhage involves bleeding into the subarachnoid space. Most subarachnoid hemorrhages are the result of a ruptured cerebral aneurysm. Presenting symptoms include headache, nuchal rigidity, photophobia, and nausea. Complications include rebleeding, vasospasm, and hydrocephalus. Arteriovenous malformations are congenital abnormal communications between arterial and venous channels that result from failure in the development of the capillary network in the embryonic brain. The vessels in the arteriovenous malformations may enlarge to form a space-occupying lesion, become weak and predispose to bleeding, and divert blood away from other parts of the brain; they can cause brain hemorrhage, seizures, headache, and other neurologic deficits.

INFECTIONS AND NEOPLASMS

Infections

Infections of the CNS may be classified according to the structure involved: the meninges, (meningitis); the brain parenchyma (encephalitis); the spinal cord (myelitis); and the brain and spinal cord (encephalomyelitis). They also may be classified by the type of invading organism: bacterial, viral, or other. In general, the pathogens enter the CNS through the bloodstream by crossing the blood-brain barrier or by direct invasion through skull fracture, a bullet hole, or rarely, by contamination during surgery or lumbar puncture.

Meningitis

Meningitis is an inflammation of the pia mater, the arachnoid, and the CSF-filled subarachnoid space. Inflammation spreads rapidly because of CSF circulation around the brain and spinal cord. The inflammation usually is caused by an infection, but chemical meningitis can occur. There are two types of acute infectious meningitis: acute pyogenic meningitis (usually bacterial) and acute lymphocytic (usually viral) meningitis.[1]

Bacterial Meningitis. Most cases of bacterial meningitis are caused by *Streptococcus pneumoniae, Haemophilus influenzae,* or *Neisseria meningitidis* (the meningococcus). The incidence of *H. influenzae*, which is the common cause of meningitis in children younger than 5 years, has declined dramatically during recent years because of vaccination against *H. influenza*. Epidemics of meningococcal meningitis occur in settings such as the military, where the recruits must reside in close contact. The very young and the very old are at highest risk for pneumococcal meningitis. Risk factors associated with contracting meningitis include head trauma with basilar skull fractures, otitis media, sinusitis or mastoiditis, neurosurgery, dermal sinus tracts, systemic sepsis, or immunocompromise.

In the pathophysiology of bacterial meningitis, the bacterial organisms replicate and undergo lysis in the CSF, releasing endotoxins or cell wall fragments. These substances initiate the release of inflammatory mediators, which set the stage for a complex but coordinated sequence of events by which neutrophils bind to and damage the endothelial cells of the

blood-brain barrier, permitting fluid to move across the capillary wall. This allows pathogens, neutrophils, and albumin to move across the endothelial wall into the CSF. As the pathogens enter the subarachnoid space, they cause inflammation, characterized by a cloudy, purulent exudate. Thrombophlebitis of the bridging veins and dural sinuses may develop, followed by congestion and infarction in the surrounding tissues. Ultimately, the meninges thicken, and adhesions form. These adhesions may impinge on the cranial nerves, giving rise to cranial nerve palsies, or may impair the outflow of CSF, causing hydrocephalus.

The most common symptoms of acute bacterial meningitis are fever and chills; headache; stiff neck; back, abdominal, and extremity pains; and nausea and vomiting. Other signs include seizures, cranial nerve palsies, and focal cerebral signs.[33] A petechial rash is found in most persons with meningococcal meningitis. These petechiae vary from pinhead size to large ecchymoses or even areas of skin gangrene that slough if the person survives. Other types of meningitis also may produce a petechial rash. Persons infected with *H. influenzae* or *S. pneumoniae* may present with difficulty in arousal and seizures, whereas those with *N. meningitidis* infection may present with delirium or coma.[33] The development of brain edema, hydrocephalus, or increased cerebral blood flow can increase ICP.

Meningeal signs (*e.g.*, photophobia and nuchal rigidity), such as those seen in subarachnoid hemorrhage, also may be present. Two assessment techniques can help determine whether meningeal irritation is present. *Kernig's sign* is resistance to extension of the leg while the person is lying with the hip flexed at a right angle. *Brudzinski's sign* is elicited when flexion of the neck results in flexion of the hip and knee. These postures are caused by stretching of the inflamed meninges from the lumbar level to the head. Stretching of the inflamed meninges is extremely painful, producing resistance to stretching. Cranial nerve damage (especially the eighth nerve, with resulting deafness) and hydrocephalus may occur as complications of pyogenic meningitis.

The diagnosis of bacterial meningitis is based on the history and physical examination, along with laboratory data. Lumbar puncture (*i.e.*, spinal tap) findings, which is necessary for accurate diagnosis, includes a cloudy and purulent CSF under increased pressure. The CSF typically contains large numbers of polymorphonuclear neutrophils (up to 90,000/mm^3), increased protein content, and reduced sugar content. Bacteria can be seen on smears and can easily be cultured with appropriate media.

Treatment includes antibiotics and corticosteroids. Optimal antibiotic treatment requires that the drug have a bactericidal effect in the CSF. Because bactericidal therapy often results in rapid lysis of the pathogen, treatment can promote the release of biologically active cell wall products into the CSF. The release of these cell wall products can increase the production of inflammatory mediators that have the potential for exacerbating the abnormalities of the blood-brain barrier and the inflammatory process. Because of evidence linking the inflammatory mediators to the pathogenesis of bacterial meningitis, adjunctive corticosteroid therapy usually is administered with or just before the first dose of antibiotics in infants and children. The adjunctive use of corticosteroid therapy in adults is a matter of controversy.

Persons who have been exposed to someone with meningococcal meningitis should be treated prophylactically with antibiotics.[34] Effective polysaccharide vaccines are available to protect against meningococcal groups A, C, Y, and W-135.[35] These vaccines are recommended for military recruits and college students, who are at increased risk of invasive meningococcal disease.

Viral Meningitis. Viral meningitis manifests in much the same way as bacterial meningitis, but the course is less severe, and the CSF findings are markedly different. There are lymphocytes in the fluid, rather than polymorphonuclear cells, the protein content is only moderately elevated, and the sugar content usually is normal. The acute viral meningitides are self-limited and usually require only symptomatic treatment. Viral meningitis can be caused by many different viruses, including mumps, coxsackievirus, Epstein-Barr virus, and herpes simplex type 2. In many cases, the virus cannot be identified.

