SAMPLE CHAPTER 15

The pages of this Sample Chapter may have slight variations in final published form.
Neurological Disorders

outline

■ Tumors
■ Seizure Disorders
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  Interim Summary
■ Disorders of Development
  Toxic Chemicals
  Inherited Metabolic Disorders
  Down Syndrome
  Interim Summary
■ Degenerative Disorders
  Transmissible Spongiform Encephalopathies
  Parkinson’s Disease
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  Alzheimer’s Disease
  Amyotrophic Lateral Sclerosis
■ Disorders Caused by Infectious Diseases
  Multiple Sclerosis
  Korsakoff’s Syndrome
  Interim Summary
Mrs. R., a divorced, fifty-year-old elementary school teacher, was sitting in her car, waiting for a traffic light to change. Suddenly, her right foot began to shake. Afraid that she would inadvertently press the accelerator and lurch forward into the intersection, she quickly grabbed the shift lever and switched the transmission into neutral. Now her lower leg was shaking, then her upper leg as well. With horrified fascination she felt her body, then her arm, begin to shake in rhythm with her leg. The shaking slowed and finally stopped. By this time the light had changed to green, and the cars behind her began honking at her. She missed that green light, but by the time the light changed again, she had recovered enough to put the car in gear and drive home.

Mrs. R. was frightened by her experience and tried in vain to think what she might have done to cause it. The next evening, some close friends visited her apartment for dinner. She found it hard to concentrate on their conversation and thought of telling them about her spell, but she finally decided not to bring up the matter. After dinner, while she was clearing the dishes off the table, her right foot began shaking again. This time she was standing up, and the contractions—much more violent than before—caused her to fall. Her friends, seated in the living room, heard the noise and came running to see what had happened. They saw Mrs. R. lying on the floor, her legs and arms held out stiffly before her, vibrating uncontrollably. Her head was thrown back and she seemed not to hear their anxious questions. The convulsion soon ceased; less than a minute later, Mrs. R. regained consciousness but seemed dazed and confused.

Mrs. R. was brought by ambulance to a hospital. After learning about her first spell and hearing her friends describe the convulsion, the emergency room physician immediately called a neurologist, who ordered a CT scan. The scan showed a small, circular white spot right where the neurologist expected it, between the frontal lobes, above the corpus callosum. Two days later, a neurosurgeon removed a small benign tumor, and Mrs. R. made an uneventful recovery.

When my colleagues and I met Mrs. R., we saw a pleasant, intelligent woman, much relieved to know that her type of brain tumor rarely produces brain damage if it is removed in time. Indeed, although we tested her carefully, we found no signs of intellectual impairment. However, if the tumor grows by infiltrating the surrounding tissue, there will be no clear-cut border between the tumor and normal tissue. If the surgeon removes the tumor, some cells may be missed, and these cells will produce a new tumor. In addition, malignant tumors often give rise to metastases. A metastasizing tumor will shed cells, which then travel through the bloodstream, lodge in capillaries, and serve as seeds for the growth of new tumors in different locations in the body.

Tumors damage brain tissue by two means: compression and infiltration. Obviously, any tumor growing in the brain, malignant or benign, can produce neurological symptoms and threaten the patient’s life. Even a benign tumor occupies space and thus pushes against the brain. The compression can directly destroy brain tissue, or it can do so indirectly by blocking the flow of cerebrospinal fluid and causing hydrocephalus. Even worse are malignant tumors, which cause both compression and infiltration. As a malignant tumor grows, it invades the surrounding region and destroys cells in its path.

Although the brain is the most protected organ, many pathological processes can damage it or disrupt its functioning. Because much of what we have learned about the functions of the human brain has been gained by studying people with brain damage, you have already encountered many neurological disorders in this book: movement disorders, such as Parkinson’s disease; perceptual disorders, such as visual agnosia and blindness caused by damage to the visual system; language disorders such as aphasia, alexia, and agraphia; and memory disorders, such as Korsakoff’s syndrome. This chapter describes the major categories of the neuropathological conditions that the brain can sustain—tumors, seizure disorders, cerebrovascular accidents, disorders of development, degenerative disorders, and disorders caused by infectious diseases—and discusses the behavioral effects of these conditions and their treatments.

**TUMORS**

A tumor is a mass of cells whose growth is uncontrolled and that serves no useful function. Some are malignant, or cancerous, and others are benign (“harmless”). The major distinction between malignancy and benignancy is whether the tumor is encapsulated: whether there is a distinct border between the mass of tumor cells and the surrounding tissue. If there is such a border, the tumor is benign; the surgeon can cut it out, and it will not regrow. However, if the tumor grows by infiltrating the surrounding tissue, there will be no clear-cut border between the tumor and normal tissue. If the surgeon removes the tumor, some cells may be missed, and these cells will produce a new tumor. In addition, malignant tumors often give rise to metastases. A metastasizing tumor will shed cells, which then travel through the bloodstream, lodge in capillaries, and serve as seeds for the growth of new tumors in different locations in the body.

Tumors damage brain tissue by two means: compression and infiltration. Obviously, any tumor growing in the brain, malignant or benign, can produce neurological symptoms and threaten the patient’s life. Even a benign tumor occupies space and thus pushes against the brain. The compression can directly destroy brain tissue, or it can do so indirectly by blocking the flow of cerebrospinal fluid and causing hydrocephalus. Even worse are malignant tumors, which cause both compression and infiltration. As a malignant tumor grows, it invades the surrounding region and destroys cells in its path. Figure

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**tumor** A mass of cells whose growth is uncontrolled and that serves no useful function.

**malignant tumor** A cancerous (literally, “harm-producing”) tumor; lacks a distinct border and may metastasize.

**benign tumor** (bee nine) A noncancerous (literally, “harmless”) tumor; has a distinct border and cannot metastasize.

**metastasis** (meh tass tis) The process by which cells break off of a tumor, travel through the vascular system, and grow elsewhere in the body.
15.1 illustrates the compressive effect of a large nonmalignant tumor. As you can see, the tumor has displaced the lateral and third ventricles. (See Figure 15.1.)

Tumors do not arise from nerve cells, which are not capable of dividing. Instead, they arise from other cells found in the brain or from metastases originating elsewhere in the body. The most common types are listed in Table 15.1. (See Table 15.1.) The most serious types of tumors are metastases and the gliomas (derived from various types of glial cells), which are usually very malignant and fast growing. Figures 15.2 and 15.3 show gliomas located in the basal ganglia and the pons, respectively. (See Figures 15.2 and 15.3.) Figure 15.4 shows an ependymoma in the lateral ventricles. (See Figure 15.4.) Some

**Figure 15.1**
A slice of a human brain, showing how a large nonmalignant tumor (a meningioma) has displaced the right side of the brain toward the left. (The dashed line indicates the location of the midline.) The right lateral ventricle is almost completely occluded.

( Courtesy of A. D’Agostino, Good Samaritan Hospital, Portland, Oregon.)

**Figure 15.2**
A slice of a human brain, showing a large glioma located in the basal ganglia, which has invaded both the left and right lateral ventricles.

( Courtesy of A. D’Agostino, Good Samaritan Hospital, Portland, Oregon.)

**Figure 15.3**
A midsagittal view of a human brain, showing a glioma located in the dorsal pons (arrowhead).

( Courtesy of A. D’Agostino, Good Samaritan Hospital, Portland, Oregon.)

**Table 15.1** Types of Brain Tumors

<table>
<thead>
<tr>
<th>Gliomas:</th>
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<tbody>
<tr>
<td>Glioblastoma multiforme (poorly differentiated glial cells)</td>
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<tr>
<td>Astrocytoma (astrocytes)</td>
</tr>
<tr>
<td>Ependymoma (ependymal cells that line ventricles)</td>
</tr>
<tr>
<td>Medulloblastoma (cells in roof of fourth ventricle)</td>
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<tr>
<td>Oligodendrocytoma (oligodendrocytes)</td>
</tr>
<tr>
<td>Meningioma (cells of the meninges)</td>
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<tr>
<td>Pituitary adenoma (hormone-secreting cells of the pituitary gland)</td>
</tr>
<tr>
<td>Neurinoma (Schwann cells or cells of connective tissue covering cranial nerves)</td>
</tr>
<tr>
<td>Metastatic carcinoma (depends on nature of primary tumor)</td>
</tr>
<tr>
<td>Angioma (cells of blood vessels)</td>
</tr>
<tr>
<td>Pinealoma (cells of pineal gland)</td>
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**glioma** (glee ah mah) A cancerous brain tumor composed of one of several types of glial cells.
tumors are sensitive to radiation and can be destroyed by a beam of radiation focused on them. Usually, a neurosurgeon first removes as much of the tumor as possible, and then the remaining cells are targeted by the radiation.

The chapter prologue described a woman whose sudden onset of seizures suggested the presence of a tumor near the top of the primary motor cortex. Indeed, she had a meningioma, an encapsulated, benign tumor consisting of cells that constitute the dura mater or arachnoid membrane. Such tumors tend to originate in the part of the dura mater that is found between the two cerebral hemispheres, or along the tentorium, the sheet of dura mater that lies between the occipital lobes and the cerebellum. (See Figure 15.5.)

**Figure 15.5**
A CT scan of a brain, showing the presence of a meningioma (round white spot indicated by the arrow).
(Courtesy of J. McA. Jones, Good Samaritan Hospital, Portland, Oregon.)

**SEIZURE DISORDERS**

Because of negative connotations that were acquired in the past, many physicians prefer not to use the term **epilepsy**. Instead, they use the phrase **seizure disorder** to refer to a condition that has many causes. Seizure disorders constitute the second most important category of neurological disorders, following stroke. A **seizure** is a period of sudden, excessive activity of cerebral neurons. Sometimes, if neurons that make up the motor system are involved, a seizure can cause a **convulsion**, which is wild, uncontrollable activity of the muscles. But not all seizures cause convulsions; in fact, most do not.

Table 15.2 presents a summary of the most important categories of seizure disorders. Two distinctions are important: **partial versus generalized seizures** and **simple versus complex** ones. **Partial seizures** have a definite focus, or source of irritation: typically, a scarred region caused by an old injury. The neurons that become involved in the seizure are restricted to a small part of the brain. **Generalized seizures** are widespread, involving most of the brain. In many cases they grow from a focus, but in some cases their origin is not discovered. Simple and complex seizures are two categories of partial seizures. **Simple partial seizures** often cause changes in consciousness but do not cause loss of consciousness. In contrast, because of their particular location and severity, **complex partial seizures** lead to loss of consciousness. (See Table 15.2.)

The most severe form of seizure is often referred to as **grand mal**. This seizure is generalized, and because it includes the motor systems of the brain, it is accompanied by convulsions. Often, before having a grand mal seizure, a person has warning symptoms, such as changes in mood or perhaps a few sudden jerks of muscular activity upon awakening. (Almost everyone sometimes experiences these jolts while falling asleep.) A few seconds before the seizure occurs, the person often experiences

**meningioma** *(men in jeb oh ma)* A benign brain tumor composed of the cells that constitute the meninges.

**seizure disorder** The preferred term for epilepsy.

**convulsion** A violent sequence of uncontrollable muscular movements caused by a seizure.

**partial seizure** A seizure that begins at a focus and remains localized, not generalizing to the rest of the brain.

**generalized seizure** A seizure that involves most of the brain, as contrasted with a partial seizure, which remains localized.

**simple partial seizure** A partial seizure, starting from a focus and remaining localized, that does not produce loss of consciousness.

**complex partial seizure** A partial seizure, starting from a focus and remaining localized, that produces loss of consciousness.

**grand mal seizure** A generalized, tonic-clonic seizure, which results in a convulsion.
an aura, which is presumably caused by excitation of neurons surrounding a seizure focus. This excitation has effects similar to those that would be produced by electrical stimulation of the region. Obviously, the nature of an aura varies according to the location of the focus. For example, because structures in the temporal lobe are involved in the control of emotional behaviors, seizures that originate from a focus located there often begin with feelings of fear and dread or, occasionally, euphoria.

The beginning of a grand mal seizure is called the tonic phase. All the patient’s muscles contract forcefully. The arms are rigidly outstretched, and the person may make an involuntary cry as the tense muscles force air out of the lungs. (At this point the patient is completely unconscious.) The patient holds a rigid posture for about 15 seconds, and then the clonic phase begins. (Clonic means “agitated.”) The muscles begin trembling, then start jerking convulsively—quickly at first, then more and more slowly. Meanwhile, the eyes roll, the patient’s face is contorted with violent grimaces, and the tongue may be bitten. Intense activity of the autonomic nervous system manifests itself in sweating and salivation. After about 30 seconds, the patient’s muscles relax; only then does breathing begin again. The patient falls into a stuporous, unresponsive sleep, which lasts for about 15 minutes. After that the patient may awaken briefly but usually falls back into an exhausted sleep that may last for a few hours.

