

PROLOGUE | It Started with Her Foot

Mrs. R., a divorced, 50-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.

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 tumors 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

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 ta sis*) The process by which cells break off of a tumor, travel through the vascular system, and grow elsewhere in the body.

Sign

TABLE 14.1 Types of Brain Tumors

Gliomas Glioblastoma multiforme (poorly differentiated glial cells)
Astrocytoma (astrocytes)
Ependymoma (ependymal cells that line ventricles)
Medulloblastoma (cells in roof of fourth ventricle)
Oligodendrocytoma (oligodendrocytes)
Meningioma (cells of the meninges)
Pituitary adenoma (hormone-secreting cells of the pituitary gland)
Neurinoma (Schwann cells or cells of connective tissue covering cranial nerves)
Metastatic carcinoma (depends on the nature of the primary tumor)
Angioma (cells of blood vessels)
Pinealoma (cells of pineal gland)

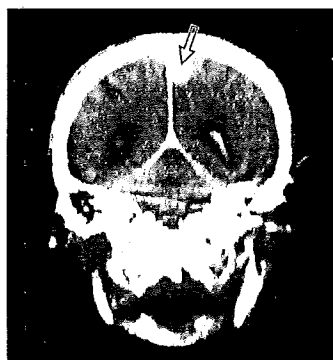


FIGURE 14.1 Meningioma. The CT scan of a brain shows the presence of a meningioma (round white spot indicated by the arrow).

J. McA. Jones.

glioma (*glee oh mah*) A cancerous brain tumor composed of one of several types of glial cells.

tumor-initiating cell Cells that originate from transformations of neural stem cells, rapidly proliferate, and give rise to a glioma.

meningioma (*men in jee 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.

both compression and infiltration. As a malignant tumor grows, it invades the surrounding region and destroys cells in its path.

Tumors do not arise from neurons, because mature neurons 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 14.1. (See *Table 14.1*.) 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. Some 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.

Evidence indicates that the malignancy of brain tumors is caused by a rare subpopulation of cells (Hadjipanayis and Van Meir, 2009). Malignant gliomas contain **tumor-initiating cells**, which originate from transformations of neural stem cells. These cells rapidly proliferate and give rise to a glioma. Because they are more resistant to chemotherapy and radiation than most tumor cells, the survival rate from these tumors is very low.

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 14.1*.)

Seizure Disorders

Because of negative connotations that were acquired in the past, some 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. At present, approximately 2.5 million people in the United States have a seizure disorder. 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. In ancient religious traditions, seizures were considered to be God's punishment or the work of demons. However, as early as the fifth century B.C., Hippocrates noted that head injuries to soldiers and gladiators sometimes led to seizures like the ones he saw in his patients, which suggested that seizures had a physical cause (Hoppe, 2006).

Table 14.2 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

TABLE 14.2 The Classification of Seizure Disorders

- I. Generalized seizures (with no apparent local onset)
 - A. Tonic-clonic (grand mal)
 - B. Absence (petit mal)
 - C. Atonic (loss of muscle tone, temporary paralysis)
- II. Partial seizures (starting from a focus)
 - A. Simple (no major change in consciousness)
 1. Localized motor seizure
 2. Motor seizure, with progression of movements as seizure spreads along the primary motor cortex
 3. Sensory (somatosensory, visual, auditory, olfactory, vestibular)
 4. Psychic (forced thinking, fear, anger, etc.)
 5. Autonomic (sweating, salivating, etc.)
 - B. Complex (with altered consciousness)
Includes 1–5, as above
- III. Partial seizures (simple or complex) evolving to generalized cortical seizure: Starts as IIA or IIB, then becomes a grand mal seizure

by an old injury, or a developmental abnormality such as a malformed blood vessel. 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 14.2*.)

The most severe form of seizure is a **tonic-clonic** seizure (sometimes called a *grand mal* seizure). This seizure is generalized, and because it includes the motor systems of the brain, it is accompanied by convulsions. Often, before having a tonic-clonic 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 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 tonic-clonic seizure is called the **tonic phase**. During this 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 thirty seconds, the patient's muscles relax; only then does breathing begin again. The patient falls into a stuporous, unresponsive sleep, which lasts for about fifteen minutes. After that the patient may awaken briefly but usually falls back into an exhausted sleep that may last for a few hours.

Other types of seizures are far less dramatic. For example, 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

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.

tonic-clonic seizure A generalized convulsive seizure that includes a tonic phase of rigidity followed by a clonic phase of jerky movements.

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 tonic-clonic seizure, in which all of the patient's skeletal muscles are contracted.

clonic phase The phase of a tonic-clonic seizure in which the patient shows rhythmic jerking movements.

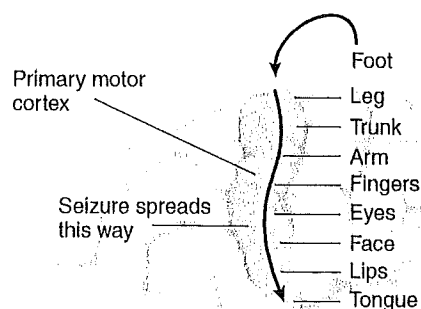


FIGURE 14.2 Primary Motor Cortex and Seizures. Mrs. R.'s seizure began in the foot region of the primary motor cortex, and as the seizure spread, more and more parts of her body became involved.

along the precentral gyrus. In the chapter prologue 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 the seizure began, it involved the foot; as it spread, it began involving the other parts of the body. (See *Figure 14.2*.) Mrs. R.'s first spell was a simple partial seizure, but her second one—much more severe—would be classed as a complex partial seizure, because she lost consciousness. A seizure beginning in the occipital lobe may produce visual symptoms such as spots of color, flashes of light, or temporary blindness; one originating in the parietal lobe can evoke somatosensations, such as feelings of pins and needles or heat and cold. Seizures in the temporal lobes may cause hallucinations that include old memories; presumably, neural circuits involved in these memories are activated by the spreading excitation. Depending on the location and extent of the seizure, the patient may or may not lose consciousness.

Children are especially susceptible to seizure disorders. Many of them do not have tonic-clonic episodes but instead have very brief seizures that are referred to as spells of **absence**. During an absence seizure, which is a *generalized* seizure disorder, they stop what they are doing and stare off into the distance for a few seconds, often blinking their eyes repeatedly. (These spells are also sometimes referred to as *petit mal* seizures.) During this time they are unresponsive, and they usually do not notice their attacks. Because absence seizures can occur up to several

hundred times each day, they can disrupt a child's performance in school. Unfortunately, many of these children are considered to be inattentive and unmotivated unless the disorder is diagnosed.

Seizures can have serious consequences; most notably, they can cause brain damage. Approximately 50 percent 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, a developmental abnormality in the brain, or the irritating effect of a growing tumor. For injuries, the development of seizures can 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. High fevers are most common in children, and approximately 3 percent of children under the age of 5 years sustain seizures associated with fevers (Berkovic et al., 2006). 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.

Genetic factors contribute to the incidence of seizure disorders (Berkovic et al., 2006). Nearly all of the genes that have been identified as playing a role in seizure disorders control the production of ion channels, which is not surprising, considering the fact that ion channels control the excitability of the neural membrane, and are responsible for the propagation of action potentials. However, most seizure disorders are caused by nongenetic factors. In the past, many cases were considered to be *idiopathic* (of unknown causes, or literally “one's own suffering”). However, the development of MRIs with more and more resolution and sensitivity has meant that small brain abnormalities responsible for triggering seizures are more likely to be seen.

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. However, 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 the region of the brain surrounding the focus (usually located in the medial temporal lobe). Most patients recover well, with their seizures eliminated or greatly reduced in frequency.

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.

Mrs. R.'s treatment, described in the chapter prologue, 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.

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 their causes and treatments.

The incidence of strokes in the United States is approximately 750,000 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. The two major types of strokes are *hemorrhagic* and *ischemic*. **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. **Ischemic strokes**—those that plug up a blood vessel and prevent the flow of blood—can be caused by thrombi 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 14.3*.)

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 blood pressure. However, if a stroke 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, and if the patient reaches an appropriately equipped and staffed stroke-treatment center soon enough, attempts will be made to dissolve or physically remove the blood clot. (I will describe these attempts later.) Even if immediate treatment is not available, the patient will receive anticoagulant drugs

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

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

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

embolus (emm bo lus) 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.

