

BIOPSYCHOLOGY, 6/e

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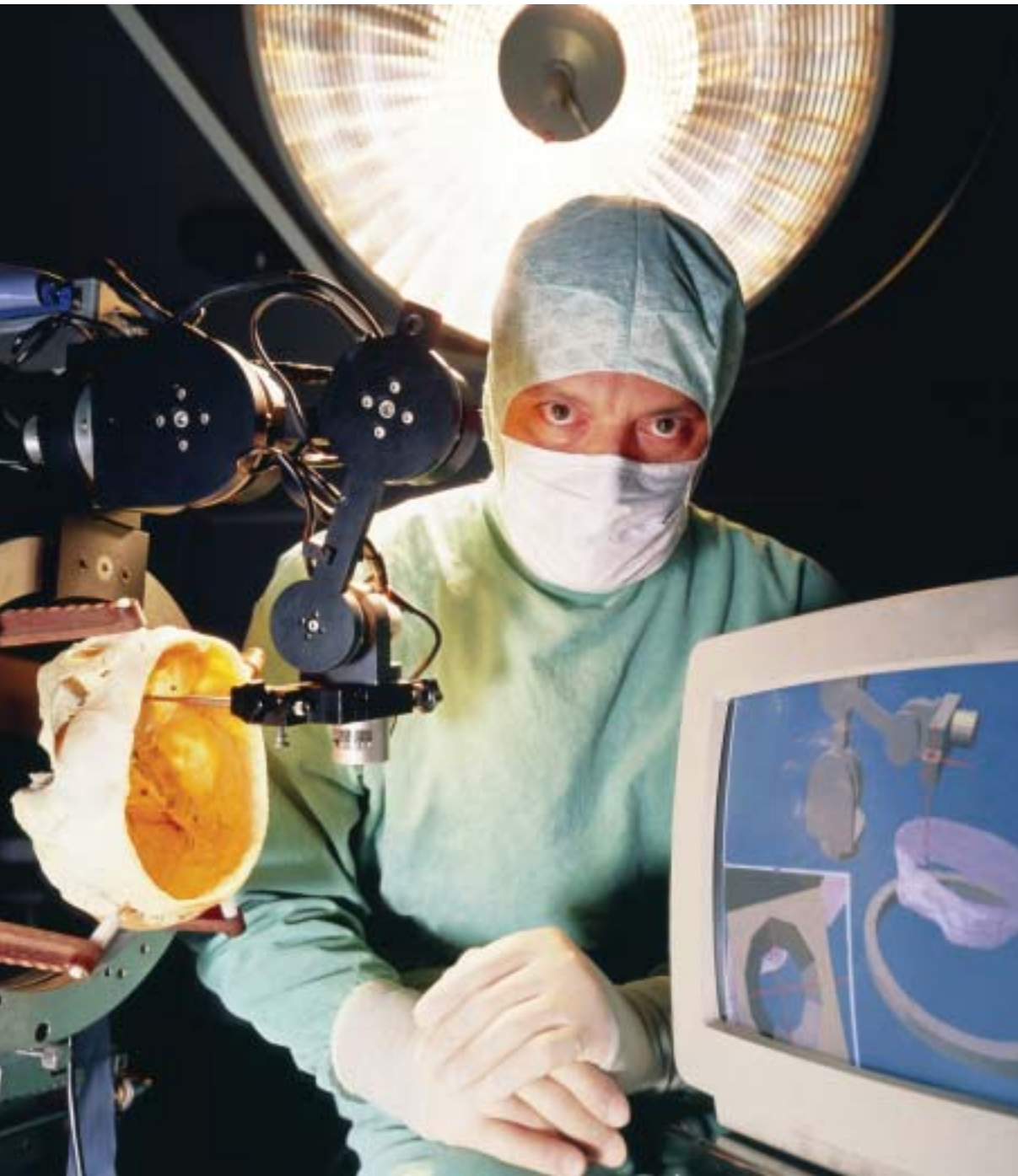
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chapter
10

Brain Damage and Neuroplasticity

Can the Brain Recover from Damage?



- 10.1** Causes of Brain Damage
- 10.2** Neuropsychological Diseases
- 10.3** Animal Models of Human Neuropsychological Diseases
- 10.4** Neuroplastic Responses to Nervous System Damage: Degeneration, Regeneration, Reorganization, and Recovery
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The study of human brain damage serves two purposes: It increases our understanding of the healthy brain, and it serves as a basis for the development of new treatments. The first three sections of this chapter focus on brain damage itself. The last two sections continue the neuroplasticity theme that was introduced in Chapter 9: The fourth focuses on the recovery and reorganization of the brain after damage, and the fifth discusses exciting new neuroplasticity-promoting treatments. But first, the continuation of the ironic case of Professor P., whom you first met in Chapter 5, relates the personal tragedy of brain damage.

The Ironic Case of Professor P.

One night Professor P. sat at his desk staring at a drawing of the cranial nerves, much like the one in Appendix III of this book. As he mulled over the location and function of each cranial nerve (see Appendix IV), the painful truth became impossible for him to deny. The irony of the situation was that Professor P. was a neuroscientist, all too familiar with what he was experiencing.

His symptoms started subtly, with slight deficits in balance. He probably wouldn't have even noticed them except that his experience as a mountaineer had taught him to pay attention to such things. Professor P. chalked these occasional lurches up to aging—after all, he thought to himself, he was past his prime, and things like this happen. Similarly, his doctor didn't seem to think that it was a problem worth looking into, but Professor P. monitored his symptoms carefully nevertheless. Three years later, his balance problems still unabated, Professor P. really started to worry. He was trying to talk with a colleague on the phone but was not having much success because of what he thought was a bad connection. Then, he changed the phone to his other ear, and all of a sudden, the faint voice on the other end became louder. He tried this switch several times over the ensuing days, and the conclusion became inescapable: Professor P. was going deaf in his right ear.

Professor P. immediately made an appointment with his doctor, who referred him to a specialist. After a cursory and poorly controlled hearing test, the specialist gave him good news. "You're fine, Professor P.; lots of people experience hearing loss when they reach middle age, and your problems are not serious enough to worry about." To this day, Professor P. regrets that he did not insist on a second opinion; his problem would have been so much easier to deal with at that stage.

It was about a year later that Professor P. sat staring at the illustration of the cranial nerves. By then he had begun to experience numbness on the right side of his mouth; he was having minor problems swallowing; and his right tear ducts were not releasing enough tears. There he sat staring at the point where the auditory and vestibular nerves come together to form cranial nerve VIII (the auditory-vestibular nerve). He knew it was there, and he knew that it was large enough to be affecting cranial nerves V through X as well, but he didn't know what it was: a tumor, a stroke, an angioma, an infection? Was he going to die? Was his death going to be terrible and lingering as his brain and intellect gradually deteriorated?

He didn't make an appointment with his doctor right away. A friend of his was conducting a brain MRI study, and Professor P. volunteered to be a control subject, knowing that his problem would show up on the scan. It did: a large tumor sitting, as predicted, on the right cranial nerve VIII.

Then, MRI in hand, Professor P. went back to his doctor, who referred him to a neurologist, who in turn referred him to a neurosurgeon. Several stressful weeks later, Professor P. found himself on life support in the intensive care unit of his local hospital, hands tied to the bed and tubes emanating seemingly from every part of his body. You see, the tumor was so convoluted that it took 6 hours to remove; and during the 6 hours that Professor P.'s brain was exposed, air entered his circulatory system, and he developed pneumonia. Near death and hallucinating from the morphine, Professor P. thought he heard his wife, Maggie, calling for help and tried to go to her assistance: That is why he was tied down. One gentle morphine-steeped professor was no match for five burly nurses intent on saving his life.

Professor P.'s auditory-vestibular nerve was transected during his surgery, which has left him permanently deaf and without vestibular function on the right side. He was also left with partial hemifacial paralysis, including serious blinking and tearing problems, but these facial symptoms have largely cleared up.

Professor P. has now returned to his students, his research, and his writing, hoping that the tumor was completely removed and that he will not have to endure another surgery. Indeed, at the very moment that I am writing these words, Professor P. is working on the forthcoming edition of his textbook. . . . If it has not yet occurred to you, I am Professor P.

Clinical Implications

the painful truth became impossible for him to deny. The irony of the situation was that Professor P.

ON THE CD



Visit the module *My Tumor and Welcome To It*. Pinel, relaxing in his own garden, describes his struggle with a brain tumor.

10.1 Causes of Brain Damage

This section provides an introduction to six causes of brain damage: brain tumors, cerebrovascular disorders, closed-head injuries, infections of the brain, neurotoxins, and genetic factors. It concludes with a discussion of programmed cell death, which mediates many forms of brain damage.

Clinical Implications

Brain Tumors

A **tumor**, or **neoplasm** (literally, “new growth”), is a mass of cells that grows independently of the rest of the body (see Wechsler-Reya & Scott, 2001). In other words, it is a cancer.

About 20% of tumors found in the human brain are **meningiomas** (see Figure 10.1)—tumors that grow between the *meninges*, the three membranes that cover the central nervous system. All meningiomas are **encapsulated tumors**—tumors that grow within their own membrane. As a result, they are particularly easy to identify on a CT scan, they can influence the function of the brain only by the pressure they exert on surrounding tissue, and they are almost always **benign tumors**—tumors that are surgically removable with little risk of further growth in the body (see Grimson et al., 1999).

Unfortunately, encapsulation is the exception rather than the rule when it comes to brain tumors. Aside from meningiomas, most brain tumors are infiltrating. **Infiltrating tumors** are those that grow diffusely through surrounding tissue. As a result, they are usually **malignant tumors**; it is difficult to remove or destroy them completely, and any cancerous tissue that remains after surgery continues to grow.

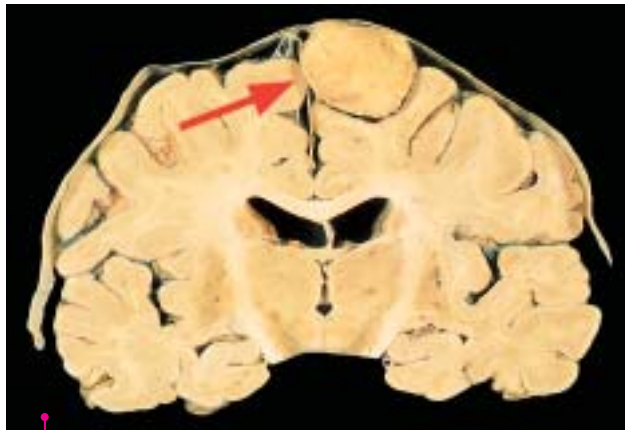


FIGURE 10.1 A meningioma. (Courtesy of Kenneth Berry, Head of Neuropathology, Vancouver General Hospital.)

About 10% of brain tumors do not originate in the brain. They grow from infiltrating tumor fragments carried to the brain by the bloodstream from some other part of the body. (The brain is a particularly fertile ground for tumor growth.) These tumors are called **metastatic tumors**; *metastasis* refers to the transmission of disease from one organ to another. Most metastatic brain tumors originate as cancers of the lungs. Obviously, the chance of recovering from a cancer that has already attacked two or more separate sites is slim at best. Figure 10.2 on page 234 illustrates the ravages of metastasis.

Fortunately, my tumor was encapsulated. Encapsulated tumors that grow on cranial nerve VIII are referred to as *acoustic neuromas* (neuromas are tumors that grow on nerves or tracts). Figure 10.3 on page 234 is an MRI scan of my acoustic neuroma, the very same scan that I took to my doctor.

Cerebrovascular Disorders

Strokes are sudden-onset cerebrovascular disorders that cause brain damage. There are two major types of strokes: those resulting from cerebral hemorrhage and those resulting from cerebral ischemia (pronounced “iss-KEEM-ee-a”). In the United States, stroke is the third leading cause of death and the most common cause of adult disability (Janardhan & Qureshi, 2004). Common consequences of stroke are amnesia, aphasia (language difficulties), paralysis, and coma. The area of dead or dying tissue produced by a stroke is called an *infarct*.

Cerebral Hemorrhage **Cerebral hemorrhage** (bleeding in the brain) occurs when a cerebral blood vessel ruptures and blood seeps into the surrounding neural tissue and damages it. Bursting aneurysms are a common cause of intracerebral hemorrhage. An **aneurysm** is a pathological balloonlike dilation that forms in the wall of a blood vessel at a point where the elasticity of the vessel wall is defective. Aneurysms can be **congenital** (present at birth) or can result from exposure to vascular poisons or infection (see Kalaria, 2001). Individuals who have aneurysms should make every effort to avoid high blood pressure.

Cerebral Ischemia **Cerebral ischemia** is a disruption of the blood supply to an area of the brain. The three main causes of cerebral ischemia are thrombosis, embolism, and arteriosclerosis. In **thrombosis**, a plug called a *thrombus* is formed and blocks blood flow at the site of its formation. A thrombus may be composed of a blood clot, fat, oil, an air bubble, tumor cells, or any

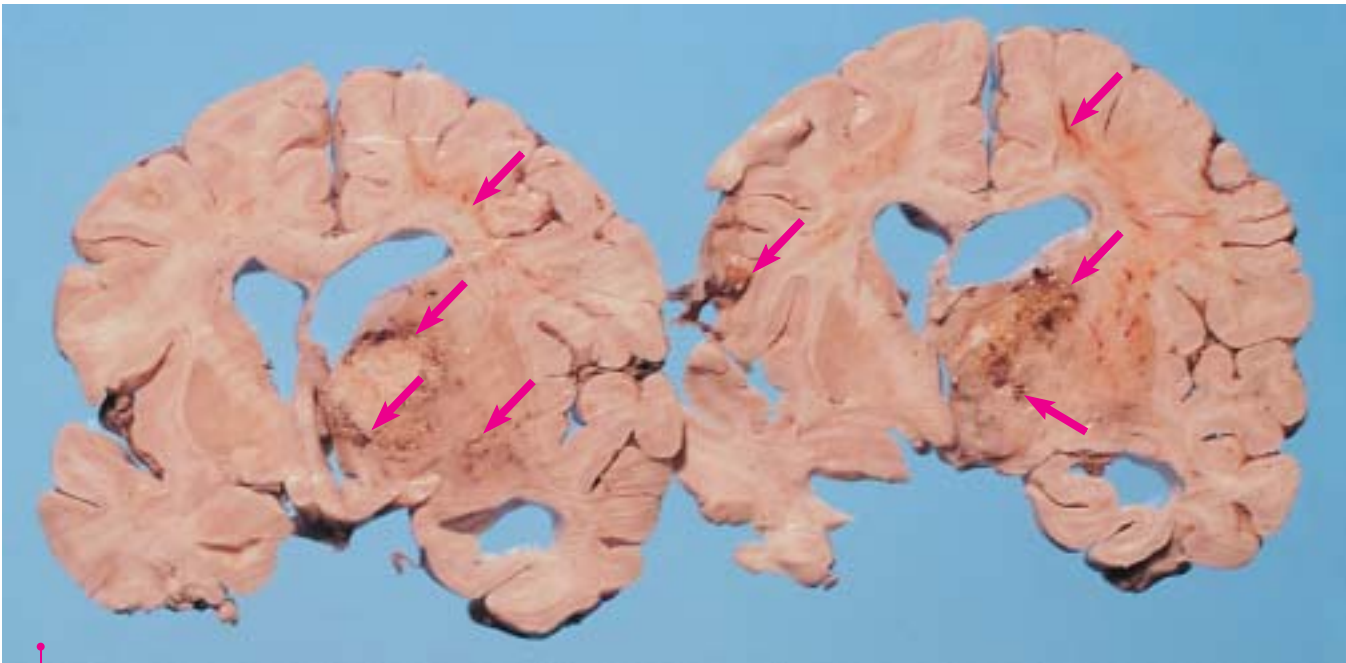


FIGURE 10.2 Multiple metastatic brain tumors. The arrows indicate some of the more advanced areas of metastatic tumor development.

combination thereof. **Embolism** is similar except that the plug, called an *embolus* in this case, is carried by the blood from a larger vessel, where it was formed, to a smaller one, where it becomes lodged; in essence, an

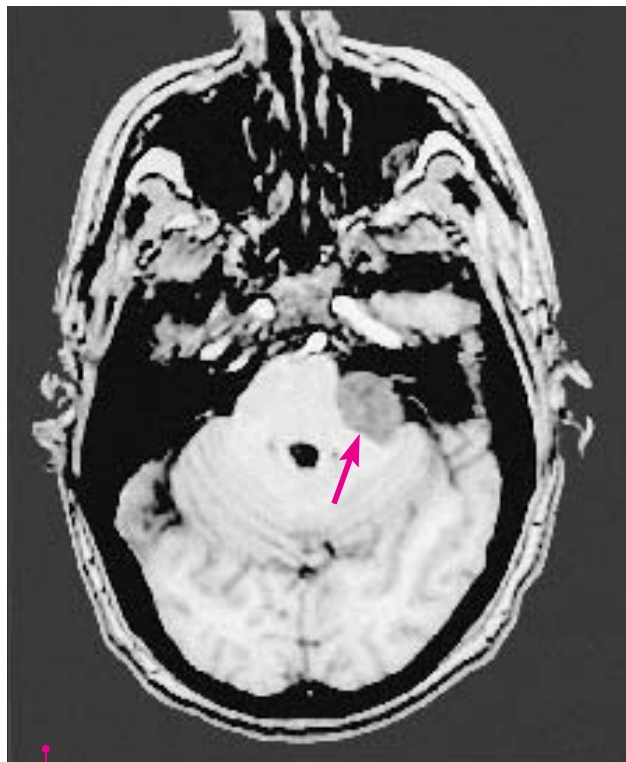


FIGURE 10.3 An MRI of Professor P's acoustic neuroma. The arrow indicates the tumor.

embolus is just a thrombus that has taken a trip. In **arteriosclerosis**, the walls of blood vessels thicken and the channels narrow, usually as the result of fat deposits; this narrowing can eventually lead to complete blockage of the blood vessels (Libby, 2002). The *angiogram* in Figure 10.4 illustrates partial blockage of one carotid artery.