Recordings made during grand mal seizures from electrodes implanted into patients’ brains show that neural firing first begins in the focus at the time of the aura; it then spreads to other regions of the brain (Adams and Victor, 1981). The activity spreads to regions surrounding the focus and then to the contralateral cortex (through the corpus callosum), the basal ganglia, the thalamus, and various nuclei of the brain stem reticular formation. At this point the symptoms begin. The excited subcortical regions feed back more excitation to the cortex, amplifying the activity there. Neurons in the motor cortex begin firing continuously, producing the tonic phase. Next, diencephalic structures begin quenching the seizure by sending inhibitory messages to the cortex. At first the inhibition comes in brief bursts; this causes the jerking movements of the clonic phase, as the muscles repeatedly relax and then contract again. Then the bursts of inhibition become more and more prolonged, and the jerks occur more and more slowly. Finally, the inhibition wins, and the patient’s muscles relax.

Other types of seizures are far less dramatic. Partial seizures involve relatively small portions of the brain. The symptoms can include sensory changes, motor activity, or both. For example, a simple partial seizure that begins in or near the motor cortex can involve jerking movements that begin in one place and spread throughout the body as the excitation spreads along the precentral gyrus. In the case described at the beginning of the chapter I described such a progression, caused by a seizure triggered by a meningioma. The tumor was pressing against the “foot” region of the left primary motor cortex. When

TABLE 15.2 The Classification of Seizure Disorders

<table>
<thead>
<tr>
<th>I. Generalized seizures (with no apparent local onset)</th>
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<tbody>
<tr>
<td>A. Tonic-clonic (grand mal)</td>
</tr>
<tr>
<td>B. Absence (petit mal)</td>
</tr>
<tr>
<td>C. Atonic (loss of muscle tone, temporary paralysis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Partial seizures (starting from a focus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Simple (no major change in consciousness)</td>
</tr>
<tr>
<td>1. Localized motor seizure</td>
</tr>
<tr>
<td>2. Motor seizure, with progression of movements as seizure spreads along the primary motor cortex</td>
</tr>
<tr>
<td>3. Sensory (somatosensory, visual, auditory, olfactory, vestibular)</td>
</tr>
<tr>
<td>4. Psychic (forced thinking, fear, anger, etc.)</td>
</tr>
<tr>
<td>5. Autonomic (e.g., sweating, salivating, etc.)</td>
</tr>
<tr>
<td>B. Complex (with altered consciousness)</td>
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<tr>
<td>Includes 1–5, above</td>
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</tbody>
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| III. Partial seizures (simple or complex) evolving to generalized cortical seizure: Starts as IIA or IIB, then becomes a grand mal seizure |

Aura A sensation that precedes a seizure; its exact nature depends on the location of the seizure focus.

Tonic phase The first phase of a grand mal seizure, in which all of the patient’s skeletal muscles are contracted.

Clonic phase The phase of a grand mal seizure in which the patient shows rhythmic jerking movements.
Seizures can have serious consequences: They can cause brain damage. Approximately 50% of patients with seizure disorders show evidence of damage to the hippocampus. The amount of damage is correlated with the number and severity of seizures the patient has had. Significant hippocampal damage can be caused by a single episode of status epilepticus, a condition in which the patient undergoes a series of seizures without regaining consciousness. The damage appears to be caused by an excessive release of glutamate during the seizure (Thompson et al., 1996).

Seizures have many causes. The most common cause is scarring, which may be produced by an injury, a stroke, or the irritating effect of a growing tumor. For injuries the development of seizures may take a considerable amount of time. Often, a person who receives a head injury from an automobile accident will not start having seizures until several months later.

Various drugs and infections that cause a high fever can also produce seizures. In addition, seizures are commonly seen in alcohol or barbiturate addicts who suddenly stop taking the drug; the sudden release from the inhibiting effects of the alcohol or barbiturate leaves the brain in a hyperexcitable condition. In fact, this condition is a medical emergency because it can be fatal.

Evidence suggests that NMDA receptors may be involved in the seizures caused by alcohol withdrawal. As you saw in Chapter 12, NMDA receptors are specialized glutamate receptors that control calcium channels. These channels open only when glutamate binds with the receptor and the membrane is depolarized. This double contingency is what seems to be responsible for at least one kind of synaptic modification involved in learning. Several studies have shown that alcohol blocks NMDA receptors (Gonzales, 1990). Perhaps, then, long-term suppression of NMDA receptors caused by chronic alcohol intake results in supersensitivity or “up-regulation,” a compensatory mechanism produced by long-term inhibition of the receptors. When an alcoholic suddenly stops drinking, the NMDA receptors, which have been suppressed for so long, suddenly rebound. The increased activity causes seizures.

Seizure disorders are treated with anticonvulsant drugs, many of which work by increasing the effectiveness of inhibitory synapses. Most disorders respond well enough that the patient can lead a normal life. In a few instances, drugs provide little or no help. Sometimes, seizure foci remain so irritable that despite drug treatment, brain surgery is required. The surgeon removes

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**Figure 15.6**

Primary motor cortex and seizures. Mrs. R.’s seizure began in the foot region of the primary motor cortex, and as the seizure spread, more and more parts of her body became involved.

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**absence** A type of seizure disorder often seen in children; characterized by periods of inattention, which are not subsequently remembered; also called petit mal seizure.

**status epilepticus** A condition in which a patient undergoes a series of seizures without regaining consciousness.
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The region of the brain surrounding the focus (almost always, the medial temporal lobe). Most patients recover well, with their seizures eliminated or greatly reduced in frequency. Mrs. R.’s treatment was a different matter; in her case the removal of a meningioma eliminated the source of the irritation and ended her seizures. No healthy brain tissue was removed.

Because seizure surgery often involves the removal of a substantial amount of brain tissue (usually from one of the temporal lobes), we might expect it to cause behavioral deficits. But in most cases the reverse is true; people’s performance on tests of neuropsychological functioning usually improves. How can the removal of brain tissue improve a person’s performance?

The answer is provided by looking at what happens in the brain not during seizures but between them. The seizure focus, usually a region of scar tissue, irritates the brain tissue surrounding it, causing increased neural activity that tends to spread to adjacent regions. Between seizures this increased excitatory activity is held in check by a compensatory increase in inhibitory activity. That is, inhibitory neurons in the region surrounding the seizure focus become more active. (This phenomenon is known as 

interictal inhibition; ictus means “stroke” in Latin.) A seizure occurs when the excitation overcomes the inhibition.

The problem is that the compensatory inhibition does more than hold the excitation in check; it also suppresses the normal functions of a rather large region of brain tissue surrounding the seizure focus. Thus, even though the focus may be small, its effects are felt over a much larger area even between seizures. Removing the seizure focus and some surrounding brain tissue eliminates the source of the irritation and makes the compensatory inhibition unnecessary. Freed from interictal inhibition, the brain tissue located near the site of the former seizure focus can now function normally, and the patient’s neuropsychological abilities will show an improvement.

CEREBROVASCULAR ACCIDENTS

You have already learned about the effects of cerebrovascular accidents, or strokes, in earlier chapters. For example, we saw that strokes can produce impairments in perception, emotional recognition and expression, memory, and language. This section will describe only their causes and treatments.

The incidence of strokes in the United States is approximately 600,000 per year. The likelihood of having a stroke is related to age; the probability doubles each decade after 45 years of age and reaches 1–2 percent per year by age 75 (Wolfe et al., 1992). The two major types of strokes are hemorrhagic and obstructive. Hemorrhagic strokes are caused by bleeding within the brain, usually from a malformed blood vessel or from one weakened by high blood pressure. The blood that seeps out of the defective blood vessel accumulates within the brain, putting pressure on the surrounding brain tissue and damaging it. Obstructive strokes—those that plug up a blood vessel and prevent the flow of blood—can be caused by thrombus or emboli. (Loss of blood flow to a region is called ischemia, from the Greek ischein, “to hold back,” and haima, “blood.”) A thrombus is a blood clot that forms in blood vessels, especially in places where their walls are already damaged. Sometimes, thrombi become so large that blood cannot flow through the vessel, causing a stroke. People who are susceptible to the formation of thrombi are often advised to take a drug such as aspirin, which helps to prevent clot formation. An embolus is a piece of material that forms in one part of the vascular system, breaks off, and is carried through the bloodstream until it reaches an artery too small to pass through. It lodges there, damming the flow of blood through the rest of the vascular tree (the “branches” and “twigs” arising from the artery). Emboli can consist of a variety of materials, including bacterial debris from an infection in the lining of the heart or pieces broken off from a blood clot. As we will see in a later section, emboli can introduce a bacterial infection into the brain. (See Figure 15.7.)

Strokes produce permanent brain damage, but depending on the size of the affected blood vessel, the amount of damage can vary from negligible to massive. If a hemorrhagic stroke is caused by high blood pressure, medication is given to reduce it. If one is caused by weak and malformed blood vessels, brain surgery may be used to seal off the faulty vessels to prevent another hemorrhage. If a thrombus was responsible for the stroke, anticoagulant drugs will be given to make the blood less likely to clot, reducing the likelihood of another stroke. If an embolus broke away from a bacterial infection, antibiotics will be given to suppress the infection.

What, exactly, causes the death of neurons when the blood supply to a region of the brain is interrupted? We might expect that the neurons simply starve to death because they lose their supply of glucose and of oxygen to metabolize it. However, research indicates that the

hemorrhagic stroke A cerebrovascular accident caused by the rupture of a cerebral blood vessel.

obstructive stroke A cerebrovascular accident caused by occlusion of a blood vessel.

ischemia (is kee mee uh) The interruption of the blood supply to a region of the body.

thrombus A blood clot that forms within a blood vessel, which may occlude it.

embolus (em bo luhs) A piece of matter (such as a blood clot, fat, or bacterial debris) that dislodges from its site of origin and occludes an artery; in the brain an embolus can lead to a stroke.
immediate cause of neuron death is the presence of excessive amounts of glutamate. In other words, the damage produced by loss of blood flow to a region of the brain is actually an excitotoxic lesion, just like one produced in a laboratory animal by the injection of a chemical such as kainic acid. (See Koroshetz and Moskowitz, 1996, for a review.)

When the blood supply to a region of the brain is interrupted, the oxygen and glucose in that region are quickly depleted. As a consequence, the sodium–potassium transporters, which regulate the balance of ions inside and outside the cell, stop functioning. Neural membranes become depolarized, which causes the release of glutamate. The activation of glutamate receptors further increases the inflow of sodium ions and causes cells to absorb excessive amounts of calcium through NMDA channels. The presence of excessive amounts of sodium and calcium within cells is toxic. The intracellular sodium causes the cells to absorb water and swell. The inflammation attracts microglia and activates them, causing them to become phagocytic. The phagocytic microglia begin destroying injured cells. Inflammation also attracts white blood cells, which can adhere to the walls of capillaries near the ischemic region and obstruct them. The presence of excessive amounts of calcium in the cells activates a variety of calcium-dependent enzymes, many of which destroy molecules that are vital for normal cell functioning. Finally, damaged mitochondria produce free radicals—molecules with unpaired electrons that act as powerful oxidizing agents. Free radicals are extremely toxic; they destroy nucleic acids, proteins, and fatty acids.

Researchers have sought ways to minimize the amount of brain damage caused by strokes. One approach has been to administer drugs that dissolve blood clots in an attempt to reestablish circulation to an ischemic brain region. This approach has met with some success. Administration of a clot-dissolving drug called tPA (tissue plasminogen activator) after the onset of a stroke has clear benefits if it is given within 3 hours (NINDS, 1995). tPA is an enzyme that converts the plasminogen, a protein present in the blood, into plasmin, an enzyme that dissolves fibrin, a protein involved in clot formation. tPA can be synthesized and released by neurons and glia in the central nervous system, and it plays a role in cell migration and neural development.

More recent research indicates that although tPA helps to dissolve blood clots and restore cerebral circulation, it also has toxic effects in the central nervous system. Both tPA and plasmin are potentially neurotoxic if they are able to cross the blood–brain barrier and reach the interstitial fluid. Evidence suggests that in cases of severe stroke, in which the blood–brain barrier is damaged, tPA increases excitotoxicity, further damages the blood–brain barrier, and may even cause cerebral hemorrhage (Benchenane et al., 2004; Klaur et al., 2004). In cases in which tPA quickly restores blood flow, the blood–brain barrier is less likely to be damaged, and the enzyme will remain in the vascular system, where it will do no harm.

**Figure 15.7**

Strokes. (a) Formation of thrombi and emboli. (b) An intracerebral hemorrhage.