Encephalitis

Encephalitis represents a generalized infection of the parenchyma of the brain or spinal cord. It usually is caused by a virus, but it also may be caused by bacteria, fungi, and other organisms. The nervous system is subjected to invasion by many viruses, such as arbovirus, poliovirus, and rabies virus. The mode of transmission may be the bite of a mosquito (arbovirus), a rabid animal (rabies virus), or ingestion (poliovirus). A common cause of encephalitis in the United States is herpes simplex virus. Less common causes of encephalitis are toxic substances such as ingested lead and vaccines for measles and mumps. Encephalitis caused by human immunodeficiency virus infection is discussed in Chapter 10.

The pathologic picture of encephalitis includes local necrotizing hemorrhage, which ultimately becomes generalized, with prominent edema. There is progressive degeneration of nerve cell bodies. The histologic picture, although rather general, demonstrates some specific characteristics. For example, the poliovirus selectively destroys the cells of the anterior horn of the spinal cord.

Encephalitis, like meningitis, is characterized by fever, headache, and nuchal rigidity. Patients experience a wide range of neurologic disturbances, such as lethargy, disorientation, seizures, focal paralysis, delirium, and coma. Diagnosis of encephalitis is made by clinical history and presenting symptoms, in addition to traditional CSF studies.

Neoplasms

For most neoplasms, the term *malignant* is used to describe the tumor's lack of cell differentiation, its invasive nature, and its ability to metastasize. However, in the brain even a well-differentiated and histologically benign tumor may grow and cause death because of its location.

Brain cancer accounts for 2% of all cancer deaths. The American Cancer Society estimates that there were 17,200 new cases and more than 13,100 deaths of brain and CNS cancers in 2001.[36] Metastasis to the brain from other sites is even more common.[37] In children, brain tumors are second only to leukemia as a cause of death from cancer, and they kill approximately 1600 children and young adults annually.

Although a number of chemical and viral agents can cause brain tumors in laboratory animals, there is no evidence that these agents directly cause brain cancer in humans. Cranial irradiation and exposure to some chemicals may lead to an in-

creased incidence of astrocytomas and meningiomas. There may also be a hereditary factor. Childhood tumors are considered to be developmental in origin.

Types of Tumors

Brain tumors can be divided into three types: primary intracranial tumors of CNS tissue (*e.g.*, neuroglial tumors [gliomas]), primary intracranial tumors that originate in the skull cavity but are not derived from the brain tissue itself (*e.g.*, meninges, pituitary gland, pineal gland), and metastatic tumors.

Primary Neuroglial Tumors. Primary intracranial neoplasms of CNS origin can be classified according to the site of origin and histologic type. They include astrocytomas, oligodendrogliomas, and ependymomas.

Collectively, the neoplasms of astrocyte origin are the most common type of primary brain tumor in the adult. Astrocytomas can be subdivided into fibrillary (filtrating) astrocytic neoplasms and pilocytic astrocytomas.[1] *Fibrillary* or *diffuse astrocytomas* account for 80% of adult primary brain tumors. They are most commonly seen in adults, but may occur at any age. Although they usually are found in the cerebral hemispheres, they also can occur in the cerebellum, brain stem, or spinal cord. These tumors are subdivided into histologic grades based on their degree of differentiation. The Word Health Organization grading system divides these tumors into three types: (1) the well differentiated lesions, designated *astrocytomas*; (2) intermediate-grade tumors, designated *anaplastic astrocytomas*; and (3) the most aggressive lesions, designated *glioblastoma multiforme*. Astrocytomas have a marked tendency to become more anaplastic with time, so a tumor beginning as an astrocytoma may develop into a glioblastoma. *Pilocytic astrocytomas* are distinguished from other astrocytomas by their cellular appearance and their benign behavior. Typically, they occur in children and young adults and usually are located in the cerebellum, but they also can be found in the floor and walls of the third ventricle, the optic chiasm and nerves, and occasionally in the cerebral hemispheres.

Oligodendrogliomas comprise approximately 5% to 15% of glial tumors. They are most common in middle life and are found in the cerebral hemispheres.[1] In general, persons with oligodendrogliomas have a better prognosis than do persons with astrocytomas.

Ependymomas are derived from the single layer of epithelium that lines the ventricles and spinal canal. Although they can occur at any age, they are most likely to occur in the first 2 decades of life.[1]

Meningiomas. Meningiomas develop from the meningothelial cells of the arachnoid and are outside the brain. They usually have their onset in the middle or later years of life. They are slow-growing, well-circumscribed, and often highly vascular tumors. They usually are benign, and complete removal is possible if the tumor does not involve vital structures.

Metastatic Tumors. The brain is a common site for metastatic tumors. They occur primarily in older persons, paralleling the increase in solid tumors that occurs with increasing age.[1] Hematopoietic tumors, such as lymphomas and leukemias, which occur in children as well as adults, may also spread to the CNS. Among the tumors that commonly metastasize to the brain are lung and breast tumors and malignant melanomas. In some cases, particularly in carcinomas arising in the lung cancer, neurologic symptoms may provide the first evidence of cancer.

Clinical Course

Brain tumors can produce either focal or generalized disorders of brain function.[37] Focal disturbances result from brain compression, tumor infiltration, disturbances in blood flow, and cerebral edema. Cysts may form in tumors and contribute to brain compression. Generalized disruption of brain function usually reflects an increase in ICP. Because the volume of the intracranial cavity is fixed, brain tumors can cause a generalized increase in ICP when they reach sufficient size. Tumors can obstruct the flow of CSF in the ventricular cavities and produce hydrocephalic dilatation of the proximal ventricles and atrophy of the cerebral hemispheres.

The clinical manifestations of brain tumors depend on the size and location of the tumor. Generalized signs and symptoms include headache, nausea, vomiting, and papilledema. The brain itself is insensitive to pain. The headache that accompanies brain tumors results from compression or distortion of pain-sensitive dural or vascular structures. It may be felt on the same side of the head as the tumor but more commonly is diffuse. In the early stages, the headache, which is caused by irritation, compression, and traction on the dural sinuses or blood vessels, is mild and occurs in the morning when the person awakens.[37] It usually disappears after the person has been up for a short time. The headache becomes more constant as the tumor enlarges and often is worsened by coughing, bending, or sudden movements of the head.