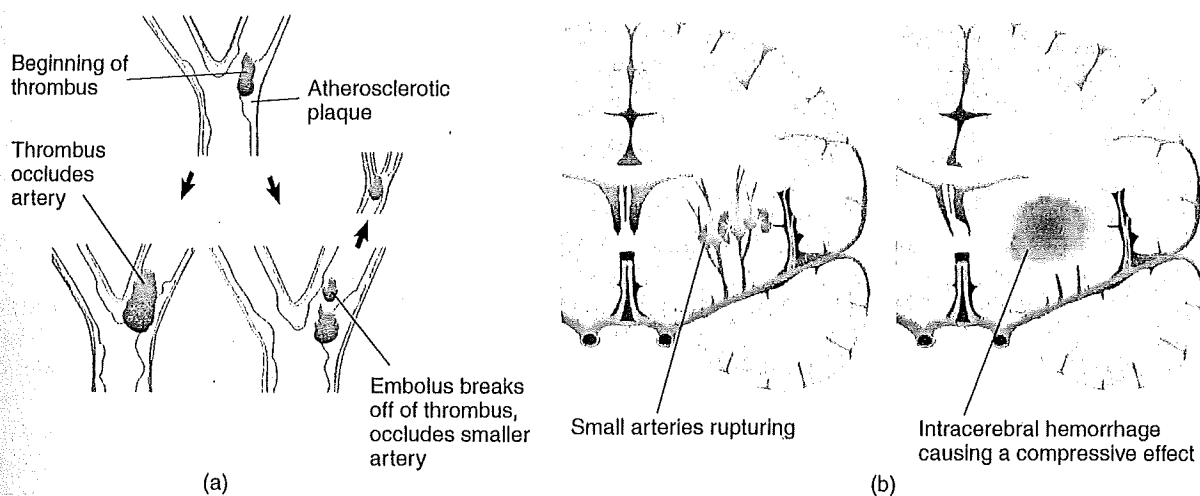
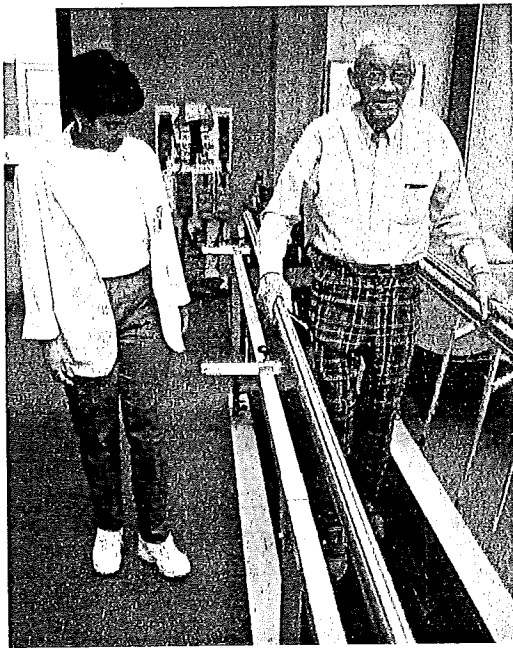


FIGURE 14.3 Strokes. (a) Formation of thrombi and emboli. (b) An intracerebral hemorrhage.



Research with both animals and humans has shown that exercise and sensory stimulation facilitate recovery of functions lost as a result of brain damage.

Paul Conklin/PhotoEdit, Inc.

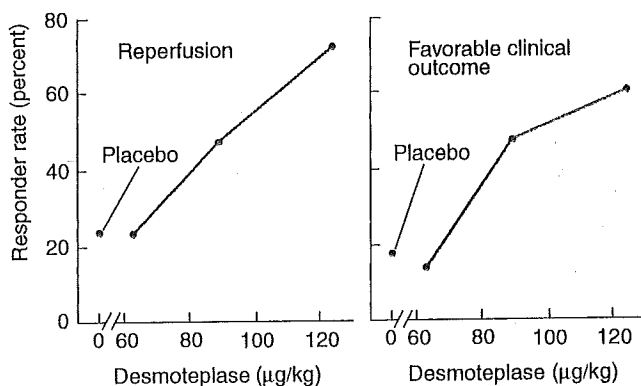


FIGURE 14.4 Desmoteplase in Treatment of Strokes. The graph shows the effects of desmoteplase and a placebo on restoration of cerebral blood flow to the affected area (*reperfusion*) and favorable clinical outcome.

Based on data from Hacke, W., Albers, G., Al-Rawi, Y., et al. *Stroke*, 2005, 36, 66–73.

to make the blood less likely to clot, reducing the likelihood of another stroke. If an embolus broke away from a mass caused by 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 will simply starve to death because they lose their supply of glucose and of oxygen to metabolize it. However, research indicates that the 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.)

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, but only if it is given within three hours (NINDS, 1995). *tPA* is an enzyme that causes the dissolution of *fibrin*, a protein involved in clot formation.

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. *tPA* is potentially neurotoxic if it is 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; Medcalf, 2011). 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.

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 indicates 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 (*reperfusion* of occluded blood vessel) and reduced clinical symptoms in a majority of patients if given up to nine hours after the occurrence of a stroke. (See **Figure 14.4**.)

Occlusions of larger cerebral blood vessels can also be removed by mechanical means (Frendl and Csiba, 2011). Two types of medical devices have been developed. Both types are inserted into a cerebral blood vessel and extended until they reach the obstruction. One type of device works like a corkscrew, grabbing the obstruction so that the surgeon can pull it out. The other type of device works by suction: Once the tip of the device touches the obstruction, a vacuum is applied and the surgeon pulls out the clot. The disadvantages of these approaches is that some clots are difficult to reach, and attempts at mechanical removal can cause perforation of the blood vessel. Trials of these procedures suggest that use of a suction device is more likely to produce clinical improvement and less likely to cause intracerebral bleeding.

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 ischemic stroke, caused by clots that form around atherosclerotic plaques in cerebral and cardiac blood vessels.

Atherosclerotic plaques often form in the internal carotid artery—the artery that supplies most of the blood flow to the cerebral hemispheres. These plaques can cause severe narrowing of the interior of the artery, greatly increasing the risk of a massive stroke. This narrowing can be visualized in an angiogram, produced by injecting a radiopaque dye into the blood and examining the artery with a computerized X-ray machine. (See *Figure 14.5*.) If the narrowing is severe, a *carotid endarterectomy* can be performed. The surgeon makes an incision in the neck that exposes the carotid artery, inserts a shunt in the artery, cuts the artery open, removes the plaque, and sews the artery back again (and the neck too, of course). Endarterectomy has been shown to reduce the risk of stroke by 50 percent in people under 75 years of age.

Another surgical treatment involves the placement of a stent in a seriously narrowed carotid artery (Yadav et al., 2004). An arterial stent is an implantable device made of a metal mesh that is used to expand and hold open a partially occluded artery. These devices were first developed for treatment of arteries that serve the heart and later modified for use in the carotid artery. The stent consists of a mesh tube made of springy metal collapsed inside a catheter—a flexible plastic tube. The surgeon cuts open a large artery in the groin and passes the catheter through large arteries up to the neck until the stent reaches the occlusion in the carotid artery. When the catheter is retracted, the stent expands, opening the narrowed artery.

Before the carotid stent received unconditional approval, a careful study funded by the U.S. government randomly assigned patients whose condition made them good candidates for the stent to one of two groups: aggressive medical management plus stent or aggressive medical management alone. Based on the successful use of stents to open cardiac arteries, the investigators expected that the study would demonstrate the success of the carotid stent. Unfortunately, the patients who received the stent had an *increased* number of strokes and their death rate was higher. (See *Figure 14.6*.)

Figure 14.6 is the only one in this book that illustrates results that fail to show beneficial effects of treatment for a disorder involving the nervous system. In the previous edition of this book I described the process of stenting in more detail and wrote that investigators had hopes that this recently developed surgical treatment would be safer and more effective than carotid endarterectomy. Rather than simply omit mention of this procedure in this edition, I have described the randomized study and presented the graph of the results to emphasize the importance of scientific research in evaluating the treatment of medical disorders. Surgeons and hospitals were getting ready to make carotid stenting a standard procedure for narrowing of the carotid artery, at a cost of at least \$20,000 and, as we now know, increased mortality. No matter how plausible and reasonable a treatment appears, only scientific research can confirm its value.

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 (Cotman, Berchtold, and Christie, 2007). For example, Taub et al. (2006) 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. A placebo group received cognitive, relaxation, and physical fitness exercises for the same amount of time. This procedure (which is called *constraint-induced movement therapy*) produced long-term improvement in the patients' ability to use the affected arm, apparently by changing connections of the primary motor cortex (Liepert et al., 2000). (See *Figure 14.7*.)

