Brain Facts

A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

Contents

Introduction

IT SETS HUMANS APART from all other species by allowing us to achieve the wonders of walking on the moon and composing masterpieces of literature, art, and music. The human brain — a spongy, three-pound mass of fatty tissue — has been compared to a telephone switchboard and a supercomputer.

But the brain is much more complicated than either of these devices, a fact scientists confirm almost daily, with each new discovery. The extent of the brain's capabilities is unknown, but it is the most complex living structure known in the universe.

This single organ controls body activities, ranging from heart rate and sexual function to emotion, learning, and memory. The brain is even thought to influence the immune system's response to disease and to determine, in part, how well people respond to medical treatments. Ultimately, it shapes our thoughts, hopes, dreams, and imaginations. In short, the brain is what makes us human.

Neuroscientists have the daunting task of deciphering the mystery of this most complex of all machines: how as many as 100 billion nerve cells are produced, grow, and organize themselves into effective, functionally active systems that ordinarily remain in working order throughout a person's lifetime.

The motivation of researchers is twofold: to understand human behavior better — from how we learn to why people have trouble getting along together — and to discover ways to prevent or cure many devastating brain disorders.

The more than 1,000 disorders of the brain and nervous system result in more hospitalizations than any other disease group, including heart disease and cancer. Neurological illnesses affect more than 50 million Americans annually, at costs exceeding $460 billion. In addition, mental disorders, excluding drug and alcohol problems, strike 44 million adults a year at a cost of some $148 billion.

Since the Decade of the Brain, which ended in 2000, neuroscience has made significant discoveries in these areas:

Genetics Disease genes have been identified that are key to several neurodegenerative disorders, including Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis. These discoveries have provided new insight into underlying disease mechanisms and are beginning to suggest new treatments. With the mapping of the human genome, neuroscientists have been able to make more rapid progress in identifying genes that either contribute to or directly cause human neurological disease. Mapping animal genomes has aided the search for genes that regulate and control many complex behaviors.

Gene-Environment Interactions Most major diseases that have a genetic basis are strongly influenced by the environment. For example, identical twins have an increased risk compared with nonidentical siblings of getting the same disease; however, if one twin gets the disease, the probability that the other will also be affected is only 30 to 60 percent. Environmental influences include many factors such as toxic substances, diet, and level of physical activity but also encompass stressful life events.

Brain Plasticity The brain possesses the ability to modify neural connections to better cope with new circumstances. Scientists have begun to uncover the molecular basis of this process, called plasticity, revealing how learning and memory occur and how declines might be reversed. These discoveries are leading to new approaches to the treatment of chronic pain.

New Drugs Researchers have gained insight into the mechanisms of molecular neuropharmacology, which provides a new understanding of the mechanisms of addiction. These advances have led to new treatments for depression and obsessive-compulsive disorder.

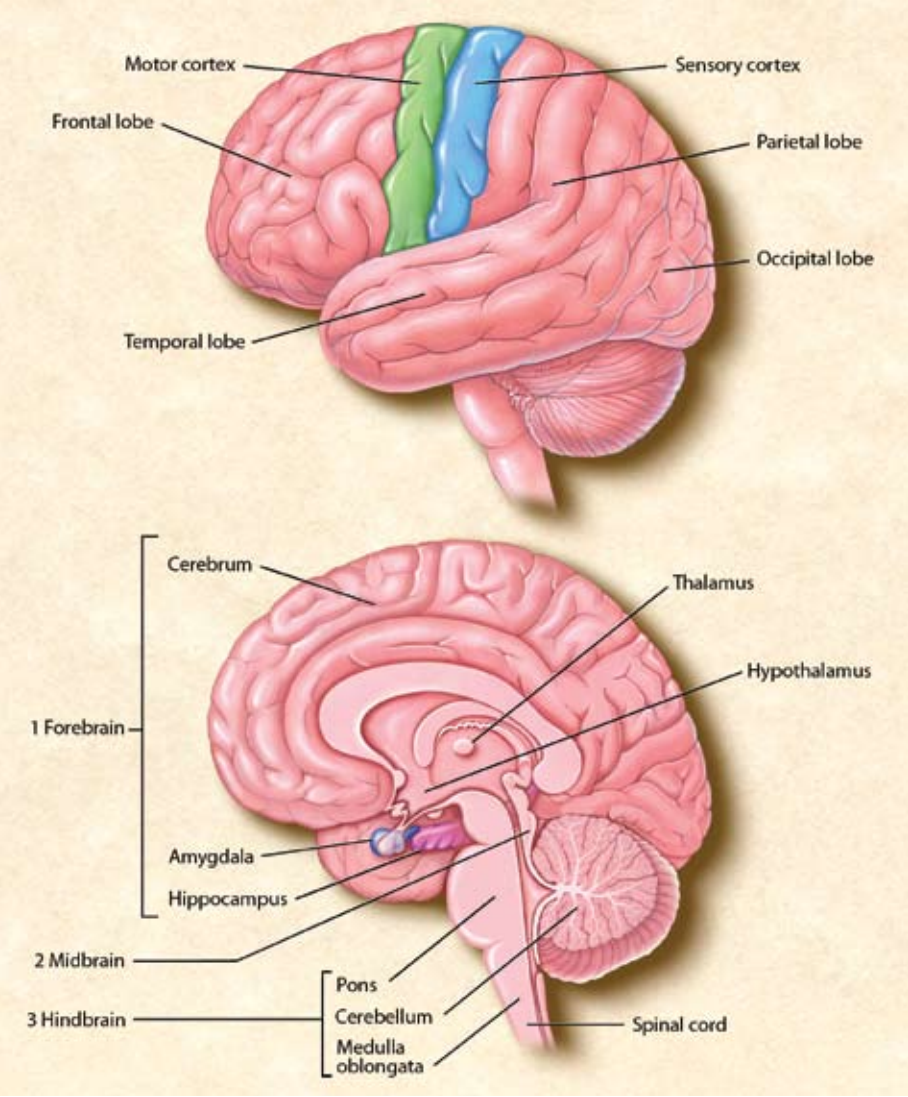
Imaging Revolutionary imaging techniques, including magnetic resonance imaging and positron emission tomography, have revealed the brain systems underlying attention, memory, and emotions and indicate dynamic changes that occur in schizophrenia and other disorders.

Cell Death The discovery of how and why neurons die, as well as the discovery of stem cells, which divide and form new neurons, has many clinical applications. This has dramatically improved the outlook for reversing the effects of injury in both the brain and the spinal cord. The first effective treatments for stroke and spinal cord injury based on these advances have been brought to clinical practice.