**free radical** A molecule with unpaired electrons; acts as a powerful oxidizing agent; toxic to cells.
As you undoubtedly know, vampire bats live on the blood of other warm-blooded animals. They make a small incision in a sleeping animal’s skin with their sharp teeth and lap up the blood with their tongues. One compound in their saliva acts as a local anesthetic and keeps the animal from awakening. Another compound (and this is the one we are interested in) acts as an anticoagulant, preventing the blood from clotting. The name of this enzyme is Desmodus rotundus plasminogen activator (DSPA), otherwise known as desmoteplase. (Desmodus rotundus is the Latin name for the vampire bat.) Research with laboratory animals indicate that unlike tPA, desmoteplase causes no excitotoxic injury when injected directly into the brain (Reddrop et al., 2005). A phase II placebo-controlled, double-blind clinical trial of desmoteplase (Hacke et al., 2005) found that desmoteplase restored blood flow and reduced clinical symptoms in a majority of patients if given up to 9 hours after the occurrence of a stroke. (See Figure 15.8.)

How can strokes be prevented? Risk factors that can be reduced by medication or changes in lifestyle include high blood pressure, cigarette smoking, diabetes, and high blood levels of cholesterol. The actions we can take to reduce these risk factors are well known, so I need not describe them here. Atherosclerosis, a process in which the linings of arteries develop a layer of plaque, deposits of cholesterol, fats, calcium, and cellular waste products, is a precursor to heart attacks (myocardial infarction) and obstructive stroke, caused by clots that form around atherosclerotic plaques in cerebral and cardiac blood vessels.

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artery. The balloon is inflated, which opens the narrowed artery and expands the stent. The balloon is deflated and removed, leaving the expanded stent in place to keep the artery open. (See Figure 15.10.)

Depending on the location of the brain damage, people who have strokes will receive physical therapy, and perhaps speech therapy, to help them recover from their disability. Several studies have shown that exercise and sensory stimulation can facilitate recovery from the effects of brain damage. For example, Taub et al. (1993) studied patients with strokes that impaired their ability to use one arm and hand. They put the unaffected arm in a sling for fourteen days and gave the patients training sessions during which the patients were forced to use the impaired arm. This procedure (which is called constraint-induced movement therapy) produced long-term improvement in the patients’ ability to use the affected arm. (See Figure 15.11.)
A study by Liepert et al. (2000) found that constraint-induced movement therapy caused changes in the connections of the primary motor cortex. The investigators used transcranial magnetic stimulation (TMS) to map the area of the contralateral motor cortex that was involved in control of the impaired arm before and after treatment. Besides improving the patients’ use of the impaired arm, the treatment caused an expansion of this region—apparently, into adjacent areas of the motor cortex—that was still present when the patients were tested 6 months later.

### Interim Summary

**Tumors, Seizure Disorders, and Cerebrovascular Accidents**

Neurological disorders have many causes. Because we have learned much about the functions of the human brain from studying the behavior of people with various neurological disorders, you have already learned about many of them in previous chapters of this book. Brain tumors are caused by the uncontrolled growth of various types of cells other than neurons. They can be benign or malignant. Benign tumors are encapsulated and thus have a distinct border; when one is surgically removed, the surgeon has a good chance of getting all of it. Tumors produce brain damage by compression and, in the case of malignant tumors, infiltration.

Seizures are periodic episodes of abnormal electrical activity of the brain. Partial seizures are localized, beginning with a focus—usually, some scar tissue caused by previous damage or a tumor. When they begin, they often produce an aura, consisting of particular sensations or changes in mood. Simple partial seizures do not produce profound changes in consciousness; complex partial seizures do. Generalized seizures may or may not originate at a single focus, but they involve most of the brain. Some seizures involve motor activity; the most serious are the grand mal convulsions that accompany generalized seizures. The convulsions are caused by involvement of the brain’s motor systems; the patient first shows a tonic phase, consisting of a few seconds of rigidity, and then a clonic phase, consisting of rhythmic jerking. Absence seizures, also called petit mal seizures, are common in children. These generalized seizures are characterized by periods of inattention and temporary loss of awareness. Seizures produced by abstinence after prolonged heavy intake of alcohol appear to be produced by supersensitivity (up-regulation) of NMDA receptors. Seizures are treated with anticonvulsant drugs and, in the case of intractable seizure disorders caused by an abnormal focus, by seizure surgery, which usually involves the medial temporal lobe.

Cerebrovascular accidents damage parts of the brain through rupture of a blood vessel or occlusion (obstruction) of a blood vessel by a thrombus or embolus. A thrombus is a blood clot that forms within a blood vessel. An embolus is a piece of debris that is carried through the bloodstream and lodges in an artery. Emboli can arise from infections within the chambers of the heart or can consist of pieces of thrombi. The lack of blood flow appears to damage neurons primarily by stimulating a massive release of glutamate, which causes inflammation, phagocytosis by activated microglia, the production of free radicals, and activation of calcium-dependent enzymes. The best current treatment for stroke is administration of a drug that dissolves clots. Tissue plasminogen activator (tPA) must be given within 3 hours of the onset of the stroke and in some cases appears to cause brain damage on its own. Desmoteplase, an enzyme secreted in the saliva of vampire bats, is effective up to 9 hours after a stroke and does not appear to cause damage. Carotid endarterectomy or insertion of a carotid stent can reduce the likelihood of a stroke in people with atherosclerotic plaque that obstruct the carotid arteries. After a stroke has occurred, physical therapy can facilitate recovery and minimize a patient’s deficits. Constraint-induced movement therapy has been shown to be especially useful in restoring useful movement of limbs following unilateral damage to the motor cortex.

### Disorders of Development

As you will see in this section, brain development can be affected adversely by the presence of toxic chemicals during pregnancy and by genetic abnormalities, both hereditary and nonhereditary. In some instances the result is mental retardation.

**Toxic Chemicals**

A common cause of mental retardation is the presence of toxins that impair fetal development during pregnancy. For example, if a woman contracts rubella (German measles) early in pregnancy, the toxic chemicals released by the virus interfere with the chemical signals that control normal development of the brain. Most women who receive good health care will be immunized for rubella to prevent them from contracting it during pregnancy.

In addition to the toxins produced by viruses, various drugs can adversely affect fetal development. For example, mental retardation can be caused by the ingestion of alcohol during pregnancy. Babies born to alcoholic
women are typically smaller than average and develop more slowly. Many of them exhibit fetal alcohol syndrome, which is characterized by abnormal facial development and deficient brain development. Figure 15.12 shows photographs of the faces of a child with fetal alcohol syndrome, of a rat fetus whose mother was fed alcohol during pregnancy, and of a normal rat fetus. As you can see, alcohol produces similar abnormalities in the offspring of both species. The facial abnormalities are relatively unimportant, of course. Much more serious are the abnormalities in the development of the brain. (See Figure 15.12.)

Recent research suggests that alcohol disrupts normal brain development by interfering with a neural adhesion protein—a protein that helps to guide the growth of neurons in the developing brain (Braun, 1996). Prenatal exposure to alcohol even appears to have direct effects on neural plasticity. Sutherland, McDonald, and Savage (1997) found that the offspring of female rats that are given moderate amounts of alcohol during pregnancy showed smaller amounts of long-term potentiation (described in Chapter 13).

A woman need not be an alcoholic to impair the development of her offspring; some investigators believe that fetal alcohol syndrome can be caused by a single alcoholic binge during a critical period of fetal development. Now that we recognize the dangers of this syndrome, pregnant women are advised to abstain from alcohol (and from other drugs not specifically prescribed by their physicians) while their bodies are engaged in the task of sustaining the development of another human being.

Inherited Metabolic Disorders

Several inherited “errors of metabolism” can cause brain damage or impair brain development. Normal functioning of cells requires intricate interactions among countless biochemical systems. As you know, these systems depend on enzymes, which are responsible for constructing or breaking down particular chemical compounds. Enzymes are proteins and therefore are produced by mechanisms involving the chromosomes, which contain the recipes for their synthesis. “Errors of metabolism” refer to genetic abnormalities in which the recipe for a particular enzyme is in error, so the enzyme cannot be synthesized. If the enzyme is a critical one, the results can be very serious.

There are at least a hundred different inherited metabolic disorders that can affect the development of the brain. The most common and best-known is called phenylketonuria (PKU). This disease is caused by an inherited lack of an enzyme that converts phenylalanine (an amino acid) into tyrosine (another amino acid). Excessive

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**F I G U R E 15.12**

A child with fetal alcohol syndrome, along with magnified views of a rat fetus. (a) Fetus whose mother received alcohol during pregnancy. (b) Normal rat fetus.

(Photographs courtesy of Katherine K. Sulik.)
amounts of phenylalanine in the blood interfere with the myelinization of neurons in the central nervous system. Much of the myelinization of the cerebral hemispheres takes place after birth. Thus, when an infant born with PKU receives foods containing phenylalanine, the amino acid accumulates, and the brain fails to develop normally. The result is severe mental retardation, with an average IQ of approximately 20 by six years of age.

Fortunately, PKU can be treated by putting the infant on a low-phenylalanine diet. The diet keeps the blood level of phenylalanine low, and myelinization of the central nervous system takes place normally. Once myelinization is complete, the dietary restraints can be relaxed somewhat, because a high level of phenylalanine no longer threatens brain development. During prenatal development a fetus is protected by its mother’s normal metabolism, which removes the phenylalanine from its circulation. However, if the mother has PKU, she must follow a strict diet during pregnancy, or her infant will be born with brain damage. If she eats a normal diet, rich in phenylalanine, the high blood level of this compound will not damage her brain, but it will damage that of her fetus.

Diagnosing PKU immediately after birth is imperative so that the infant’s brain is never exposed to high levels of phenylalanine. Consequently, many governments have passed laws that mandate a PKU test for all newborn babies. The test is inexpensive and accurate, and it has prevented many cases of mental retardation.

Other genetic errors of metabolism can be treated in similar fashion. For example, untreated pyridoxine dependency results in damage to cerebral white matter, to the thalamus, and to the cerebellum. It is treated by large doses of vitamin B6. Another error of metabolism, galactosemia, is an inability to metabolize galactose, a sugar found in milk. If it is not treated, it, too, causes damage to cerebral white matter and to the cerebellum. The treatment is use of a milk substitute that does not contain galactose. (Galactosemia should not be confused with lactose intolerance, which is caused by an insufficient production of lactase, the digestive enzyme that breaks down lactose. Lactose intolerance leads to digestive disturbance, not brain damage.)

Some other inherited metabolic disorders cannot yet be treated successfully. For example, Tay-Sachs disease, which occurs mainly in children of Eastern European Jewish descent, causes the brain to swell and damage itself against the inside of the skull and against the folds of the dura mater than encase it. The neurological symptoms begin by 4 months of age and include an exaggerated startle response to sounds, listlessness, irritability, spasticity, seizures, dementia, and finally, death.

Tay-Sachs disease is one of several metabolic “storage” disorders. All cells contain sacs of material encased in membrane, called lysosomes (“dissolving bodies”). These sacs constitute the cell’s rubbish-removal system; they contain enzymes that break down waste substances that cells produce in the course of their normal activities. The broken-down waste products are then recycled (used by the cells again) or excreted. Metabolic storage disorders are genetic errors of metabolism in which one or more vital enzymes are missing. Particular kinds of waste products cannot be destroyed by the lysosomes, so they accumulate. The lysosomes get larger and larger, the cells get larger and larger, and eventually the brain begins to swell and become damaged.

Researchers investigating hereditary errors of metabolism hope to prevent or treat these disorders in several ways. Some will be treated like PKU or galactosemia, by avoiding a constituent of the diet that cannot be tolerated. Others, such as pyridoxine dependency, will be treated by administering a substance that the body requires. Still others may be cured some day by the techniques of genetic engineering. Viruses infect cells by inserting their own genetic material into them and thus taking over the cells’ genetic machinery, using it to reproduce themselves. Perhaps one day, researchers will develop special viruses that will “infect” an infant’s cells with genetic information that is needed to produce the enzymes that the cells lack, leaving the rest of the cells’ functions intact. Such viruses have already yielded useful results, such as the development of bacteria that produce human insulin. Some day they might cure human genetic disorders as well.

**Down Syndrome**

Down syndrome is a congenital disorder that results in abnormal development of the brain, producing mental retardation in varying degrees. Congenital does not necessarily mean hereditary; it simply refers to a disorder that is born with. Down syndrome is caused not by the inheritance of a faulty gene but by the possession of an extra twenty-first chromosome. The syndrome is closely associated with the mother’s age; in most cases something goes wrong with some of her ova, resulting in the presence of two (rather than one) twenty-first chromosomes. When fertilization occurs, the addition of the father’s

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**pyridoxine dependency** (peer i dox een) A metabolic disorder in which an infant requires larger-than-normal amounts of pyridoxine (vitamin B6) to avoid neurological symptoms.