Much of the damage produced by cerebral ischemia takes a day or two to develop fully, and, paradoxically,

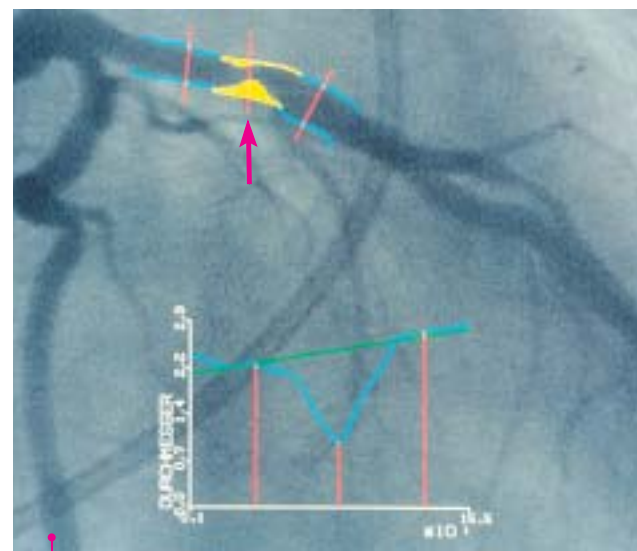


FIGURE 10.4 An angiogram that illustrates narrowing of the carotid artery (see arrow), the main pathway of blood to the brain. Compare this angiogram with the normal angiogram in Figure 5.1.

some of the brain's own neurotransmitters play a key role in its development (Wahlgren & Ahmed, 2004). Much of the brain damage associated with stroke is a consequence of excessive release of excitatory amino acid neurotransmitters, in particular **glutamate**, the brain's most prevalent excitatory neurotransmitter.

Here is how this mechanism is thought to work (see Dirnagl, Iadecola, & Moskowitz, 1999). After a blood vessel becomes blocked, many of the blood-deprived neurons become overactive and release excessive quantities of glutamate. The glutamate in turn overactivates glutamate receptors in the membranes of postsynaptic neurons; the glutamate receptors that are most involved in this reaction are the **NMDA (N-methyl-D-aspartate)**

receptors. As a result, large numbers of Na^+ and Ca^{2+} ions enter the postsynaptic neurons.

The excessive internal concentrations of Na^+ and Ca^{2+} ions affect the postsynaptic neurons in two ways: They trigger the release of excessive amounts of glutamate from them, thus spreading the toxic cascade to yet other neurons; and they trigger a sequence of internal reactions that ultimately kill the postsynaptic neurons. (See Figure 10.5.)

Ischemia-induced brain damage has three important properties (Kriegelstein, 1997). First, it takes a while to develop. Soon after a temporary cerebral ischemic episode, say, one 10 minutes in duration, there usually is little or no evidence of brain damage; however,

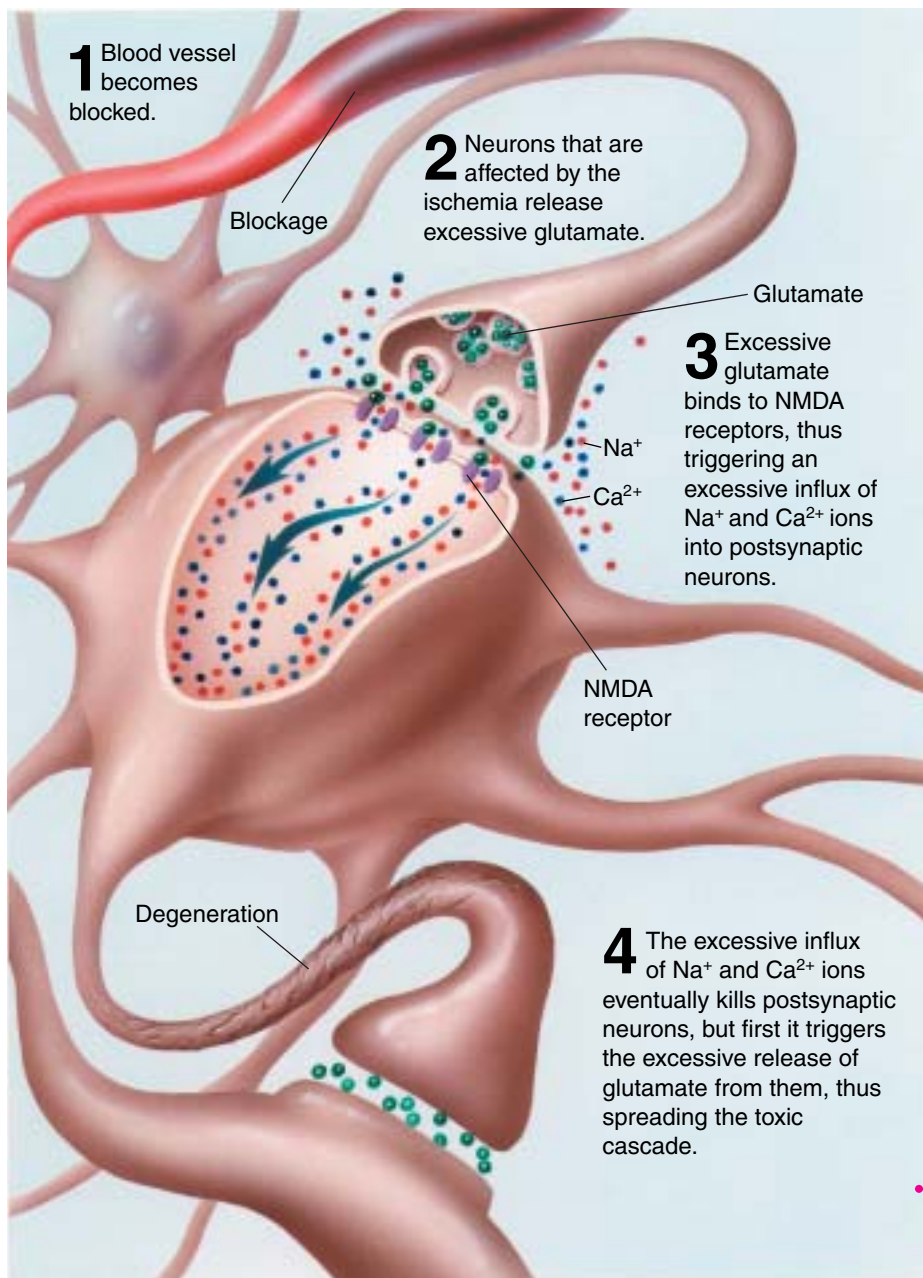


FIGURE 10.5 The cascade of events by which the stroke-induced release of glutamate kills neurons.

substantial neuron loss can often be detected a day or two later. Second, ischemia-induced brain damage does not occur equally in all parts of the brain; particularly susceptible are neurons in certain areas of the hippocampus (Ohtaki et al., 2003). Third, the mechanisms of ischemia-induced damage vary somewhat from structure to structure within the brain.

An exciting implication of the discovery that excessive glutamate release causes much of the brain damage associated with stroke is the possibility of preventing stroke-related brain damage by blocking the glutamatergic cascade. The search is on for a glutamate antagonist that is effective and safe for use in human stroke victims (Leker & Shohami, 2002; Lo, Dalkara, & Moskowitz, 2003). Several have proved to be effective in laboratory animals, but so far none has been shown to limit brain damage from strokes in humans. Wahlgren and Ahmed (2004) have argued that if such treatments are to be effective, they need to be initiated in the ambulance, not hours later in the hospital.

Closed-Head Injuries

It is not necessary for the skull to be penetrated for the brain to be seriously damaged. In fact, any blow to the head should be treated with extreme caution, particularly when confusion, sensorimotor disturbances, or loss of consciousness ensues. Brain injuries produced by blows that do not penetrate the skull are called *closed-head injuries*.

Contusions are closed-head injuries that involve damage to the cerebral circulatory system. Such damage produces internal hemorrhaging, which results in a hematoma. A **hematoma** is a localized collection of clotted blood in an organ or tissue—in other words, a bruise.

It is paradoxical that the very hardness of the skull, which protects the brain from penetrating injuries, is the major factor in the development of contusions. Contusions from closed-head injuries occur when the brain slams against the inside of the skull. As Figure 10.6 illustrates, blood from such injuries can accumulate in the *subdural space*—the space between the dura mater and arachnoid membrane—and severely distort the surrounding neural tissue.

It may surprise you to learn that contusions frequently occur on the side of the brain opposite the side struck by a blow. The reason for such so-called **contrecoup injuries** is that the blow causes the brain to strike the inside of the skull on the other side of the head.

When there is a disturbance of consciousness following a blow to the head and there is no evidence of a contusion or other structural damage, the diagnosis is **concussion**. It is commonly assumed that concussions entail a temporary disruption of normal cerebral function with no long-term damage. However, the punch-drunk syndrome suggests otherwise. The **punch-**

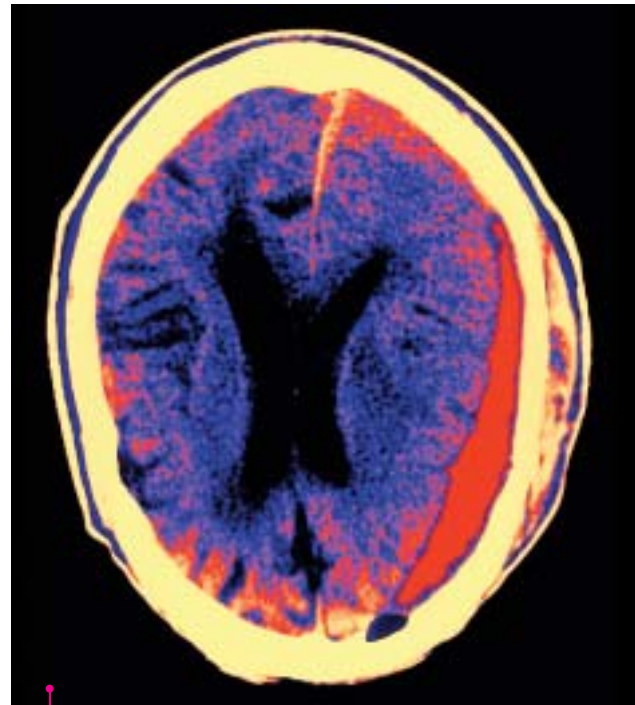


FIGURE 10.6 A CT scan of a subdural hematoma. Notice that the subdural hematoma has displaced the left lateral ventricle.

drunk syndrome is the **dementia** (general intellectual deterioration) and cerebral scarring that is observed in boxers and other individuals who experience repeated concussions. If there were no damage associated with a single concussion, the effects of many concussions could not summate to produce severe damage (McCrorry & Berkovic, 1998).

One of the most dangerous aspects of concussion is the complacency with which it is regarded. Flippant references to it, such as “having one’s bell rung,” do little to communicate its hazards.

The Case of Jerry Quarry, Ex-Boxer

Jerry Quarry thumps his hard belly with both fists. Smiles at the sound. Like a stone against a tree.

“Feel it,” he says proudly, punching himself again and again.

He pounds big, gnarled fists into meaty palms. Cocks his head. Stares. Vacant blue eyes. Punch-drunk at 50. Medical name: *Dementia pugilistic* [punch-drunk syndrome]. Cause: Thousands of punches to the head.

A top heavyweight contender in the 1960s and ’70s, Quarry now needs help shaving, showering, putting on shoes and socks. Soon, probably, diapers. His older brother, James, cuts meat into little pieces so he won’t choke. Jerry smiles like a kid. Shuffles like an old man.

Clinical Implications

Thinking Critically

Slow, slurred speech. Random thoughts snagged on branches in a dying brain. Memories twisted. Voices no one else hears. (Steve Wiltstein, Associated Press, 1995)

Infections of the Brain

An invasion of the brain by microorganisms is a *brain infection*, and the resulting inflammation is **encephalitis**. There are two common types of brain infections: bacterial infections and viral infections.

Bacterial Infections When bacteria infect the brain, they often lead to the formation of *cerebral abscesses*—pockets of pus in the brain. They also often attack and inflame the meninges, creating a disorder known as **meningitis**, which is fatal in 25% of adults (Nau & Brück, 2002). Penicillin and other antibiotics sometimes eliminate the infection, but they cannot reverse brain damage that has already been produced.

Syphilis is one bacterial brain infection you have likely heard about. Syphilis bacteria are passed from infected to noninfected individuals through contact with genital sores. The infecting bacteria then go into a dormant stage for several years before they become virulent and attack many parts of the body, including the brain. The syndrome of insanity and dementia that results from a syphilitic infection is called **general paresis**.

Syphilis has a particularly interesting history (see Klawans, 1990). The first Europeans to visit America stripped the natives of their gold and left smallpox in return. But the deal was not totally one-sided; the booty carried back to Europe by Columbus's sailors and the adventurers that followed included a cargo of syphilis bacteria. Until then, syphilis had been restricted to the Americas, but it quickly spread to the rest of the world.

Viral Infections There are two types of viral infections of the nervous system: those that have a particular affinity for neural tissue and those that attack neural tissue but have no greater affinity for it than for other tissues.

Rabies, which is usually transmitted through the bite of a rabid animal, is a well-known example of a viral infection that has a particular affinity for the nervous system. The fits of rage caused by the virus's effects on the brain increase the probability that rabid animals that normally attack by biting (e.g., dogs, cats, raccoons, bats, and mice) will spread the disorder. Although the effects of the rabies virus on the brain are ultimately lethal, the virus does have one redeeming feature: It does not usually attack the brain for at least a month after it has been contracted, thus allowing time for a preventive vaccination.

The *mumps* and *herpes* viruses are common examples of viruses that can attack the nervous system but have no special affinity for it. Although these viruses sometimes spread into the brain, they typically attack other tissues of the body.

Viruses may play a far greater role in neuropsychological disorders than is currently thought. Their involvement in the *etiology* (cause) of disorders is often difficult to recognize because they may lie dormant for many years before producing symptoms.