Vomiting occurs with or without preceding nausea and is a common symptom of increased ICP and brain stem compression. Direct stimulation of the vomiting center, which is located in the medulla, may contribute to the vomiting that occurs with brain tumors. The vomiting may be projectile. Vomiting caused by brain tumor usually is unrelated to meals and often is associated with headache. Papilledema (edema of the optic disk) results from increased ICP and obstruction of the CSF pathways. It is associated with decreased visual acuity, diplopia, and deficits in the visual fields. Visual defects associated with papilledema often are the reason that persons with brain tumor seek medical care.

Personality and mental changes are common with brain tumors. Persons with brain tumors often are irritable initially and later become quiet and apathetic. They may become forgetful, seem preoccupied, and appear to be psychologically depressed. Because of the mental changes, a psychiatric consultation may be sought before a diagnosis of brain tumor is made.

Focal signs and symptoms are determined by the location of the tumor. Tumors arising in the frontal lobe may grow to large size, increase the ICP, and cause signs of generalized brain dysfunction before focal signs are recognized. Tumors that impinge on the visual system cause visual loss or visual field defects long before generalized signs develop. Certain areas of the brain have a relatively low threshold for seizure activity; tumors arising in relatively silent areas of the brain may produce focal epileptogenic discharges. Temporal lobe tumors often produce seizures as their first symptom. Hallucinations of smell or hearing and déjà vu phenomena are common focal manifestations of temporal lobe tumors. Brain stem tumors commonly produce upper and lower motoneuron signs, such as weakness of facial muscles and ocular palsies that occur with or without

involvement of sensory or long motor tracts. Cerebellar tumors often cause ataxia of gait.

Diagnosis and Treatment. Diagnostic procedures for brain tumor include physical and neurologic examinations, visual field and funduscopic examination, CT scans and MRI, skull x-ray films, technetium pertechnetate brain scans, electroencephalography, and cerebral angiography. Physical examination is used to assess motor and sensory function. Because the visual pathways travel through many areas of the cerebral lobes, detection of visual field defects can provide information about the location of tumors. Although CT scanning is used as a screening test, MRI scans are more sensitive than CT scans for mass lesions and can be diagnostic when a clinically suspected tumor is not detected by CT scanning. Skull x-ray films are used to detect calcified areas in a neoplasm or erosion of skull structures caused by tumors. Cerebral angiography can be used to locate a tumor and visualize its vascular supply, information that is important when planning surgery.

The three general methods for treatment of brain tumors are surgery, irradiation, and chemotherapy. Surgery is part of the initial management of virtually all brain tumors; it establishes the diagnosis and achieves tumor removal in many cases. The use of chemotherapy for brain tumors is somewhat limited by the blood-brain barrier. Chemotherapeutic agents can be administered intravenously, intra-arterially, intrathecally (*i.e.*, into the spinal canal), or intraventricularly.

In summary, infections of the CNS may be classified according to the structures involved (*e.g.*, meningitis, encephalitis) or the type of organism causing the infection. The damage caused by infection may predispose to hydrocephalus, seizures, or other neurologic defects.

Brain tumors account for 2% of all cancer deaths and are the second most common type of cancer in children. Primary brain tumors can arise from any structure in the cranial cavity. Most begin in brain tissue, but the pituitary, the pineal region, and the meninges also are sites of tumor development. Brain tumors cause generalized or focal disturbances in brain function. Generalized disruption of brain function usually reflects an increase in ICP. General symptoms such as headache, nausea, vomiting, mental changes, and papilledema usually reflect an increase in ICP. Focal symptoms, such disorders of motor function, result from brain compression, tumor infiltration, disturbances in blood flow, and cerebral edema.

SEIZURE DISORDERS

Seizures, sometimes called *convulsions*, are paroxysmal motor, sensory, or cognitive manifestations of spontaneous, abnormally synchronous discharges of collections of neurons in the cerebral cortex. Approximately 2 million persons in the United States experience recurrent seizures.[38] Seizure activity is the most common disorder encountered in pediatric neurology, and among adults, its incidence is exceeded only by cerebrovascular disorders. In most persons, the first seizure episode occurs before 20 years of age. After 20 years of age, a seizure is caused most often by a structural change, trauma, tumor, or stroke.

KEY CONCEPTS

SEIZURES

- Seizures are paroxysmal motor, sensory, or cognitive manifestations of spontaneous, abnormally synchronous electrical discharges from collections of neurons in the cerebral cortex that are thought to result directly or indirectly from changes in excitability of single neurons or groups of neurons.
- Partial seizures originate in a small group of neurons in one hemisphere with secondary spread of seizure activity to other parts of the brain. Simple partial seizures usually are confined to one hemisphere and do not involve loss of consciousness. Complex partial seizures begin in a localized area, spread to both hemispheres, and involve impairment of consciousness.
- Generalized seizures show simultaneous disruption of normal brain activity in both hemispheres from the onset. They include unconsciousness and varying bilateral degrees of symmetric motor responses with evidence of localization to one hemisphere. Absence seizures are generalized nonconvulsive seizure events that are expressed mainly by brief periods of unconsciousness. Tonic-clonic seizures involve unconsciousness along with both tonic and clonic muscle contractions.

A seizure represents the clinical manifestations of an abnormal, uncontrolled electrical discharge from a group of neurons. This uncontrolled neuronal activity causes signs and symptoms that vary according to the location of the originating focus of seizure activity, involvement of surrounding neurons, and spread to other parts of the brain. These signs and symptoms can include strange sensations and perceptions (*e.g.*, hallucinations), unusual or repetitive muscle movements, autonomic visceral activity, and the onset of a confusional state or loss of consciousness.

Many theories have been proposed to explain the cause of the abnormal brain electrical activity that occurs with seizures. Seizures may be caused by alterations in cell membrane permeability or distribution of ions across the neuronal cell membranes. Another cause may be decreased inhibition of cortical or thalamic neuronal activity or structural changes that alter the excitability of neurons. Neurotransmitter imbalances such as an acetylcholine excess or γ-aminobutyric acid (GABA, an inhibitory neurotransmitter) deficiency have been proposed as causes.