In some cases of brain damage or spinal cord damage, patients are unable to perform useful limb movements, even after intensive therapy. In such cases, investigators have attempted to devise brain-computer interfaces that permit the patient to control electronic and mechanical devices to perform useful actions. Developers of such interfaces have implanted arrays of microelectrodes directly into the patient's motor cortex and have applied surface

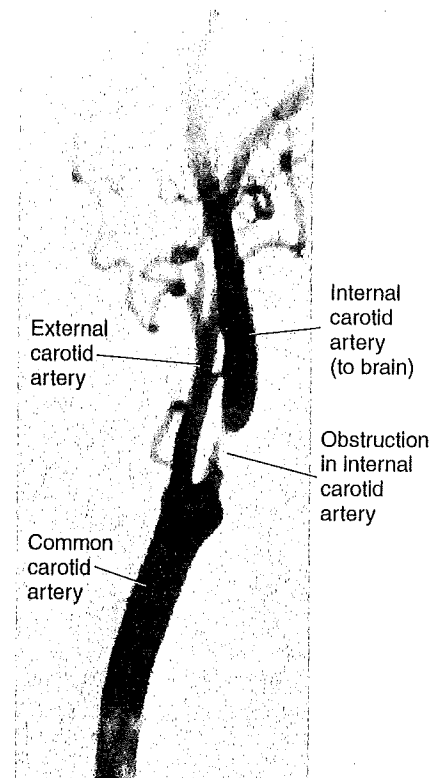


FIGURE 14.5 Atherosclerotic Plaque.

An angiogram shows an obstruction in the internal carotid artery caused by an atherosclerotic plaque.

From Stapf, C., and Mohr, J.P. *Annual Review of Medicine*, 2002, 53, 453-475. Reprinted with permission.

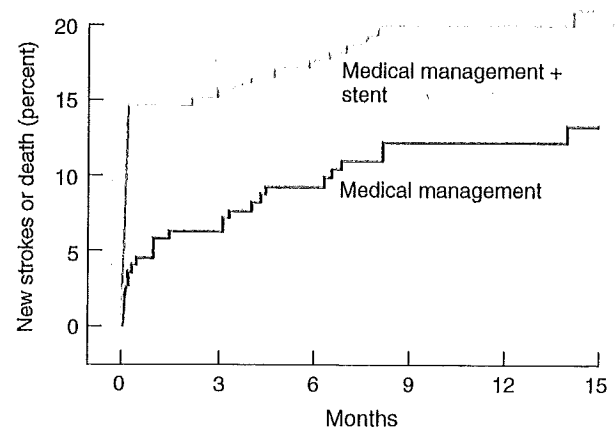


FIGURE 14.6 Effects of Carotid Stents. The graph shows that the rate of strokes and deaths in the fifteen months after insertion of a carotid stent was higher than that of patients who received medical management alone.

Based on data from Chimowitz et al., 2011.

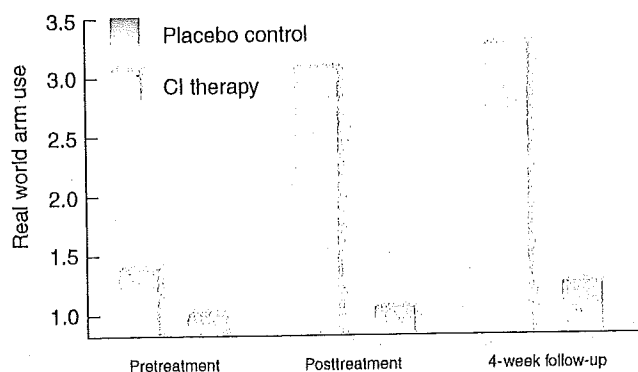


FIGURE 14.7 Constraint-Induced Movement Therapy. The graph shows the effects of CI therapy and placebo therapy on the use of a limb whose movement was impaired by a stroke.

Based on data from Taub, E., Uswatte, F., King, D. K., et al. *Stroke*, 2006, 37, 1045–1049.

electrodes to measure changes in EEG activity transmitted through the skull and scalp. These devices, while still experimental, permit patients to move prosthetic hands, perform actions with multi-jointed robotic arms, and move the cursor of a computer display and operate the computer (Wolpaw and McFarland, 2004; Hochberg et al., 2006).

Traumatic Brain Injury

Traumatic brain injury (TBI) is a serious health problem (Chen and D’Esposito, 2010). In the United States alone, approximately 1.4 million people are treated and released from an emergency department, 270,000 people are hospitalized, and 52,000 people die from TBI. Undoubtedly, many other people receive brain injuries but not a diagnosis. Almost a third of deaths caused by injury involve TBI. Traumatic brain injury can be caused by a projectile or a fall against a sharp object that fractures the

skull, causing the brain to be wounded by the object or a piece of the broken skull. Closed-head injuries do not involve penetration of the brain, but these injuries can also cause severe injury or death.

Penetrating brain injuries (also called open-head injuries) obviously affect the portion of the brain that is damaged by the object or the bone. In addition, damage to blood vessels can deprive parts of the brain of their normal blood supply, and the accumulation of blood within the brain can cause further damage by exerting pressure within the brain. Closed-head injury—for example, caused by a blow with a blunt object against the right side of a person’s forehead—will bruise the right frontal lobe as it comes into violent contact with the inside of the skull. (This blow to the brain is known as the *coup*.) The brain will then recoil in the opposite direction and smash against the left posterior region of the skull. (This blow is known as the *contrecoup*.) In many cases, the contrecoup can produce more damage than the coup.

Closed-head injury can damage more than the cerebral cortex at the point of the coup or contrecoup. Bundles of axons can be torn and twisted, blood vessels can be ruptured, and cerebrospinal fluid can distort the walls of the ventricles. And as we saw in the section on seizure disorders, traumatic brain injury can be followed several months later by a chronic seizure disorder. People who are most likely to sustain TBI include combat veterans, people who participate in sports such as boxing or American football, and motorcyclists and skiers who do not wear helmets.

Even mild cases of TBI can greatly increase a person’s risk of sustaining deficits that are not immediately obvious but which manifest themselves as the person ages. For example, the likelihood of Alzheimer’s disease is much higher in a person who has received blows to the head earlier in life. Besides causing obvious physical trauma to the brain, TBI results in increased levels of adenosine and glutamate in the traumatized brain tissue. The increased glutamate converts adenosine from its normal role as an anti-inflammatory agent to an agent that promotes inflammation, which causes further damage. Treatment with a drug that inhibits the release of glutamate can prevent this switch in the role of extracellular adenosine (Dai et al., 2010).

Treatment of the long-term behavioral and cognitive effects of TBI involve the same strategies as those employed in the treatment of brain damage caused by cerebrovascular accidents.

SECTION SUMMARY

Tumors, Seizure Disorders, Cerebrovascular Accidents, and Traumatic Brain Injury

Neurological disorders have many causes. 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. Malignant gliomas contain tumor-initiating cells, derived from neural stem cells which are resistant to chemotherapy and radiation.

Section Summary *(continued)*

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 convulsions that accompany tonic-clonic 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 can be produced by abstinence after prolonged heavy intake of alcohol; these appear to be produced by a sudden release from inhibition. 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. (Seizure surgery is described in the chapter epilogue.)

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

best current treatment for stroke is administration of a drug that dissolves clots. Tissue plasminogen activator (tPA) must be given within three 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 nine hours after a stroke and does not appear to cause brain damage. Procedures are being developed to remove blood clots mechanically from obstructed cerebral blood vessels. Carotid endarterectomy can reduce the likelihood of a stroke in people with atherosclerotic plaque that obstructs the carotid arteries. Unfortunately, insertion of a carotid stent has been found to increase the likelihood of subsequent strokes. 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.

Traumatic brain injury is a serious health problem. The damage caused by closed-head injuries is usually less obvious than that caused by penetrating brain injuries, but both can cause substantial deficits. Even mild cases of TBI can increase a person's risk of sustaining deficits later in life and increase the likelihood of Alzheimer's disease. Drug treatments are being developed to reduce the symptoms of TBI.

Thoughtful Question

If a contestant in a boxing match manages to hit the other person's head hard enough to cause him to fall to the ground, unconscious, he wins the match. Having read about the effects of traumatic brain injury, what do you think about competitions like these?

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—especially during the third to fourth week (Sulik, 2005). 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 14.8 shows photographs of the faces of a child with fetal alcohol syndrome, of a mouse fetus whose mother was fed alcohol during pregnancy, and of a normal mouse 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 14.8*.)

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

fetal alcohol syndrome A birth defect caused by ingestion of alcohol by a pregnant woman; includes characteristic facial anomalies and faulty brain development.