Neurotoxins

The nervous system can be damaged by exposure to any one of a variety of toxic chemicals, which can enter general circulation from the gastrointestinal tract, from the lungs, or through the skin. For example, heavy metals such as mercury and lead can accumulate in the brain and permanently damage it, producing a **toxic psychosis** (chronic insanity produced by a neurotoxin). Have you ever wondered why Alice in Wonderland's Mad Hatter was a mad hatter and not a mad something else? In 18th- and 19th-century England, hatmakers were commonly driven mad by the mercury employed in the preparation of the felt used to make hats. In a similar vein, the word *crackpot* originally referred to the toxic psychosis observed in some people in England—primarily the poor—who steeped their tea in cracked ceramic pots with lead cores.

Sometimes, the very drugs used to treat neurological disorders prove to have toxic effects. For example, some of the antipsychotic drugs introduced in the early 1950s produced effects of distressing scope. By the late 1950s, millions of psychotic patients were being maintained on these new drugs. However, after several years of treatment, many of the patients developed a motor disorder termed **tardive dyskinesia (TD)**. Its primary symptoms are involuntary smacking and sucking movements of the lips, thrusting and rolling of the tongue, lateral jaw movements, and puffing of the cheeks. Safer antipsychotic drugs have since been developed.

Brain damage from the effects of recreational drugs is also a serious problem. You learned in Chapter 1 that alcohol produces brain damage through a combination of its direct neurotoxic effects and its effects on thiamine metabolism. Do you remember the case of Jimmie G.?

Some neurotoxins are *endogenous* (produced by the patient's own body). For example, the body can produce antibodies that attack particular components of the nervous system (see Newsom-Davis & Vincent, 1991).

Genetic Factors

Normal human cells have 23 pairs of chromosomes; however, sometimes accidents of cell division occur, and the fertilized egg ends up with an abnormal chromosome or with an abnormal number of normal chromosomes. Then, as the fertilized egg divides and redivides, these chromosomal anomalies are duplicated in every cell of the body.

Most neuropsychological diseases of genetic origin are caused by abnormal recessive genes that are passed from parent to offspring. (In Chapter 2, you learned about

one such disorder, *phenylketonuria*.) Inherited neuropsychological disorders are rarely associated with dominant genes because dominant genes that disturb neuropsychological function tend to be eliminated from the gene pool—every individual who carries one is at a major survival and reproductive disadvantage. In contrast, individuals who inherit one abnormal recessive gene do not develop the disorder, and the gene is passed on to future generations.

There are, however, two possible situations in which neurological disorders can be associated with dominant genes. One is the case in which an abnormal dominant gene manifests itself only in rare environmental circumstances. The other is the case in which an abnormal dominant gene is not expressed until the individual is well past puberty.

Down syndrome is a genetic disorder that is caused not by a faulty gene, but by a genetic accident, which occurs in 0.15% of births. The usual cause is an accident that happens during ovulation. During ovulation an extra chromosome 21 is created in the egg; thus, when the egg is fertilized, there are three rather than two in the zygote. The consequences of the superfluous chromosome 21 are unfortunate. In addition to characteristic disfigurement—flattened skull and nose, folds of skin over the inner corners of the eyes, and short fingers (see Figure 10.7)—intellectual development is retarded, and there are often serious medical complications. The probability of giving birth to a child with Down syndrome increases with advancing maternal age (Carothers et al., 2001).

Rapid progress is being made in locating and characterizing the faulty genes that are associated with some neuropsychological disorders. Once this goal is achieved, it will open up a variety of new treatment and prevention strategies, such as splicing in healthy genes to replace faulty ones and developing specific DNA-binding proteins that can enter neurons and block the expression of faulty genes.

Programmed Cell Death

You learned in Chapter 9 that neurons and other cells have genetic programs for suicide, that the process by which cells destroy themselves is called **apoptosis** (pronounced “A-poe-toe-sis”), and that apoptosis plays a critical role in early development by eliminating some of the excessive neurons that are initially created. Apoptosis also plays a role in brain damage. Indeed, each of the six causes of brain damage that have already been discussed in this chapter (tumors, cerebrovascular disorders, closed-head injuries, infections, toxins, and genetic factors) appears to produce its effect, in part, by activating apoptotic programs of self-destruction (Allsop & Fazakerley, 2000; Dirnagl, Simon, & Hallenbeck, 2003; Nijhawan, Honarpour, & Wang, 2000).

It was once assumed that the death of neurons following brain damage was totally necrotic—*necrosis* is passive cell death resulting from injury. It now seems that if cells are not damaged too severely, they will attempt to marshal enough resources to commit suicide. However, cell death is not an either-or situation: Some damaged and dying cells display signs of both necrosis and apoptosis (see Elibol et al., 2001).

It is easy to understand why apoptotic mechanisms have evolved: Apoptosis is clearly more adaptive than necrosis. In necrosis, the damaged neuron swells and breaks apart, beginning in the axons and dendrites and ending in the cell body. This fragmentation leads to inflammation, which can damage other cells in the vicinity. Necrotic cell death is quick, it is typically complete in a few hours. In contrast, apoptotic cell death is slow, typically requiring a day or two. Apoptosis of a neuron proceeds gradually, starting with shrinkage of the cell body. Then, as parts of the neuron die, the resulting debris is packaged in vesicles. As a result, there is no inflammation, and damage to nearby cells is kept to a minimum.

FIGURE 10.7 A child with Down syndrome before and after plastic surgery. The purpose of these photographs is not to promote cosmetic surgery but to challenge our culture’s reaction to patients with Down syndrome. The little girl on the left and the little girl on the right are the same girl; they deserve the same respect and consideration. (Courtesy of Kenneth E. Salyer, Director, International Craniofacial Institute.)



10.2 Neuropsychological Diseases

The preceding section focused on the causes of human brain damage. This section considers five diseases that are associated with brain damage: epilepsy, Parkinson's disease, Huntington's disease, multiple sclerosis, and Alzheimer's disease.

Clinical Implications

Epilepsy

The primary symptom of **epilepsy** is the epileptic seizure, but not all persons who suffer seizures are considered to have epilepsy. It is not uncommon for an otherwise healthy person to have a seizure during temporary illness or following exposure to a convulsive agent. The label *epilepsy* is applied to only those patients whose seizures appear to be generated by their own chronic brain dysfunction. About 1% of the population are diagnosed as epileptic at some point in their lives.

In view of the fact that epilepsy is characterized by epileptic seizures—or, more accurately, by spontaneously recurring epileptic seizures—you might think that the task of diagnosing this disorder would be an easy one. But you would be wrong. The task is made difficult by the diversity and complexity of epileptic seizures. You are probably familiar with seizures that take the form of **convulsions** (motor seizures); these often involve tremors (*clonus*), rigidity (*tonus*), and loss of both balance and consciousness. But many seizures do not take this form; instead, they involve subtle changes of thought, mood, or behavior that are not easily distinguishable from normal ongoing activity.

There are many causes of epilepsy. Indeed, all of the causes of brain damage that have been described in this chapter—including viruses, neurotoxins, tumors, and blows to the head—can cause epilepsy, and over 70 different faulty genes have been linked to it (Noebels, 2003). Many cases of epilepsy appear to be associated with faults at inhibitory synapses that cause large numbers of neurons to fire in synchronous bursts (Köhling, 2002).

The diagnosis of epilepsy rests heavily on evidence from electroencephalography (EEG). The value of scalp electroencephalography in confirming suspected cases of epilepsy stems from the fact that epileptic seizures are associated with bursts of high-amplitude EEG spikes, which are often apparent in the scalp EEG during an attack (see Figure 10.8), and from the fact that individual spikes often punctuate the scalp EEGs of epileptics between attacks. (Cohen et al., 2002). Although the observation of spontaneous epileptic discharges is incontrovertible evidence of epilepsy, the failure to observe them does not always mean that the patient is not epileptic. It could mean that the patient is epileptic but did not happen to experience epileptic discharges during the test or

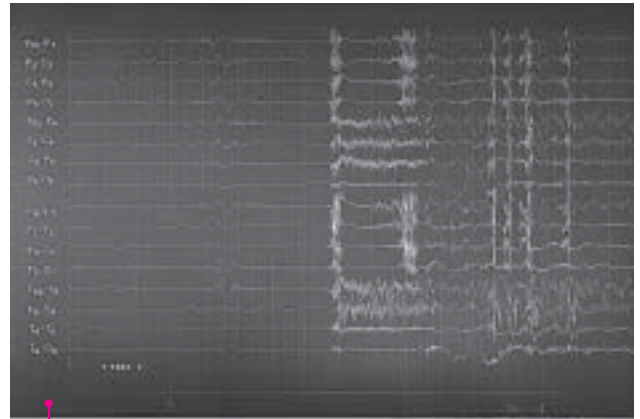


FIGURE 10.8 Cortical electroencephalogram (EEG) record from various locations on the scalp during the beginning of a complex partial seizure. The letters and numbers to the left of each trace indicate the conventional locations of the electrodes over the frontal (F), temporal (T), parietal (P), and occipital (O) lobes.

that epileptic discharges did occur during the test but were not recorded through the scalp electrodes.

Some epileptics experience peculiar psychological changes just before a convulsion. These changes, called **epileptic auras**, may take many different forms—for example, a bad smell, a specific thought, a vague feeling of familiarity, a hallucination, or a tightness of the chest. Epileptic auras are important for two reasons. First, the nature of the auras provides clues concerning the location of the epileptic focus. Second, because the epileptic auras experienced by a particular patient are often similar from attack to attack, they warn the patient of an impending convulsion.

Once an individual has been diagnosed as epileptic, it is usual to assign the epilepsy to one of two general categories—*partial epilepsy* or *generalized epilepsy*—and then to one of their respective subcategories. The various seizure types are so different from one another that epilepsy is best viewed not as a single disease but as a number of different, but related, diseases. Supporting this view is the fact that epilepsy has no single cause; almost any kind of brain disturbance can cause seizures.

Partial Seizures A **partial seizure** is a seizure that does not involve the entire brain. The epileptic neurons at a focus begin to discharge together in bursts, and it is this synchronous bursting of neurons (see Figure 10.9 on page 240) that produces epileptic spiking in the EEG. The synchronous activity may stay restricted to the focus until the seizure is over, or it may spread to other areas of the brain—but, in the case of partial seizures, not to

FIGURE 10.9 The bursting of an epileptic neuron, recorded by extracellular unit recording.



the entire brain. The specific behavioral symptoms of a partial epileptic seizure depend on where the disruptive discharges begin and into what structures they spread. Because partial seizures do not involve the entire brain, they are not usually accompanied by a total loss of consciousness or equilibrium.

There are two major categories of partial seizures: simple and complex. **Simple partial seizures** are partial seizures whose symptoms are primarily sensory or motor or both; they are sometimes called *Jacksonian seizures* after the famous 19th-century neurologist Hughlings Jackson. As the epileptic discharges spread through the sensory or motor areas of the brain, the symptoms spread systematically through the body.

In contrast, **complex partial seizures** are often restricted to the temporal lobes, and those who experience them are often said to have *temporal lobe epilepsy*. During a complex partial seizure, the patient engages in compulsive, repetitive, simple behaviors commonly referred to as *automatisms* (e.g., doing and undoing a button) and in more complex behaviors that appear almost normal. The diversity of complex partial seizures is illustrated by the following four cases.

The Subtlety of Complex Partial Seizures: Four Cases

Clinical Implications

A war veteran subject to many automatisms read in the newspaper about a man who had embraced a woman in a park, followed her into a women's toilet, and then boarded a bus. From the description given, he realized he was the man.

One morning a doctor left home to answer an emergency call from the hospital and returned several hours later, a trifle confused, feeling as though he had experienced a bad dream. At the hospital he had performed a difficult . . . [operation] with his usual competence, but later had done and said things deemed inappropriate.

A young man, a music teacher, when listening to a concert, walked down the aisle and onto the platform, circled the piano, jumped to the floor, did a hop, skip, and jump up the aisle, and regained his senses when part way home. He often found himself on a trolley [bus] far from his destination.

A man in an attack went to his employer and said, "I have to have more money or [I] quit." Later, to his sur-

prise, he found that his salary had been raised. (Lennox, 1960, pp. 237–238.)

Although patients appear to be conscious throughout their complex partial seizures, they usually have little or no subsequent recollection of them. About half of all cases of epilepsy are of the complex partial variety—the temporal lobes are particularly susceptible to epileptic discharges.

Generalized Seizures **Generalized seizures** involve the entire brain. Some begin as focal discharges that gradually spread through the entire brain. In other cases, the discharges seem to begin almost simultaneously in all parts of the brain. Such sudden-onset generalized seizures may result from diffuse pathology or may begin focally in a structure, such as the thalamus, that projects to many parts of the brain.

Like partial seizures, generalized seizures occur in many forms. One is the **grand mal** (literally, "big trouble") **seizure**. The primary symptoms of a grand mal seizure are loss of consciousness, loss of equilibrium, and a violent *tonic-clonic convulsion*—a convulsion involving both tonus and clonus. Tongue biting, urinary incontinence, and *cyanosis* (turning blue from excessive extraction of oxygen from the blood during the convulsion) are common manifestations of grand mal convulsions. The **hypoxia** (shortage of oxygen supply to tissue, for example, to the brain) that accompanies a grand mal seizure can itself cause brain damage, some of which develops slowly after the attack and is mediated by the excessive release of excitatory amino acid neurotransmitters.

A second major category of generalized seizure is the **petit mal** (literally, "small trouble") **seizure** (see Crunelli & Leresche, 2002). Petit mal seizures are not associated with convulsions; their primary behavioral symptom is the *petit mal absence*—a disruption of consciousness that is associated with a cessation of ongoing behavior, a vacant look, and sometimes fluttering eyelids. The EEG of a petit mal seizure is different from that of other seizures; it is a bilaterally symmetrical **3-per-second spike-and-wave discharge** (see Figure 10.10). Petit mal seizures are most common in children, and they frequently cease at puberty. They often go undiagnosed; thus, children with petit mal epilepsy are sometimes considered to be "daydreamers" by their parents and teachers.

Although there is no cure for epilepsy, the frequency and severity of seizures can often be reduced by anti-

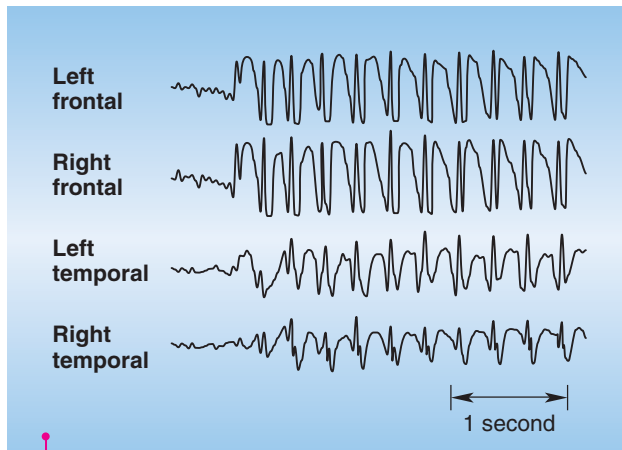


FIGURE 10.10 The bilaterally symmetrical, 3-per-second spike-and-wave EEG discharge that is associated with petit mal epileptic seizures.

convulsant medication. Brain surgery is sometimes prescribed in life-threatening situations.

Parkinson's Disease

Parkinson's disease is a movement disorder of middle and old age that affects about 0.5% of the population (see Strickland & Bertoni, 2004). It is about 2.5 times more prevalent in males than in females (see Sawada & Shimohama, 2000; Wooten et al., 2004).

The initial symptoms of Parkinson's disease are mild—perhaps no more than a slight stiffness or tremor of the fingers—but they inevitably increase in severity with advancing years. The most common symptoms of the full-blown disorder are a tremor that is pronounced during inactivity but not during voluntary movement or sleep, muscular rigidity, difficulty initiating movement, slowness of movement, and a masklike face. Pain and depression often develop before the motor symptoms become severe.

Although Parkinson's patients often display some cognitive deficits, dementia is not typically associated with the disorder. In essence, Parkinson's disease victims are thinking people trapped inside bodies they cannot control. Do you remember from Chapter 4 the case of “The Lizard”—Roberto Garcia d’Orta?