Provoked and Unprovoked Seizures

Clinically, seizures may be categorized as unprovoked (primary or idiopathic) or provoked (secondary or acute symptomatic).[39] Provoked or symptomatic seizures include febrile seizures, seizures precipitated by systemic metabolic conditions,

and those that follow a primary insult to the CNS. Unprovoked or idiopathic seizures are those for which no identifiable cause can be determined.

The most common subgroup of seizures under the category of provoked seizures is that of febrile seizures in children.[40] They are associated with a high fever, usually with a temperature higher than 104 °F. Seizures can also be precipitated by systemic or metabolic disturbances, and primary CNS insults also fall into the category of provoked seizures. Transient systemic metabolic disturbances may precipitate seizures. Examples include electrolyte imbalances, hypoglycemia, hypoxia, hypocalcemia, and alkalosis. Toxemia of pregnancy, water intoxication, uremia, and CNS infections such as meningitis also may precipitate a seizure. The rapid withdrawal of sedative-hypnotic drugs, such as alcohol or barbiturates, is another cause of seizures. Approximately 5% to 10% of those who sustain a CNS insult, such as occurs with cerebral bleeding, edema, or neuronal damage, experience a seizure. Treatment of the immediate cause of these seizures often results in their disappearance.

Multiple episodes or frequent recurrences of apparently unprovoked seizures are considered a seizure disorder. The terms *seizure disorder* and *epileptic syndrome* often are used interchangeably. However, the term *seizure disorder* is often preferred because of the negative connotations associated with the term *epilepsy*. A seizure disorder can be defined as a syndrome in which there is a tendency to have recurrent, paroxysmal seizure activity without evidence of a reversible metabolic cause. It is a chronic condition for which long-term medication may be appropriate.

CHART 37-1 Classification of Epileptic Seizures

Partial Seizures

Simple partial seizures (no impairment of consciousness)
- With motor symptoms
- With sensory symptoms
- With autonomic signs
- With psychic symptoms

Complex partial seizures (impairment of consciousness)
- Simple partial onset followed by impaired consciousness
- Impairment of consciousness at onset

Partial seizures evolving to secondarily generalized seizures
- Simple partial leading to generalized seizures
- Complex partial leading to generalized seizures

Unclassified Seizures

Classification not possible because of inadequate or incomplete data

Generalized Seizures

Absence seizures (typical or atypical)
Atonic seizures
Myoclonic seizures
Clonic seizures
Tonic
Tonic-clonic seizures

(Adapted from Commission on Classification and Terminology of the International League Against Epilepsy [1981]. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 22, 489)

Classification

The International Classification of Epileptic Seizures is based on symptoms during the seizure and EEG activity. It divides seizures into two broad categories: partial seizures, in which the seizure begins in a specific or focal area of one cerebral hemisphere, and generalized seizures, which begin simultaneously in both cerebral hemispheres[41] (Chart 37-1).

Partial Seizures

Partial or focal seizures are the most common type of seizure among newly diagnosed cases in all persons older than 10 years of age. Partial seizures can be subdivided into three major groups: simple partial (consciousness is not impaired), complex partial (impairment of consciousness), and secondarily generalized partial seizures.

Simple Partial Seizures. Simple partial seizures usually involve only one hemisphere and are not accompanied by loss of consciousness or responsiveness. These seizures also have been referred to as *elementary partial seizures, partial seizures with elementary symptoms,* or *focal seizures*. Simple partial seizures are classified according to motor signs, sensory symptoms, autonomic manifestations, and psychic symptoms.

The observed clinical signs and symptoms depend on the area of the brain where the abnormal neuronal discharge is taking place. If the motor area of the brain is involved, the earliest symptom is motor movement corresponding to the location of onset on the contralateral side of the brain. The motor movement may remain localized or may spread to other cortical areas, with sequential involvement of body parts in an epileptic-type "march," known as a *Jacksonian seizure*. If the sensory portion of the brain is involved, there may be no observable clinical manifestations. Sensory symptoms correlating with the location of seizure activity on the contralateral side of the brain may involve somatic sensory disturbance (*e.g.*, tingling and crawling sensations) or special sensory disturbance (*i.e.*, visual, auditory, gustatory, or olfactory phenomena). When abnormal cortical discharge stimulates the autonomic nervous system, flushing, tachycardia, diaphoresis, hypotension or hypertension, or pupillary changes may be evident.

The term *prodrome* or *aura* traditionally has meant a sensory warning sign of impending seizure activity that affected persons could recognize or describe because they were conscious. Simple partial seizures may progress to complex partial seizures or generalized tonic-clonic seizures that result in unconsciousness.

Complex Partial Seizures. Complex partial seizures involve impairment of consciousness and often arise from the temporal lobe. The seizure begins in a localized area of the brain but may progress rapidly to involve both hemispheres. These seizures also may be referred to as *temporal lobe seizures* or *psychomotor seizures*.

Complex partial seizures often are accompanied by automatisms. Automatisms are repetitive, nonpurposeful activity, such as lip smacking, grimacing, patting, or rubbing clothing. Confusion during the postictal state (after a seizure) is common. Hallucinations and illusional experiences such as *déjà vu*

(familiarity with unfamiliar events or environments) or *jamais vu* (unfamiliarity with a known environment) have been reported. There may be overwhelming fear, uncontrolled forced thinking or a flood of ideas, and feelings of detachment and depersonalization.

Secondarily Generalized Partial Seizures. These seizures are focal at onset but then become generalized as the seizure activity spreads, involving deeper structures of the brain, such as the thalamus or the reticular formation. Discharges spread to both hemispheres, resulting in progression to tonic-clonic seizure activity. These seizures may start as simple or complex partial seizures and may be preceded by an aura. The aura, often a stereotyped peculiar sensation that precedes the seizure, is the result of partial seizure activity. A history of an aura is clinically useful to identify the seizure as partial and not generalized in onset. However, absence of an aura does not reliably exclude a focal onset because many partial seizures generalize too rapidly to generate an aura.