**galactosemia** (ga lak tow see mee uh) An inherited metabolic disorder in which galactose (milk sugar) cannot easily be metabolized.

**Tay-Sachs disease** A heritable, fatal, metabolic storage disorder; lack of enzymes in lysosomes causes accumulation of waste produces and swelling of cells of the brain.

**Down syndrome** A disorder caused by the presence of an extra twenty-first chromosome, characterized by moderate to severe mental retardation and often by physical abnormalities.
The twenty-first chromosome makes three, rather than two. The extra chromosome presumably causes biochemical changes that impair normal brain development. The development of amniocentesis, a procedure whereby some fluid is withdrawn from a pregnant woman’s uterus through a hypodermic syringe, has allowed physicians to identify fetal cells with chromosomal abnormalities and thus to determine whether the fetus carries Down syndrome.

Down syndrome, described in 1866 by John Langdon Down, occurs in approximately 1 out of 700 births. An experienced observer can recognize people with this disorder; they have round heads; thick, protruding tongues that tend to keep the mouth open much of the time; stubby hands; short stature; low-set ears; and somewhat slanting eyelids. They are slow to learn to talk, but most do talk by 5 years of age. The brain of a person with Down syndrome is approximately 10 percent lighter than that of a normal person, the convolutions (gyri and sulci) are simpler and smaller, the frontal lobes are small, and the superior temporal gyrus (the location of Wernicke’s area) is thin. After age 30 the brain develops abnormal microscopic structures and begins to degenerate. Because this degeneration resembles that of Alzheimer’s disease, it will be discussed in the next section.

Although the occurrence of any form of mental retardation is a tragedy, people with Down syndrome are often only moderately retarded. Given proper training, many of them can function well with only minimal supervision.

**Interim Summary**

**Disorders of Development**

Developmental disorders can result in brain damage serious enough to cause mental retardation. During pregnancy the fetus is especially sensitive to toxins, such as alcohol or chemicals produced by some viruses. Several inherited metabolic disorders can also impair brain development. For example, phenylketonuria is caused by the lack of an enzyme that converts phenylalanine into tyrosine. Brain damage can be averted by feeding the infant a diet low in phenylalanine, so early diagnosis is essential. Other inherited metabolic disorders include pyridoxine dependency, which can be treated by vitamin B6, and galactosemia, which can be treated with a diet that does not contain milk sugar. Storage disorders, such as Tay-Sachs disease, are caused by the inability of cells to destroy waste products within the lysosomes, which causes the cells to swell and eventually die. So far, these disorders cannot be treated. Down syndrome is produced by the presence of an extra twenty-first chromosome. The brain development of people with Down syndrome is abnormal, and after age 30 their brains develop features similar to those of people with Alzheimer’s disease.

**Degenerative Disorders**

Many disease processes cause degeneration of the cells of the brain. Some of these conditions injure particular kinds of cells, a fact that provides the hope that research will uncover the causes of the damage and find a way to halt it and prevent it from occurring in other people.

**Transmissible Spongiform Encephalopathies**

The outbreak of bovine spongiform encephalopathy (BSE, or “mad cow disease”) in Great Britain in the late 1980s and early 1990s brought a peculiar form of brain disease to public attention. BSE is a transmissible spongiform encephalopathy (TSE)—a contagious brain disease ("encephalopathy") whose degenerative process gives the brain a spongelike (or Swiss cheese-like) appearance. Besides BSE, these diseases include Creutzfeldt-Jakob disease, fatal familial insomnia, and kuru, which affect humans, and scrapie, which primarily affects sheep. Although scrapie cannot be transmitted to humans, BSE can, and it produces a variant of Creutzfeldt-Jakob disease. Although they can have a long incubation period, TSEs are ultimately fatal.

Unlike other transmissible diseases, TSEs are caused not by microorganisms, but by simple proteins, which have been called prions, or “protein infectious agents” (Prusiner, 1982). Prion proteins are found primarily in the membrane of neurons, where they are believed to play a role in synaptic function. They are resistant to proteolytic enzymes—enzymes that are able to destroy proteins by breaking the peptide bonds that hold a protein’s amino acids together. Prion proteins are also resistant to levels of heat that denature normal proteins, which explains why cooking meat from cattle with BSE does not

**transmissible spongiform encephalopathy** A contagious brain disease whose degenerative process gives the brain a spongelike appearance; caused by accumulation of misfolded prion protein.

**prion** (pree on) A protein that can exist in two forms that differ only in their three-dimensional shape; accumulation of misfolded prion protein is responsible for transmissible spongiform encephalopathies.
most cases of this disease are determined largely by their three-dimensional shapes. The only difference between PrPc and PrPSc is the way the protein is folded. Once misfolded PrPSc is introduced into a cell, it causes normal PrPc to become misfolded too, and the process of this transformation ultimately kills them. (See Hetz et al., 2003, for a review.)

A familial form of Creutzfeldt-Jakob disease is transmitted as a dominant trait, caused by a mutation of the PRNP gene located on the short arm of chromosome 20, which codes for the human prion protein gene. However, most cases of this disease are sporadic. That is, they occur in people without a family history of prion protein disease. Prion protein diseases are unique not only because they can be transmitted by means of a simple protein, but also because they can also be genetic or sporadic—and the genetic and sporadic forms can be transmitted to others. The most common form of transmission of Creutzfeldt-Jakob disease in humans is through transplantation of tissues such as dura mater or corneas, harvested from cadavers that were infected with a prion disease. One form of human prion protein disease, kuru, was transmitted through cannibalism: Out of respect to their recently departed relatives, members of a South Pacific tribe ate their brains and sometimes thus contracted the disease. This practice has since been abandoned.

Whatever role normal PrPc plays, it does not seem to be essential for the life of a cell. Bueler et al. (1993) found that mice with a targeted mutation of the prion protein gene showed normal development and behavior, despite the fact that their cells produced absolutely no prion protein. Moreover, they did not develop mouse scrapie when they were inoculated with the misfolded prions that cause this disease. Normal mice inoculated with these prions died within six months.

Some investigators (for example, Bailey, Kandel, and Si, 2004) have suggested that a prionlike mechanism could play a role in the establishment and maintenance of long-term memories. Long-term memories can last for decades, and prion proteins, which are resistant to the destructive effects of enzymes, might maintain synaptic changes for long periods of time. Criado et al. (2005) found that mice with a targeted mutation against the PRNP gene showed deficits in a spatial learning task and in establishment of long-term potentiation in the dentate gyrus. In addition, Papassotirioupolos et al. (2005) found that people with a particular allele of the prion protein gene remembered 17 percent more information 24 hours after a word list–learning task than a different allele. (Both alleles are considered normal and are not associated with a prion protein disease.)

Mallucci et al. (2003) prepared a genetically modified mouse strain whose neurons produced an enzyme at 12 weeks of age that destroyed normal prion protein. When the animals were a few weeks of age, the experimenters infected them with misfolded mouse scrapie prions. Soon thereafter, the animals began to develop spongy holes in their brains, indicating that they were infected with mouse scrapie. Then, at 12 weeks, the enzyme became active and started destroying normal PrPc. Although analysis showed that glial cells in the brain still contained misfolded PrPSc, the disease process stopped. Neurons stopped making normal PrPc, which could no longer be converted into PrPSc, so the mice went on to live normal lives. The disease process continued to progress in mice without the special enzyme, and these animals soon died. The authors concluded that the process of conversion of PrPc to PrPSc is what kills cells.

How might misfolded prion protein kill neurons? As we will see later in this chapter, the brains of people with several other degenerative diseases, including Parkinson’s disease, Alzheimer’s disease, amyotrophic lateral sclerosis, and Huntington’s disease contain aggregations of misfolded proteins (Soto, 2003). As we saw in Chapter 3, cells contain the means by which they can commit suicide—a process known as apoptosis. Apoptosis can be triggered either externally, by a chemical signal telling the cell it is no longer needed (for example, during development), or internally, by evidence that biochemical processes in the cell have become disrupted so that the cell is no longer functioning properly. Perhaps the accumulation of misfolded, abnormal proteins provides such a signal. Apoptosis involves production of “killer enzymes” called caspases. Mallucci et al. (2003) suggest that inactivation of caspase-12, the enzyme that appears to be responsible for the death of neurons infected with PrPSc, may provide a treatment that could arrest the progress of transmissible spongiform encephalopathies. Let’s hope they are right.

**Parkinson’s Disease**

One of the most common degenerative neurological disorders, Parkinson’s disease, is caused by degeneration of the nigrostriatal system—the dopamine-secreting neurons of the substantia nigra that send axons to the basal ganglia. It is estimated that 1 in 10,000 people in the United States have Parkinson’s disease, and the number of cases is expected to increase as the population ages.

Spinal cord neurons that project to the basal ganglia release the neurotransmitter dopamine, which acts on postsynaptic receptors in the basal ganglia. Dysfunction of the basal ganglia affects the motor system, leading to a variety of symptoms including tremors, rigidity, and bradykinesia (slow movements). The hallmark of Parkinson’s disease is a decrease in dopamine levels in the substantia nigra, which is responsible for the loss of dopaminergic neurons.

The precise mechanisms that underlie the neurodegeneration in Parkinson’s disease are not fully understood. Risk factors include age, genetic predisposition, and exposure to certain environmental toxins. Genetic factors, such as mutations in the parkin gene, can cause familial cases of Parkinson’s disease. Environmental factors, including exposure to pesticides and occupational chemicals, may also contribute to the development of the disease.

Currently, there is no cure for Parkinson’s disease, but several treatments are available to manage symptoms and improve quality of life. Medications, such as levodopa (L-dopa), are commonly used to increase dopamine levels in the brain. Other treatments include deep brain stimulation, which involves surgical implantation of a small device that delivers electrical impulses to specific areas of the brain to modulate abnormal neural activity. Physical therapy and exercise are also important for maintaining mobility and delaying the progression of symptoms.

Parkinson’s disease is a chronic, progressive condition, and the course of the disease can vary widely from person to person. Early detection and treatment can help manage symptoms effectively, allowing patients to maintain their independence and quality of life for as long as possible.
Parkinson’s disease is seen in approximately 1 percent of people over 65 years of age. The primary symptoms of Parkinson’s disease are muscular rigidity, slowness of movement, a resting tremor, and postural instability. For example, once a person with Parkinson’s disease is seated, he or she finds it difficult to rise. Once the person begins walking, he or she has difficulty stopping. Thus, a person with Parkinson’s disease cannot easily pace back and forth across a room. Reaching for an object can be accurate, but the movement usually begins only after a considerable delay. Writing is slow and labored, and as it progresses, the letters get smaller and smaller. Postural movements are impaired. A normal person who is bumped while standing will quickly move to restore balance—for example, by taking a step in the direction of the impending fall or by reaching out with the arms to grasp onto a piece of furniture. However, a person with Parkinson’s disease fails to do so and simply falls. A person with this disorder is even unlikely to put out his or her arms to break the fall.

Parkinson’s disease also produces a resting tremor—vibratory movements of the arms and hands that diminish somewhat when the individual makes purposeful movements. The tremor is accompanied by rigidity; the joints appear stiff. However, the tremor and rigidity are not the cause of the slow movements. In fact, some patients with Parkinson’s disease show extreme slowness of movements but little or no tremor.

Examination of the brains of patients who had Parkinson’s disease shows, of course, the near-disappearance of nigrostriatal dopaminergic neurons. Many surviving dopaminergic neurons show Lewy bodies, abnormal circular structures found with the cytoplasm. Lewy bodies have a dense protein core, surrounded by a halo of radiating fibers (Forno, 1996). (See Figure 15.14.) Although most cases of Parkinson’s disease do not appear to have genetic origins, researchers have discovered that the mutation of a particular gene located on chromosome 4 will produce this disorder (Polymeropoulos et al., 1996). This gene produces a protein known as α-synuclein, which is normally found in the presynaptic terminals and is thought to be involved in synaptic transmission in dopaminergic neurons (Moore et al., 2005). The mutation produces what is known as a toxic gain of function because it produces a protein that results in effects that are toxic to the cell. Mutations that cause toxic gain of function are normally dominant because the toxic substance is produced whether one or both members of the pair of chromosomes contains the mutated gene. Abnormal

**Lewy body** Abnormal circular structures with a dense core consisting of α-synuclein protein; found in the cytoplasm of nigrostriatal neurons in people with Parkinson’s disease.

**α-synuclein** A protein normally found in the presynaptic membrane, where it is apparently involved in synaptic plasticity. Abnormal accumulations are apparently the cause of neural degeneration in Parkinson’s disease.

**toxic gain of function** Said of a genetic disorder caused by a dominant mutation that involves a faulty gene that produces a protein with toxic effects.
α-synuclein becomes misfolded and forms aggregations, especially in dopaminergic neurons (Goedert, 2001). The dense core of Lewy bodies consists primarily of these aggregations, along with neurofilaments and synaptic vesicle proteins.