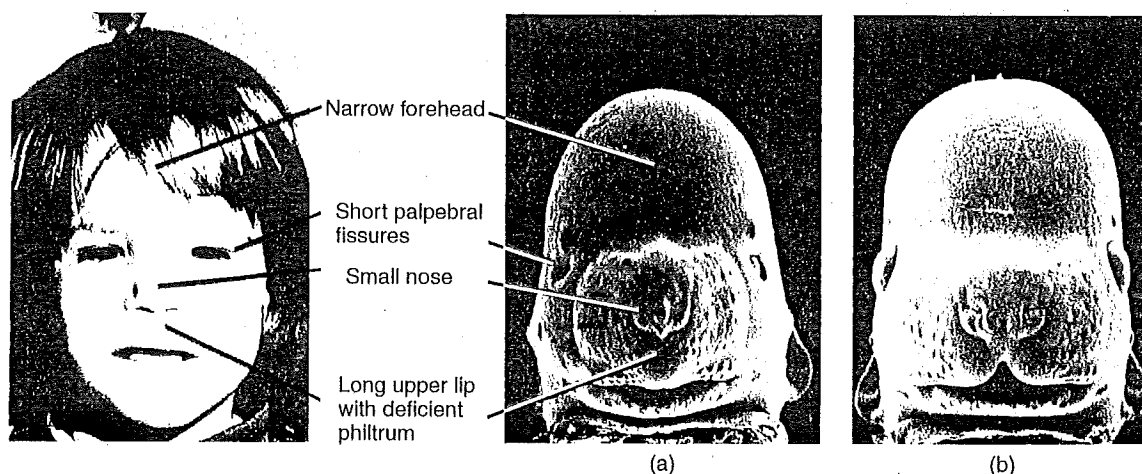


FIGURE 14.8 Facial Malformations in Fetal Alcohol Syndrome. The photographs show a child with fetal alcohol syndrome, along with magnified views of mouse fetuses. (a) Fetus whose mother received alcohol during pregnancy. (b) Normal mouse fetus.

Kathleen K. Sulik.

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” are 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 amounts of phenylalanine in the blood interfere with the myelination of neurons in the central nervous system. Much of the myelination 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 6 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 myelination of the central nervous system takes place normally. 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.

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 that 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. Because of this, particular kinds of waste products cannot be destroyed by the lysosomes, so they accumulate. The lysosomes get

phenylketonuria (PKU) (*fee nul kee ta new ree uh*) A hereditary disorder caused by the absence of an enzyme that converts the amino acid phenylalanine to tyrosine; the accumulation of phenylalanine causes brain damage unless a special diet is implemented soon after birth.

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

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, like PKU, will be treated by avoiding a constituent of the diet that cannot be tolerated. Others will be treated by administering a substance that the body requires. Still others may be cured some day by the techniques of genetic engineering. Researchers hope to develop genetically modified viruses that will insert into the infant's cells genetic information needed to produce the enzymes that the cells lack, leaving the rest of the cells' functions intact.

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 one 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. In fact, a small portion of the twenty-first chromosome, which includes approximately 300 genes, contains the critical region (Belichenko et al., 2010). 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 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. If efforts to develop effective therapies for Alzheimer's disease are successful, they might also be useful in preventing the degeneration seen in the brains of people with Down syndrome.



People with Down syndrome, caused by the presence of an extra twenty-first chromosome, are often only mildly retarded, and many of them can function well with only minimal supervision.

Mika/Corbis Images.

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.

SECTION 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. 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. A study with an animal model of Down syndrome suggests that administration of GABA antagonists might be useful.

Thought Exercise

Suppose that you were in charge of a governmental or charitable agency that had a lot of money to spend on research. What kinds of approaches do you think would be the most effective in preventing developmental disorders caused by behavior (for example, fetal alcohol syndrome) and by genetic factors?

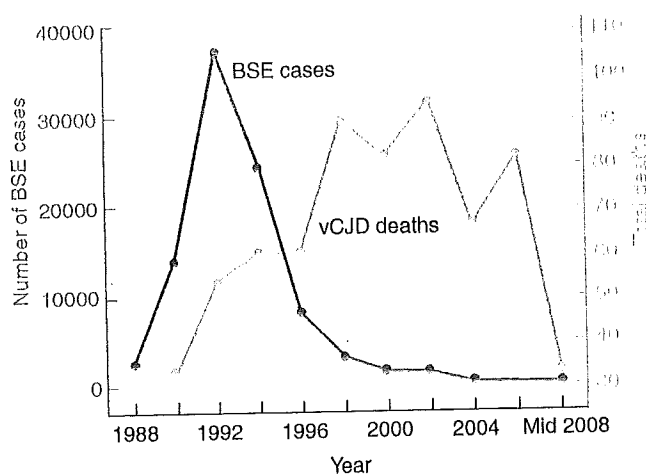


FIGURE 14.9 Bovine Spongiform Encephalopathy and Creutzfeldt-Jakob Disease. The graph shows the number of cases of BSE in cattle and variant Creutzfeldt-Jakob disease (vCJD) in humans in Great Britain between 1988 and March 31, 2008.

Based on data from OIE-World Organisation for Animal Health and the CJD Surveillance Unit.

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

prion (*pre* 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.

sporadic disease A disease that occurs rarely and is not obviously caused by heredity or an infectious agent.

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, thereby preventing 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 fatal contagious brain disease (“encephalopathy”) whose degenerative process gives the brain a sponglike (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. Scrapie cannot be transmitted to humans, but BSE can, and it produces a variant of Creutzfeldt-Jakob disease. (See *Figure 14.9*.)

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 and in preservation of the myelin sheath (Popko, 2010). Prion proteins are resistant to levels of heat that denature normal proteins, which explains why cooking meat from cattle with BSE does not destroy the infectious agent. The sequence of amino acids of normal prion protein (PrP^c) and infectious prion (PrP^{Sc}) are identical. How, then, can two proteins with the same amino acid sequences have such different effects? The answer is that the functions of proteins are determined largely by their three-dimensional shapes. The only difference between PrP^c and PrP^{Sc} is the way the protein is folded. Once misfolded PrP^{Sc} is introduced into a cell, it causes normal PrP^c to become misfolded as well. The process of this transformation ultimately kills them. (See Miller, 2009, 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 Creutzfeldt-Jakob 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 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 of people who 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 (Gajdusek, 1977).

A study by Steele et al. (2006) suggests that normal prion protein plays a role in neural development and differentiation in fetuses and neurogenesis in adults. The investigators produced a genetically engineered strain of mice that produced increased amounts of PrP^c and found increased numbers of proliferating cells in the subventricular zone, as well as more neurons in the dentate gyrus, compared with normal mice. Mice with a targeted mutation against the prion protein gene had fewer proliferating cells. Málaga-Trillo et al. (2009) found that a targeted mutation against the prion protein gene in zebra fish produced serious developmental anomalies.

Mallucci et al. (2003) created 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

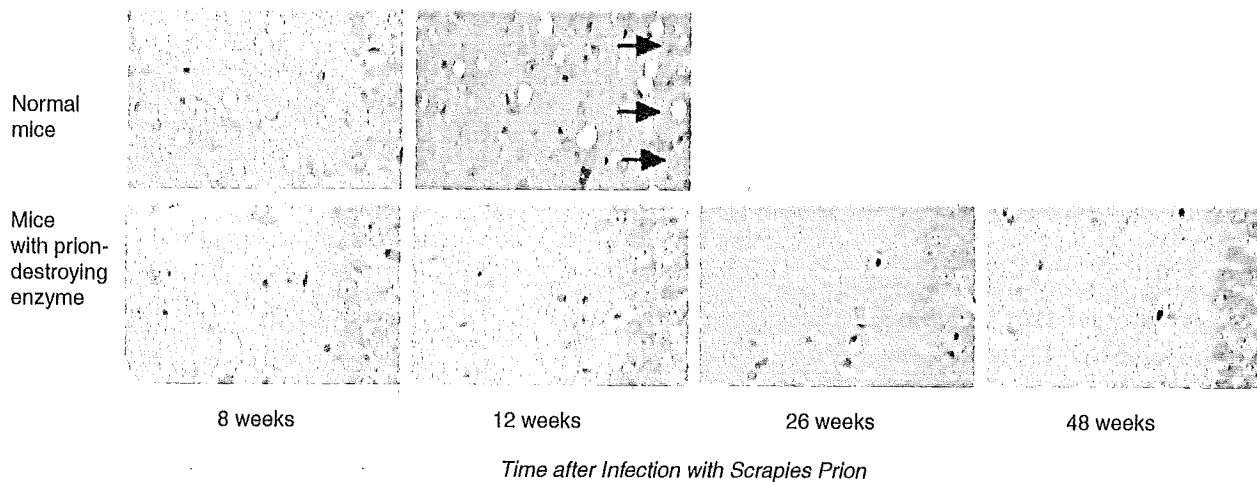


FIGURE 14.10 Experimental Treatment of a Prion Protein Infection. Neural death was prevented and early spongiosis was reversed in scrapie-infected mice after a genetically engineered enzyme began to destroy PrPc at 12 weeks of age. Arrows point to degenerating neurons in mice without the prion-destroying enzyme. Spongiosis is seen as holes in the brain tissue (arrowheads).