Generalized Seizures

Generalized seizures begin with initial involvement of both hemispheres. Generalized-onset seizures are the most common type in young children. These seizures are classified as primary or generalized when clinical signs, symptoms, and supporting EEG changes indicate involvement of both hemispheres at onset. The clinical symptoms include unconsciousness and involve varying degrees of symmetric bilateral motor responses without evidence of localization to one hemisphere.

These seizures are divided into four broad categories: absence seizures (typical and atypical), atonic seizures, myoclonic seizures, and major motor (tonic-clonic) seizures.[41]

Absence Seizures. Absence seizures, formerly referred to as *petit mal seizures*, are generalized, nonconvulsive epileptic events and are expressed mainly as disturbances in consciousness. Absence seizures typically occur only in children and cease in adulthood or evolve to generalized motor seizures. Children may present with a history of school failure that predates the first evidence of seizure episodes. Although *typical absence seizures* have been characterized as a blank stare, motionlessness, and unresponsiveness, motion occurs in many cases of typical absence seizures. This motion may take the form of automatisms such as lip smacking, mild clonic motion (usually in the eyelids), increased or decreased postural tone, and autonomic phenomena. There often is a brief loss of contact with the environment. The seizure usually lasts only a few seconds, and then the child is able to resume normal activity immediately. The manifestations often are so subtle that they may pass unnoticed.

Atypical absence seizures are similar to typical absence seizures except for greater alterations in muscle tone and less abrupt onset and cessation. In practice, it is difficult to distinguish typical from atypical absence seizures without benefit of supporting EEG findings. Because automatisms and unresponsiveness are common to complex partial seizures, the latter may be mistakenly labeled as absence seizures. However, it is important to distinguish between the two types of seizures because the drug treatment is different. Medications that are effective for partial seizures may increase the frequency of absence seizures.

Atonic Seizures. In atonic or akinetic seizures, there is a sudden, split-second loss of muscle tone leading to slackening of the jaw, drooping of the limbs, or falling to the ground. These seizures also are known as *drop attacks*.

Myoclonic Seizures. Myoclonic seizures involve brief involuntary muscle contractions induced by stimuli of cerebral origin. A myoclonic seizure involves bilateral jerking of muscles, generalized or confined to the face, trunk, or one or more extremities. Tonic seizures are characterized by a rigid, violent contraction of the muscles, fixing the limbs in a strained position. Clonic seizures consist of repeated contractions and relaxations of the major muscle groups.

Tonic-Clonic Seizures. Tonic-clonic seizures, formerly called *grand mal seizures*, are the most common major motor seizure. Frequently, a person has a vague warning (probably a simple partial seizure) and experiences a sharp tonic contraction of the muscles with extension of the extremities and immediate loss of consciousness. Incontinence of bladder and bowel is common. Cyanosis may occur from contraction of airway and respiratory muscles. The tonic phase is followed by the clonic phase, which involves rhythmic bilateral contraction and relaxation of the extremities. At the end of the clonic phase, the person remains unconscious until the RAS begins to function again. This is called the *postictal phase*. The tonic-clonic phases last approximately 60 to 90 seconds.

Unclassified Seizures

Unclassified seizures are those that cannot be placed in one of the previous categories. These seizures are observed in the neonatal and infancy periods. Determination of whether the seizure is focal or generalized is not possible. Unclassified seizures are difficult to control with medication.

Diagnosis and Treatment

The diagnosis of seizure disorders is based on a thorough history and neurologic examination, including a full description of the seizure. The physical examination and laboratory studies help exclude any metabolic disease (*e.g.*, hyponatremia) that could precipitate seizures. Skull radiographs and CT or MRI scans are used to identify structural defects. One of the most useful diagnostic tests is the EEG, which is used to record changes in the brain's electrical activity. It is used to support the clinical diagnosis of epilepsy, to provide a guide for prognosis, and to assist in classifying the seizure disorder.

The first rule of treatment is to protect the person from injury during a seizure, preserve brain function by aborting or preventing seizure activity, and treat any underlying disease. Persons with epilepsy should be advised to avoid situations that could be dangerous or life threatening if seizures occur.

Anticonvulsant Medications

Since the late 1970s, the therapy for epilepsy has changed drastically because of an improved classification system, the ability to measure serum anticonvulsant levels, and the availability of potent new anticonvulsant drugs. With proper drug management, 60% to 80% of persons with epilepsy can obtain good seizure control.

More than 20 drugs are available in the United States for the treatment of epilepsy.[42] Antiseizure drugs act mainly by suppressing repetitive firing of isolated neurons that act as epileptogenic foci for seizure activity or by inhibiting the transmission of electrical impulses involved in seizure activity. Because of their selective mechanisms of action, different drugs are used to treat the different types of seizures. For example, ethosuximide is the drug of choice for absence seizures, but it is not effective for tonic-clonic seizures that progress from partial seizures.

The goal of pharmacologic treatment is to bring the seizures under control with the least possible disruption in lifestyle and minimum side effects from medication. When possible, a single drug should be used. Monotherapy eliminates drug interactions and additive side effects. Determining the proper dose of the anticonvulsant drug is often a long and tedious process, which can be very frustrating for the person with epilepsy. Often blood tests are used to determine that the blood concentration is within the therapeutic range. Consistency in taking the medication is essential. Anticonvulsant drug use never should be discontinued abruptly. Special consideration is needed when a person taking an anticonvulsant medication becomes ill and must take additional medications. Some drugs act synergistically, and others interfere with the actions of anticonvulsant medications. This situation needs to be carefully monitored to avoid overmedication or interference with successful seizure control.

Women of childbearing age require special consideration concerning fertility, contraception, and pregnancy. Many of the drugs interact with oral contraceptives; some affect hormone function or decrease fertility. All such women should be advised to take folic acid supplementation. For women with epilepsy who become pregnant, antiseizure drugs increase the risk of congenital abnormalities and other perinatal complications.

Surgical Therapy

Surgical treatment may be an option for persons with epilepsy that is refractory to drug treatment.[43] With the use of modern neuroimaging and surgical techniques, a single epileptogenic lesion can be identified and removed without leaving a neurologic deficit.