Another hereditary form of Parkinson’s disease is caused by mutation of a gene on chromosome 6 that produces a gene that has been named parkin (Kitada et al., 1998). This mutation causes a loss of function, which makes it a recessive disorder. If a person carries only a mutated parkin gene on only one chromosome, the normal allele on the other chromosome can produce a sufficient amount of normal parkin for normal cellular functioning. Normal parkin plays a role in ferrying defective or misfolded proteins to the proteasomes—organelles responsible for destroying these proteins (Moore et al., 2005). This mutation permits high levels of defective parkin in the action of proteasomes. Parkin assists in the tagging of abnormal or misfolded proteins with numerous molecules of ubiquitin, a small, compact globular protein. Ubiquitination (as this process is called) targets the abnormal proteins for destruction by the proteasomes, which break them down into their constituent amino acids. Defective parkin fails to ubiquitinate abnormal proteins, and they accumulate in the cell, eventually killing it. For some reason, dopaminergic neurons are especially sensitive to this accumulation. (See Figure 15.15.)

Several other mutations have been discovered that produce Parkinson’s disease. UCH-L1 is involved in the ubiquitin-proteasome system. DJ-1 plays a role in stabilizing messenger RNA and modulating its expression, and PINK1 is somehow involved with mitochondria (Vila and Przedborski, 2004). In addition, an epidemiological study found the existence of a mutation in mitochondrial DNA that caused Parkinson’s disease, which was transmitted from mother to child (Swerdlow et al., 1998). (Sperm cells pass no mitochondrial DNA into a fertilized egg; all mitochondrial DNA is inherited from the mother.)

The overwhelming majority of the cases of this Parkinson’s disease (approximately 95 percent) are sporadic. That is, they occur in people without a family history of Parkinson’s disease. What, then, triggers the accumulation of α-synuclein and the destruction of dopaminergic neurons? Research suggests that Parkinson’s disease may be caused by toxins present in the environment, by faulty metabolism, or by unrecognized infectious disorders. For example, the insecticides rotenone and paraquat can also cause Parkinson’s disease—and, presumably, so can other unidentified toxins. All of these chemicals inhibit mitochondrial functions, which leads to the aggregation of misfolded α-synuclein, especially in dopaminergic neurons. These accumulated proteins eventually kill the cells (Dawson and Dawson, 2003).

As we saw in Chapter 4, the standard treatment for Parkinson’s disease is L-DOPA, the precursor of dopamine. An increased level of L-DOPA in the brain causes a patient’s remaining dopaminergic neurons to produce and secrete more dopamine and, for a time, alleviates the symptoms of the disease. But this compensation does not work indefinitely; eventually, the number of nigrostriatal dopaminergic neurons declines to such a low level that the symptoms become worse. In addition, high levels of L-DOPA produce side effects by acting on dopaminergic systems other than the nigrostriatal system. Some patients—especially those whose symptoms began when they were relatively young—become bedridden, scarcely able to move.

Another drug, deprenyl, is often given to patients with Parkinson’s disease, usually in conjunction with L-DOPA. As we saw in Chapter 4, several people acquired the symptoms of Parkinson’s disease after taking an illicit drug contaminated with MPTP. Subsequent studies with laboratory animals revealed that the toxic effects of MPTP could be prevented by administration of deprenyl, a drug that inhibits the activity of the enzyme MAO-B. The original rationale for administering deprenyl to patients with Parkinson’s disease was that it might prevent unknown toxins from producing further damage.

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**FIGURE 15.14**

A photomicrograph of the substantia nigra of a patient with Parkinson’s disease. A Lewy body is indicated by the arrow.

(Photograph courtesy of Dr. Don Born, University of Washington.)

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**parkin** A protein that plays a role in ferrying defective or misfolded proteins to the proteasomes; mutated parkin is a cause of familial Parkinson’s disease.

**loss of function** Said of a genetic disorder caused by a recessive gene that fails to produce a protein that is necessary for good health.

**proteasome** An organelle responsible for destroying defective or degraded proteins within the cell.

**ubiquitin** A protein that attaches itself to faulty or misfolded proteins and thus targets them for destruction by proteasomes.
to dopaminergic neurons. In addition, Kumar and Andersen (2004) note that there is an age-related increase in MAO-B activity that might increase the level of oxidative stress in dopaminergic neurons. The intracellular breakdown of dopamine by MAO-B causes the formation of hydrogen peroxide, which can damage cells. Thus, a beneficial effect of MAO-B inhibitors might be to decrease normal, age-related oxidative stress. Ironically, cigarette smokers have a lower incidence of Parkinson’s disease, perhaps because compounds in tobacco inhibit MAO-B activity (Fowler et al., 2003). Of course, the increased incidence of lung cancer, emphysema, and other smoking-related diseases far outweighs any potential benefits effects on the incidence of Parkinson’s disease.

What are the effects of the loss of dopaminergic neurons on normal brain functioning? Functional imaging studies have shown that akinesia (difficulty in initiating movements) was associated with decreased activation of the supplementary motor area and that tremors are associated with abnormalities of a neural system involving the pons, midbrain, cerebellum, and thalamus (Grafton, 2004). A functional imaging study by Buhmann et al. (2003) studied drug-naïve patients with akinetic hemiparkinsonism—difficulty in initiating movements on one side of the body. (Parkinson’s disease often affects one side of the body more than the other, especially early in the course of the disease.) The investigators found decreased activation of the supplementary motor area and the primary motor cortex contralateral to the affected side while the patients performed a task that required them to touch a finger to their thumb. When the patients were given a dose of L-DOPA, the activation of these regions increased, and their motor performance improved. In fact, the improvements in motor performance were positively correlated with the increased brain activation.

Neurosurgeons have been developing three stereotaxic procedures designed to alleviate the symptoms of Parkinson’s disease that no longer respond to treatment with L-DOPA. The first one, transplantation of fetal tissue, attempts to reestablish the secretion of dopamine in the neostriatum. The tissue is obtained from the substantia nigra of aborted human fetuses and implanted into the caudate nucleus and putamen by means of stereotaxically guided needles. As we saw in Chapter 5, PET scans have shown that dopaminergic fetal cells are able to grow in their new host and secrete dopamine, reducing the patient’s symptoms—at least, initially. In a study of 32 patients with fetal tissue transplants, Freed (2002) found that those whose symptoms had previously responded to L-DOPA were most likely to benefit from the surgery. Presumably, these patients had a sufficient number of basal ganglia neurons with receptors that could be stimulated by the dopamine secreted by either the medication or the transplanted tissue. Unfortunately, many transplant patients later developed severe, persistent dyskinesias—troublesome, and often painful, involuntary movements. As a result, fetal transplants are no longer recommended (Olanow et al., 2003).

One potential source of dopaminergic neurons could come from cultures of stem cells—undifferentiated cells that have the ability, if appropriately stimulated, to develop into a variety of types of cells, including dopaminergic neurons (Snyder and Olanow, 2005). A significant advantage of human stem cells is that large numbers of cells could be transplanted, thus increasing the numbers of surviving cells in the patients’ brains.

Another procedure has a long history, but only recently have technological developments in imaging methods and electrophysiological techniques led to an increase in its popularity. The principal output of the
basal ganglia comes from the internal division of the globus pallidus (GPi). (The caudate nucleus, putamen, and globus pallidus are the three major components of the basal ganglia.) This output, which is directed through the thalamus to the motor cortex, is inhibitory. Furthermore, a decrease in the activity of the dopaminergic input to the caudate nucleus and putamen causes an increase in the activity of the GPi. Thus, damage to the GPi might be expected to relieve the symptoms of Parkinson’s disease. (See Figure 15.16.)

In the 1950s, Leksell and his colleagues performed pallidotomies (surgical destruction of the internal division of the globus pallidus) in patients with severe Parkinson’s disease (Svennilson et al., 1960; Laitinen, Bergenheim, and Hariz, 1992). The surgery often reduced the rigidity and enhanced the patient’s ability to move. Unfortunately, the surgery occasionally made the patient’s symptoms worse and sometimes resulted in partial blindness. (The optic tract is located next to the GPi.)

With the development of l-DOPA therapy in the late 1960s, pallidotomies were abandoned. However, it eventually became evident that l-DOPA worked for a limited time and that the symptoms of Parkinson’s disease would eventually return. For that reason, in the 1990s,

**FIGURE 15.16**
The major connections of the basal ganglia and associated structures. Excitatory connections are shown as black lines; inhibitory connections are shown as red lines. Many connections, such as the inputs to the substantia nigra, are omitted for clarity. Two regions that have been targets of stereotaxic surgery for Parkinson’s disease—the internal division of the globus pallidus and the subthalamus—are outlined in gray. Damage to these regions reduces inhibitory input to the thalamus and facilitates movement.

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**internal division of the globus pallidus (GPi)** A division of the globus pallidus that provides inhibitory input to the motor cortex via the thalamus; sometimes stereotactically lesioned to treat the symptoms of Parkinson’s disease.
neurosurgeons again began experimenting with pallidotomies, first with laboratory animals and then with humans (Graybiel, 1996; Lai et al., 2000). This time, they used MRI scans to find the location of the GP, and then inserted an electrode into the target region. They could then pass low-intensity, high-frequency stimulation through the electrode, thus temporarily disabling the region around its tip. If the patient’s rigidity disappeared (obviously, the patient is awake during the surgery), then the electrode was in the right place. To make the lesion, the surgeon passed radiofrequency current of sufficient strength to heat and destroy the brain tissue. The results of this procedure have been so promising that several neurological teams have begun promoting its use in the treatment of relatively young patients whose symptoms no longer respond to L-DOPA. PET studies have found that after pallidotomy the metabolic activity in the pre-motor and supplementary motor areas of the frontal lobes, normally depressed in patients with Parkinson’s disease, returns to normal levels (Grafton et al., 1995), a result indicating that lesions of the GP, do indeed release the motor cortex from inhibition.

Neurosurgeons have also targeted the subthalamus in patients with advanced Parkinson’s disease. As Figure 15.16 shows, the subthalamus has an excitatory effect on the GP; thus, damage to the subthalamus decreases the activity of this region and removes some of the inhibition on motor output. (See Figure 15.16.) Normally, damage to the subthalamus causes involuntary jerking and twitching movements. However, in people with Parkinson’s disease, damage to this region brings motor activity, which is normally depressed, back to normal (Guridi and Obeso, 2001).

The third stereotaxic procedure aimed at relieving the symptoms of Parkinson’s disease involves implanting electrodes in the subthalamic nucleus and attaching a device that permits the patient to electrically stimulate the brain through the electrodes. (See Figure 15.17.) According to some studies, deep brain stimulation is as effective as brain lesions in suppressing tremors and has fewer adverse side effects (Simuni et al., 2002; Speelman et al., 2002). In addition, a 3-year follow-up study found no evidence of cognitive deterioration of patients who received implants for deep-brain stimulation (Funkiewiez et al., 2004). The fact that either lesions or stimulation alleviates tremors suggests that the stimulation has an inhibitory effect on subthalamic neurons, but this hypothesis has not yet been confirmed.

**Huntington’s Disease**

Another basal ganglia disease, Huntington’s disease, is caused by degeneration of the caudate nucleus and putamen. Whereas Parkinson’s disease causes a poverty of movements, Huntington’s disease causes uncontrollable ones, especially jerky limb movements. The movements of Huntington’s disease look like fragments of purposeful movements but occur involuntarily. This disease is progressive, includes cognitive and emotional changes, and eventually causes death, usually within 10–15 years after the symptoms begin.

The symptoms of Huntington’s disease usually begin in the person’s thirties and forties but can sometimes begin in the early twenties. The first signs of neural degeneration occur in the putamen, in a specific group of inhibitory neurons—GABAergic medium spiny neurons. Damage to these neurons removes some inhibitory control exerted on the premotor and supplementary motor areas of the frontal cortex. Loss of this control leads to...
involuntary movements. As the disease progresses, neural degeneration is seen in many other regions of the brain, including the cerebral cortex.

Huntington’s disease is a hereditary disorder, caused by a dominant gene on chromosome 4. In fact, the gene has been located, and its defect has been identified as a repeated sequence of bases that code for the amino acid glutamine (Collaborative Research Group, 1993). This repeated sequence causes the gene product—a protein called huntingtin (htt)—to contain an elongated stretch of glutamine. Abnormal htt becomes misfolded and forms aggregations that accumulate in the nucleus. Longer stretches of glutamine are associated with patients whose symptoms began at a younger age, a finding that indicates that this abnormal portion of the huntingtin molecule is responsible for the disease. These facts suggest that the mutation causes the disease through a toxic gain of function—that abnormal htt causes harm. In fact, the cause of death of neurons in Huntington’s disease is apoptosis (cell “suicide”). Li et al. (2000) found that HD mice lived longer if they were given a caspase inhibitor, which suppresses apoptosis. Abnormal htt may trigger apoptosis by impairing the function of the ubiquitin-protease system, which activates caspase, one of the enzymes involved in apoptosis (Hague, Klaffke, and Bandmann, 2005).