From Mallucci, G., Dickinson, A., Linehan, J., Klöhn, P. C., et al. *Science*, 2003, 302, 871-874. © Copyright 2003. Reprinted with permission from AAAS.

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. The mere presence of PrPsc in the brain (found in nonneuronal cells) does not cause the disease. Figure 14.10 shows the development of spongiform degeneration and its disappearance after the PrPc-destroying enzyme became active at 12 weeks of age. (See *Figure 14.10*.)

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, frontotemporal dementia, amyotrophic lateral sclerosis, and Huntington's disease, also contain aggregations of misfolded proteins (Miller, 2009; Lee et al., 2010). We will also see that although these misfolded proteins are not prions, the disease process can be transmitted to the brains of other animals by inoculating them with the proteins. 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

An important degenerative neurological disorder, 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. 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.

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

caspase A "killer enzyme" that plays a role in apoptosis, or programmed cell death.

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.

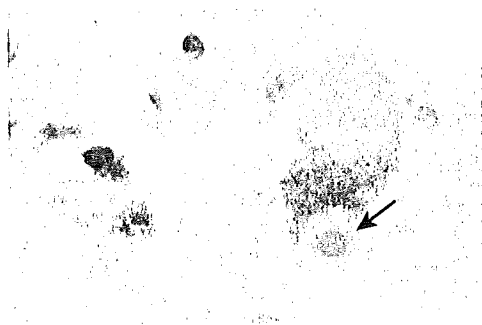


FIGURE 14.11 Lewy Bodies. A photomicrograph of the substantia nigra of a patient with Parkinson's disease shows a Lewy body, indicated by the arrow.

Dr. Don Born.

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.

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.

have a dense protein core, surrounded by a halo of radiating fibers (Forno, 1996). (See **Figure 14.11**.) 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 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 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, and the person will not develop Parkinson's disease. 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 protein to accumulate in dopaminergic neurons and ultimately damage them. **Figure 14.12** illustrates the role of 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 14.12**.)

The overwhelming majority of the cases of 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. The L-DOPA activates DA neurons in the mesolimbic/mesocortical system and produces side effects such as hallucinations and delusions. 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 the prologue and epilogue of 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 this drug 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 to dopaminergic neurons. Many studies (for example, Mizuno et al., 2010; Zhao et al., 2011) confirm that administration of deprenyl slows the progression of Parkinson's disease, especially if deprenyl therapy begins soon after the onset of the disease. However, the benefits of deprenyl and other inhibitors of MAO-B

appear to be reduction in symptoms. The drugs do not appear to retard the degeneration of dopaminergic neurons (Williams, 2010).

Neurosurgeons have developed 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 thirty-two 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, transplants of dopaminergic fetal cells are no longer recommended (Olanow et al., 2003).

Further examination of the fate of fetal transplants has shown that although the transplanted cells can survive and form connections with neurons in the recipient's tissue, these cells eventually develop deposits of α -synuclein. Studies with animal models of Parkinson's disease show that misfolded α -synuclein is transferred from the recipient's own neurons to the grafted neurons (Kordower et al., 2011). As many investigators have noted, misfolded proteins responsible for several neurodegenerative diseases, including Parkinson's disease, can be transferred from cell to cell in the brain where they induce further protein misfolding, just like prion proteins (Lee et al., 2011). It appears that adding healthy cells to the basal ganglia of patients with Parkinson's disease will ultimately fail unless a way is found to stop the process that results in the deposition of misfolded α -synuclein.

Another therapeutic procedure involves destruction of the **internal division of the globus pallidus (GP_i)**. The output of the GP_p, which is directed through the subthalamic nucleus (STN) to the motor cortex, is inhibitory. The decreased release of dopamine in the caudate nucleus and putamen that is seen in patients with Parkinson's disease causes an *increase* in the activity of the GP_i. Thus, damage to the GP_i might be expected to relieve the symptoms of Parkinson's disease. (See *Figure 14.13*.)

In fact, that is exactly what happens (Graybiel, 1996; Lai et al., 2000). Neurosurgeons insert an electrode into the GP_i and then pass radiofrequency current through the electrode that heats and destroys the brain tissue. PET studies have found that after the surgery, the metabolic activity in the premotor and supplementary motor areas of the frontal lobes, normally depressed in patients with Parkinson's disease, returns to normal levels (Grafton et al., 1995). This result indicates that lesions of the GP_i do indeed release the motor cortex from inhibition. Using the same reasoning, neurosurgeons have also successfully treated the symptoms of Parkinson's disease by targeting the subthalamic nucleus, which provides an excitatory input to the GP_i.

The third stereotaxic procedure aimed at relieving the symptoms of Parkinson's disease involves implanting electrodes in the STN or the GP_i and attaching a device that permits the patient to electrically stimulate the brain through the electrodes. According to some studies, **deep brain stimulation (DBS)** of the subthalamic nucleus is as effective as brain lesions in suppressing tremors and has fewer adverse side effects (Esselink et al., 2009). In addition, a three-year follow-up study found no evidence of cognitive deterioration in patients who received implants for deep brain stimulation (Funkiewiez et al., 2004). Notably, DBS treats only the motor symptoms of Parkinson's disease, not the affective and cognitive symptoms such as depression and dementia.

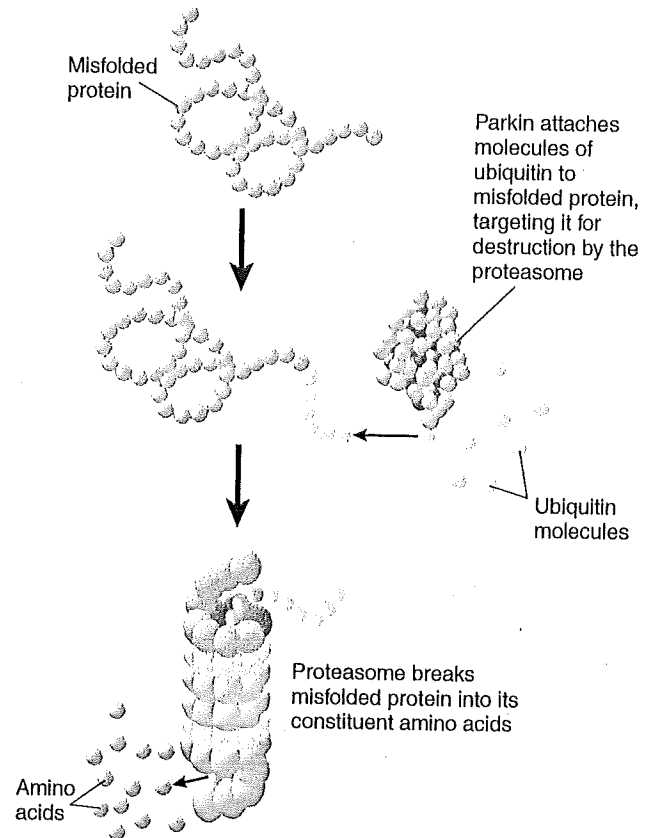


FIGURE 14.12 The Role of Parkin in Parkinson's Disease. Parkin is involved in the destruction of abnormal or misfolded proteins by the ubiquitin-proteasome system. If parkin is defective because of a mutation, abnormal or misfolded proteins cannot be destroyed, so they accumulate in the cell. If α -synuclein is defective because of a mutation, parkin is unable to tag it with ubiquitin, and it accumulates in the cell.

internal division of the globus pallidus (GP_i) A division of the globus pallidus that provides inhibitory input to the motor cortex via the thalamus; sometimes stereotaxically lesioned to treat the symptoms of Parkinson's disease.

deep brain stimulation (DBS) A surgical procedure that involves implanting electrodes in a particular region of the brain and attaching a device that permits the electrical stimulation of that region through the electrodes.