Like epilepsy, Parkinson's disease seems to have no single cause; faulty genes, brain infections, strokes, tumors, traumatic brain injury, and neurotoxins have all been implicated in specific cases (see Greenamyre & Hastings, 2004). However, in the majority of cases, no cause is obvious, and there is no family history of the disorder (see Calne et al., 1987).

Parkinson's disease is associated with degeneration of the **substantia nigra**—the midbrain nucleus whose neurons project via the **nigrostriatal pathway** to the **striatum** of the basal ganglia. Although *dopamine* is normally the

major neurotransmitter released by most neurons of the substantia nigra, there is little dopamine in the substantia nigra and striatum of long-term Parkinson's patients.

As you saw in the case of d’Orta, the symptoms of Parkinson's disease can be alleviated by injections of **L-dopa**—the chemical from which dopamine is synthesized. However, L-dopa is rarely a permanent solution; it typically becomes less and less effective with continued use, until its side effects (e.g., involuntary movements; see Bezard, Brotchie, & Gross, 2001) outweigh its benefits. This is exactly what happened to d’Orta. L-Dopa therapy gave him a 3-year respite from his disease, but ultimately it became totally ineffective. His prescription was then changed to another dopamine agonist, and again his condition improved—but again the improvement was only temporary. We will return to d’Orta’s roller-coaster case later in this chapter.

About 10 different gene mutations have been linked to Parkinson's disease (see Dawson & Dawson, 2003; Le & Appel, 2004). This has led many people to believe that a cure is just around the corner. However, it is important to realize that each of these gene mutations has been discovered in a different family, each of which had members suffering from a rare form of early-onset Parkinson's disease that runs in families. Thus, these mutations are unlikely to be factors in typical forms of the disease. Still, the study of the effects of these gene mutations may eventually lead to a better understanding of the physiological changes that underlie the symptoms of the disorder (see Vila, Wu, & Przedborski, 2001).

Thinking
Critically

Huntington's Disease

Like Parkinson's disease, **Huntington's disease** is a progressive motor disorder of middle and old age; but, unlike Parkinson's disease, it is rare, it has a strong genetic basis, and it is associated with severe dementia.

The first motor signs of Huntington's disease are often increased fidgetiness; as the disorder develops, rapid, complex, jerky movements of entire limbs (rather than individual muscles) begin to predominate. Eventually the motor and intellectual deterioration become so severe that sufferers are incapable of feeding themselves, controlling their bowels, or recognizing their own children. There is no cure; death typically occurs about 15 years after the appearance of the first symptoms.

Huntington's disease is passed from generation to generation by a single dominant gene; thus, all of the individuals carrying the gene develop the disorder, as do about half their offspring. The Huntington's gene is readily passed from parent to child because the first symptoms of the disease do not appear until the parent is well past the peak reproductive years (at about age 40).

The abnormal dominant gene that causes Huntington's disease was identified and characterized in 1993.

The abnormal protein produced by the Huntington's gene has also been isolated and characterized. However, the precise effect of this protein, which has been named *huntingtin*, has not yet been determined (see McMurray, 2001). Curiously, huntingtin is produced in all parts of the brains of Huntington's sufferers, yet brain damage is largely restricted to the striatum and cerebral cortex (see DiFiglia et al., 1997; Jakel & Maragos, 2000).

If one of your parents were to develop Huntington's disease, the chance would be 50/50 that you too would develop it. If you were in such a situation, would you want to know whether or not you would suffer the same fate? Medical geneticists have developed a test that can tell relatives of Huntington's patients whether they are carrying the gene (Gilliam, Gusella, & Lehrach, 1987; Martin, 1987). Some choose to take the test, and some do not. One advantage of the test is that it permits the relatives of Huntington's patients who have not inherited the gene to have children without the fear of passing on the disorder.

Clinical Implications

Shortly after the first edition of this textbook appeared in print, I received the letter reproduced on the next page. I have altered it slightly to protect the identity of its author and his family. It speaks for itself.

Multiple Sclerosis

Multiple sclerosis (MS), is a progressive disease that attacks the myelin of axons in the CNS. It is particularly disturbing because it typically attacks young people just as they are beginning their adult life. First, there are microscopic areas of degeneration on myelin sheaths; but eventually there is a breakdown of both the myelin and the associated axons, along with the development of many areas of hard scar tissue (*sclerosis* means "hardening"). Figure 10.11 illustrates degeneration in the white matter of a patient with multiple sclerosis.

Diagnosing multiple sclerosis is difficult because the nature and severity of the disorder depend on the number, size, and position of the sclerotic lesions. Furthermore, in some cases, there are lengthy periods of remission (up to 2 years), during which the patient seems almost normal; however, these are usually just oases in the progression of the disorder. Common symptoms of advanced multiple sclerosis are visual disturbances, muscular weakness, numbness, tremor, and **ataxia** (loss of motor coordination).

Epidemiological studies of multiple sclerosis have provided evidence of the environmental and genetic factors that influence its development. **Epidemiology** is the study of the various factors, such as diet, geographic location, age, sex, and race, that influence the distribution of a disease in the general population.

Evidence that environmental factors influence the development of multiple sclerosis comes from the finding that the incidence of multiple sclerosis is far greater in

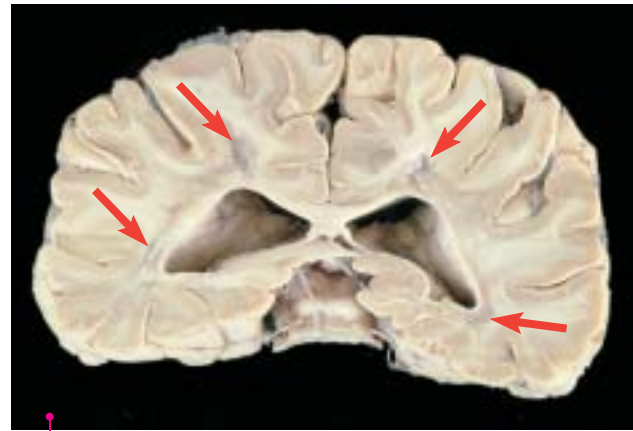


FIGURE 10.11 Areas of sclerosis (see arrows) in the white matter of a patient with MS.

people who spent their childhood in a cool climate, even if they subsequently moved to a warm climate. In contrast, evidence of genetic involvement comes from the finding that multiple sclerosis is rare among certain groups, such as Africans and Asians, even when they live in environments in which the incidence of the disease is high in other groups. The disorder occurs in 0.15% of Caucasians and is about twice as common in females (Steinman et al., 2002). Research indicates that there is a strong genetic predisposition to multiple sclerosis, with involvement of a large number of different genes, each making a small contribution (Hemmer, Archelos, & Hartung, 2002).

Multiple sclerosis is an *autoimmune disorder*—a disorder in which the body's immune system attacks part of the body, as if it were a foreign substance. In multiple sclerosis, myelin is the focus of the faulty immune reaction. Indeed, an animal model of multiple sclerosis, termed **experimental autoimmune encephalomyelitis**, can be induced by injecting laboratory animals with myelin and a preparation that stimulates the immune system. One of the puzzles of multiple sclerosis is that the healing response of *remyelination*, which occurs in animal models and in the early stages of most human cases, eventually fails (Franklin, 2002).

There are a number of drugs that retard the progression of multiple sclerosis or block some of its symptoms. However, there is no cure.

Alzheimer's Disease

Alzheimer's disease is the most common cause of *dementia*. It sometimes appears in individuals as young as 40, but the likelihood of its development becomes greater with advancing years. About 10% of the general population over the age of 65 suffer from the disease, and the proportion is about 35% in those over 85 (St. George-Hyslop, 2000).

Alzheimer's disease is progressive. Its early stages are often characterized by a selective decline in memory; its

Mr. Walter S. Miller
1500 N. Severn-Langdon Rd.
Manchester, Connecticut 22022
Z9/900-854
August 5, 1991

Dr. John P. J. Pinel
Department of Psychology
University of British Columbia
Vancouver, B. C. Canada V6T.1Y7.

Dear Dr. Pinel:

I am worried about my children and their future. In fact, I am worried sick. After reading your book I feel that you are my friend and I have nowhere else to turn.

My wife came down with Huntington's disease 7 years ago, and today she can't walk or take care of herself. I have three young children. Where can I take them to see if they have inherited my wife's infected cells? I am presently incarcerated, which adds to my psychological pain. I look to be released soon, and could take my wife and kids just about anywhere to find help and get answers.

Any kind of advice that you could give us would be greatly appreciated by me and my family. I wish to thank you for any assistance that you can give.

God bless you and give you and yours His love and peace! I remain with warmest personal regards.

Very truly yours,

Walter S. Miller

Walter S. Miller

WSM:

THE UNIVERSITY OF BRITISH COLUMBIA



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2136 West Mall
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Tel: (604) 822-2755
Fax: (604) 822-6923

November 25, 1991

Mr. Walter S. Miller
1500 N. Severn-Langdon Road
Manchester, Connecticut 22022
U.S.A.

Dear Mr. Miller:

I was saddened to learn of your unhappy state of affairs. In requesting my advice, I hope that you understand that I am a scientist, not a physician. In any case, the following is my assessment.

If your wife does in fact have Huntington's disease and not some other neurological disorder, each of your children has a 50/50 chance of developing Huntington's disease in adulthood. I am sure that you are aware that there is currently no cure.

I advise you to seek the advice of a local neurologist, who can explain your options to you and provide you with the advice and support that you sorely need. You must decide whether or not to subject your children to the tests that are required to determine whether or not they are carrying the Huntington's gene. One option would be to wait for your children to reach legal age and then allow them to make the decision for themselves. Some people whose parents develop Huntington's disease decide to take the test; others decide not to. In either case, it is extremely important for them not to risk passing on the Huntington's gene to future generations.

I am sorry that I cannot provide you with a more optimistic assessment, but your children's situation is too serious for me to be less than totally frank. Again, please consult a neurologist as soon as possible.

Do not lose hope. There is a chance (1/8) that none of your children is carrying the Huntington's gene. I wish you, your wife, and your children good fortune.

Cordially,

John P. J. Pinel
Professor

intermediate stages are marked by confusion, irritability, anxiety, and deterioration of speech; and in its advanced stages, the patient deteriorates to the point that even simple responses such as swallowing and controlling the bladder are difficult. Alzheimer's disease is terminal.

Because Alzheimer's disease is not the only cause of dementia, it cannot be diagnosed with certainty on the basis of its behavioral symptoms—definitive diagnosis of Alzheimer's disease must await autopsy. The two defining characteristics of the disease are neurofibrillary tangles and amyloid plaques. *Neurofibrillary tangles* are threadlike tangles of protein in the neural cytoplasm, and *amyloid plaques* are clumps of scar tissue composed of degenerating neurons and a protein called **amyloid**, which is present in normal brains in only very small amounts. In addition, there is substantial neuron loss. The presence of amyloid plaques in the brain of a patient who died of Alzheimer's disease is illustrated in Figure 10.12.

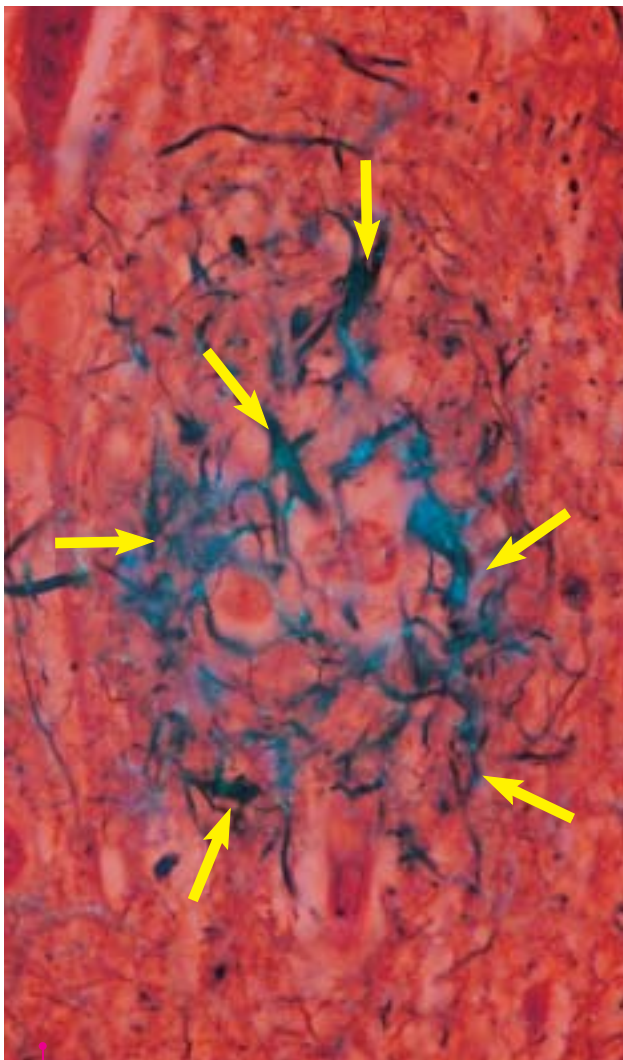


FIGURE 10.12 Amyloid plaques (see arrows) in the brain of a patient with Alzheimer's disease.

Although neurofibrillary tangles, amyloid plaques, and neuron loss tend to occur throughout the brains of Alzheimer's patients, they are more prevalent in some areas than in others. For example, they are particularly prevalent in medial temporal lobe structures such as the *entorhinal cortex*, *amygdala*, and *hippocampus*—all structures that are involved in various aspects of memory (see Collie & Maruff, 2000; Selkoe, 2002). They are also prevalent in the inferior temporal cortex, posterior parietal cortex, and prefrontal cortex—all areas that mediate complex cognitive functions. (See Figure 10.13.)

There is a difficulty in studying the genetics of Alzheimer's disease: Its carriers often die of natural causes before their Alzheimer's symptoms can be manifested. Nevertheless, it is clear that Alzheimer's disease has a major genetic component. People with an Alzheimer's victim in their immediate family have a 50% chance of being stricken by the disease if they survive into their 80s (Breitner, 1990).

Much of the research on the genetics of Alzheimer's disease has focused on rare early-onset *familial* forms of the disease. Several gene mutations have been found to be associated with early-onset Alzheimer's disease, and all of them have been implicated in the synthesis of amyloid or *tau*, a protein found in neurofibrillary tangles (see St. George-Hyslop, 2000).

The massive research effort currently aimed at developing a cure for Alzheimer's disease is fueled by a combination of two factors. One is the severity of the problem. The other is that a major advance seems feasible—because Alzheimer's is a disease of old age, the number of cases could be halved by a treatment that would slow its development by even 5 years.

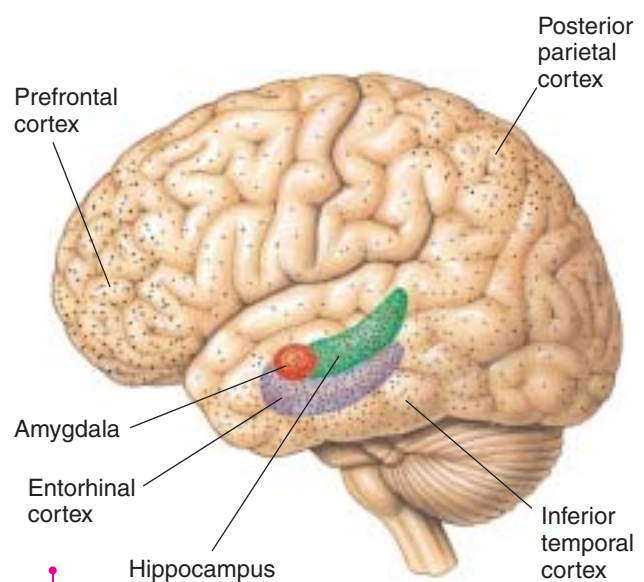


FIGURE 10.13 The typical distribution of neurofibrillary tangles and amyloid plaques in the brains of patients with advanced Alzheimer's disease. (Based on Goedert, 1993, and Selkoe, 1991.)



SCAN YOUR BRAIN

This is a good place for you to pause to scan your brain. Are you ready to progress to the following section, which discusses animal models of some of the disorders that you have just

learned about? Fill in the following blanks. The correct answers are provided at the bottom of this page. Before proceeding, review material related to your errors and omissions.