Brain Development New principles and newly discovered molecules responsible for guiding nervous system development now give scientists a better understanding of certain disorders of childhood. Together with the discovery of stem cells, these advances are pointing to novel strategies for helping the brain or spinal cord regain functions lost as a result of injury or developmental dysfunction.

Federal neuroscience research funding of more than $5 billion annually and private support will continue to expand our knowledge of the brain in the years ahead.

This book provides only a glimpse of what is known about the nervous system, the disorders of the brain, and some of the exciting avenues of research that promise new therapies for many neurological diseases.



THE BRAIN. Cerebral cortex (top image). This part of the brain is divided into four sections: the occipital lobe, the temporal lobe, the parietal lobe, and the frontal lobe. Functions, such as vision, hearing, and speech, are distributed in selected regions. Some regions are associated with more than one function. Major internal structures (bottom image). The (1) forebrain is credited with the highest intellectual functions — thinking, planning, and problem-solving. The hippocampus is involved in memory. The thalamus serves as a relay station for almost all the information coming into the brain. Neurons in the hypothalamus serve as relay stations for internal regulatory systems by monitoring information coming in from the autonomic nervous system and commanding the body through those nerves and the pituitary gland. On the upper surface of the (2) midbrain are two pairs of small hills, colliculi, collections of cells that relay specific sensory information from sense organs to the brain. The (3) hindbrain consists of the pons and medulla oblongata, which help control respiration and heart rhythms, and the cerebellum, which helps control movement as well as cognitive processes that require precise timing.

THE TOLL OF SELECTED BRAIN AND NERVOUS SYSTEM DISORDERS ON AMERICANS*

Condition	Total Cases	Cost per Year (U.S. dollars)
Sleep Disorders	70 million	100 billion
Hearing Loss	32 million	2.5 billion
All Depressive Disorders	20.9 million	70 billion
Traumatic Brain Injury	5.3 million	60 billion
Stroke	5.2 million	51 billion
Alzheimer's Disease	5 million	148 billion
Schizophrenia	2 million	32.5 billion
Parkinson's Disease	1 million	5.6 billion
Multiple Sclerosis	400,000	10.6 billion
Spinal Cord Injury	250,000	10 billion
Huntington's Disease	30,000	2 billion

** Estimates provided by the Centers for Disease Control and Prevention, National Institutes of Health, and voluntary organizations.*

The Neuron

A SPECIALIZED CELL designed to transmit information to other nerve cells, muscle, or gland cells, the neuron is the basic working unit of the brain. The brain is what it is because of the structural and functional properties of interconnected neurons. The brain contains between 1 billion and 100 billion neurons, depending on the species.

The neuron consists of a *cell body*, *dendrites*, and an *axon*. The cell body contains the nucleus and cytoplasm. The electrically excitable axon extends from the cell body and often gives rise to many smaller branches before ending at *nerve terminals*. *Dendrites* extend from the neuron cell body and receive messages from other neurons. *Synapses* are the contact points where one neuron communicates with another. The dendrites and cell body are covered with synapses formed by the ends of axons from other neurons.

Neurons signal by transmitting electrical impulses along their axons, which can range in length from a tiny fraction of an inch to three feet or more. Many axons are covered with a layered *myelin* sheath, which speeds the transmission of electrical signals along the axon. This sheath is made of specialized cells called oligodendrocytes in the brain and Schwann cells in the peripheral nervous system.

Nerve impulses involve the opening and closing of *ion channels*, which are selectively permeable, water-filled molecular tunnels that pass through the cell membrane and allow ions — electrically charged atoms — or small molecules to enter or leave the cell. The flow of these ions creates an electrical current that produces tiny voltage changes across the neuron's cell membrane.

The ability of a neuron to generate an electrical impulse depends on a difference in charge between the inside and outside of the cell. When a nerve impulse begins, a dramatic reversal in the electrical potential occurs at one point on the cell's membrane, when the neuron switches from an internal negative charge to a positive charge state. The change, called an *action potential*, then passes along the membrane of the axon at speeds up to several hundred miles per hour. In this way, a neuron may be able to fire impulses multiple times every second.

Upon reaching the end of an axon, these voltage changes trigger the release of *neurotransmitters*, the brain's chemical messengers. Neurotransmitters are released at nerve terminals, diffuse across the intrasynaptic space, and bind to receptors on the surface of the target cell (often another neuron but also possibly a muscle or gland cell).

These receptors act as on-and-off switches for the next cell. Each receptor has a distinctly shaped region that selectively recognizes a particular chemical messenger. A neurotransmitter fits into this region in much the same way that a key fits into a lock. And when the transmitter is in place, this interaction alters the target cell's membrane potential and triggers a response, such as the generation of an action potential, contraction of a muscle, stimulation of enzyme activity, or inhibition of neurotransmitter release from the target cell.

Increased understanding of neurotransmitters in the brain and of the action of drugs on these chemicals — gained largely through animal research — guides one of the largest fields in neuroscience. Armed with this information, scientists hope to understand the circuits responsible for disorders such as Alzheimer's disease and Parkinson's disease. Sorting out the various chemical circuits is vital to understanding how the brain stores memories, why sex is such a powerful motivation, and what makes up the biological basis of mental illness.

Neurotransmitters and neuromodulators

Acetylcholine The first neurotransmitter, identified about 75 years ago, was acetylcholine (ACh). This chemical is released by neurons connected to voluntary muscles (causing them to contract) and by neurons that control the heartbeat. ACh also serves as a transmitter in many regions of the brain.

ACh is formed at the axon terminals. When an action potential arrives at the nerve terminal, the electrically charged calcium ion rushes in, and ACh is released into the synapse, where it attaches to ACh receptors on the target cells. On voluntary muscles, this opens sodium channels and causes the muscle to contract. ACh is then broken down by the enzyme acetylcholinesterase and resynthesized in the nerve terminal. Antibodies that block one type of receptor for ACh cause *myasthenia gravis*, a disease characterized by fatigue and muscle weakness.

Much less is known about ACh in the brain. Recent discoveries suggest, however, that it may be critical for normal attention, memory, and sleep. Because ACh-releasing neurons die in Alzheimer's patients, finding ways to restore this neurotransmitter is one goal of current research. Drugs that inhibit acetylcholinesterase are presently the main drugs used to treat Alzheimer's disease.

Amino acids Amino acids, widely distributed throughout the body and the brain, serve as the building blocks of proteins. Certain amino acids can also serve as neurotransmitters in the brain.