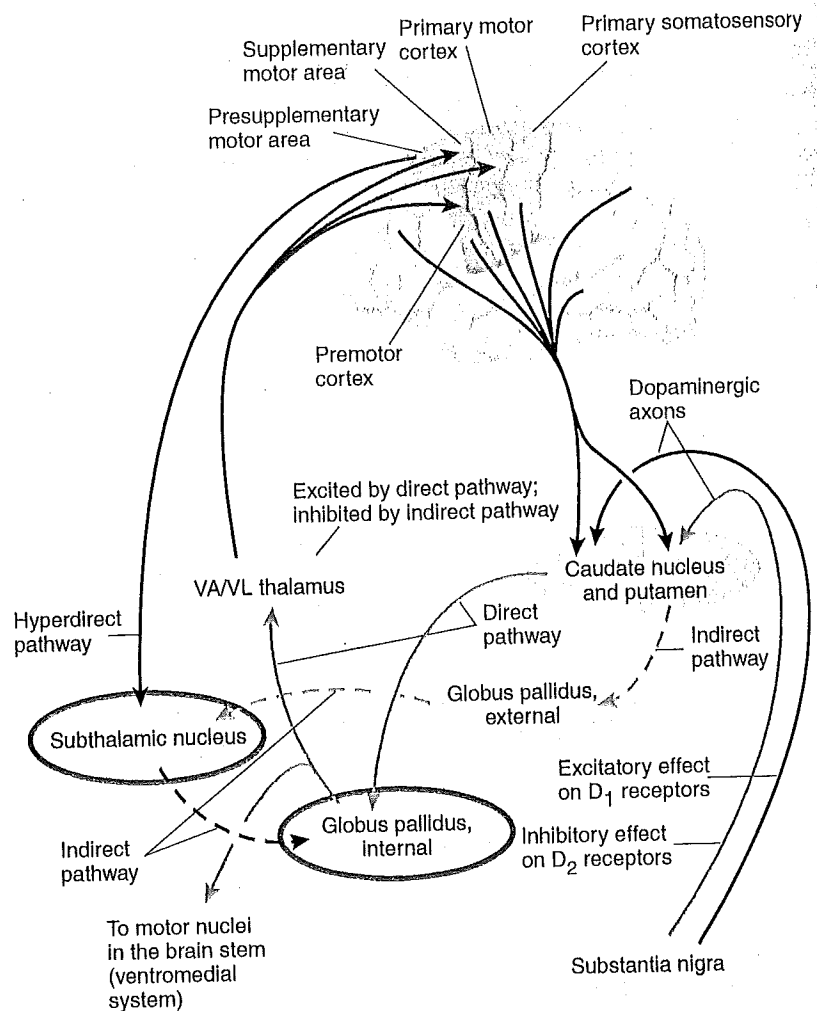


FIGURE 14.13 Connections of the Basal Ganglia. This schematic shows the major connections of the basal ganglia and associated structures. Excitatory connections are shown as black lines; inhibitory connections are shown as red lines. Many connections, such as the inputs to the substantia nigra, are omitted for clarity. Two regions that have been targets of stereotaxic surgery for Parkinson's disease—the internal division of the globus pallidus and the subthalamic nucleus—are outlined in gray. Damage to these regions reduces inhibitory input to the thalamus and facilitates movement. Deep brain stimulation of these regions produces similar effects.

Researchers have been attempting to develop strategies of gene therapy to treat the symptoms of Parkinson's disease. Kaplitt et al. (2007) introduced a genetically modified virus into the subthalamic nucleus of patients with Parkinson's disease that delivered a gene for GAD, the enzyme responsible for the biosynthesis of the major inhibitory neurotransmitter, GABA. The production of GAD turned some of the excitatory, glutamate-producing neurons in the subthalamic nucleus into inhibitory, GABA-producing neurons. As a result, the activity of the GP_i decreased, the activity of the supplementary motor area increased, and the symptoms of the patients improved. A larger double-blind clinical trial confirmed the efficacy and safety of this procedure (LeWitt et al. 2011). (See *Figure 14.14*.)

Huntington's Disease

Huntington's disease An inherited disorder that causes degeneration of the basal ganglia; characterized by progressively more severe uncontrollable jerking movements, writhing movements, dementia, and finally death.

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. The disease is progressive, includes cognitive and emotional changes, and eventually causes death, usually within ten to fifteen years after the symptoms begin.

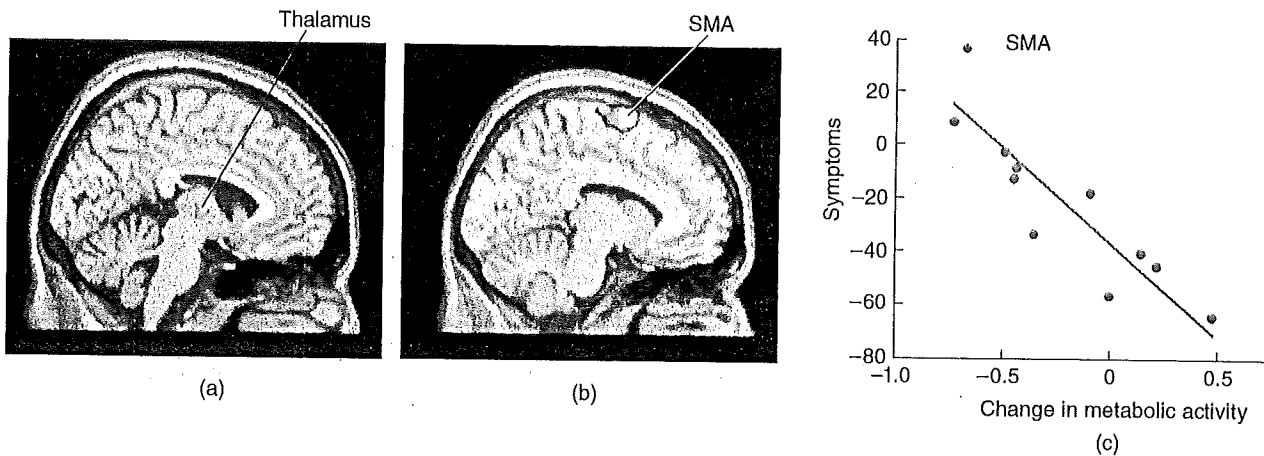


FIGURE 14.14 Gene Therapy of Parkinson's Disease. The gene for GAD, the enzyme responsible for biosynthesis of GABA, was delivered to cells in the subthalamic nucleus of patients with Parkinson's disease by means of a genetically modified virus. Functional MRI scans show (a) decreased activation of the subthalamic nucleus and (b) increased activation of the supplementary motor area. (c) The graph shows the relation between changes in the activation of the supplementary motor area and symptoms of Parkinson's disease.

From Kaplitt, M. G., Feigin, A., Tang, C., et al. *Lancet*, 2007, 369, 2097–2105. Reprinted with permission.

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. 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 (Hague, Klaffke, and Bandmann, 2005).

At present there is no treatment for Huntington's disease. However, Southwell, Ko, and Patterson (2009) prepared a special type of antibody that acts intracellularly (an *intrabody*) called Hap1. This antibody targets a portion of the huntingtin protein. Tests with five different experimental models of Huntington's disease in mice found that insertion of the Hap1 gene into the animals' brains suppressed production of mutant htt and improved the animal's disease symptoms. Another approach by DiFiglia and her colleagues (DiFiglia et al., 2007; Pfister et al., 2009) involves injection of small interfering RNAs (siRNA) into the striatum that blocked the transcription of the htt genes—and hence the production of mutant htt—in this region. The treatment decreases the size of inclusion bodies in striatal neurons, prolongs the life of the striatal neurons, and reduces the animals' motor symptoms.

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, called **Alzheimer's disease**, occurs in approximately 10 percent of the population above the age of 65 and almost 50 percent

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.

dementia (*da men sha*) 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.

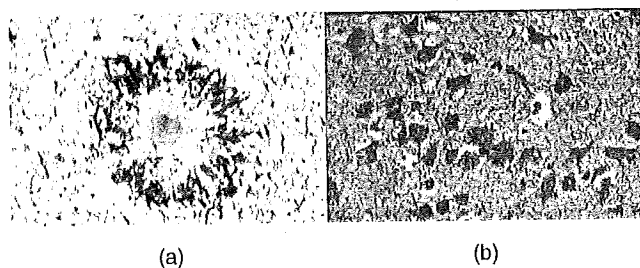


FIGURE 14.15 Microscopic Features of Alzheimer's Disease. The photomicrographs from deceased patients with Alzheimer's disease show (a) an amyloid plaque, filled with β -amyloid protein and (b) neurofibrillary tangles.

Dennis J. Selkoe.

amyloid plaque 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 ($A\beta$) (amm iloyd) A protein found in excessive amounts in the brains of patients with Alzheimer's disease.