- The two major categories of epileptic seizures are _____ and _____.
- _____ are simple repetitive responses that occur during complex partial seizures.
- The disorder characterized by tremor at rest is _____ disease.
- Parkinson's disease is associated with degeneration in the _____ dopamine pathway.
- _____ disease is passed from generation to generation by a single dominant gene.
- Genetic studies of Parkinson's disease and Alzheimer's disease have focused on early-onset _____ forms of the disorder.
- Experimental autoimmune encephalomyelitis is an animal model _____ of _____.
- The most common cause of dementia is _____ disease.
- Two major neuropathological symptoms of Alzheimer's disease are _____ tangles and _____ plaques.

One factor complicating the search for a treatment or cure for Alzheimer's disease is that it is still not clear which symptom is primary (see Lee, 2001; Mudher & Lovestone, 2002). This is a key issue because an effective treatment is most likely to be developed only by research focusing on the primary symptom. The most popular candidate is the amyloid plaques; the *amyloid hypothesis* holds that the development of these plaques is the primary symptom of the disorder, which causes all other symptoms (see Hardy & Selkoe, 2002). However, others believe that the development of tau and neurofibrillary tangles is the primary symptom, and still others support other contenders—for example, a disruption of calcium regulation—for this role (see LaFerla, 2002).

The first efforts to develop treatments for Alzheimer's disease focused on the fact that declines in ace-

tylcholine levels were among the earliest neurochemical changes appearing in patients. Cholinergic agonists are still sometimes prescribed, but, except for a few minor benefits early in the disorder, they have proven ineffective. Several other treatment approaches are currently under development (see Hardy & Selkoe, 2002). Arguably, the most promising of these is the *immunotherapeutic approach* (see Ingram, 2001; Schenk, 2002). This approach has used an amyloid vaccine to reduce plaque deposits and improve performance on memory tasks in a transgenic mouse model of Alzheimer's disease (which we'll discuss further in the next section). Human trials have been mixed: Therapeutic effects have been observed, but dangerous inflammation occurred in the CNSs of 5% of the patients (see Monsonego & Weiner, 2003).



10.3 Animal Models of Human Neuropsychological Diseases

The first two sections of this chapter focused on neuropsychological diseases and their causes, but they also provided some glimpses into the ways in which researchers have attempted to solve the many puzzles of neurological dysfunction. This section focuses on one of these ways: the experimental investigation of animal models. Because the experimentation necessary to identify the neuropathological basis of human neuropsychological diseases is seldom possible on the patients themselves, animal models of the diseases play an important role in such investigation (see Cenci, Whishaw, & Schallert, 2002).

It is important to appreciate that even the best animal models of neuropsychological diseases display only some of the features of the diseases they are modeling (see Maries et al., 2003). Consequently, animal models must be employed with caution. Studying an animal model is

Evolutionary Perspective

Thinking Critically

Scan Your Brain answers: (1) partial and generalized in either order, (2) Automatism, (3) Parkinson's, (4) nigrostriatal, (5) Huntington's, (6) familial, (7) multiple sclerosis, (8) Alzheimer's, (9) neurofibrillary and amyloid.

like exploring a section of an unknown maze. One enters an unfamiliar section with little more than a hope that its exploration will prove fruitful, and it is only after each of its arms has been carefully explored that it is possible to know whether the decision to enter the section was wise. In the same way, it is not possible to evaluate animal models of neuropsychological dysfunction that are currently under investigation until each has been thoroughly explored. Surely, only a few animal models will lead toward the goals of understanding and prevention, but only time and effort can tell which ones these are.

This section of the chapter discusses three animal models that are currently the focus of intensive investigation: the kindling model of epilepsy, the transgenic mouse model of Alzheimer's disease, and the MPTP model of Parkinson's disease.

Kindling Model of Epilepsy

In 1969, Goddard, McIntyre, and Leech delivered one mild electrical stimulation per day to rats through implanted amygdalar electrodes. There was no behavioral response to the first few stimulations, but soon each stimulation began to elicit a convulsive response. The first convulsions were mild, involving only a slight tremor of the face. However, with each subsequent stimulation, the elicited convulsions became more generalized, until each convulsion involved the entire body. The progressive development and intensification of convulsions elicited by a series of periodic brain stimulations became known as the **kindling phenomenon**.

Although kindling is most frequently studied in rats subjected to repeated amygdalar stimulation, it is a remarkably general phenomenon. For example, kindling has been reported in mice (Leech & McIntyre, 1976), rabbits (Tanaka, 1972), cats (Adamec, 1990), dogs (Wauquier, Ashton, & Melis, 1979), and various primates (Wada, 1990a). Moreover, kindling can be produced by the repeated stimulation of many brain sites other than the amygdala, and it can be produced by the repeated application of initially subconvulsive doses of convulsive chemicals (Cain, 1986; Mori & Wada, 1990; Post et al., 1990).

There are many interesting features of kindling (see Racine & Burnham, 1984; Wada, 1990b), but two warrant emphasis. The first is that the neural changes underlying kindling are permanent. A subject that has been kindled and then left unstimulated for several months still responds to each low-intensity stimulation with a generalized convulsion (Goddard, McIntyre, & Leech, 1969; Wada & Sato, 1974). The second is that kindling is produced by distributed, as opposed to massed, stimulations. If the intervals between successive stimulations are shorter than an hour or two, it usually requires many more stimulations to kindle a subject; and under normal circumstances, no kindling at all occurs at intervals of less than about 20 minutes (Racine et al., 1973).

Much of the interest in kindling stems from the fact that it models epilepsy in two ways. First, the convulsions elicited in kindled animals are similar in many respects to those observed in some types of human epilepsy. Second, the kindling phenomenon itself is comparable to the **epileptogenesis** (the development, or genesis, of epilepsy) that can follow a head injury: Some individuals who at first appear to have escaped serious injury after a blow to the head begin to experience convulsions a few weeks later, and these convulsions sometimes begin to recur more and more frequently and with greater and greater intensity.

It must be stressed that the kindling model as it is applied in most laboratories is different from epilepsy in one important respect. You will recall from earlier in this chapter that epilepsy is a disease in which epileptic attacks recur spontaneously; in contrast, kindled convulsions are elicited. However, a model that overcomes this shortcoming has been developed in several species. If subjects are kindled for a very long time—about 300 stimulations in rats—a syndrome can be induced that is truly epileptic, in the sense that the subjects begin to display spontaneous seizures and continue to display them even after the regimen of stimulation is curtailed (e.g., Pinel, 1981; Shouse et al., 1990; Wada, Sato, & Corcoran, 1974).

One interesting and potentially important development in the study of kindling is that some researchers have started to focus on *interictal behavior* (behavior that occurs in epileptics between their seizures). For some human epileptics, particularly those who suffer from complex partial seizures, pathological changes in interictal behavior are more distressing and more difficult to treat than the seizures themselves (Leung, Ma, & McLachlan, 2000). Several studies of kindling have shown that kindled subjects display a variety of changes in interictal emotional behavior that are similar to those observed in human epileptics (Kalynchuk, 2000; Wintink et al., 2003).

Transgenic Mouse Model of Alzheimer's Disease

Perhaps the most exciting development in the study of Alzheimer's disease has been the transgenic model of the disorder. **Transgenic** refers to animals into which the genes of another species have been introduced (see Carter et al., 1999).

One difficulty in studying Alzheimer's disease is that only humans and a few related primates develop amyloid plaques, considered by many to be the primary symptom of the disorder. As a result, experimental studies of Alzheimer's disease have been difficult to conduct, and fundamental questions of causation have been difficult to address. For example, the causal role of amyloid plaques in Alzheimer's disease has not yet been sorted out: Some investigators believe that amyloid deposition triggers neuron degeneration, thereby causing the

behavioral symptoms; others believe that the amyloid plaques are the result, not the cause, of the neural degeneration (Neve & Robakis, 1998). This lack of progress in answering fundamental causal questions about Alzheimer's disease is why the development of the transgenic mouse model of the disorder is such an important contribution.

There are several forms of the transgenic mouse model. In one (Hsiao et al., 1996), genes that accelerate the synthesis of human amyloid are injected into newly fertilized mouse eggs, which are then injected into a foster mother to develop. When the transgenic mice mature, their brains contain many amyloid plaques like those of human Alzheimer's patients. Moreover, the distribution of the amyloid plaques is comparable to that observed in human Alzheimer's patients, with the highest concentrations occurring in structures of the medial temporal lobes (e.g., hippocampus, amygdala, and entorhinal cortex).

Although the transgenic mice of Hsiao and her colleagues arguably provide the best animal model of Alzheimer's disease, the model is not without its problems. For example, the mice show no neurofibrillary tangles, and the degree of memory impairment changes little as the mice mature and develop more plaques. However, an animal model does not have to mimic the human disorder in every respect to be useful: As you learned in the preceding section, the transgenic mouse model of Alzheimer's disease has been used to develop an amyloid vaccine that is being tested on human patients.

MPTP Model of Parkinson's Disease

The preeminent animal model of Parkinson's disease grew out of an unfortunate accident, which resulted in the following anomalous cases of Parkinson's disease.

The Case of the Frozen Addicts

Clinical Implications

Parkinson's disease... rarely occurs before the age of 50. It was somewhat of a surprise then to see a group of young drug addicts at our hospital in 1982 who had developed symptoms of severe and what proved to be irreversible parkinsonism. The only link between these patients was the recent use of a new "synthetic heroin." They exhibited virtually all of the typical motor features of Parkinson's disease, including the classic triad of bradykinesia (slowness of movement), tremor and rigidity of their muscles. Even the subtle features, such as seborrhea (oiliness of the skin) and micrographia (small handwriting), that are typical of Parkinson's disease were present. After tracking down samples of this substance, the offending agent was tentatively identified as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

or MPTP. . . . There has been no sign of remission, and most are becoming increasingly severe management problems. (Langston, 1985, p. 79)

Researchers immediately turned the misfortune of these few to the advantage of many by developing a much-needed animal model of Parkinson's disease (Langston, 1986). It was quickly established that nonhuman primates respond like humans to MPTP. The brains of primates exposed to MPTP have cell loss in the substantia nigra similar to that observed in the brains of Parkinson's patients. Considering that the substantia nigra is the major source of the brain's dopamine, it is not surprising that the level of dopamine is greatly reduced in both the MPTP model and in the naturally occurring disorder. However, it is curious that in a few monkeys MPTP produces a major depletion of dopamine without producing any gross motor symptoms (Taylor et al., 1990).

The MPTP animal model has already benefitted patients with Parkinson's disease. For example, it was discovered that **deprenyl**, a monoamine agonist, blocks the effects of MPTP in an animal model, and it was subsequently shown that deprenyl administered to early Parkinson's patients retards the progression of the disease (Tetrad & Langston, 1989)—see Figure 10.14

Several transgenic mouse models of Parkinson's disease have been developed. However, the MPTP model is still regarded as the best (Beal, 2001).

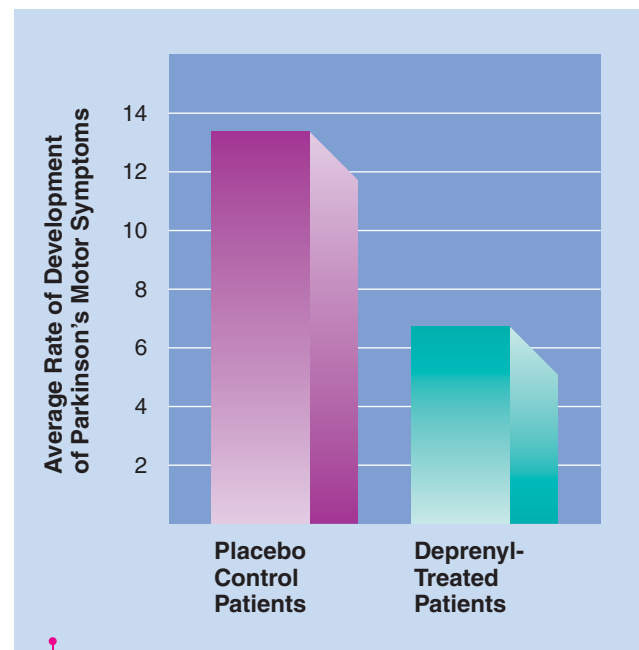


FIGURE 10.14 Average rate of motor symptom development in early Parkinson's patients treated with deprenyl (a monoamine oxidase inhibitor) or with a placebo. Deprenyl slowed the progression of the disease by 50%. (Based on Tetrad and Langston, 1989.)

10.4

Neuroplastic Responses to Nervous System Damage: Degeneration, Regeneration, Reorganization, and Recovery

Damage to the nervous system may trigger four neuroplastic responses: degeneration, regeneration, reorganization, and recovery of function. Each of these four responses is discussed in this section.

Neural Degeneration

A widely used method for the controlled study of the responses of neurons to damage is to cut their axons. Two kinds of neural degeneration (deterioration) ensue: anterograde degeneration and retrograde degeneration (see Coleman & Perry, 2002; Raff, Whitmore, & Finn, 2002). **Anterograde degeneration** is the degeneration of the **distal segment**—the segment of a cut axon between the cut and the synaptic terminals. **Retrograde degeneration** is the degeneration of the **proximal segment**—the segment of a cut axon between the cut and the cell body.

Anterograde degeneration occurs quickly following *axotomy*, because the cut separates the distal segment of the axon from the cell body, which is the metabolic center of the neuron. The entire distal segment becomes badly swollen within a few hours, and it breaks into fragments within a few days.

The course of retrograde degeneration is different; it progresses gradually back from the cut to the cell body. In about 2 or 3 days, major changes become apparent in the cell bodies of most axotomized neurons. These early cell body changes are either degenerative or regenerative in nature. Early degenerative changes to the cell body (e.g., a decrease in size) suggest that the neuron will ultimately die—usually by apoptosis but sometimes by necrosis or a combination of both (Syntichaki & Tavernarakis, 2003). Early regenerative changes (e.g., an increase in size) indicate that the cell body is involved in a massive synthesis of the proteins that will be used to replace the degenerated axon. But early regenerative changes in the cell body do not guarantee the long-term survival of the neuron; if the regenerating axon does not manage to make synaptic contact with an appropriate target, the neuron eventually dies.

Sometimes, degeneration spreads from damaged neurons to neurons that are linked to them by synapses; this is called **transneuronal degeneration**. In some cases, transneuronal degeneration spreads from damaged neurons to the neurons on which they synapse; this is called *anterograde transneuronal degeneration*. And in some cases, it spreads from damaged neurons to the neurons that synapse on them; this is called *retrograde transneuronal degeneration*. Neural and transneuronal degeneration are illustrated in Figure 10.15.

Neural Regeneration

Neural regeneration—the regrowth of damaged neurons—does not proceed as successfully in mammals and other higher vertebrates as it does in most invertebrates and lower vertebrates. The capacity for accurate axonal growth, which is possessed by higher vertebrates during their original development, is lost once they reach maturity. Regeneration is virtually nonexistent in the CNS of adult mammals, and is at best a hit-or-miss affair in the PNS.

In the mammalian PNS, regrowth from the proximal stump of a damaged nerve usually begins 2 or 3 days after axonal damage. What happens next depends on the nature of the injury (see Tonge & Golding, 1993); there are three possibilities. First, if the original Schwann cell myelin sheaths remain intact, the regenerating peripheral axons grow through them to their original targets at a rate of a few millimeters per day. Second, if the peripheral nerve is severed and the cut ends become separated by a few millimeters, regenerating axon tips often grow into incorrect sheaths and are guided by them to incorrect destinations; that is why it is often difficult to regain the coordinated use of a limb affected by nerve damage even if there has been substantial regeneration. And third, if the cut ends of a severed mammalian peripheral nerve become widely separated or if a lengthy section of the nerve is damaged, there may be no meaningful regeneration at all; regenerating axon tips grow in a tangled mass around the proximal stump, and the neurons ultimately die. These three patterns of mammalian peripheral nerve regeneration are illustrated in Figure 10.16 on page 250.