The neurotransmitters *glycine* and *gamma-aminobutyric acid* (GABA) inhibit the firing of neurons. The activity of GABA is

increased by *benzodiazepines* (e.g., Valium) and by anticonvulsant drugs. In Huntington's disease, a hereditary disorder that begins during midlife, the GABA-producing neurons in brain centers that coordinate movement degenerate, thereby causing uncontrollable movements.

Glutamate and *aspartate* act as excitatory signals, activating, among others, *N-methyl-d-aspartate* (NMDA) receptors, which have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in a developing animal. The stimulation of NMDA receptors may promote beneficial changes in the brain, whereas overstimulation can cause nerve cell damage or cell death in trauma and stroke.

Key questions remain about the NMDA receptor's precise structure, regulation, location, and function. Developing drugs to block or stimulate activity at NMDA receptors holds promise for improving brain function and treating neurological and psychiatric disorders.

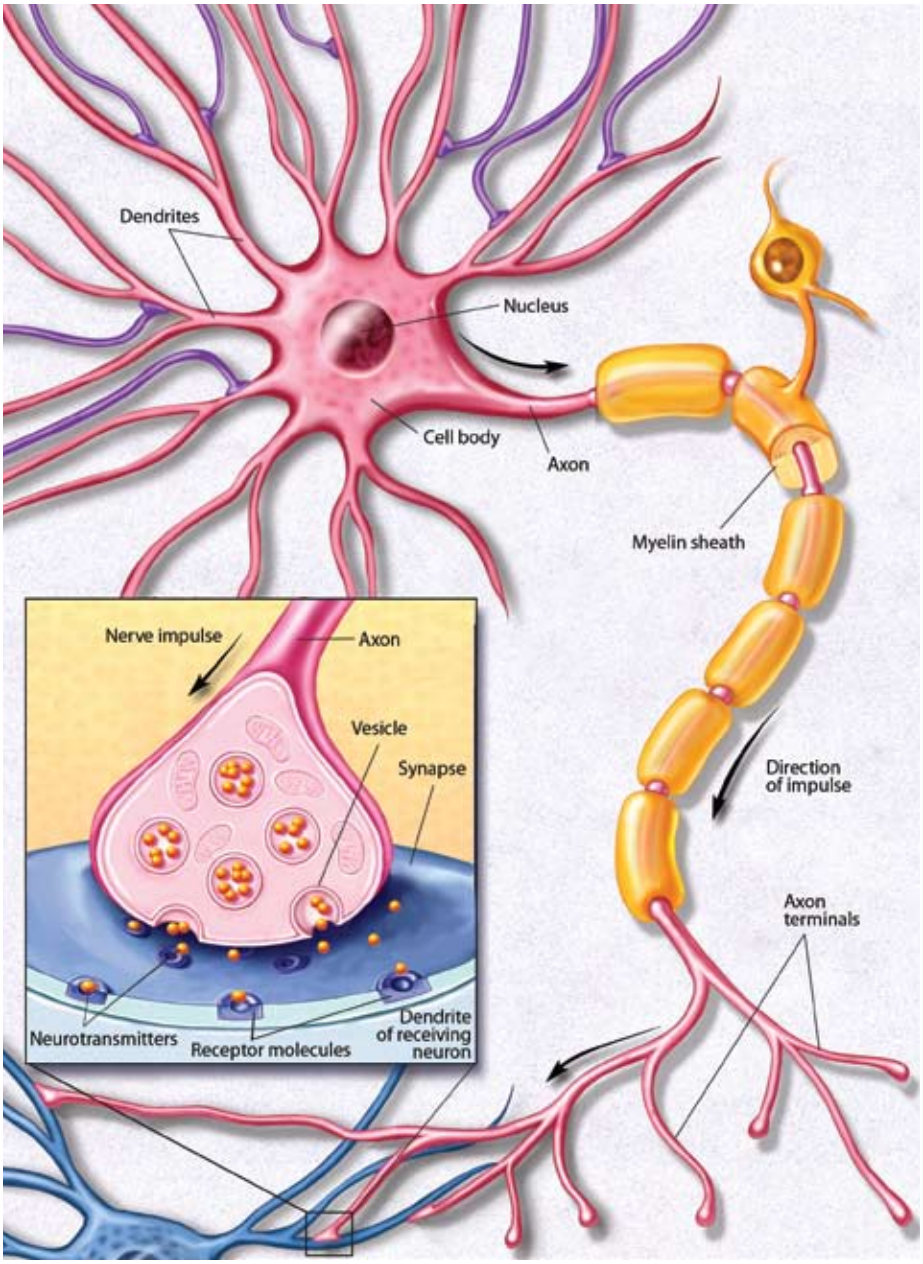
Catecholamines

Dopamine and *norepinephrine* are widely present in the brain and peripheral nervous system. Dopamine is present in three principal circuits in the brain; these circuits control movement, cause psychiatric symptoms such as psychosis, and regulate hormonal responses.

The dopamine circuit that regulates movement has been directly linked to disease. Due to dopamine deficits in the brain, people with Parkinson's disease show symptoms including muscle tremors, rigidity, and difficulty in moving. Thus, medical scientists have found that the administration of *levodopa*, a substance from which dopamine is synthesized, is an effective treatment for Parkinson's, allowing patients to walk and perform skilled movements more successfully.

Another dopamine circuit is thought to be important for cognition and emotion; abnormalities in this system have been implicated in schizophrenia. Because drugs that block certain dopamine receptors in the brain are helpful in diminishing psychotic symptoms, learning more about dopamine is important to understanding mental illness.

In a third circuit, dopamine regulates the endocrine system. Dopamine directs the hypothalamus to manufacture hormones and hold them in the pituitary gland for release into the bloodstream or to trigger the release of hormones held within cells in the pituitary.



NEURON. A neuron fires by transmitting electrical signals along its axon. When signals reach the end of the axon, they trigger the release of neurotransmitters that are stored in pouches called vesicles. Neurotransmitters bind to receptor molecules on the surfaces of adjacent neurons. The point of virtual contact is known as the synapse.

Nerve fibers containing norepinephrine are present throughout the brain. Deficiencies in this transmitter occur in patients with Alzheimer's disease, Parkinson's disease, and *Korsakoff's syndrome*, a cognitive disorder associated with chronic alcoholism. Thus, researchers believe norepinephrine may play a role in both learning and memory. Norepinephrine is also secreted by the sympathetic nervous system in the periphery to regulate heart rate and blood pressure. Acute stress increases the release of norepinephrine from sympathetic nerves and the adrenal medulla.