Generalized Convulsive Status Epilepticus

Seizures that do not stop spontaneously or occur in succession without recovery are called *status epilepticus*. There are as many types of status epilepticus as there are types of seizures. Tonic-clonic status epilepticus is a medical emergency and, if not promptly treated, may lead to respiratory failure and death.

The disorder occurs most frequently in the young and old. Morbidity and mortality rates are highest in elderly persons and persons with acute symptomatic seizures, such as those related to anoxia or cerebral infarction.[44] Approximately one third of patients have no history of a seizure disorder, and in another one third, status epilepticus occurs as an initial manifestation of epilepsy.[44]

Treatment consists of appropriate life-support measures. If status epilepticus is caused by neurologic or systemic disease, the cause needs to be identified and treated immediately. Medications are given to control seizure activity.

In summary, seizures are caused by spontaneous, uncontrolled, paroxysmal, transitory discharges from cortical centers in the brain. Seizures may occur as a reversible symptom of another disease condition or as a recurrent condition called *epilepsy*. Epileptic seizures are classified as partial or generalized seizures. Partial seizures have evidence of local onset, beginning in one hemisphere. They include simple partial seizures, in which consciousness is not lost, and complex partial seizures, which begin in one hemisphere but progress to involve both. Because consciousness is not lost, an aura is now considered to be part of a simple partial seizure. Generalized seizures involve both hemispheres and include unconsciousness and rapidly occurring, widespread, bilateral symmetric motor responses. They include minor motor seizures, such as absence and akinetic seizures, and major motor or grand mal seizures.

DEMENTIAS

Dementia is a syndrome of intellectual deterioration severe enough to interfere with occupational or social performance. It may involve disturbances in memory, language use, perception, and motor skills and may interrupt the ability to learn necessary skills, solve problems, think abstractly, and make judgments. The dementias include Alzheimer's disease, multi-infarct dementia, Pick's disease, Creutzfeldt-Jakob disease, Wernicke-Korsakoff syndrome, and Huntington's chorea.

Depression is the most common treatable illness that may masquerade as dementia, and it must be excluded when a diagnosis of dementia is considered. This is important because cognitive functioning usually returns to baseline levels after depression is treated.

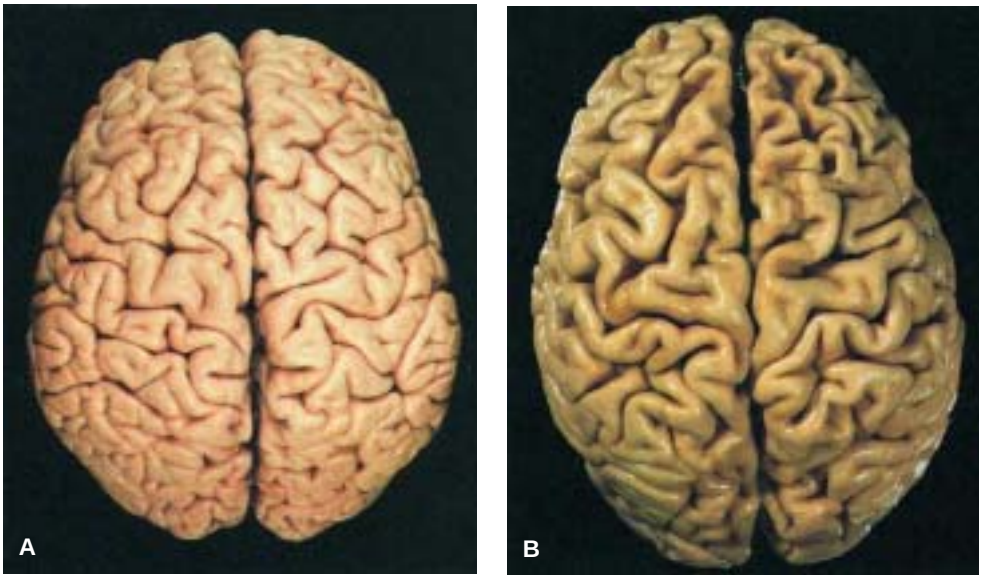
Alzheimer's Disease

Dementia of the Alzheimer's type occurs in middle or late life and accounts for 50% to 70% of all cases of dementia. The disorder affects approximately 4 million Americans and may be the fourth leading cause of death in the United States.[45] The risk of Alzheimer's disease increases with age, and it occurs in nearly half of persons 85 years of age and older.

Pathophysiology

Alzheimer's disease is characterized by cortical atrophy and loss of neurons, particularly in the parietal and temporal lobes (Fig. 37-21). With significant atrophy, there is ventricular enlargement (*i.e.*, hydrocephalus) from the loss of brain tissue. Neurochemically, Alzheimer's disease has been associated with a decrease in the level of choline acetyltransferase activity in the cortex and hippocampus. This enzyme is required for the synthesis of acetylcholine, a neurotransmitter that is associated with memory. The reduction in choline acetyltransferase is quantitatively related to the numbers of neuritic plaques and severity of dementia.

The major microscopic features of Alzheimer's disease are the presence of amyloid-containing neuritic plaques and neurofibrillary tangles.[8] The neurofibrillary tangles, which



■ **FIGURE 37-21** ■ Alzheimer's disease. (**A**) Normal brain. (**B**) The brain of a patient with Alzheimer's disease shows cortical atrophy, characterized by slender gyri and prominent sulci. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1511]. Philadelphia: Lippincott Williams & Wilkins)

are found in the cytoplasm of abnormal neurons, consist of fibrous proteins that are wound around each other in a helical fashion. These tangles are resistant to chemical or enzymatic breakdown, and they persist in brain tissue long after the neuron in which they arose has died and disappeared. The senile plaques are patches or flat areas composed of clusters of degenerating nerve terminals arranged around a central core of β-amyloid (Aβ).[8] These plaques are found in areas of the cerebral cortex that are linked to intellectual function. Aβ is a fragment of a much larger membrane-spanning amyloid precursor protein (APP). The function of APP is unclear, but it appears to be associated with the cytoskeleton of nerve fibers. Normally, the degradation of APP involves enzymatic cleavage, with formation of soluble nonpathogenic fragments. In Alzheimer's disease, cleavage of the APP molecule results in the formation of the less soluble Aβ peptide, which tends to aggregate into the amyloid fibrils found in the senile plaques.[8]

Some plaques and tangles can be found in the brains of older persons who do not show cognitive impairment. The number and distribution of the plaques and tangles appear to contribute to the intellectual deterioration that occurs with Alzheimer's disease. In persons with the disease, the plaques and tangles are found throughout the neocortex and in the hippocampus and amygdala, with relative sparing of the primary sensory cortex.[1] Hippocampal function in particular may be compromised by the pathologic changes that occur in Alzheimer's disease. The hippocampus is crucial to information processing, acquisition of new memories, and retrieval of old memories. The development of neurofibrillary tangles in the entorhinal cortex and superior portion of the hippocampal gyrus interferes with cortical input and output, thereby isolating the hippocampus from the remainder of the cortex and rendering it functionless.