Why do mammalian PNS neurons regenerate, and mammalian CNS neurons do not? The obvious answer is that PNS neurons are inherently capable of regeneration while CNS neurons are not, but this answer has proved to be incorrect. CNS neurons are capable of regeneration if they are transplanted to the PNS, whereas PNS neurons are not capable of regeneration if they are transplanted to the CNS. Clearly, there is something about the environment of the PNS that promotes regeneration and something about the environment of the CNS that does not (Goldberg & Barres, 2000). Schwann cells are the key.

Schwann cells, which myelinate PNS axons, promote regeneration in the mammalian PNS by producing both neurotrophic factors and cell-adhesion molecules (CAMs). The neurotrophic factors released by Schwann cells stimulate the growth of new axons, and the cell-adhesion molecules on the cell membranes of Schwann cells provide the paths along which regenerating PNS

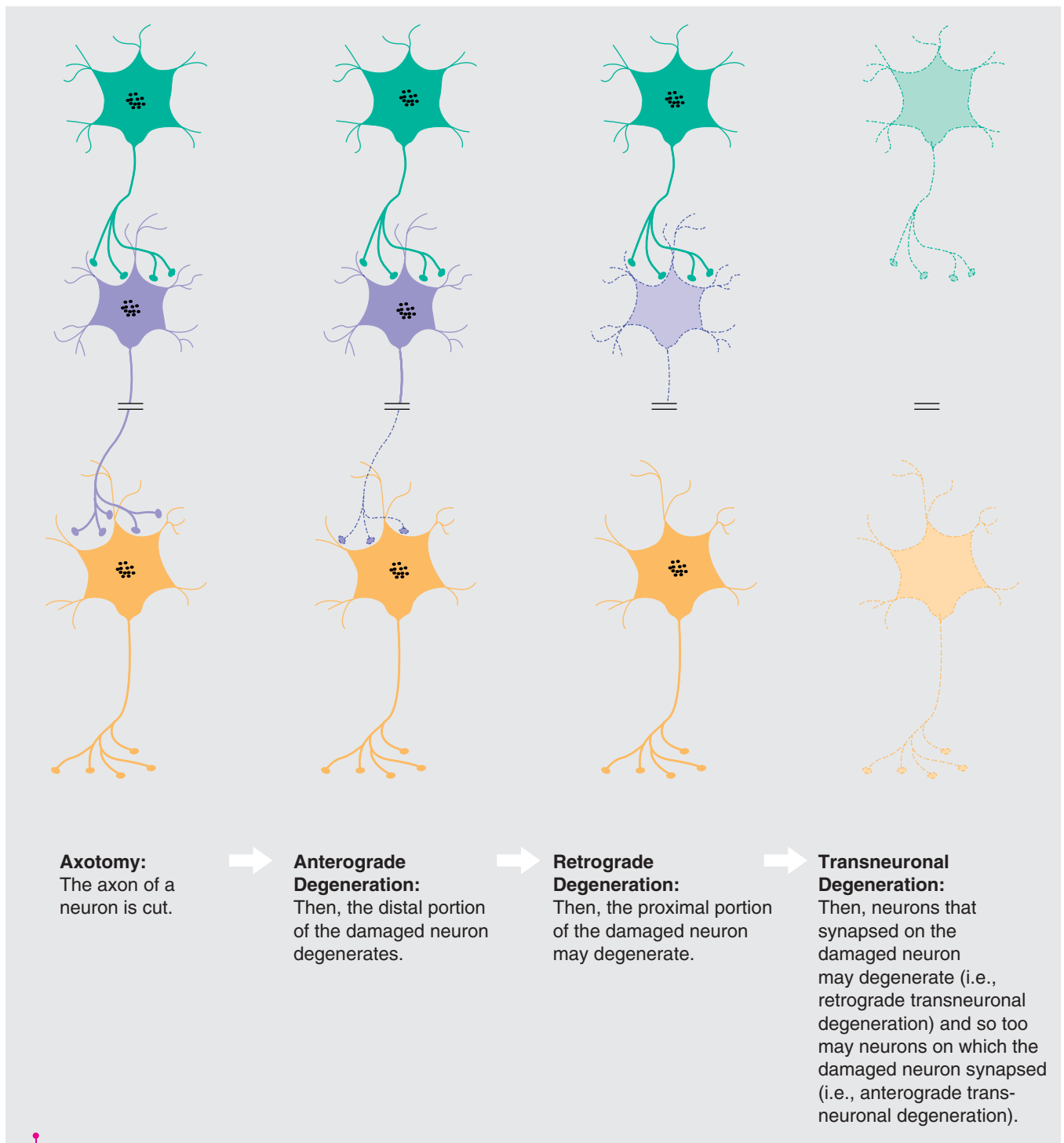


FIGURE 10.15 Neuronal and transneuronal degeneration following axotomy.

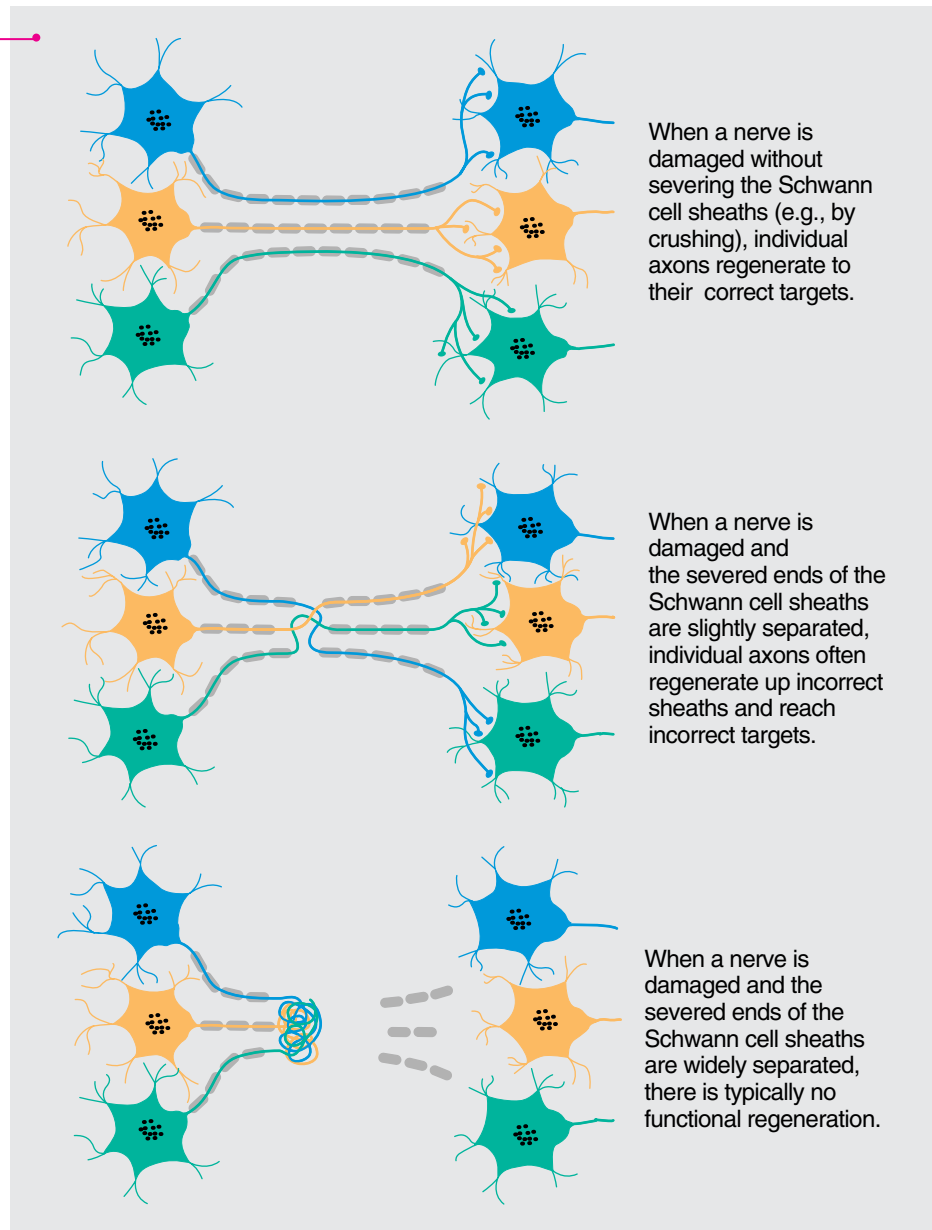
axons grow. In contrast, **oligodendroglia**, which myelinate CNS axons, do not stimulate or guide regeneration; indeed, they release factors that actively block regeneration (Filbin, 2003; Fournier & Strittmatter, 2001).

In contrast to neural regeneration in mammals, that in lower vertebrates is extremely accurate. It is accurate

in both the CNS and the PNS, and it is accurate even when the regenerating axons do not grow into remnant Schwann cell myelin sheaths. The accuracy of regeneration in lower vertebrates offers hope of a medical breakthrough: If the factors that promote accurate regeneration

Evolutionary Perspective

FIGURE 10.16 Three patterns of axonal regeneration in mammalian peripheral nerves.



in lower vertebrates can be identified and applied to the human brain, it might be possible to cure currently untreatable brain injuries.

When an axon degenerates, axon branches grow out from adjacent healthy axons and synapse at the sites vacated by the degenerating axon; this is called **collateral sprouting**. Collateral sprouts may grow out from the axon terminal branches or the nodes of Ranvier on adjacent neurons. Collateral sprouting is illustrated in Figure 10.17.

Neural Reorganization

It has long been assumed that major changes in mammalian nervous systems were limited to the period of early development: Adult mammalian nervous systems were

thought to be limited to the subtle functional changes that mediate learning and memory. However, as you learned in Chapter 9, it was recently discovered that adult mammalian brains retain the ability to reorganize themselves in response to experience. They also retain the ability to reorganize themselves in response to damage.

Examples of Cortical Reorganization Following Nervous System Damage

Most studies of neural reorganization following damage have focused on adult sensory and motor systems (see Donoghue, 1995; Wall, Xu, & Wang, 2002). Sensory and motor systems are ideally suited to the study of neural reorganization because of their topographic layout. The damage-induced reorganization of the primary sensory and motor systems has been studied in two fundamentally different condi-

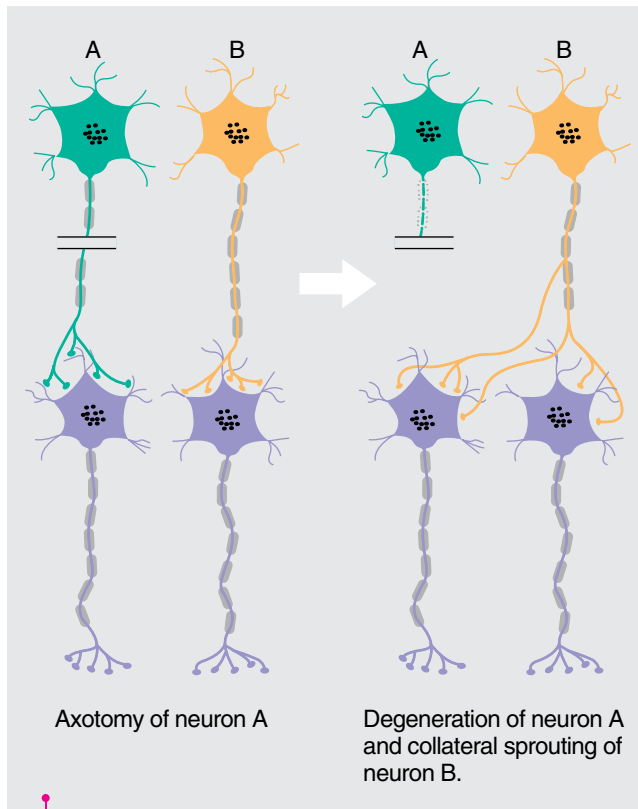


FIGURE 10.17 Collateral sprouting after neural degeneration.

tions: following damage to peripheral nerves and following damage to the primary cortical areas (Buonomano & Merzenich, 1998). Let's consider some studies that illustrate these two approaches.

Kaas and colleagues (1990) assessed the effect of making a small lesion in one retina and removing the other. Several months after the retinal lesions were made, primary visual cortex neurons that originally had receptive fields in the lesioned area of the retina were found to have receptive fields in the area of the retina next to the lesion; remarkably, this change began within minutes of the lesion (Gilbert & Wiesel, 1992).

Pons and colleagues (1991) mapped the primary somatosensory cortex of monkeys whose contralateral arm sensory neurons had been cut 10 years before. They found that the cortical face representation had systematically expanded into the original arm area. This study created a stir because the scale of the reorganization was far greater than had been assumed to be possible: The primary somatosensory cortex face area had expanded its border by well over a centimeter, likely as a consequence of the particularly long (10-year) interval between surgery and testing.

Jenkins and Merzenich (1987) removed the area of monkey somatosensory cortex that responded to touches of the palm of the contralateral hand. Several weeks later, they found that neurons adjacent to the lesion now responded to touches of the palm.

Working with rats, Sanes, Suner, and Donoghue (1990) transected the motor neurons that controlled the muscles of the rats' *vibrissae* (whiskers). A few weeks later, stimulation of the area of motor cortex that had previously elicited vibrissae movement now activated other muscles of the face. This result is illustrated in Figure 10.18.

Mechanisms of Neural Reorganization Two kinds of mechanisms have been proposed to account for the reorganization of neural circuits: a strengthening of existing connections, possibly through release from inhibition, and the establishment of new connections by collateral sprouting (see O'Leary, Ruff, & Dyck, 1994). Support for the first mechanism comes from two observations: Reorganization often occurs too quickly to be explained by neural growth, and rapid reorganization never involves changes of more than 2 millimeters of cortical surface. Support for

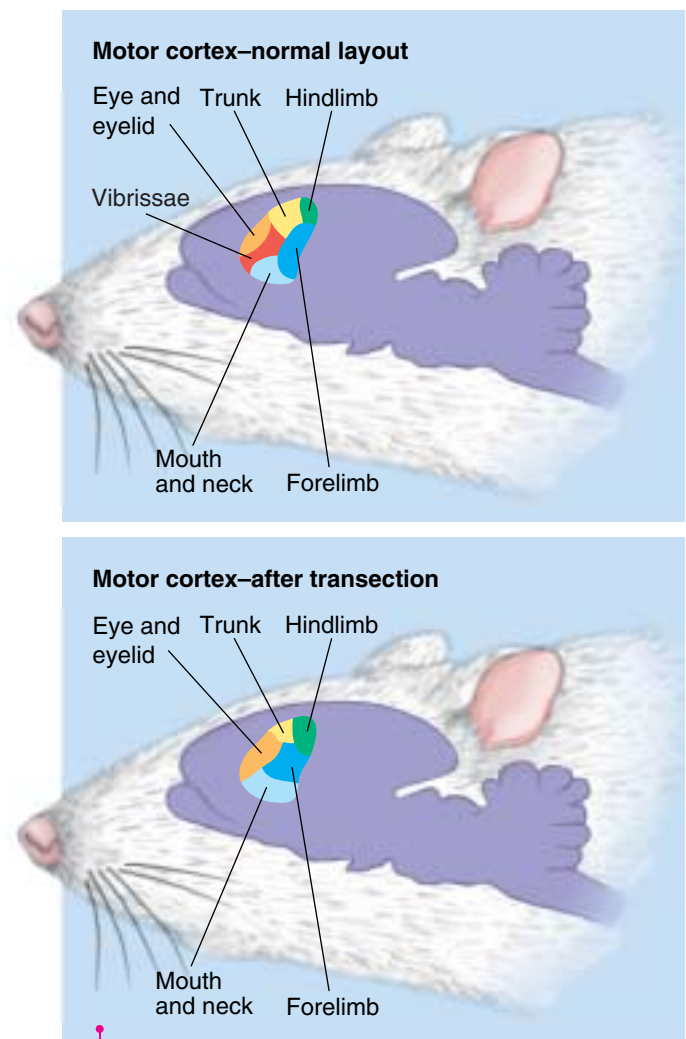


FIGURE 10.18 Reorganization of the rat motor cortex following transection of the motor neurons that control movements of the vibrissae. The motor cortex was mapped by brain stimulation before transection and then again a few weeks after. (Adapted from Sanes, Suner, & Donoghue, 1990.)

the second mechanism comes from the observation that the magnitude of long-term reorganization can be too great to be explained by changes in existing connections. Figure 10.19 illustrates how these two mechanisms might account for the reorganization that occurs after damage to a peripheral somatosensory nerve.