Serotonin This neurotransmitter is present in the brain and other tissues, particularly blood platelets and the lining of the digestive tract. In the brain, serotonin has been implicated in sleep, mood, depression, and anxiety. Because serotonin controls the different switches affecting various emotional states, scientists believe these switches can be manipulated by analogs, chemicals with molecular structures similar to that of serotonin. Drugs that alter serotonin's action, such as *fluoxetine*, relieve symptoms of depression and obsessive-compulsive disorder.

Peptides These are chains of amino acids linked together. Peptides differ from proteins, which are much larger and have more complex combinations of amino acids.

In 1973, scientists discovered receptors for opiates on neurons in several regions of the brain, suggesting that the brain must make substances very similar to opium. Shortly thereafter, scientists made their first discovery of an opiate produced by the brain that resembles morphine, an opium derivative used medically to kill pain. They named it *enkephalin*, literally meaning "in the head." Soon after, other types of opioid peptides, *endorphins*, were discovered. Endorphins, whose name comes from endogenous morphine, act like opium or morphine to kill pain or cause sleepiness.

The precise role of the naturally occurring opioid peptides is unclear. A simplistic hypothesis is that they are released by brain neurons in times of stress to minimize pain and enhance adaptive behavior. The presence of opioid peptides may explain, for example, why injuries received during the stress of combat are often not noticed until hours later. Neurons containing these opioid peptides, however, are not limited to pain-sensing circuits.

Opioids and their receptors are closely associated with pathways in the brain that are activated by painful or tissue-damaging stimuli. These signals are transmitted to the *central nervous system* — the brain and spinal cord — by special sensory nerves, small myelinated fibers, and tiny unmyelinated *C fibers*. Scientists have discovered that some C fibers contain a peptide called *substance P* that causes the sensation of burning pain. The active component of chili peppers, *capsaicin*, causes the release of substance P.

Trophic factors Researchers have discovered several small proteins in the brain that are necessary for the development, function, and survival of specific groups of neurons. These small proteins are made in brain cells, are released locally in the brain, and bind to receptors expressed by specific neurons. Researchers also have identified genes that code for receptors and are involved in the signaling mechanisms of trophic factors. These findings are expected to result in a greater understanding of how trophic factors work in the brain. This information should also prove useful for the design of new therapies for brain disorders of development and for degenerative diseases, including Alzheimer's disease and Parkinson's disease.

Hormones In addition to the nervous system, the *endocrine system* is a major communication system of the body. While the nervous system uses neurotransmitters as its chemical signals, the endocrine system uses hormones for its chemical signals. The pancreas, kidneys, heart, adrenal glands, gonads, thyroid, parathyroid, thymus, and pituitary gland are sources of hormones. The endocrine system works in large part through the pituitary gland, which secretes hormones into the blood. Because fragments of endorphins are released from the pituitary gland into the bloodstream, they might also function as endocrine hormones. This system is very important for the activation and control of basic behavioral activities such as sex, emotion, responses to stress, and the regulation of body functions, including growth, reproduction, energy use, and metabolism. Actions of hormones show the brain to be very malleable and capable of responding to environmental signals.

The brain contains receptors for thyroid hormones and the six classes of steroid hormones — *androgens*, *estrogens*, *progestins*, *glucocorticoids*, *mineralocorticoids*, and *vitamin D*. The receptors are found in selected populations of neurons in the brain and relevant organs in the body. Thyroid and steroid hormones bind to receptor proteins that in turn bind to DNA and regulate the action of genes. This can result in long-lasting changes in cellular structure and function.

The brain has receptors for many hormones; for example, the metabolic hormones *insulin*, insulinlike growth factor, *ghrelin*, and *leptin*. These hormones are taken up from the blood and act to affect neuronal activity and certain aspects of neuronal structure.

In response to stress and changes in our *biological clocks*, such as day and night cycles and jet lag, hormones enter the blood and travel to the brain and other organs. In the brain, hormones alter the production of gene products that participate in synaptic neurotransmission as well as the structure of brain cells. As a result, the circuitry of the brain and its capacity for neurotransmission are changed over a course of hours to days. In this way, the brain adjusts its performance and control of behavior in response to a changing environment. Hormones are important agents of protection and adaptation, but stress

and stress hormones, such as the glucocorticoid cortisol, can also alter brain function, including learning. Severe and prolonged stress can cause permanent brain damage.

Reproduction in females is a good example of a regular, cyclic process driven by circulating hormones: The neurons in the hypothalamus produce *gonadotropin-releasing hormone* (GnRH), a peptide that acts on cells in the pituitary. In both males and females, this causes two hormones — the *follicle-stimulating hormone* (FSH) and the *luteinizing hormone* (LH) — to be released into the bloodstream. In males, these hormones are carried to receptors on cells in the testes, where they release the male hormone testosterone, an androgen, into the bloodstream. In females, FSH and LH act on the ovaries and cause the release of the female hormones estrogen and progesterone. Testosterone, estrogen, and progesterone are often referred to as sex hormones.

In turn, the increased levels of testosterone in males and estrogen in females act back on the hypothalamus and pituitary to decrease the release of FSH and LH. The increased levels of sex hormones also induce changes in cell structure and chemistry that lead to an increased capacity to engage in sexual behavior. Sex hormones also exert widespread effects on many other functions of the brain such as attention, motor control, pain, mood, and memory.

Sexual differentiation of the brain is caused by sex hormones acting in fetal and early postnatal life, although recent evidence points to genes on the Y chromosome contributing to this process. Scientists have found statistically and biologically significant differences between the brains of men and women that are similar to sex differences found in experimental animals. These include differences in the size and shape of brain structures in the hypothalamus and the arrangement of neurons in the cortex and hippocampus. Sex differences go well beyond sexual behavior and reproduction and affect many brain regions and functions, ranging from mechanisms for perceiving pain and dealing with stress to strategies for solving cognitive problems. Although differences exist, the brains of men and women are more similar than they are different.

Anatomical differences have also been reported between the brains of heterosexual and homosexual men. Research suggests that hormones and genes act early in life to shape the brain in terms of sex-related differences in structure and function, but scientists are still putting together all the pieces of this puzzle.

Gases Scientists identified a new class of neurotransmitters that are gases. These molecules — *nitric oxide* and *carbon monoxide* — do not act like other neurotransmitters. Being gases, they are not stored in any structure, certainly not in synaptic storage structures. Instead, they are made by enzymes as they are needed and released from neurons by diffusion. Rather than acting at receptor sites, these gases simply diffuse into adjacent neurons and act upon chemical targets, which may be enzymes.