It is likely that Alzheimer's disease is caused by several factors that interact differently in different persons. Progress on the genetics of inherited early-onset Alzheimer's disease shows that mutations in at least three genes—the APP gene on chromosome 21; presenilin-1 (PS1), a gene on chromosome 14; and presenilin-2 (PS2), a gene on chromosome 1—can cause Alzheimer's disease in certain families.[8,46,47] The APP gene is associated with an autosomal dominant form of early-onset Alzheimer's disease and can be tested clinically. Persons with Down's syndrome (trisomy 21) experience the pathologic changes of Alzheimer's disease and a comparable decline in cognitive functioning at a relatively young age. Virtually all persons with Down's syndrome who survive past 50 years experience the full-blown pathologic features of dementia. Because the APP gene is located on chromosome 21, it is thought that the additional dosage of the gene product in trisomy 21 predisposes to accumulation of BAP.[8] There is some indication that PS1 and PS2 are mutant proteins that alter the processing of APP.[8] A fourth gene, an allele of the apolipoprotein E gene, APOE e4, has been identified as a risk factor for late-onset Alzheimer's disease.

Clinical Course

Alzheimer's-type dementia follows an insidious and progressive course. The hallmark symptoms are loss of short-term memory and a denial of such memory loss, with eventual disorientation, impaired abstract thinking, apraxias, and changes in personality and affect. Three stages of Alzheimer's dementia have been identified, each characterized by progressive degenerative changes.

The *first stage*, which may last for 2 to 4 years, is characterized by short-term memory loss that often is difficult to differentiate from the normal forgetfulness that occurs in the elderly, and usually is reported by caregivers and denied by the patient. Although most elderly have trouble retrieving from memory incidental information and proper names, persons with Alzheimer's disease randomly forget important and unimportant details. They forget where things are placed, get lost easily, and have trouble remembering appointments and performing novel tasks. Mild changes in personality, such as lack

of spontaneity, social withdrawal, and loss of a previous sense of humor, occur during this stage.

As the disease progresses, the person with Alzheimer's disease enters the *second* or *confusional stage* of dementia. This stage may last several years and is marked by a more global impairment of cognitive functioning. During this stage, there are changes in higher cortical functioning needed for language, spatial relationships, and problem solving. Depression may occur in persons who are aware of their deficits. There is extreme confusion, disorientation, lack of insight, and inability to carry out the activities of daily living. Personal hygiene is neglected, and language becomes impaired because of difficulty in remembering and retrieving words. Wandering, especially in the late afternoon or early evening, becomes a problem. The *sundown syndrome*, which is characterized by confusion, restlessness, agitation, and wandering, may become a daily occurrence late in the afternoon. Some persons may become hostile and abusive toward family members. Persons who enter this stage become unable to live alone and should be assisted in making decisions about supervised placement with family members or friends or in a community-based facility.

Stage 3 is the terminal stage. It usually is relatively short (1 to 2 years) compared with the other stages, but it has been known to last for as long as 10 years.[48] The person becomes incontinent, apathetic, and unable to recognize family or friends. It usually is during this stage that the person is institutionalized.

Diagnosis and Treatment

Alzheimer's disease is essentially a diagnosis of exclusion. There are no peripheral biochemical markers or tests for the disease. The diagnosis can be confirmed only by microscopic examination of tissue obtained from a cerebral biopsy or at autopsy. The diagnosis is based on clinical findings. A diagnosis of Alzheimer's disease requires the presence of dementia established by clinical examination, mental status tests, and the absence of systemic or brain disorders that could account for the memory or cognitive deficits.[48,49] Brain imaging, CT scan, or MRI is done to exclude other brain disease. Metabolic screening should be done for known reversible causes of dementia, such as vitamin B_{12} deficiency, thyroid dysfunction, and electrolyte imbalance.

There is no curative treatment for Alzheimer's dementia. Drugs are used primarily to slow the progression and to control depression, agitation, or sleep disorders. Two major goals of care are maintaining the person's socialization and providing support for the family. Day care and respite centers are available in many areas to provide relief for caregivers and appropriate stimulation for the patient.

Although there is no current drug therapy that is curative for Alzheimer's disease, some show promise in terms of slowing the progress of the disease. Several drugs have been shown to be effective in slowing the progression of the disease by potentiating the available acetylcholine. The drugs—tacrine, donepezil, rivastigmine, and galantamine—inhibit acetylcholinesterase, preventing the metabolism of endogenous acetylcholine. Thus far, such therapy has not halted disease progression, but it can establish a meaningful plateau in decline.[50] There also is interest in the use of agents such as antioxidants (*e.g.*, vitamin E, ginkgo) and anti-inflammatory agents to prevent or delay the onset of the disease.

Other Types of Dementia

Vascular Dementia

Dementia associated with cerebrovascular disease does not result directly from atherosclerosis, but rather is caused by multiple infarctions throughout the brain, thus the name *vascular* or *multi-infarct dementia*. Approximately 20% to 25% of dementias are vascular in origin, and the incidence is closely associated with hypertension. Other contributing factors are arrhythmias, myocardial infarction, peripheral vascular disease, diabetes mellitus, and smoking. The usual onset is between the ages of 55 and 70 years. The disease differs from Alzheimer's dementia in its presentation and tissue abnormalities. The onset may be gradual or abrupt, the course usually is a stepwise progression, and there should be focal neurologic symptoms related to local areas of infarction.