Recovery of Function after Brain Damage

Understanding the mechanisms that underlie the recovery of function after nervous system damage is a high priority for neuroscientists. If these mechanisms were understood, steps could be taken to promote recovery. However, recovery of function after nervous system damage is a poorly understood phenomenon.

Little is known about recovery of function after nervous system damage for two reasons. The first is that it is difficult to conduct controlled experiments on populations of brain-damaged patients. The second is that nervous system damage may result in a variety of compensatory changes that can easily be confused with true recovery of function. For example, any improvement in the week or two after damage could reflect a decline in *cerebral edema* (brain swelling) rather than a recovery from the neural damage itself, and any gradual improvement in the months after damage could reflect the learning of new cognitive and behavioral strategies (i.e., substitution of functions) rather than the return of lost functions (see Wilson, 1998). Consequently, true recovery of function is less common than most believe (see

Thinking Critically

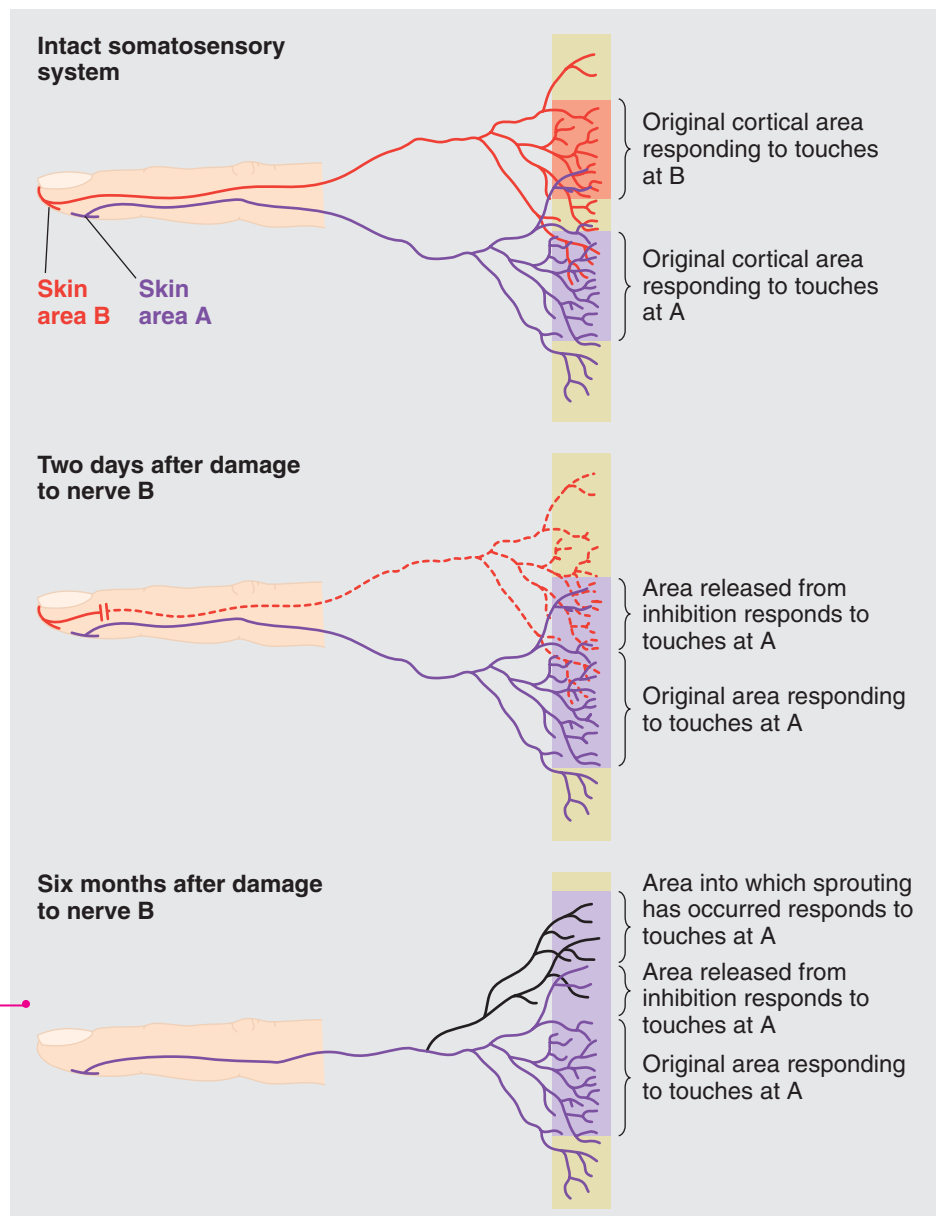


FIGURE 10.19 The two-stage model of neural reorganization: (1) strengthening of existing connections through release from inhibition and (2) establishment of new connections by collateral sprouting.

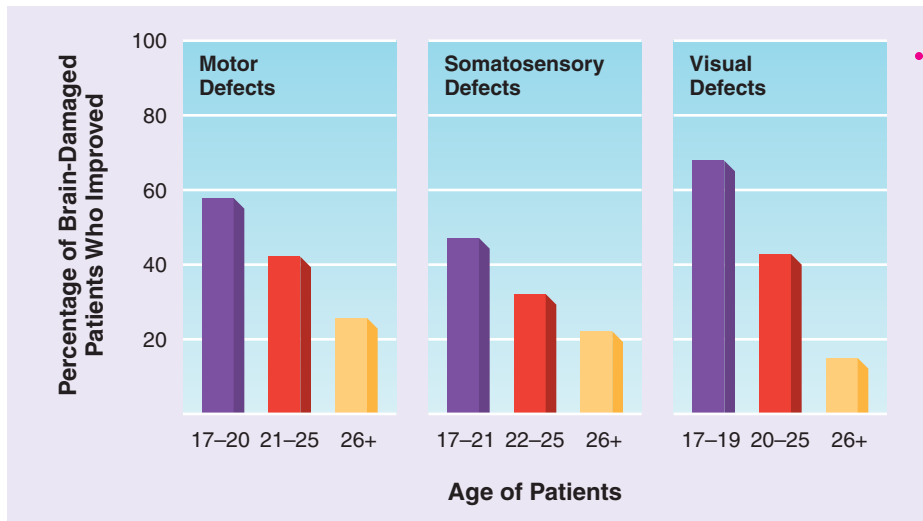


FIGURE 10.20 Percentage of patients showing improvement following brain injury. Teuber (1975) assessed the deficits of brain-damaged soldiers within a week of their injury and again 20 years later.

Figure 10.20). However, substantial recovery of function is most likely when lesions are small and the patient is young (see Payne & Lomber, 2001).

Cognitive reserve (roughly equivalent to education and intelligence) is thought to play an important role in the apparent recovery of cognitive function after brain damage. Kapur (1997) conducted a biographical study of doctors and neuroscientists with brain damage, and he observed a great deal of cognitive recovery. He concluded that the observed improvement did not occur because these patients had actually recovered lost cognitive function but because their cognitive reserve allowed them to accomplish cognitive tasks in alternative ways.

The mechanisms of recovery of function remain unknown. It seems likely that neural reorganization contributes to recovery, but so far most of the evidence

for this hypothesis has been indirect (see Hallett, 2001). The strongest evidence comes from a study in which the degree of motor recovery in stroke patients was found to be correlated with the degree of motor cortex reorganization (Lipert et al., 2000).

For years, neural reorganization seemed to be the only explanation for recovery from CNS damage. However, the discovery of adult neurogenesis raised another possibility: Perhaps the growth of new neurons plays a role in such recovery, particularly when the damage affects the hippocampus. It has recently been shown (see Kokaia & Lindvall, 2003) that cerebral ischemia, which preferentially damages the hippocampus, increases adult neurogenesis; that many of the new cells become part of the hippocampus; and that these new cells establish synapses and develop into mature neurons—see Figure 10.21.

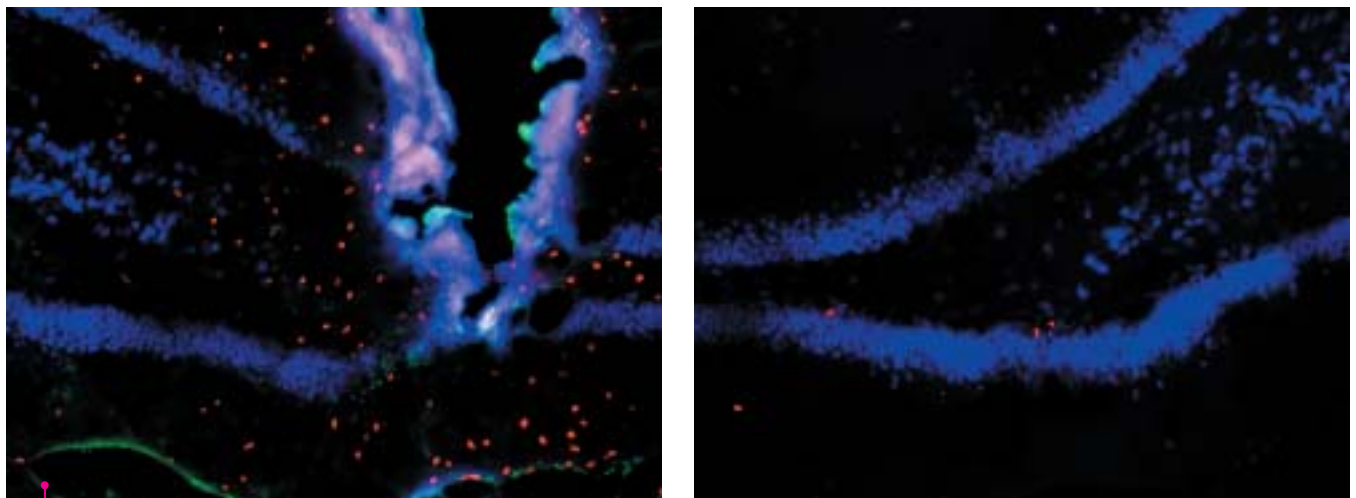


FIGURE 10.21 Increased neurogenesis in the dentate gyrus following damage. The left panel shows (1) ion electrolytic lesion in the dentate gyrus (damaged neurons are stained turquoise) and (2) the resulting increase in the formation of new cells (stained red), many of which develop into mature neurons (stained dark blue). The right panel displays the comparable control area in the unlesioned hemisphere, showing the normal number of new cells (stained red). (These beautiful images are courtesy of my good friends Carl Ernst and Brian Christie, Department of Psychology, University of British Columbia.)

It is thus possible that an increase in adult neurogenesis contributes to recovery from stroke, but there is currently no direct evidence for this attractive hypothesis. However, if this hypothesis is proven, exercise—which has been

shown to increase adult neurogenesis (Holmes et al., 2004; Van Praag et al., 2002)—could prove to be therapeutic for patients with hippocampal damage.

10.5

Neuroplasticity and the Treatment of Nervous System Damage

The study of neuroplasticity is currently one of the most active and exciting areas of research in neuroscience. This section reveals the major reason for all the excitement: The dream that recent discoveries about neuroplasticity—with which you are now familiar—can be applied to the treatment of brain damage in human patients.

Evolutionary Perspective

The following four subsections describe research on some major new treatment approaches. Most of this research has focused on animal models, but some of it has progressed to clinical trials with human patients.

Reducing Brain Damage by Blocking Neurodegeneration

Several studies have shown that it may be possible to reduce brain damage by blocking neural degeneration in human patients. For example, in one study, Xu and colleagues (1999) induced cerebral ischemia in rats by limiting blood flow to the brain. This had two major effects in the control group of rats: It produced damage in the hippocampus, a structure that is particularly susceptible to ischemic damage, and it produced deficits in the rats' performance in the Morris water maze (see Chapter 5). The hippocampuses of rats in the experimental group were treated with viruses genetically engineered to release *apoptosis inhibitor protein*. Amazingly, the apoptosis inhibitor protein prevented both the loss of hippocampal neurons and the deficits in Morris water maze performance.

In addition to apoptosis inhibitor protein, several other neurochemicals have been shown to block the degeneration of damaged neurons. The most widely studied of these is *nerve growth factor* (see Sofroniew, Howe, & Mobley, 2001). You may be surprised to learn that estrogens have a similar effect (see Behl, 2002; Sawada & Shimohama, 2000; Stein, 2001; Wise et al., 2001). **Estrogens** are a class of steroid hormones that are released in large amounts by the *ovaries* (the female gonads). These hormones have several important effects on the maturation of the female body, which you will learn about in Chapter 13, but they also have a variety of influences on the brain. Estrogens have been shown to limit or delay neuron death in animal models and in cell cultures, and there are also some supportive findings from human patients. These neuroprotective effects of estrogens may

explain why several brain disorders (e.g., Parkinson's disease) are more prevalent in males than in females.

In general, molecules that limit neural degeneration also promote regeneration. This point leads us to the next subsection.

Promoting Recovery from CNS Damage by Promoting Regeneration

Although regeneration does not normally occur in the mammalian CNS, several studies have shown that it can be induced. The following three studies are particularly promising because they have shown that such regeneration can be associated with functional recovery.

Eitan and colleagues (1994) transected the left optic nerves of rats. In the control rats, the retinal ganglion cells, which compose the left optic nerve, permanently degenerated. The experimental rats received injections of an agent that is toxic to oligodendrocytes, thus eliminating these cells' ability to block regeneration. In these experimental subjects, the optic nerves regenerated, and 6 weeks after the injury, evoked potentials could be recorded from the optic nerve in response to light flashes presented to the left eye.

Cheng, Cao, and Olson (1996) transected the spinal cords of rats, thus rendering them *paraplegic* (paralyzed in the posterior portion of their bodies). The researchers then transplanted sections of myelinated peripheral nerve across the transection. As a result, spinal cord neurons regenerated through the implanted Schwann cell myelin sheaths, and the regeneration allowed the rats to regain use of their hindquarters.

A similar study involved transplanting *olfactory ensheathing cells* rather than Schwann cells. Olfactory ensheathing cells, which are similar to Schwann cells, were selected because the olfactory system is unique in its ability to support continual growth of axons from new PNS neurons into the CNS (i.e., into the olfactory bulbs). Li, Field, and Raisman (1998) made lesions in the corticospinal tract of rats and then implanted bridges of olfactory ensheathing cells across the lesion. Axons grew through the lesion, and the motor function of the affected paw was partially restored. Although it is not yet clear how this recovery occurs, these findings have generated considerable optimism (see Barnett & Chang, 2004; Edgerton & Roy, 2002; Keyvan-Fouladi, Li, & Raisman, 2002).

Promoting Recovery from CNS Damage by Neurotransplantation

A few years ago, the idea of brain transplantation was little more than science fiction. Today, the treatment of brain damage by transplanting neural tissue is approaching reality. Efforts to treat CNS damage by neurotransplantation have taken two different approaches (see Björklund & Lindvall, 2000). The first is to transplant fetal tissue; the second is to transplant stem cells.

Transplanting Fetal Tissue The first approach to neurotransplantation was to replace a damaged structure with fetal tissue that would develop into the same structure. Could the *donor* tissue develop and become integrated into the *host* brain, and in so doing alleviate the symptoms? This approach focused on Parkinson's disease. Parkinson's patients lack the dopamine-releasing cells of the nigrostriatal pathway: Could they be cured by transplanting the appropriate fetal tissue into the site?

Early signs were positive. Bilateral transplantation of fetal substantia nigra cells was successful in treating the MPTP monkey model of Parkinson's disease (Bankiewicz et al., 1990; Sladek et al., 1987). Fetal substantia nigra transplants survived in the MPTP-treated monkeys; they innervated adjacent striatal tissue, released dopamine, and, most importantly, alleviated the severe poverty of movement, tremor, and rigidity produced by the MPTP.

Soon after the favorable effects of neurotransplants in the MPTP monkey model were reported, neurotransplantation was offered as a treatment for Parkinson's disease at major research hospitals. The results of the first case studies were promising. The fetal substantia nigra implants survived, and they released dopamine into the host striatum (see Sawle & Myers, 1993). More importantly, some of the patients improved.