While exact functions for carbon monoxide have not been determined, nitric oxide has already been shown to play several important roles. For example, nitric oxide neurotransmission governs erection in the penis. In nerves of the intestine, it governs the relaxation that contributes to the normal movements of digestion. In the brain, nitric oxide is the major regulator of the intracellular messenger molecule — *cyclic GMP.* In conditions of excess glutamate release, as occurs in stroke, neuronal damage following the stroke may be attributable in part to nitric oxide.

Second messengers

Substances that trigger biochemical communication within cells, after the action of neurotransmitters at their receptors, are called second messengers; these intracellular effects may be responsible for long-term changes in the nervous system. They convey the chemical message of a neurotransmitter (the first messenger) from the cell membrane to the cell's internal biochemical machinery. Second-messenger effects may endure for a few milliseconds to as long as many minutes.

An example of the initial step in the activation of a second-messenger system involves *adenosine triphosphate* (ATP), the chemical source of energy in cells. ATP is present throughout the cytoplasm of all cells. For example, when norepinephrine binds to its receptors on the surface of the neuron, the activated receptor binds a G protein on the inside of the membrane. The activated G protein causes the enzyme *adenylyl cyclase* to convert ATP to *cyclic adenosine monophosphate* (cAMP). The second messenger, cAMP, exerts a variety of influences within the cell, ranging from changes in the function of ion channels in the membrane to changes in the expression of genes in the nucleus, rather than acting as a messenger between one neuron and another.

Second messengers also are thought to play a role in the manufacture and release of neurotransmitters and in intracellular movements and carbohydrate metabolism in the *cerebrum* — the largest part of the brain, consisting of two hemispheres — as well as the processes of growth and development. In addition, direct effects of second messengers on the genetic material of cells may lead to long-term alterations in cellular functioning and ultimately in behavior.

Brain Development

THE CELLS OF THE NERVOUS SYSTEM

connect with one another in trillions of remarkably specific patterns that form and change over the course of an organism's life. These connections develop among various types of neurons, a process that begins in the embryo. First, appropriate types of neurons must arise in appropriate numbers and migrate to appropriate places. The axons and dendrites that form the connections then extend from these nerve cells, and the growth of axons must be guided over long distances so they reach the appropriate targets. Axons must recognize specific target cells. The connections that form initially then mature, with the activity and experience of early postnatal life playing a key role in their refinement. The degree of complexity in the brain, and therefore the amount of interaction required to regulate its development, is far greater than in other organs of the body. Scientists studying development are working to reveal how these complicated processes of connecting and reshaping occur.

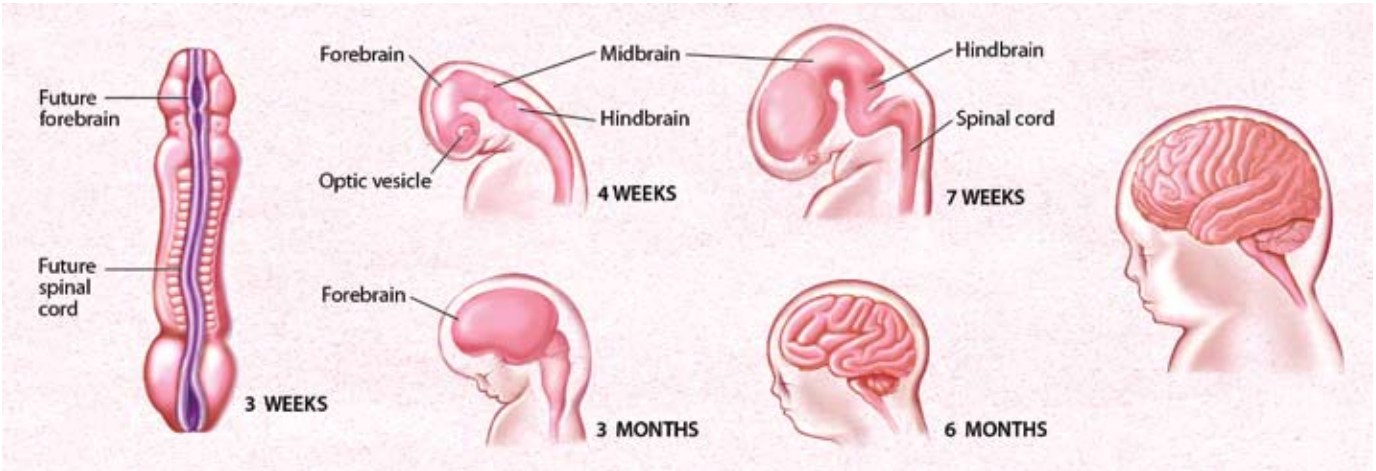
Many initial steps in brain development are similar across species, although later steps are different. By studying these similarities and differences, scientists can learn about normal human brain development and can learn how brain abnormalities, such as mental retardation and other disorders, can be prevented or treated.

Advances in the study of brain development have become increasingly relevant for medical treatments. For example, several diseases that most scientists once thought were purely disorders of adult function are now being considered in developmental terms, including schizophrenia. Other research suggests that genes that are important for brain development may also play a role in susceptibility to autism spectrum disorders. And by applying knowledge about how connections form during development, regeneration following injury to the brain now is viewed as distinctly possible.