Pick's Disease

Pick's disease is a rare form of dementia characterized by atrophy of the frontal and temporal areas of the brain. The neurons in the affected areas contain cytoplasmic inclusions called *Pick bodies*. The average age at onset of Pick's disease is 38 years. The disease is more common in women than men. Behavioral manifestations may be noticed earlier than memory deficits, taking the form of a striking absence of concern and care, a loss of initiative, echolalia (*i.e.*, automatic repetition of anything said to the person), hypotonia, and incontinence. The course of the disease is relentless, with death ensuing within 2 to 10 years. The immediate cause of death usually is infection.

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease is a rare transmissible form of dementia thought to be caused by an infective protein agent called a *prion*.[51] Similar diseases occur in animals, including scrapie in sheep and goats, and bovine spongiform encephalitis (BSE; mad cow disease) in cows. The pathogen is resistant to chemical and physical methods commonly used for sterilizing medical and surgical equipment. The disease reportedly has been transmitted through corneal transplants and human growth hormone obtained from cadavers.

Creutzfeldt-Jakob disease causes degeneration of the pyramidal and extrapyramidal systems and is distinguished most readily by its rapid course. Affected persons usually are demented within 6 months of onset. The disease is uniformly fatal, with death often occurring within months, although a few persons may survive for several years.[1] The early symptoms consist of abnormalities in personality and visual-spatial coordination. Extreme dementia, insomnia, and ataxia follow as the disease progresses.[51]

Wernicke-Korsakoff Syndrome

Wernicke-Korsakoff syndrome results from chronic alcoholism. Wernicke's disease is characterized by acute weakness and paralysis of the extraocular muscles, nystagmus, ataxia, and confusion. The affected person also may have signs of peripheral neuropathy. The person has an unsteady gait and reports diplopia. There may be signs attributable to alcohol withdrawal, such as delirium, confusion, and hallucinations. This disorder is caused by a deficiency of thiamine (vitamin B_1), and many of the symptoms are reversed when nutrition is improved with supplemental thiamine.

The Korsakoff component of the syndrome involves the chronic phase with severe impairment of recent memory. There often is difficulty in dealing with abstractions, and the person's capacity to learn is defective. Confabulation (*i.e.*, recitation of imaginary experiences to fill in gaps in memory) probably is the most distinctive feature of the disease. Polyneuritis also is common. Unlike Wernicke's disease, Korsakoff's psychosis does not improve significantly with treatment.

Huntington's Disease

Huntington's disease is a rare hereditary disorder characterized by chronic progressive chorea, psychological changes, and dementia. The disease is inherited as an autosomal dominant disorder with complete penetrance, meaning that anyone inheriting the gene will eventually experience the disease. The age of onset most commonly is in the fourth and fifth decades, often after affected persons have passed the gene on to their children.[1] Juvenile- or early-onset cases can occur and are more likely to be associated with inheritance from the father than from the mother.

The responsible gene (which encodes a protein called *huntingtin*) has located on chromosome 4.[1] The presence of the mutant huntingtin gene leads to localized death of brain cells. The first and most severely affected neurons are those of the basal ganglia. There is symmetric atrophy of caudate nucleus and lesser involvement of the putamen. There also is atrophy of the frontal cortex. Although the exact mechanisms whereby the mutant gene produces its effects is unclear, it is likely that it causes cell loss by some combination of activation of apoptotic pathways and impairment of normal metabolic processes in susceptible neurons.

Depression and personality changes are the most common early psychological manifestations; memory loss often is accompanied by impulsive behavior, moodiness, antisocial behavior, and a tendency toward emotional outbursts.[52] Other early signs of the disease are lack of initiative, loss of spontaneity, and inability to concentrate. Fidgeting or restlessness may represent early signs of dyskinesia, followed by choreiform and some dystonic posturing. Eventually, progressive rigidity and akinesia (rather than chorea) develop in association with dementia.

There is no cure for Huntington's disease. The treatment is largely symptomatic. Drugs may be used to treat the dyskinesias and behavioral disturbances. The discovery of a marker probe for the gene locus has enabled testing that can predict whether a person will experience the disease.

In summary, cognitive disorders can be caused by any disorder that permanently damages large cortical or subcortical areas of the hemispheres. The most common cause of dementia is Alzheimer's disease, which is a major health problem among the elderly. It is characterized by cortical atrophy and loss of neurons, the presence of neuritic plaques, granulovacuolar degeneration, and cerebrovascular deposits of amyloid. The disease follows an insidious and progressive course that begins with memory impairment and terminates in an inability to recognize family or friends and the loss of control over bodily functions. Multi-infarct dementia is associated with vascular disease and Pick's disease with atrophy of the frontal and temporal lobes. Creutzfeldt-Jakob disease is a rare transmissible form of dementia. Wernicke-Korsakoff syndrome results from chronic alcoholism. Huntington's disease is a rare hereditary disorder characterized by chronic and progressive chorea, psychological change, and dementia.

REVIEW QUESTIONS

- Differentiate cerebral hypoxia from ischemia and focal from global ischemia.
- Compare cytotoxic and vasogenic cerebral edema in terms of pathophysiology and distribution with brain tissue.
- Characterize the role of excitatory amino acids as a common pathway for neurologic disorders.
- Compare the brain damage associated with concussion, diffuse axonal injury, contusion, and intracerebral hemorrhage and hematoma.
- State the determinants of intracranial pressure and describe compensatory mechanisms used to prevent large changes in intracranial pressure when there are changes in brain, blood, and cerebrospinal fluid volumes.
- Compare the causes of communicating and noncommunicating hydrocephalus.
- Define consciousness and trace the rostral-to-caudal progression of unconsciousness in terms of arousal and cognition, pupillary changes, muscle tone and motor function, and respiration.
- Compare the pathologies of ischemic and hemorrhagic stroke.
- Compare the pathology, manifestations, and outcomes associated with meningitis and encephalitis.
- List the major categories of brain tumors and interpret the meaning of *benign* and *malignant* as related to brain tumors.
- Differentiate between the origin of seizure activity in partial and generalized forms of epilepsy and compare the manifestations of simple partial seizures with those of complex partial seizures and major and minor motor seizures.

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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