Normal htt is found in cells throughout the body, but it occurs in especially high levels in neurons and in cells of the testes. The protein plays a critical role in development: O’Kusky et al. (1999) found that mice with a knockout of the gene that codes for huntingtin die before embryonic day 8.5. Heterozygous knockout mice, with one good htt gene, survive to adulthood, but because of the decreased level of htt, they show excessive motor activity and degeneration of neurons in the basal ganglia and subthalamic nuclei. These findings suggest that the mutation responsible for Huntington’s disease may also cause brain damage through a loss of function. One of the most important functions of normal htt in adulthood appears to be facilitation of the production and transport of brain-derived neurotrophic factor (BDNF). BDNF is a chemical that is necessary for survival of neurons in the caudate nucleus and putamen. This chemical is produced in the cerebral cortex and transported through axons to the basal ganglia. Abnormal htt interferes with BDNF activity in the caudate nucleus and putamen in two ways. First, its presence inhibits the expression of the BDNF gene (Zuccato et al., 2001, 2003). Second, it interferes with the transport of BDNF from the cerebral cortex to the basal ganglia (Gauthier et al., 2004).

Researchers have debated the role played by the accumulations of misfolded htt in the nucleus (known as inclusion bodies) in development of the disease. These inclusions could cause neural degeneration, they could have a protective role, or they could play no role at all.

A study by Arrasate et al. (2004) strongly suggests that inclusion bodies actually protect neurons. The investigators prepared tissue cultures from rat striatal neurons that they infected with genes that expressed fragments of abnormal htt. Some of the neurons that produced the mutant htt formed inclusion bodies; others did not. Arrasate and her colleagues used a robotic microscope to see what happened to the cells over a period of almost 10 days. They found that the inclusion bodies appeared to have a protective function. Neurons that contained inclusion bodies had lower levels of mutant htt elsewhere in the cell, and these neurons lived longer than those without these accumulations. (See Figure 15.18.)

At present there is no treatment for the disorder, but researchers hope that the recent progress made in understanding the origins of this disorder holds promise for the development of a cure.

**FIGURE 15.18**

A photomicrograph of two neurons that have been infected with genes that express fragments of abnormal huntingtin. The lower one shows an inclusion body (orange), and the upper one does not. Arresate et al. (2004) found that neurons with inclusion bodies survived longer than those without inclusion bodies. Blue ovals are the nuclei of uninfected neurons.

(Photograph courtesy of Steven Finkbeiner, Gladstone Institute of Neurological Disease and the University of California, San Francisco.)

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**huntingtin (htt)** A protein that may serve to facilitate the production and transport of brain-derived neurotrophic factor. Abnormal huntingtin is the cause of Huntington’s disease.
Alzheimer’s Disease

Several neurological disorders result in dementia, a deterioration of intellectual abilities resulting from an organic brain disorder. A common form of dementia is called Alzheimer’s disease, which occurs in approximately 10 percent of the population above the age of sixty-five and almost 50 percent of people older than eighty-five years. It is characterized by progressive loss of memory and other mental functions. At first, people may have difficulty remembering appointments and sometimes fail to think of words or other people’s names. As time passes, they show increasing confusion, and increasing difficulty with tasks such as balancing a checkbook. The memory deficit most critically involves recent events, and thus it resembles the anterograde amnesia of Korsakoff’s syndrome. If people with Alzheimer’s disease venture outside alone, they are likely to get lost. They eventually become bedridden, then become completely helpless, and finally succumb (Terry and Davies, 1980).

Alzheimer’s disease produces severe degeneration of the hippocampus, entorhinal cortex, neocortex (especially the association cortex of the frontal and temporal lobes), nucleus basalis, locus coeruleus, and raphe nuclei. Figure 15.19 shows photographs of the brain of a patient with Alzheimer’s disease and of a normal brain. You can see how much wider the sulci are in the patient’s brain, especially in the frontal and temporal lobes, indicating substantial loss of cortical tissue. (See Figure 15.19.)

Earlier, I mentioned that the brains of patients with Down syndrome usually develop abnormal structures that are also seen in patients with Alzheimer’s disease: amyloid plaques and neurofibrillary tangles. Amyloid plaques are extracellular deposits that consist of a dense core of a protein known as β-amyloid, surrounded by degenerating axons and dendrites, along with activated microglia and reactive astrocytes, cells that are involved in destruction of damaged cells. Eventually, the phagocytic glial cells destroy the degenerating axons and dendrites, leaving only a core of β-amyloid (usually referred to as Aβ).

Neurofibrillary tangles consist of dying neurons that contain intracellular accumulations of twisted filaments of hyperphosphorylated tau protein. Normal tau protein serves as a component of microtubules, which provide the cells’ transport mechanism. During the

dementia (də meⁿ she) A loss of cognitive abilities such as memory, perception, verbal ability, and judgment; common causes are multiple strokes and Alzheimer’s disease.
Alzheimer’s disease A degenerative brain disorder of unknown origin; causes progressive memory loss, motor deficits, and eventual death.
amyloid plaque (ə'māloid) An extracellular deposit containing a dense core of β-amyloid protein surrounded by degenerating axons and dendrites and activated microglia and reactive astrocytes.
β-amyloid (Aβ) A protein found in excessive amounts in the brains of patients with Alzheimer’s disease.
neurofibrillary tangle (ni'ərofībril'arē ĭl'ar ĭ) A dying neuron containing intracellular accumulations of β-amyloid and twisted protein filaments that formerly served as the cell’s internal skeleton.
tau protein A protein that normally serves as a component of microtubules, which provide the cell’s transport mechanism.

progression of Alzheimer’s disease, excessive amounts of phosphate ions become attached to strands of tau protein, thus changing its molecular structure. Abnormal filaments are seen in the soma and proximal dendrites of pyramidal cells in the cerebral cortex, which disrupt transport of substances within the cell, and the cell dies, leaving behind a tangle of protein filaments. (See Figure 15.20.)

Formation of amyloid plaques is caused by the production of a defective form of A\(\beta\). The production of A\(\beta\) takes several steps. First, a gene encodes the production of the \(\beta\)-amyloid precursor protein (APP), a chain of approximately 700 amino acids. APP is then cut apart in two places by enzymes known as secretases to produce A\(\beta\). The first, \(\beta\)-secretase, cuts the “tail” off of an APP molecule. The second, \(\gamma\)-secretase (gamma-secretase), cuts the “head” off. The result is a molecule of A\(\beta\) that contains either 40 or 42 amino acids. (See Figure 15.21.)

The location of the second cut of the APP molecule by \(\gamma\)-secretase determines which form is produced. In normal brains, 90–95 percent of the A\(\beta\) molecules are of the short form; the other 5–10 percent are of the long form. In patients with Alzheimer’s disease the proportion of long A\(\beta\) rises to as much as 40 percent of the total. High concentrations of the long form have a tendency to fold themselves improperly and form aggregations, which have toxic effects on the cell. (As we saw earlier in this chapter, abnormally folded prions and \(\alpha\)-synuclein proteins form aggregations that cause brain degeneration.) Small amounts of long A\(\beta\) can easily be cleared from the cell. The molecules are given a ubiquitin tag that marks them for destruction, and they are transported to the proteasomes, where they are rendered harmless. However, this system cannot keep up with abnormally high levels of production of long A\(\beta\).

Figure 15.22 shows the abnormal accumulation of A\(\beta\) in the brain of a person with Alzheimer’s disease. Klunk and his colleagues (Klunk et al., 2003; Mathis et al., 2005) developed a chemical that binds with A\(\beta\) and readily crosses the blood–brain barrier. They gave the patient and a healthy control subject an injection of a radioactive form of this chemical and examined their brains with a PET scanner. You can see the accumulation of the protein in the patient’s cerebral cortex. (See Figure 15.22.) The ability to measure the levels of A\(\beta\) in the brains of Alzheimer’s patients will enable researchers to evaluate the effectiveness of potential treatments for the disease. And if such a treatment is devised, the ability to identify the accumulation of A\(\beta\) early in the development of the disease will make it possible to begin a patient’s treatment before significant degeneration—and the accompanying decline in cognitive abilities—has occurred.

**β amyloid precursor protein (APP)** A protein produced and secreted by cells that serves as the precursor for β-amyloid protein.

**secretase (see cre tays)** A class of enzymes that cut the β-amyloid precursor protein into smaller fragments, including β-amyloid.
Research has shown that at least some forms of Alzheimer’s disease appear to run in families and thus appear to be hereditary. Because the brains of people with Down syndrome (caused by an extra twenty-first chromosome) also contain deposits of Aβ, some investigators hypothesized that the twenty-first chromosome may be involved in the production of this protein. In fact, St. George-Hyslop et al. (1987) found that chromosome 21 does contain the gene that produces APP.

Since the discovery of the APP gene, several studies have found specific mutations of this gene that produce familial Alzheimer’s disease (Martinez et al., 1993; Farlow et al., 1994). In addition, other studies have found numerous mutations of two presenilin genes, found on chromosomes 1 and 14, that also produce Alzheimer’s disease. Abnormal APP and presenilin genes all cause the defective long form of Aβ to be produced (Hardy, 1997). The two presenilin proteins, PS1 and PS2, appear to be subunits of γ-secretase, which is not a simple enzyme but consists of a large multiprotein complex (De Strooper, 2003).

Yet another genetic cause of Alzheimer’s disease is a mutation in the gene for apolipoprotein E (ApoE), a glycoprotein that transports cholesterol in the blood and also plays a role in cellular repair. One allele of the ApoE gene, known as E4, increases the risk of late-onset Alzheimer’s disease, apparently by interfering with the removal of the long form of Aβ from the extracellular space in the brain (Roses, 1997; Price and Sisodia, 1998; Mahley and Rall, 2000). The ApoE2 allele may actually protect people from developing Alzheimer’s disease (Wilhelmus et al., 2005). Traumatic brain injury is also a serious risk factor for Alzheimer’s disease. For example, examination of the brains of people who have sustained closed head injuries (including those that occur during prize fights) often reveals a widespread distribution of amyloid plaques. Risk of Alzheimer’s disease following traumatic brain injury is especially high in people who possess the ApoE4 allele (Lesné et al., 2005; Luukinen et al., 2005).

As we saw earlier, the brains of Alzheimer’s patients contain abnormal forms of two types of proteins: Aβ and tau. It appears that excessive amounts of abnormal Aβ, but not tau protein, are responsible for the disease. Mutations in the Aβ precursor, APP, produce both forms of abnormal proteins and cause the development of both amyloid plaques and neurofibrillary tangles. However, mutations in the gene for tau protein (found on chromosome 17) produce only neurofibrillary tangles. The result of these mutations is a disorder known as frontotemporal dementia, which causes degeneration of the frontal and temporal cortex along with the symptoms of Parkinson’s disease (Goate, 1998; Goedert and Spillantini, 2000).

It appears that the presence of excessive amounts of Aβ in the cytoplasm of cells, not the formation of amyloid plaques themselves, is the cause of neural degeneration (Bossy-Wetzel, Schwarzenbacher, and Lipton, 2004). Aβ oligomers (aggregations of several Aβ molecules) activate microglia, causing an inflammatory response that triggers the release of toxic cytokines—chemicals produced by the immune system that normally destroy infected cells. Aβ oligomers also trigger an excessive release of glutamate by glial cells, which causes excitotoxicity because of excessive inflow of calcium ions through neural NMDA receptors. They also cause synaptic dysfunction and suppress the formation of long-term potentiation, perhaps because of interference of axonal and dendritic transport.

A study by Buckner et al. (2005) suggests that increases in Aβ—and subsequent degeneration—are first seen in regions of the brain that have the highest default activity—activity that occurs when a person is resting and not working on a task or solving a problem. Figure 15.23 shows lateral and medial views of a human cerebrum, showing regions of high default activity, deposition of

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**presenilin** (pres sen ill in) A protein produced by a faulty gene that causes β-amyloid precursor protein to be converted to the abnormal short form; may be a cause of Alzheimer’s disease.

**apolipoprotein E (ApoE)** (ay po ly op proh teen) A glycoprotein that transports cholesterol in the blood and plays a role in cellular repair; presence of the E4 allele of the apoE gene increases the risk of late-onset Alzheimer’s disease.
Aβ, disruption of metabolism, and cortical atrophy. (See Figure 15.23.)