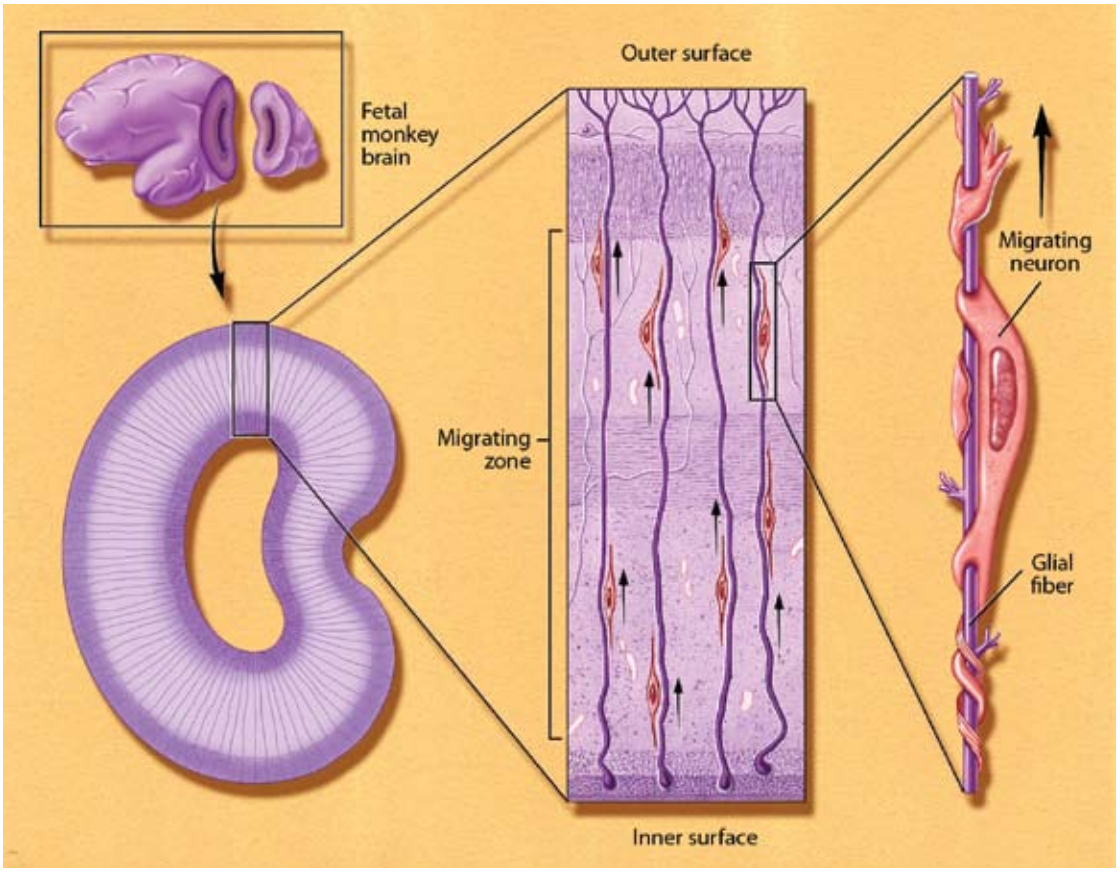
Knowing how the brain is put together is essential for understanding its ability to reorganize in response to external influences or injury. These studies also shed light on brain functions such as learning and memory. The brain evolves from the embryo to the adult stage, and during infancy and childhood it possesses unique attributes that contribute to differences in learning ability as well as vulnerability to specific brain disorders. Neuroscientists are beginning to discover some general principles that underlie developmental processes, many of which overlap in time.

Birth of neurons and brain wiring

Three to four weeks after conception, one of the two cell layers of the gelatinlike human embryo, about one-tenth of an inch long, starts to thicken and build up along the middle. As the cells continue to divide and this flat neural plate grows, parallel ridges, similar to the creases in a paper airplane, rise across its surface. Within a few days, the ridges fold in toward each other and fuse to form the hollow neural tube. The top of the tube thickens into three bulges that form the hindbrain, midbrain, and forebrain. The first signs of the eyes and the hemispheres of the brain appear later in development.



BRAIN DEVELOPMENT. The human brain and nervous system begin to develop at about three weeks' gestation with the closing of the neural tube (left image). By four weeks, major regions of the human brain can be recognized in primitive form, including the forebrain, midbrain, hindbrain, and optic vesicle (from which the eye develops). Irregular ridges, or convolutions, are clearly seen by six months.



NEURON MIGRATION. A cross-sectional view of the occipital lobe (which processes vision) of a three-month-old monkey fetus brain (center) shows immature neurons migrating along glial fibers. These neurons make transient connections with other neurons before reaching their destination. A single migrating neuron, shown about 2,500 times its actual size (right), uses a glial fiber as a guiding scaffold. To move, it needs adhesion molecules, which recognize the pathway, and contractile proteins to propel it along.

The embryo has three layers that undergo many interactions in order to grow into organ, bone, muscle, skin, or neural tissue. Skin and neural tissue arise from one layer, the *ectoderm*, in response to signals provided by the adjacent layer, the *mesoderm*.

A number of molecules interact to determine whether the ectoderm becomes neural tissue or develops in another way to become skin. Studies of spinal cord development in frogs show that one major mechanism depends on specific proteins that inhibit the activity of other proteins. In areas where no inhibition occurs, the tissue becomes skin. In areas where proteins secreted from the mesoderm do lead to inhibition, the tissue becomes neural.

Once the ectodermal tissue has acquired its neural fate, more signaling interactions determine which type of brain cell forms. The mature nervous system contains a vast array of cell types, which can be divided into two main categories: the neurons, responsible primarily for signaling, and supporting cells called glial cells.

Researchers are finding that the destiny of neural tissue depends on a number of elements, including cell position within the nervous system, that define the environmental signals to which the cells are exposed. For example, a key factor in spinal cord development is a secreted protein called *sonic hedgehog* that is similar to a signaling protein found in flies. The protein, initially secreted from mesodermal tissue lying beneath the developing spinal cord, marks directly adjacent neural cells to become a specialized class of glial cells. Cells farther away are exposed to lower concentrations of sonic hedgehog, and they become the motor neurons that control muscles. An even lower concentration promotes the formation of interneurons, which relay messages to other neurons, not muscles.

A combination of signals also determines the type of chemical messages, or neurotransmitters, that a neuron will use to communicate with other cells. For some cells, such as motor neurons, the type of neurotransmitter is fixed, but for other neurons, it is a matter of choice. Scientists found that when certain neurons are maintained in a dish with no other cell types, they produce the neurotransmitter norepinephrine. In contrast, if the same neurons are maintained with other cells, such as cardiac, or heart, tissue, they produce the neurotransmitter acetylcholine. Since all neurons have the genes required to produce these molecules, it is the turning on of a particular set of genes that begins the production of specific neurotransmitters. Many researchers believe that the signal to engage the gene and, therefore, the final determination of the chemical messengers that a neuron produces, is influenced by factors coming from the targets themselves.

Neurons are initially produced along the central canal in the neural tube. These neurons then migrate from their birthplace to a final destination in the brain. They collect together to form each of the various brain structures and acquire specific ways of transmitting nerve messages. Their axons grow long distances to find and connect with appropriate partners, forming elaborate and specific circuits. Finally, sculpting action eliminates redundant or improper connections, honing the specific purposes of the circuits that remain. The result is a precisely elaborated adult network of 100 billion neurons capable of body movement, perception, emotion, and thought.

As neurons are produced, they move from the neural tube's *ventricular zone*, or inner surface, to near the border of the *marginal zone*, or outer surface. After neurons stop dividing, they form an intermediate zone where they gradually accumulate as the brain develops.