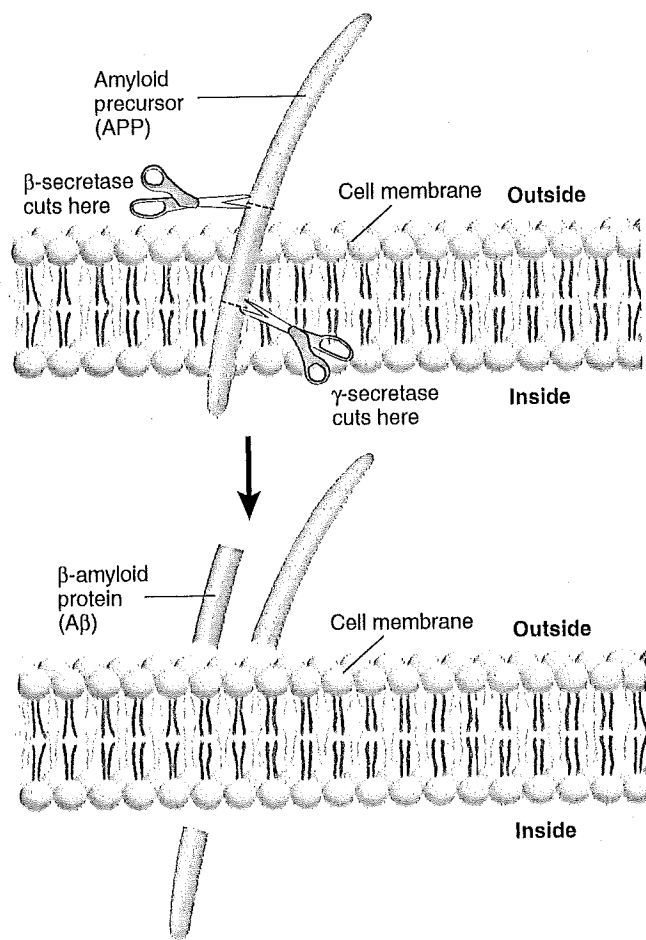


FIGURE 14.16 β -Amyloid Protein. The schematic shows the production of β -amyloid protein ($A\beta$) from the amyloid precursor protein.

of people older than 85 years. The 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. The degeneration produces 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).

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 $A\beta$).

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 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 14.15.)

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 **β -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, β -secretase, cuts the "tail" off of an APP molecule. The second, γ -secretase (gamma-secretase), cuts the "head" off. The result is a molecule of $A\beta$ that contains either forty or forty-two amino acids. (See Figure 14.16.)

The location of the second cut of the APP molecule by γ -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 α -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 $A\beta$.

Acetylcholinergic neurons in the basal forebrain are among the first cells to be affected in Alzheimer's disease. $A\beta$ serves as a ligand for the **p75 neurotrophic receptor**, a receptor that normally responds to stress signals and stimulates apoptosis (Sotthibundhu et al., 2008). Basal forebrain ACh neurons contain high levels of these receptors; thus, once the level of long-form $A\beta$ reaches a sufficiently high level, these neurons begin to die.

Figure 14.17 shows the abnormal accumulation of A β in the brain of a person with Alzheimer's disease. Klunk and his colleagues (Klunk et al., 2003; Mathis et al., 2005) developed PiB, a chemical that binds with A β and readily crosses the blood-brain barrier. They gave the patient and a healthy control subject an injection of a radioactive form of PiB and examined their brains with a PET scanner. You can see the accumulation of the protein in the patient's cerebral cortex. (See Figure 14.17.) The ability to measure the levels of A β in the brains of Alzheimer's patients will enable researchers to evaluate the effectiveness of potential treatments for the disease. When such a treatment is devised, the ability to identify the accumulation of A β 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.

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 A β , 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 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 A β 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 A β from the extracellular space in the brain (Roses, 1997; Bu, 2010). In contrast, the ApoE2 allele may actually protect people from developing Alzheimer's disease. 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 (Bu, 2010). Obesity, hypertension, high cholesterol levels, and diabetes are also risk factors, and these factors, too, are exacerbated by the presence of the ApoE4 allele (Martins et al., 2006).

Although the studies I have cited indicate that genetically triggered production of abnormal A β 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 relationship between increased number of years of formal education and cognitive performance, even in people whose brains contained significant concentrations of amyloid plaques. For example, people who had received some postgraduate education had significantly higher cognitive test scores than people with the same concentration of amyloid plaques but less formal education. 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.

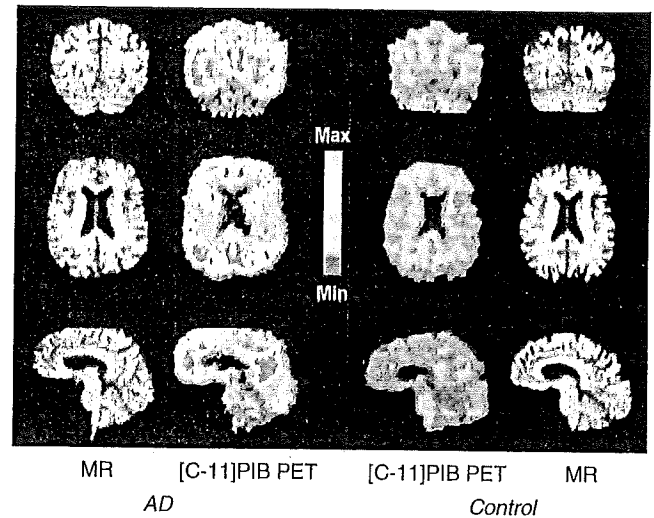


FIGURE 14.17 Detection of β -Amyloid Protein. The PET scans show the accumulation of β -amyloid protein (A β) in the brains of a patient with Alzheimer's disease. AD = Alzheimer's disease, MR = structural magnetic resonance image, [C-11]PiB PET = PET scan of brains after an injection of a radioactive ligand for A β .

Courtesy of William Klunk, Western Psychiatric Institute and Clinic, Pittsburgh, PA.

neurofibrillary tangle (new row fibrillary) A dying neuron containing intracellular accumulations of 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.

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

secretase (see cre tayss) A class of enzymes that cut the β -amyloid precursor protein into smaller fragments, including β -amyloid.

presenilin (pre 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 po 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.

Billings et al. (2007) performed an experiment 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. The investigators began training the mice early in life on the water maze task, described in Chapter 12. The mice were trained at three-month intervals between the ages of 2 to 18 months. This training delayed the accumulation of A β and led to a slower decline of the animals' performance. This study lends support to the conclusion that intellectual activity (if I can use that term for mice) delays the appearance of Alzheimer's disease.

Like the transmissible spongiform encephalopathies caused by misfolded prion proteins, the misfolded A β responsible for Alzheimer's disease can also be propagated from cell to cell, and from animal to animal. Kane et al. (2000) prepared a dilute suspension of homogenized brain tissue taken from deceased patients with Alzheimer's disease and injected some of the liquid into the brains of mice. Three months later, they found profuse development of amyloid plaques and vascular deposits of A β . Even more unsettling, Eisele et al. (2009) coated stainless-steel wires with minute amounts of misfolded A β and implanted them in the brains of mice. This procedure, too, induced β -amyloidosis in the recipients—even when the wires had been boiled before they were implanted. As we saw, prion proteins retain their infective potency even after being heated to the boiling point. Apparently, misfolded A β retains its ability to act as a seed that induces misfolding in a recipient brain. Fortunately, Eisele and her colleagues found that plasma sterilization of the wires blocked the ability of the A β to trigger the production of misfolded protein, so it is unlikely that Alzheimer's disease could be transmitted by means of surgical instruments.

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 neural 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 immunological research with AD mice. Schenk et al. (1999) and Bard et al. (2000) attempted to sensitize the immune system against A β . They injected AD mice with a vaccine that, they hoped, would stimulate the immune system to destroy A β . The treatment worked: The vaccine sup-

pressed 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.

A clinical trial with Alzheimer's patients attempted to destroy A β by sensitizing the patient's immune systems to the protein (Monson 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 A β protein. Twenty of these patients generated antibodies against A β , which slowed the course of the disease, presumably because their immune systems began destroying A β 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 A β antibodies to those who did not. As Figure 14.18 shows, antibody production significantly reduced cognitive decline. (See Figure 14.18.)

One of the patients whose immune system generated antibodies against A β 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 A β from many regions of the cerebral cortex. Unfortunately, the injections of the A β antigen caused an inflammatory reaction in the brains of 5 percent of the patients, so the clinical trial was terminated. New approaches to immunotherapy are now being prepared that will (we hope) avoid inflammatory reactions (Fu et al., 2010).

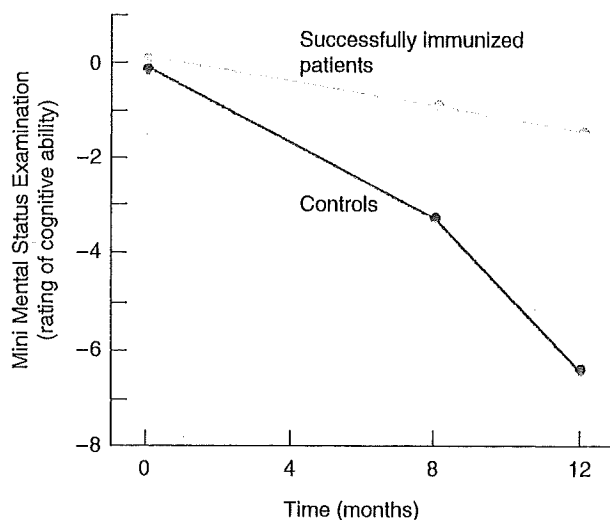


FIGURE 14.18 Immunization Against A β . The graph shows the effect of immunization against A β on the cognitive decline of patients who generated A β antibodies (successfully immunized patients) and those who did not (controls).