Although the studies I have cited indicate that genetically triggered production of abnormal Aβ plays an important role in the development of Alzheimer’s disease, the fact is that most forms of Alzheimer’s disease are sporadic, not hereditary. So far, the strongest known nongenetic risk factor for Alzheimer’s disease (other than age) is traumatic brain injury. Another factor, level of education, has also been shown to play an important role. The Religious Orders Study, supported by the U.S. National Institute on Aging, measures the cognitive performance of older Catholic clergy (priests, nuns, and monks) and examines their brains when they die. A report by Bennett et al. (2003) found a positive relation between increased number of years of formal education and cognitive performance, even in people whose brains contained significant numbers of amyloid plaques. For example, people who had received some postgraduate education had significantly higher cognitive test scores than people with the same number of amyloid plaques but less formal education. Thus, formal education appears to enable a person to maintain a higher level of cognitive performance even in the face of brain degeneration. Ninety percent of the people who are participating in the study received some college education. It is possible that if people with much less formal education were studied, an even stronger relationship between education and resistance to dementia would be seen. Of course, it is possible that variables such as individual differences in cognitive ability affect the likelihood that a person will pursue advanced studies, and these differences, by themselves, could play an important role. In any case, engaging in vigorous intellectual activity (and adopting a lifestyle that promotes good general health) is probably the most important thing a person can do to stave off the development of dementia.

Acting on observations that people who had been treated with anti-inflammatory drugs (for diseases such as rheumatoid arthritis or leprosy) seemed to have a particularly low rate of Alzheimer’s disease, Rogers et al. (1993) administered indomethacin, a nonsteroid anti-inflammatory drug (NSAID) or a placebo to 44 patients with mild to moderate symptoms of Alzheimer’s disease. They found that the cognitive performance of the drug-treated patients improved by 1.3 percent over the 6-month period, while that of the placebo patients declined by 8.4 percent. As Rogers noted, “We lost about 20 percent of our placebo patients because they went down hill behaviorally, so much that they wouldn’t take medicine or sit for the test anymore. . . . This didn’t happen with the indomethacin patients” (Schnabel, 1993, p. 1719). As you might expect, these findings have stimulated further research, and drug companies are trying to develop even more effective anti-inflammatory drugs. Several studies (for example, Sastre et al., 2003; Weggen et al., 2003) suggest that NSAIDs reduce the production of Aβ by modulating the activity of secretases. Another possibility is that they reduce the inflammatory activity of microglia (Klegeris and McGeer, 2005).

Currently, the only approved pharmacological treatments for Alzheimer’s disease are acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and an NMDA receptor antagonist (memantine). Because acetylcholinergic neurons are among the first to be damaged in Alzheimer’s disease and because these neurons play a role in cortical activation and memory, drugs that inhibit the destruction of ACh and hence enhance its activity have been found to provide a modest increase in cognitive activity of patients with this disease. However, these drugs have no effect on the process of neuronal degeneration and do not prolong patients’ survival. Memantine, a noncompetitive NMDA receptor blocker, appears to produce a slight improvement in symptoms of dementia by retarding excitotoxic destruction of acetylcholinergic neurons caused by the entry of excessive amounts of calcium (Rogawski and Wenk, 2003).

Perhaps the most promising approaches to the prevention of Alzheimer’s disease come from recent
research with AD mice—a strain of genetically modified mice that contain a mutant human gene for APP that leads to the development of Alzheimer’s disease. Schenk et al. (1999) and Bard et al. (2000) attempted to sensitize the immune system against Aβ. They injected AD mice with a vaccine that, they hoped, would stimulate the immune system to destroy Aβ. The treatment worked: The vaccine suppressed the development of amyloid plaques in the brains of mice that received the vaccine from an early age and halted or even reversed the development of plaques in mice that received the vaccine later in life. Using a different approach, Dovey et al. (2001) developed a drug that inhibits γ-secretase and found that this drug reduced the levels of Aβ in the brains of AD mice. However, Saura et al. (2004) found that a targeted mutation against the genes responsible for the γ-secretase complex resulted in neural degeneration, which suggests that γ-secretase plays an important role in normal cellular function.

A clinical trial with Alzheimer’s patients attempted to destroy Aβ by sensitizing the patient’s immune system to the protein (Monsonego and Weiner, 2003). In a double-blind study, thirty patients with mild-to-moderate Alzheimer’s disease were given injections of a portion of the Aβ protein. Twenty of these patients generated antibodies against Aβ, which slowed the course of the disease, presumably because their immune systems began destroying Aβ in their brain and reducing the neural destruction caused by the accumulation of this protein. Hock et al. (2003) compared the cognitive abilities of the patients who generated Aβ antibodies to those who did not. As Figure 15.24 shows, antibody production significantly reduced cognitive decline. (See Figure 15.24.)

One of the patients whose immune system generated antibodies against Aβ died of a pulmonary embolism (a blood clot in a blood vessel serving the lungs). Nicoll et al. (2003) examined this patient’s brain and found evidence that the immune system had removed Aβ from many regions of the cerebral cortex. Unfortunately, the injection of the Aβ antigen caused an inflammatory reaction in the brains of 5 percent of the patients, so the clinical trial was terminated. Monsonego and Weiner (2003) suggest two possible solutions to this problem: preparation of a vaccine using a different portion of the Aβ protein or attempting to establish a passive immunity by administering antibodies developed in tissue cultures. Efforts to produce a better vaccine are currently underway. In addition, Hartman et al. (2005) found that passive immunization of AD mice with an anti-Aβ antibody decreased the formation of amyloid plaques and reduced the learning deficit and decline in hippocampal long-term potentiation that normally occurs in these animals. (See Figure 15.25.) Whether passive immunization could retard the progression of Alzheimer’s disease in humans without causing an inflammatory reaction is still an unanswered question. In any event, all of us who look forward to growing old and retaining our cognitive abilities should hope that one of these approaches is successful.

**Amyotrophic Lateral Sclerosis**

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder that attacks spinal cord and cranial nerve motor neurons (Bruijn, Miller, and Cleveland (2004). The incidence of this disease is approximately 5 in 100,000. The symptoms include spasticity (increased tension of muscles, causing stiff and awkward movements), exaggerated stretch reflexes, progressive weakness and muscular atrophy, and, finally, paralysis. Death usually occurs 5–10 years after the onset of the disease as a result of failure of respiratory muscles. The muscles that control eye movements are spared. Cognitive abilities are rarely affected.

Ten percent of the cases of ALS are hereditary; the other 90 percent are sporadic. Of the hereditary cases, 10–20 percent are caused by a mutation in the gene that produces the enzyme superoxide dismutase 1 (SOD1), found on chromosome 21. This mutation causes a toxic gain...
of function that leads to protein misfolding and aggregation, impaired axonal transport, and mitochondrial dysfunction. It also impairs glutamate reuptake into glial cells, which increases extracellular levels of glutamate and causes excitotoxicity in motor neurons (Bossy-Wetzel, Schwarzenbacher, and Lipton, 2004).

The primary cause of sporadic ALS appears to be an abnormality in RNA editing. In most cases, proteins are produced by a two-step process: a copy of an active gene is transcribed to a strand of messenger RNA, which is then translated into a sequence of amino acids at a ribosome. However, in some cases, enzymes alter RNA molecules between transcription and translation so that a different protein is produced. In sporadic ALS, faulty editing of RNA that codes for a particular glutamate receptor subunit (GluR2) in motor neurons results in the production of glutamate AMPA receptors that admit increased amounts of calcium ions into these neurons. As a result, the cells die from excitotoxicity Kawahara et al. (2004) examined the spinal cords and brains of five patients who had died of ALS and found evidence for deficient RNA editing in spinal cord motor neurons of all of them. All of the motor neurons from people without ALS showed normal RNA editing. Kuner et al. (2005) produced a genetic mutation in mice that caused the production of AMPA receptors with increased calcium permeability. The mice sustained late-onset degeneration of spinal cord motor neurons and movement deficits similar to those of ALS. Kawahara et al. (2005) produced an animal model of ALS by inserting mutated human SOD1 genes into rats. They found no evidence for abnormal RNA editing in the degenerating motor neurons of these animals, which suggests that sporadic and familial ALS are caused by different mechanisms.

The only current pharmacological treatment for ALS is riluzole, a drug that reduces glutamate-induced excitotoxicity, probably by decreasing the release of glutamate. Clinical trials found that patients treated with riluzole lived an average of 1–3 months longer than those who received a placebo (Bensimon, Lacomblez, and Meininger, 1994). However, a study by Kaspar et al. (2003) using mice with a genetically engineered SOD1 mutation provides some hope of a more effective treatment, at least for familial ALS. The authors injected a harmless virus that contained a gene that causes the production of insulin-like growth factor-1 (IGF-1) into leg muscles of mice. The virus was taken up by terminal buttons of motor neurons and carried by means of retrograde axoplasmic flow to the cell bodies of these neurons, located in the ventral horn of the spinal cord. The inserted gene triggered the production of IGF-1, a protein that has been shown to prolong the lives of injured motor neurons, at least partly by blocking caspase activation. The animals lived 30 percent longer than mice treated with a placebo if the treatment started before the onset of physical symptoms and 18 percent longer if treatment was started after symptom onset. (See Figure 15.26.) The advantages of this treatment are that the virus used to insert the gene into the motor neurons is harmless to humans as well as mice and that the gene expression lasts for a long time. According to Kaspar and his colleagues, a clinical trial of this procedure in humans is being designed.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune demyelinating disease. At scattered locations within the central nervous system, myelin sheaths are attacked by the person’s immune system, leaving behind hard patches of debris
called sclerotic plaques. (See Figure 15.27.) The normal transmission of neural messages through the demyelinated axons is interrupted. Because the damage occurs in white matter located throughout the brain and spinal cord, a wide variety of neurological disorders are seen.

Multiple sclerosis afflicts women somewhat more frequently than men, and the disorder usually occurs in people in their late twenties or thirties. People who spend their childhood in places far from the equator are more likely to come down with the disease than are those who live close to the equator. Hence, it is likely that some disease contracted during a childhood spent in a region in which the virus is prevalent causes the person’s immune system to attack his or her own myelin. Perhaps a virus weakens the blood–brain barrier, allowing myelin protein into the general circulation and sensitizing the immune system to it, or perhaps the virus attaches itself to myelin. In addition, people born during the late winter and early spring are at higher risk, which suggests that infections contracted by a pregnant woman (for example, a viral disease contracted during the winter) may also increase susceptibility to this disease. In any event, the process is a long-lived one, lasting for many decades.

Only two treatments for multiple sclerosis have shown any promise. The first is interferon β, a protein that modulates the responsiveness of the immune system. Administration of interferon β has been shown to reduce the frequency and severity of attacks and slow the progression of neurological disabilities in some patients with multiple sclerosis (Arnason 1999). However, the treatment is only partially effective. Another partially effective treatment is glatiramer acetate (also known as copaxone or copolymer-1). Glatiramer acetate is a mixture of synthetic peptides composed from random sequences of the amino acids tyrosine, glutamate, alanine, and lysine. This compound was first produced in an attempt to induce the symptoms of multiple sclerosis in laboratory animals. An experimentally induced demyelinating disease known as experimental allergic encephalitis (EAE) can be produced in laboratory animals by injecting them with protein found in myelin. The immune system then becomes sensitized to myelin protein.
and attacks the animal’s own myelin sheaths. Glatiramer acetate turned out to do just the opposite; rather than causing EAE, it prevented its occurrence, apparently by stimulating certain cells of the immune system to secrete anti-inflammatory chemicals such as interleukin 4, which suppress the activity of immune cells that would otherwise attack the patient’s myelin (Farina et al., 2005). As you might expect, researchers tested glatiramer acetate in people with MS and found that the drug reduced the symptoms of patients who showed the relapsing-remitting form of the disease: periodic occurrences of neurological symptoms followed by partial remissions. The drug is now approved for treatment of this disorder. A structural MRI study by Sormani et al. (2005) found a reduction of 20–54 percent in white-matter lesions in 95 percent of patients treated with glatiramer acetate.

Although interferon β and glatiramer acetate provide some relief, neither treatment halts the progression of MS. We still need better forms of therapy. Because the symptoms of MS are often episodic—new or worsening symptoms followed by partial recovery—patients and their families often attribute the changes in the symptoms to whatever has happened recently. For example, if the patient has taken a new medication or gone on a new diet and the symptoms get worse, the patient will blame the symptoms on the medication or diet. Conversely, if the patient gets better, he or she will credit the medication or diet.