The migration of neurons occurs in most structures of the brain but is particularly prominent in the formation of a large cerebral cortex in primates, including humans. In this structure, neurons slither from the place of origin near the ventricular surface, along non-neuronal fibers that form a trail, to their proper destination. Proper neuron migration requires multiple mechanisms, including the recognition of the proper path and the ability to move long distances. One mechanism for long-distance migration is the movement of neurons along elongated fibers that form transient scaffolding in the fetal brain. In another mode, inhibitory interneurons migrate tangentially across the brain. Many external forces, such as alcohol, cocaine, or radiation, prevent proper neuronal migration and result in misplacement of cells, which may lead to mental retardation or epilepsy. Furthermore, mutations in genes that regulate migration have been shown to cause some rare genetic forms of retardation and epilepsy in humans.

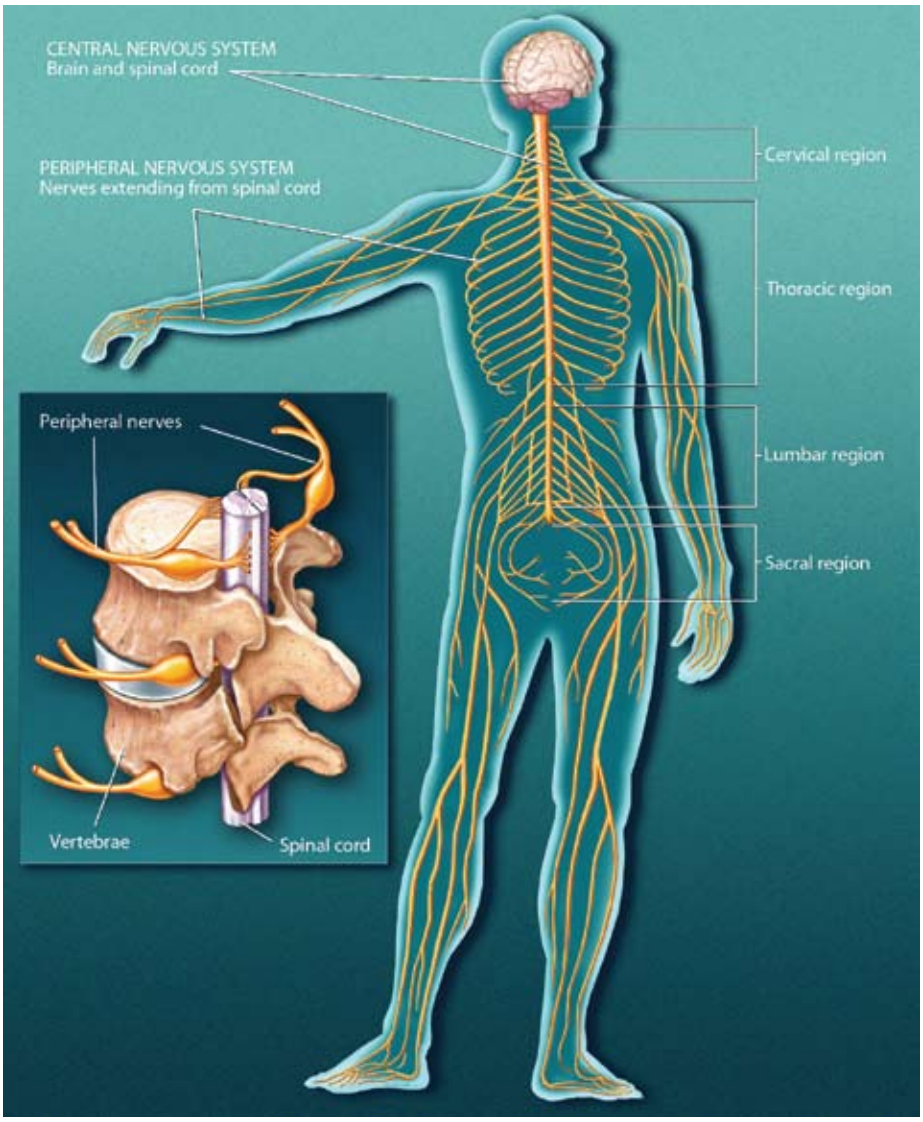
Once the neurons reach their final location, they must make the proper connections for a particular function to occur; for example, vision or hearing. They do this through their axons. These thin appendages can stretch out a thousand times longer than the cell body from which they arise. The journey of most axons ends when they meet thicker appendages, called dendrites, on other neurons. These target neurons can be located at a considerable distance, sometimes at the opposite side of the brain. In the case of a motor neuron, the axon may travel from the spinal cord all the way down to a foot muscle.

Axon growth is directed by growth cones. These enlargements of the axon's tip actively explore the environment as they seek out their precise destination. Researchers have discovered many special molecules that help guide growth cones. Some molecules lie on the cells that growth cones contact, whereas others are released from sources found near the growth cone. The growth cones, in turn, bear molecules that serve as receptors for the environmental cues. The binding of particular signals with receptors tells the growth cone whether to move forward, stop, recoil, or change direction. These signaling molecules include proteins with names such as netrin, semaphorin, and ephrin. In most cases, these are families of related molecules; for example, researchers have identified at least 15 semaphorins and at least 10 ephrins.

Perhaps the most remarkable finding is that most of these proteins are common to worms, insects, and mammals, including humans. Each protein family is smaller in flies or worms than in mice or people, but its functions are quite similar. It has therefore been possible to use the simpler animals to gain knowledge that can be applied directly to humans. For example, the first netrin was discovered in a worm and shown to guide neurons around the worm's "nerve ring." Later, vertebrate netrins were found to guide axons around the mammalian spinal cord. Receptors for netrins were found in worms and proved invaluable in finding the corresponding, and related, human receptors.

Once axons reach their targets, they form synapses, which permit electric signals in the axon to jump to the next cell, where they can either provoke or prevent the generation of a new signal. The regulation of this transmission at synapses, and the integration of inputs from the thousands of synapses each neuron receives, are responsible for the astounding information-processing capacity of the brain. For processing to occur properly, the connections must be highly specific. Some specificity arises from the mechanisms that guide each axon to its proper target area. Additional molecules mediate *target recognition*, whereby the axon chooses the proper neuron, and often the proper part of the target, once it arrives at its destination. Several of these recognition molecules have been identified in the past few years.