The results of these case studies triggered a large-scale double-blind evaluation study of patients suffering from advanced Parkinson's disease. The study was extremely thorough; it even included placebo controls—patients who received surgery but no implants. The initial results were encouraging: Although control patients showed no improvement, the implants survived in the experimental patients, and some displayed a modest improvement. Unfortunately, however, about 15% of these patients started to display a variety of uncontrollable writhing and chewing movements about a year after the surgery (Greene et al., 1999).

The results of this first double-blind placebo-controlled clinical trial of the effectiveness of fetal tissue transplants created widespread debate (see Dunnett, Björklund, & Lindvall, 2001). The incidence of adverse motor side effects is likely to stifle future attempts to develop neurotransplantation as a treatment for Parkinson's disease. However, many still believe that this is an extremely promising therapeutic approach, but that the

large-scale clinical trial was premature. Researchers do not yet know how to maximize the survival and growth of neurotransplants and how to minimize their side effects. It is important to achieve a balance between the pressure to develop new treatments quickly and the need to base treatments on a carefully constructed foundation of scientific understanding (see Döbrössy & Dunnett, 2001).

In Chapter 4, you were introduced to Roberto Garcia d'Orta—the Lizard. D'Orta, who suffered from Parkinson's disease, initially responded to L-dopa therapy; but, after 3 years of therapy, his condition worsened. Then he responded to treatment with a dopamine agonist, but again the improvement was only temporary. D'Orta, was in a desperate state when he heard about *adrenal medulla autotransplantation* (transplanting a patient's own adrenal medulla cells into her or his striatum, usually for the treatment of Parkinson's disease). Adrenal medulla cells release small amounts of dopamine, and there were some early indications that adrenal medulla autotransplantation might alleviate the symptoms of Parkinson's disease.

D'Orta demanded adrenal medulla autotransplantation from his doctor. When his doctor refused, on the grounds that the effectiveness of the treatment was still in doubt, d'Orta found himself another doctor—a neurosurgeon who was not nearly so cautious.

The Case of Roberto Garcia d'Orta: The Lizard Gets an Autotransplant

Roberto flew to Juarez. The neurosurgeon there greeted him with open arms. As long as Roberto could afford the cost, he'd be happy to do an adrenal implant on him. . . .

Were there any dangers?

The neurosurgeon seemed insulted by the question. If Señor d'Orta didn't trust him, he could go elsewhere. . . .

Roberto underwent the procedure.

He flew back home two weeks later. He was no better. He was told that it took time for the cells to grow and make the needed chemicals. . . .

Then I received an unexpected call from Roberto's wife. Roberto was dead. . . .

He'd died of a stroke. . . . Had the stroke been a complication of his surgery? It was more than a mere possibility. (Klawans, 1990, pp. 63–64)

Transplanting Stem Cells In Chapter 9, you learned about *embryonic neural stem cells*, which are *multipotent* (having the capacity to develop into many types of mature neurons). Investigators are trying to develop procedures for repairing brain damage by injecting embryonic neural stem cells into the damaged site. Once

injected, the stem cells could develop and replace the damaged cells, under guidance from surrounding tissue. This line of research received a major boost from the development of renewable cultures of stem cells (see Wakayama et al., 2001), which can serve as a source for transplantation and research (Gage, 2000). The study by McDonald and colleagues (1999) illustrates the potential of this method.

McDonald and colleagues injected embryonic neural stem cells into an area of spinal damage. Their subjects were rats that had been rendered paraplegic by a blow. The stem cells migrated to different areas around the damaged area, where they developed into mature neurons. Remarkably, the rats receiving the implants became capable of supporting their weight with their hindlimbs and walking, albeit awkwardly.

The study by McDonald and colleagues and several similar ones triggered widespread media attention and a frenzy of research activity. Effective treatment for severe CNS damage appeared to be within reach. However, it quickly became apparent that much research still needs to be done (see Rossi & Cattaneo, 2002; Wexler & Palmer, 2002). First, effective methods of propagating populations of neural stem cells must be developed (see Gottlieb, 2002). Because sources of embryonic stem cells have been limited by law in some parts of the world, efforts have focused on harvesting neural stem cells from adult brains or on trying to cause other types of adult stem cells (e.g., blood stem cells) to develop into neural stem cells. Neither approach has as yet achieved unqualified success (see Temple, 2001; Wagers et al., 2002). Second, techniques for promoting the survival and appropriate maturation of the neural stem cells once they have been implanted need to be developed. Third, the factors that promote the establishment of correct connections with surviving cells need to be identified. And fourth, methods for encouraging functional recovery have to be developed. For example, little attention has been paid to the behavioral treatment of patients with neural stem cell implants, which is likely to be an important factor in their recovery. In short, although therapeutic neural stem cell transplantation is one of the most exciting subjects of investigation in all of neuroscience, the ultimate goal is an ambitious one whose achievement will take longer than once thought (see Zoghbi, Gage, & Choi, 2000).

Promoting Recovery from CNS Damage by Rehabilitative Training

Several demonstrations of the important role of experience in the organization of the developing and adult brain kindled a renewed interest in the use of rehabilitative training to promote recovery from CNS damage.

The following innovative rehabilitative training programs were derived from such findings.

Clinical Implications

Strokes Small strokes produce a core of brain damage, which is often followed by a gradually expanding loss of neural function around this core. Nudo and colleagues (1996) produced small *ischemic lesions* (lesions produced by an interruption of blood supply) in the hand area of the motor cortex of monkeys. Then, 5 days later, a program of hand training and practice was initiated. During the ensuing 3 or 4 weeks, the monkeys plucked hundreds of tiny food pellets from food wells of different sizes. This practice substantially reduced the expansion of cortical damage. The monkeys that received the rehabilitative training also showed greater recovery in the use of their affected hand.

One of the principles that has emerged from the study of neurodevelopment is that neurons seem to be in a competitive situation: They compete with other neurons for synaptic sites and neurotrophins, and the losers die. Weiller and Rijntjes (1999) designed a rehabilitative program based on this principle, tested it on monkeys, and then tested it on unilateral stroke patients who had difficulty using one arm. Their procedure, called *constraint-induced therapy* (Taub, Uswatte, & Elbert, 2002), was to tie down the functioning arm for 2 weeks while the affected arm received intensive training. Performance with the affected arm improved markedly over the 2 weeks, and there was an increase in the area of motor cortex controlling that arm.

Spinal Injury In one approach to treating patients with spinal injuries (see Rossignol, 2000; Wolpaw & Tennissen, 2001), patients incapable of walking were supported by a harness over a moving treadmill. With most of their weight supported and the treadmill providing appropriate feedback, the patients gradually learned to make walking movements. Then, as they improved, the amount of support was gradually reduced. In one study using this technique, over 90% of the trained patients eventually became independent walkers, compared with only 50% of those receiving conventional physiotherapy.

Phantom Limbs Most amputees continue to experience limbs that have been amputated—a condition referred to as **phantom limb**. The most striking feature of phantom limbs is their reality. Their existence is so compelling that a patient may try to jump out of bed onto a nonexistent leg or to lift a cup with a nonexistent hand. In most cases, the amputated limb behaves like a normal limb; for example, as an amputee walks, a phantom arm seems to swing back and forth in perfect coordination with the intact arm. However, sometimes an amputee feels that the amputated limb is stuck in a peculiar position. For example, one amputee felt that his phantom arm extended straight out from the shoulder, and as a result, he turned sideways whenever he passed through doorways (Melzack, 1992).

About 50% of amputees experience chronic severe pain in their phantom limbs. A typical complaint is that an amputated hand is clenched so tightly that the fingernails are digging into the palm of the hand. Occasionally, phantom limb pain can be treated by having the amputee concentrate on opening the amputated hand. However, when this does not work, the pain can become so intense that desperate measures are attempted.

Based on the premise that phantom limb pain results from irritation at the stump, many efforts to control it involved cutting off the stump or surgical destruction of various parts of the neural pathway between the stump and the cortex. Unfortunately, none of these surgical interventions provided patients with relief from the pain or eliminated the phantom limb (see Melzack, 1992). Still, the idea that phantom limbs and phantom limb pain result from irritation of nerves in the stump persisted. There seemed to be no other possibility.

This chapter ends with the stories of two patients suffering from phantom limb pain and their exceptional doctor. The patients were Tom and Philip, and their physician was the neuropsychologist V. S. Ramachandran. In the process of treating Tom and Philip, Dr. Ramachandran solved a long-standing neuropsychological puzzle and developed a new treatment to boot.

The Cases of Tom and Philip: Phantom Limbs and Ramachandran

Dr. Ramachandran read an article about a study you have already encountered in this chapter, the study by Pons and colleagues (1991). In this study, severing

Clinical Implications

the sensory neurons in the arms of monkeys led to a reorganization of somatosensory cortex: The area of the somatosensory cortex that originally received input from the damaged arm now received input from areas of the body normally mapped onto adjacent areas of somatosensory cortex. Ramachandran was struck by a sudden insight: Perhaps phantom limbs were not in the stump at all, but in the brain; perhaps the perception of a phantom arm originated from parts of the body that now innervated the original arm area of the somatosensory cortex (see Ramachandran & Blakeslee, 1998).

Thinking Critically

Excited by his hypothesis, Dr. Ramachandran asked one of his patients, Tom, if he would participate in a simple test. He touched various parts of Tom's body and asked Tom what he felt. Remarkably, when he touched the side of Tom's face on the same side as his amputated arm, Tom felt sensations from various parts of his phantom hand as well as his face. Indeed, when

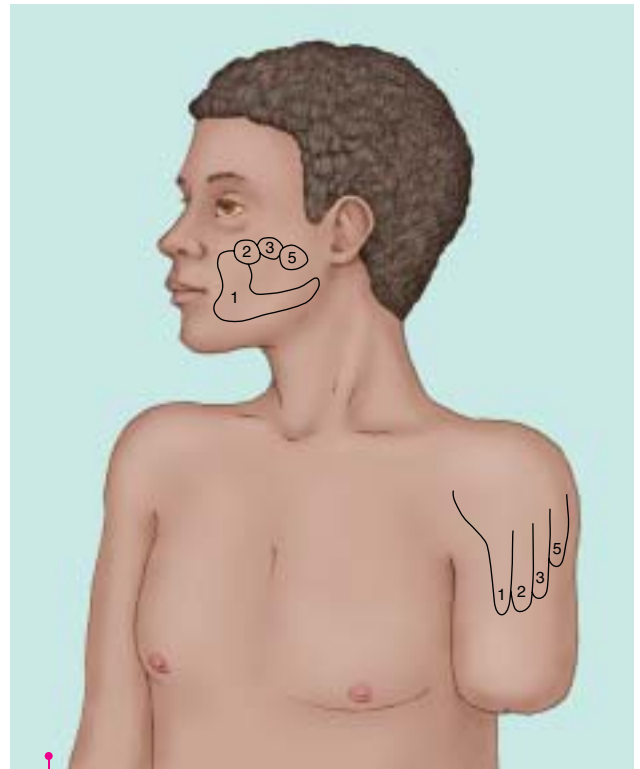


FIGURE 10.22 The places on Tom's body where touches elicited sensations in his phantom hand. (Adapted from Ramachandran & Blakeslee, 1998.)

some warm water was dropped on his face, he felt it running down his phantom hand. A second map of his hand was found on his shoulder (see Figure 10.22).

Philip, another patient of Dr. Ramachandran, suffered from severe chronic pain in his phantom arm. For a decade, Philip had been unable to move the joints of the phantom arm: It was frozen in an awkward position (Ramachandran & Rogers-Ramachandran, 2000), and Philip suffered great pain in all of its joints, particularly the elbow.

Dr. Ramachandran applied a bit of biopsychological ingenuity to the problem. Could he relieve Philip's pain by teaching him to move his phantom arm? Knowing how important feedback is in movement (see Chapter 8), Dr. Ramachandran constructed a special feedback apparatus for Philip. This was a box divided in two by a vertical mirror. Philip was instructed to put his good right hand into the box through a hole in the front and view it through a hole in the top. When he looked at his hand, he could see it and its mirror image. He was instructed to put his phantom limb in the box and try to position it, as best he could, so that it corresponded to the mirror image of his good hand. Then, he was instructed to make synchronous, bilaterally symmetrical movements of his arms—his actual

Thinking Critically

right arm and his phantom left arm—while viewing his good arm and its mirror image.

“Oh my God! Oh my God, doctor! This is unbelievable. It’s mind-boggling.” He was jumping up and down like a kid. “My left arm is plugged in again. It’s as if I’m in the past. . . . I can move my arm again. I can feel my elbow moving, my wrist moving. It’s all moving again. (Ramachandran & Blakeslee, 1998, pp. 47–48)

But when Philip shut his eyes or removed his arms from the apparatus, his phantom limb was frozen once again. . . . and the pain was as bad as ever. So, Ramachandran sent Philip home with the box and instructions to use it. Three weeks later, Philip phoned.

“Doctor,” he exclaimed, “it’s gone!”
 “What’s gone?” (I thought maybe he had lost the mirror box.)
 “My phantom is gone.”

“What are you talking about?”

“You know, my phantom arm, which I had for 10 years. It doesn’t exist anymore. All I have is my phantom fingers and palm dangling from my shoulder.”

. . . “Philip—does this bother you?”

“No, no, no. . . . On the contrary. You know the excruciating pain that I always had in my elbow? . . . Well, now I don’t have an elbow and I don’t have that pain anymore.” (Ramachandran & Blakeslee, 1998, p. 49)

I hope that I have managed to communicate to you some of the excitement that is being generated by the discovery that the adult human brain is plastic. The possibilities of applying neuroplastic processes to repair brain damage are truly exciting. I am optimistic that there will soon be a breakthrough because, as you have just learned, progress is being made on so many different fronts.

Themes Revisited

Because this entire chapter dealt with clinical issues, the clinical implications tab made numerous appearances. In particular, it drew attention to the many cases that appeared in the chapter: the ironic case of Professor P.; Jerry Quarry, the punch-drunk ex-boxer; the cases of complex partial epilepsy; Walter S. Miller, the man whose wife had Huntington’s disease; the cases of MPTP poisoning; and Tom and Philip, the amputees with phantom limbs.

The chapter stressed clear thinking about biopsychology in several places. Attention was drawn to thinking about the cumulative effects of concussions, about the relation between genes and Parkinson’s disease, about animal models of disease, about the identity of

the primary symptom of Alzheimer’s disease, and about recovery of function. Particularly interesting were the insightful approaches that Dr. Ramachandran took in treating Tom and Philip, who suffered from phantom limb pain.

The evolutionary perspective was also highlighted at several points. You were introduced to the concept of animal models, which is based on the comparative approach, and you learned that most of the research on neural regeneration and reorganization following brain damage has been done with animal models. Finally, you learned that research into the mechanisms of neural regeneration has been stimulated by the fact that this process occurs accurately in some species.

ON THE CD

See Hard Copy for additional readings for Chapter 10.



Evolutionary Perspective

Clinical Implications

Thinking Critically

Think about It

1. An epileptic is brought to trial for assault. The lawyer argues that her client is not a criminal and that the assaults in question were psychomotor attacks. She points out that her client takes her medication faithfully, but that it does not help. The prosecution lawyer argues that the defendant has a long history of violent assault and must be locked up. What do you think the judge should do?
2. Describe a bizarre incident you have observed that you think in retrospect might have been a complex partial or petit mal seizure.
3. The more that is known about a disease, the easier it is to diagnose; and the more accurately it can be diagnosed, the easier it is to find things out about it. Explain and discuss.

4. Total dementia often creates less suffering than partial dementia. Discuss.
5. In order to be useful, animal models do not have to have all of the features of the disorder they are modeling. Discuss.
6. Major breakthroughs in the treatment of CNS damage are on the horizon. Discuss.
7. The first evaluation of the effectiveness of neurotransplantation in the treatment of Parkinson’s disease suggested that the treatment, as administered, was not effective. What do you think should be the next step?

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Key Terms

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 Aneurysm (p. 233)
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 Arteriosclerosis (p. 234)
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