**Korsakoff’s Syndrome**

The last degenerative disorder I will discuss, Korsakoff’s syndrome, is neither hereditary nor contagious. It is caused by environmental factors—usually (but not always) involving chronic alcoholism. The disorder actually results from a thiamine (vitamin B₁) deficiency caused by the alcoholism (Adams, 1969; Haas, 1988). Because alcoholics receive a substantial number of calories from the alcohol they ingest, they usually eat a poor diet, and their vitamin intake is consequently low. Furthermore, alcohol interferes with intestinal absorption of thiamine. The ensuing deficiency produces brain damage. Thiamine is essential for a step in metabolism: the carboxylation of pyruvate, an intermediate product in the breakdown of carbohydrates, fats, and amino acids. Korsakoff’s syndrome sometimes occurs in people who have been severely malnourished and have then received intravenous infusions of glucose; the sudden availability of glucose to the cells of the brain without adequate thiamine with which to metabolize it damages the cells, probably because they accumulate pyruvate. Hence, standard medical practice is to administer thiamine along with intravenous glucose to severely malnourished patients.

As we saw in Chapter 13, the brain damage incurred in Korsakoff’s syndrome causes anterograde amnesia. Although degeneration is seen in many parts of the brain, the damage that characterizes this disorder occurs in the mammillary bodies, located at the base of the brain, in the posterior hypothalamus. (See Figure 15.28.)

**Interim Summary**

**Degenerative Disorders**

Transmissible spongiform encephalopathies such as Creutzfeldt-Jakob disease, scrapie, and bovine spongiform encephalopathy (“mad cow disease”) are unique among contagious diseases: They are produced by a simple protein molecule, not by a virus or microbe. The sequence of amino acids of normal prion protein (PrPc) and infectious prion protein (PrPSc) are identical, but their three-dimensional shapes differ in the way that they are folded. Somehow, the presence of a misfolded prion protein in a neuron causes normal prion proteins to become misfolded, and a chain reaction ensues. The transformation of PrPc into PrPSc kills the cell, apparently by triggering apoptosis. Creutzfeldt-Jakob disease is heritable as well as transmissible, but the most common form is sporadic—of unknown origin. Normal prion protein may play a role in the establishment and maintenance of long-term memories.

Parkinson’s disease is caused by degeneration of dopamine-secreting neurons of the substantia nigra that send
axons to the basal ganglia. Study of rare hereditary forms of Parkinson’s disease reveals that the death of these neurons is caused by the aggregation of misfolded protein, α-synuclein. One mutation produces defective α-synuclein, and another produces defective parkin, a protein that assists in the tagging of abnormal proteins for destruction by the proteasomes. The accumulation of α-synuclein can also be triggered by some toxins, which suggests that nonhereditary forms of the disease may be caused by toxic substances present in the environment. Treatment of Parkinson’s disease includes administration of L-DOPA, implantation of fetal dopaminergic neurons in the basal ganglia, stereotaxic destruction of a portion of the globus pallidus or subthalamus, and implantation of electrodes that enable the patient to electrically stimulate the subthalamus. Fetal transplants have turned out to be less successful than they had initially appeared to be.

Huntington’s disease, an autosomal-dominant hereditary disorder, produces degeneration of the caudate nucleus and putamen. Mutated huntingtin misfolds and forms aggregations that accumulate in the nucleus of GABAergic neurons in the putamen. Although the primary effect of mutated huntingtin is gain of toxic function, the disease also appears to involve a loss of function; normal huntingtin facilitates the production and transport of BDNF, a protein necessary for survival of neurons in the striatum. Evidence also suggests that inclusion bodies have a protective function and that damage is done by mutated huntingtin dispersed throughout the cell.

Alzheimer’s disease, another degenerative disorder, involves much more of the brain; the disease process eventually destroys most of the hippocampus and cortical gray matter. The brains of affected individuals contain many amyloid plaques, which contain a core of misfolded long-form Aβ protein surrounded by degenerating axons and dendrites, and neurofibrillary tangles, composed of dying neurons that contain intracellular accumulations of twisted filaments of tau protein. Hereditary forms of Alzheimer’s disease involve defective genes for the amyloid precursor protein (APP), for the secretases that cut APP into smaller pieces, or for apolipoprotein E (ApoE), a glycoprotein involved in transport of cholesterol and the repair of cell membranes. Anti-inflammatory drugs may be useful in fighting this disorder. Another promising treatment is vaccination against Aβ, but a way must be found to avoid triggering an inflammatory reaction. Temporary reduction of symptoms is seen in some patients who are treated with anticholinergic drugs or drugs that serve as NMDA antagonists.

Amyotrophic lateral sclerosis is a degenerative disorder that attacks motor neurons. Ten percent of the cases are hereditary, caused by a mutation of the gene for SOD1; the other 90 percent are sporadic. The primary cause of sporadic ALS appears to be an abnormality in RNA editing, which results in the production of AMPA receptor subunits that permit the entry of excessive amounts of calcium into the cells. The only pharmacological treatment is riluzole, a drug that reduces glutamate-induced excitotoxicity. A virally introduced gene for IGF-1 has shown promise in an animal model of ALS.

Multiple sclerosis, a demyelinating disease, is characterized by periodic attacks of neurological symptoms, usually with partial remission between attacks. The damage appears to be caused by the body’s immune system, which attacks the protein contained in myelin. Most investigators believe that a viral infection early in life somehow sensitizes the immune system to myelin protein. The only effective treatments for MS are interferon β and glatiramer acetate, a mixture of synthetic peptides that appears to stimulate certain immune cells to secrete anti-inflammatory chemicals.

Korsakoff’s syndrome is usually a result of chronic alcohol abuse, but it can also be caused by malnutrition that results in a thiamine deficiency. The most obvious location of brain damage is the mammillary bodies, but damage also occurs in many other parts of the brain.

### Disorders Caused by Infectious Diseases

Several neurological disorders can be caused by infectious diseases, transmitted by bacteria, fungi or other parasites, or viruses. The most common are encephalitis and meningitis. **Encephalitis** is an infection that invades the entire brain. The most common cause of encephalitis is a virus that is transmitted by mosquitoes, which pick up the infectious agent from horses, birds, or rodents.

The symptoms of acute encephalitis include fever, irritability, and nausea, often followed by convulsions, delirium, and signs of brain damage, such as aphasia or paralysis. Unfortunately, there is no specific treatment besides supportive care, and between 5 and 20 percent of the cases are fatal; 20 percent of the survivors show some residual neurological symptoms.

**Encephalitis** *(en sef’ a lye’ tis)* An inflammation of the brain; caused by bacteria, viruses, or toxic chemicals.
Encephalitis can also be caused by the herpes simplex virus, which is the cause of cold sores (or “fever blisters”) that most people develop in and around their mouth from time to time. Normally, the viruses live quietly in the trigeminal nerve ganglia nodules on the fifth cranial nerve that contain the cell bodies of somatosensory neurons that serve the face. The viruses proliferate periodically, traveling down to the ends of nerve fibers, where they cause sores to develop in mucous membrane. Unfortunately, they occasionally (but rarely) go the other way into the brain. Herpes encephalitis is a serious disease; the virus attacks the frontal and temporal lobes in particular and can severely damage them.

Two other forms of viral encephalitis are probably already familiar to you: polio and rabies. Acute anterior poliomyelitis (“polio”) is fortunately very rare in developed countries since the development of vaccines that immunize people against the disease. The virus causes specific damage to motor neurons of the brain and spinal cord: neurons in the primary motor cortex; in the motor nuclei of the thalamus, hypothalamus, and brain stem; in the cerebellum; and in the ventral horns of the gray matter of the spinal cord. Undoubtedly, these motor neurons contain some chemical substance that either attracts the virus or in some way makes the virus become lethal to them.

Rabies is caused by a virus that is passed from the saliva of an infected mammal directly into a person’s flesh by means of a bite wound. The virus travels through peripheral nerves to the central nervous system and there causes severe damage. It also travels to peripheral organs, such as the salivary glands, which makes it possible for the virus to find its way to another host. The symptoms include a short period of fever and headache, followed by anxiety, excessive movement and talking, difficulty in swallowing, movement disorders, difficulty in speaking, seizures, confusion, and, finally, death within two to seven days of the onset of the symptoms. The virus has a special affinity for cells in the cerebellum and hippocampus, and damage to the hippocampus probably accounts for the emotional changes that are seen in the early symptoms.

Fortunately, the incubation period for rabies lasts up to several months while the virus climbs through the peripheral nerves. (If the bite is received in the face or neck, the incubation time will be much shorter because the virus has a smaller distance to travel before it reaches the brain.) During the incubation period a person can receive a vaccine that will confer an immunity to the disease; the person’s own immune system will destroy the virus before it reaches the brain.

Several infectious diseases cause brain damage even though they are not primarily diseases of the central nervous system. One such disease is acquired immune deficiency syndrome (AIDS). Records of autopsies have revealed that at least 75 percent of people who died of AIDS show evidence of brain damage (Levy and Breidenstein, 1989). The brain damage often results in a syndrome called AIDS dementia, which is characterized by a loss of cognitive and motor functions. At first the patients may become forgetful, they may think and reason more slowly, and they may have word-finding difficulties (anomia). Eventually, they may become almost mute. Motor deficits may begin with tremor and difficulty in making complex movement but then may progress so much that the patient becomes bedridden (Maj, 1990).

Evidence suggests that the cause of AIDS dementia may be the entry of excessive amounts of calcium into neurons. For several years, researchers have been puzzled by the fact that although AIDS certainly causes neural damage, neurons are not themselves infected by the HIV virus (the organism responsible for the disease). Lipton et al. (1990) found that the cause of neural death appears to be the entry of excessive amounts of calcium. (As we saw earlier, the death of neurons caused by several different types of pathology involves the entry of excessive amounts of Ca2+.) Lipton and his colleagues (Lipton, 1996, 1997) suggest that virus-infected astrocytes and white blood cells may be the cause of the calcium inflow. The infection causes these cells to secrete excitotoxic substances (including glutamate) that activate NMDA receptors. The investigators suggest that the drugs being developed to reduce the damage caused by strokes may also be useful in treating AIDS dementia. In fact, a clinical trial of nimodipine, a drug that blocks calcium channels, found no signs of toxicity, and further studies will investigate the effectiveness of this drug in preventing the development of neurological symptoms (Navia et al., 1998).

Another category of infectious diseases of the brain actually involves inflammation of the meninges, the layers of connective tissue that surround the central nervous system. Meningitis can be caused by viruses or bacteria. The symptoms of all forms include headache, a stiff neck, and, depending on the severity of the disorder, convulsions, confusion or loss of consciousness, and sometimes death. The stiff neck is one of the most important symptoms. Neck movements cause the meninges to stretch; because they are inflamed, the stretch causes severe pain. Thus, the patient resists having his or her neck moved.

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**herpes simplex virus** (her peez) A virus that normally causes cold sores near the lips but that can also cause brain damage.

**acute anterior poliomyelitis** (poh lee oh my a lye tee) A viral disease that destroys motor neurons of the brain and spinal cord.

**rabies** A fatal viral disease that causes brain damage; usually transmitted through the bite of an infected animal.

**meningitis** (men in jee tee) An inflammation of the meninges; can be caused by viruses or bacteria.
The most common form of viral meningitis usually does not cause significant brain damage. However, various forms of bacterial meningitis do. The usual cause is spread of a middle-ear infection into the brain, introduction of an infection into the brain from a head injury, or the presence of emboli that have dislodged from a bacterial infection present in the chambers of the heart. Such an infection is often caused by unclean hypodermic needles; therefore, drug addicts are at particular risk for meningitis (as well as many other diseases). The inflammation of the meninges can damage the brain by interfering with circulation of blood or by blocking the flow of cerebrospinal fluid through the subarachnoid space, causing hydrocephalus. In addition, the cranial nerves are susceptible to damage. Fortunately, bacterial meningitis can usually be treated effectively with antibiotics. Of course, early diagnosis and prompt treatment are essential, because neither antibiotics nor any other known treatment can repair a damaged brain.

**Interim Summary**

**Disorders Caused by Infectious Diseases**

Infectious diseases can damage the brain. Encephalitis, usually caused by a virus, affects the entire brain. One form is caused by the herpes simplex virus, which infects the trigeminal nerve ganglia of most of the population. This virus tends to attack the frontal and temporal lobes. The polio virus attacks motor neurons in the brain and spinal cord, resulting in motor deficits or even paralysis. The rabies virus, acquired by an animal bite, travels through peripheral nerves and attacks the brain, particularly the cerebellum and hippocampus. An AIDS infection also produces brain damage, perhaps because infected white blood cells and astrocytes release excitotoxic chemicals that open calcium channels that permit a lethal dose of the ion to enter the cells of the brain. Meningitis is an infection of the meninges, caused by viruses or bacteria. The bacterial form, which is usually more serious, is generally caused by an ear infection, a head injury, or an embolus from a heart infection.

**Suggested Readings**


**Additional Resources**

The Companion Website for this text contains additional resources, including Practice Tests and Weblinks with up-to-date information about topics discussed in this chapter.

[www.ablongman.com/pob9e](http://www.ablongman.com/pob9e)