Based on data from Hock, C., Konietzko, U., Streffer, J. R., et al. *Neuron*, 2003, 38, 547–554.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder that attacks spinal cord and cranial nerve motor neurons (Zinman and Cudkowicz, 2011). 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 five to ten years after the onset of the disease as a result of failure of the respiratory muscles. The muscles that control eye movements are spared. Cognitive abilities are rarely affected.

Among all cases of ALS, 10 percent 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). And like the other degenerative brain disorders that I have described that involve misfolded proteins, mutant SOD1 can be transmitted from cell to cell, as prion proteins do. However, there is presently no evidence that the disease can be transmitted between individuals (Münch and Bertolotti, 2011).

SOD1 normally functions as a detoxifying enzyme found in the cytoplasm and mitochondria. It converts superoxide radicals to molecular oxygen and hydrogen peroxide (Milani et al., 2011). Superoxide radicals are naturally present in the cytoplasm, but become toxic in sufficiently high concentrations.

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 approximately two months longer than those who received a placebo (Miller et al., 2003). Clearly, research to find more effective therapies is warranted.

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*. 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.

The symptoms of multiple sclerosis often flare up and then decrease, to be followed by another increase in symptoms after varying periods of time. In most cases, this pattern (*remitting-relapsing MS*) is followed by *progressive MS* later in the course of the disease. Progressive MS is characterized by a slow, continuous increase in the symptoms of the disease.

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 promise (Aktas, Keiseier, and Hartung, 2009). 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

amyotrophic lateral sclerosis (ALS)
A degenerative disorder that attacks
the spinal cord and cranial nerve motor
neurons.

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, but it turned out to actually reduce them. Interferon β and glatiramer acetate are effective only for the remitting-relapsing form of MS, and not the progressive form.

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. One encouraging approach to treatment of MS is the transplantation of autologous hemopoietic stem cells—transplants of adult stem cells taken from a patient's own blood or bone marrow. A clinical trial with twenty-one MS patients reported significant improvements in neurological symptoms at the end of thirty-seven months (Burt et al., 2009).

Because the symptoms of remitting-relapsing MS are 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. The best way to end exploitation of MS patients by people selling useless treatments is to develop genuinely effective therapies.

SECTION 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 (PrP^c) and infectious prion protein (PrP^{Sc}) 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 PrP^c into PrP^{Sc} 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 neural development and neurogenesis, which may in turn affect 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 subthalamic nucleus, and implantation of electrodes that enable the patient to electrically stimulate the subthalamic nucleus. Fetal transplants of dopaminergic neurons have turned out to be less successful than they had initially appeared to be, probably because the α -synuclein is transferred to the grafted neurons from the recipient's own neurons. A trial of gene therapy designed to reduce excitation in the subthalamic nucleus obtained promising results.

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; a targeted mutation in mice against the *htt* gene is fatal. Evidence also suggests that inclusion bodies have

Section Summary *(continued)*

a protective function and that damage is done by mutated huntingtin dispersed throughout the cell. Animal studies that targeted intracellular antibodies against a portion of htt and that transferred small interfering RNA targeted against the htt gene have produced promising results.

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 A β protein surrounded by degenerating axons and dendrites, as well as 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. Preliminary studies with mice and people with Alzheimer's disease suggest that vaccination against A β may be helpful in treatment of this disorder. Temporary reduction of symptoms is seen in some patients who are treated with anticholinergic drugs or drugs that serve as NMDA antagonists. Exercise and intellectual stimulation appear to delay the onset of Alzheimer's disease, and obesity, high cholesterol levels, and diabetes are significant risk factors.

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 only pharmacological treatment is riluzole, a drug that reduces glutamate-induced excitotoxicity. Misfolded proteins involved in a variety of degenerative diseases, including α -synuclein, A β , tau protein, and SOD1, can transmit infection from cell to cell and in some cases from individual to individual in a manner that resembles the transmission of misfolded prion protein.

Multiple sclerosis, a demyelinating disease, is characterized by periodic attacks of neurological symptoms, usually with partial remission between attacks (remitting-relapsing MS), followed by progressive MS later in life. 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 remitting-relapsing MS are interferon β and glatiramer acetate, a mixture of synthetic peptides that appears to stimulate certain immune cells to secrete anti-inflammatory chemicals. Experimental transplantation of autologous hemopoietic stem cells shows some promise.

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 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") has fortunately been 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,

encephalitis (*en seff a lye tis*) An inflammation of the brain; caused by bacteria, viruses, or toxic chemicals.

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 tis*) 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.

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 thus 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 caused by the human immunodeficiency virus (HIV), the cause of 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 Bredesen, 1989). Brain damage associated with an HIV infection can produce a range of syndromes, from mild neurocognitive disorder to HIV-associated dementia (also called *AIDS dementia complex*, or *ADC*). Neuropathology caused by HIV infection is characterized by damage to synapses and death of neurons in the hippocampus, cerebral cortex, and basal ganglia (Mattson, Haughey, and Nath, 2005; Valcour et al., 2011). Aggressive treatment with combination antiretroviral therapy, if started soon after the infection is discovered, can prevent or minimize damage to the brain. However, active viruses can persist in the brain even when they cannot be detected in the blood, so the patients' cognitive abilities and affective state should be carefully monitored. If the viral infection is not treated, the brain damage progresses and leads to a loss of cognitive and motor functions; this is the leading cause of cognitive decline in people under 40 years of age. 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).

For several years, researchers have been puzzled by the fact that although an HIV infection certainly causes neural damage, neurons are not themselves infected by the virus. Instead, the viruses live and replicate in the brain's astrocytes. The neuropathology appears to be caused by the glycoprotein *gp120* envelope that coats the RNA that is responsible for the AIDS infection. The *gp120* binds with other proteins that trigger apoptosis (cell suicide) (Mattson, Haughey, and Nath, 2005; Alirezai et al., 2007).

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. Therefore, the patient resists having his or her neck moved.

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.

meningitis (*men in jy tis*) An inflammation of the meninges; can be caused by viruses or bacteria.

SECTION 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 HIV infection can also produce brain damage when the gp120 protein envelope of the HIV virus binds with other proteins that trigger apoptosis. Aggressive treatment with combination antiretroviral therapy can minimize brain damage. 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.

EPILOGUE | Seizure Surgery

Mrs. R's surgery was performed to remove a noncancerous brain tumor that, incidentally, produced seizures. As I mentioned in this chapter, neurosurgeons occasionally perform surgery specifically to remove brain tissue that contains a seizure focus. Such an operation, called *seizure surgery*, is performed only when drug therapy is unsuccessful.

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.

As I mentioned in this chapter, seizures often occur after a head injury, but only after a delay of several months. The cause of the

delay is related to some properties of neurons that make learning possible. Goddard (1967) implanted electrodes in the brains of rats and administered a brief, weak electrical stimulus once a day. At first the stimulation produced no effects, but after several days the stimulation began to trigger small, short seizures. As days went by, the seizures became larger and longer until the animal was finally having full-blown tonic-clonic convulsions. Goddard called the phenomenon *kindling*, because it resembled the way a small fire can be kindled to start a larger one.

Kindling appears to be analogous to learning, and it presumably involves changes in synaptic strength like those seen in long-term potentiation. It can most easily be induced in the temporal lobe, which is the place where seizure foci are most likely to occur. The probable reason for the delayed occurrence of seizures after a head injury is that it takes time for kindling to occur. The irritation produced by the brain injury eventually causes increased synaptic strength in excitatory synapses located nearby.

Kindling has become an animal model of focal-seizure disorders, and it has proved useful in research on the causes and treatment of these disorders. For example, Silver, Shin, and McNamara (1991) produced seizure foci in rats through kindling and compared the effects of some commonly used medications on both seizures (the electrical events within the brain) and convulsions (the motor manifestations of the seizures). They found that one of the drugs they tested prevented the convulsions but left seizures intact, whereas another prevented both seizures and convulsions. Because each seizure is capable of producing some brain damage through overstimulation of neurons (especially those in the hippocampal formation, which become especially active during a seizure), the goal of medical treatment should be the elimination of seizures, not simply the convulsions that accompany them. Research with the animal model of kindling will undoubtedly contribute to the effective treatment of focal-seizure disorders.