Researchers also have had success identifying the ways in which the synapse differentiates once contact has been made. The tiny portion of the axon that contacts the dendrite becomes specialized for the release of neurotransmitters, and the tiny portion of the dendrite that receives the contact becomes specialized to receive and respond to the signal. Special molecules pass between the sending and receiving cells to ensure that the contact is formed properly and that the sending and receiving specializations are precisely matched. These processes ensure that the synapse can transmit signals quickly and effectively. Finally, still other molecules coordinate the maturation of the synapse after it has formed, so that it can accommodate the changes that occur as our bodies mature and our behavior changes. Defects in some of these molecules are now thought to confer susceptibility to disorders such as autism,



SPINAL CORD AND NERVES. The mature central nervous system (CNS) consists of the brain and spinal cord. The brain sends nerve signals to specific parts of the body through peripheral nerves, known as the peripheral nervous system (PNS). Peripheral nerves in the cervical region serve the neck and arms; those in the thoracic region serve the trunk; those in the lumbar region serve the legs; and those in the sacral region serve the bowels and bladder. The PNS consists of the somatic nervous system that connects voluntary skeletal muscles with cells specialized to respond to sensations, such as touch and pain. The autonomic nervous system is made of neurons connecting the CNS with internal organs. It is divided into the sympathetic nervous system, which mobilizes energy and resources during times of stress and arousal, and the parasympathetic nervous system, which conserves energy and resources during relaxed states.

and the loss of others may underlie the degradation of synapses that occurs during aging.

Many axons in the brain require a sheath of myelin to enhance the speed of conduction. The process of wrapping axons in myelin occurs last and can take years to complete in some areas of the brain.

Paring back

After growth, the neural network is pared back to create a more efficient system. Only about half the neurons generated during development survive to function in the adult. Entire populations of neurons are removed through apoptosis, programmed cell death initiated in the cells. Apoptosis is activated if a neuron loses its battle with other neurons to receive life-sustaining chemical signals called trophic factors. These factors are produced in limited quantities by target tissues. Each type of trophic factor supports the survival of a distinct group of neurons. For example, nerve growth factor is important for sensory neuron survival. Recently, it has become clear that apoptosis is maintained into adulthood and constantly held in check. On the basis of this idea, researchers have found that injuries and some neurodegenerative diseases kill neurons not directly by the damage they inflict but rather by activating the cells' own death programs. This discovery — and its implication that death need not follow insult — have led to new avenues for therapy.

Brain cells also form too many connections at first. For example, in primates, the projections from the two eyes to the brain initially overlap and then sort out to separate territories devoted to one eye or the other. Furthermore, in the young primate cerebral cortex, the connections between neurons are greater in number than and twice as dense as those in an adult primate. Communica-

tion between neurons with chemical and electrical signals is necessary to weed out the connections. The connections that are active and generating electrical currents survive, whereas those with little or no activity are lost. Thus, the circuits of the adult brain are formed, at least in part, by sculpting away incorrect connections to leave only the correct ones.

Critical periods

Although most of the neuronal cell death occurs in the embryo, the paring down of connections occurs in large part during critical periods in early postnatal life. These are windows of time during development when the nervous system must obtain certain critical experiences, such as sensory, movement, or emotional input, to develop properly. These periods are characterized by high learning rates.

After a critical period, connections diminish in number and are less subject to change, but the ones that remain are stronger, more reliable, and more precise. Injury or deprivation, either sensory or social, occurring at a certain stage of postnatal life may affect one aspect of development, whereas the same injury at a different period may affect another aspect.

Scientists hope that new insight into brain development will lead to treatments for those with learning disabilities, brain damage, and neurodegenerative disorders and will help us understand aging.

In one example, if a monkey is raised from birth to 6 months of age with one eyelid closed, the animal permanently loses useful vision in that eye because of diminished use. This gives cellular meaning to the saying "use it or lose it." Loss of vision is caused by the actual loss of functional connections between that eye and neurons in the visual cortex. This finding has led to earlier and better treatment for the eye disorders of congenital cataracts and "crossed eyes" in children.

Research also shows that enriched environments can bolster brain development. For example, studies show that animals brought up in toy-filled surroundings have more branches on their neurons and more connections than isolated animals. In one recent study, scientists found that enriched environments resulted in more neurons in a brain area involved in memory.

Many people have observed that children can learn languages with greater proficiency than adults, and recent research suggests that the heightened activity of the critical period may contribute to this robust learning. Interestingly, compared with adults, children have an increased incidence of certain disorders that involve excessive brain activity, such as epilepsy. Many epilepsy syndromes appear during childhood and fade away by adulthood. Brain development in people continues into the early 20s — even the brain of an adolescent is not completely mature. One of the later aspects of brain development is the completion of myelination of the axons connecting one brain area to another. This process starts around birth and moves from the back of the brain to the front: The frontal lobes are the last to become "connected" with fast-conducting myelinated axons. Major functions of the frontal lobes are judgment, insight, and impulse control, and so the acquisition of these attributes becomes the last step in the creation of an adult human brain.

Scientists hope that new insight into brain development will lead to treatments for those with learning disabilities, brain damage, and neurodegenerative disorders and will help us understand aging. Research results indicate the need to understand processes related to normal function of the brain at each of its major stages and suggest that this information might lead to better age-specific therapies for brain disorders.

Sensation and Perception

VISION. Our wonderful sense of sight allows us to perceive the world around us, from the genius of Michelangelo's Sistine Chapel ceiling to mist-filled vistas of a mountain range. Vision is one of our most delicate and complicated senses. It is also the most intensively studied. About one-fourth of the human brain is involved in visual processing, more than for any other sense. More is known about vision than any other vertebrate sensory system, with most of the information derived from studies of monkeys and cats.

Vision begins with light passing through the *cornea*, which does about three-quarters of the focusing, and then the *lens*, which adjusts the focus. Both combine to produce a clear image of the visual world on the sheet of *photoreceptors* in the *retina*. Photoreceptors absorb light and send electrical signals to nearby neurons lining the back of the eye.

As in a camera, the image on the retina is reversed: Objects to the right of center project images to the left part of the retina and vice versa; objects above the center project to the lower part and vice versa. The size of the pupil, which regulates how much light enters the eye, is controlled by the *iris*. The shape of the lens is altered by the muscles just behind the iris so that near or far objects can be brought into focus on the retina.

Photoreceptors, about 125 million in each human eye, are neurons specialized to turn light into electrical signals. They occur in two forms. *Rods* are most sensitive to dim light and do not convey color.

Cones work in bright light and are responsible for acute detail, black-and-white vision, and color vision. The human eye contains three types of cones, each sensitive to a different range of colors. Because their sensitivities overlap, cones work in combination to convey information about all visible colors. You might be surprised to know that we can see thousands of colors using only three types of cones, but computer monitors use a similar process to generate a spectrum of colors using only three kinds of phosphors: red, green, and blue.

Primates, including humans, have well-developed vision using two eyes, called binocular vision. Visual signals pass from each eye along the million or so fibers of the optic nerve to the optic chiasm, where some nerve fibers cross over, so both sides of the brain receive signals from both eyes. Consequently, the left halves of both retinas project to the left visual cortex and the right halves project to the right visual cortex.

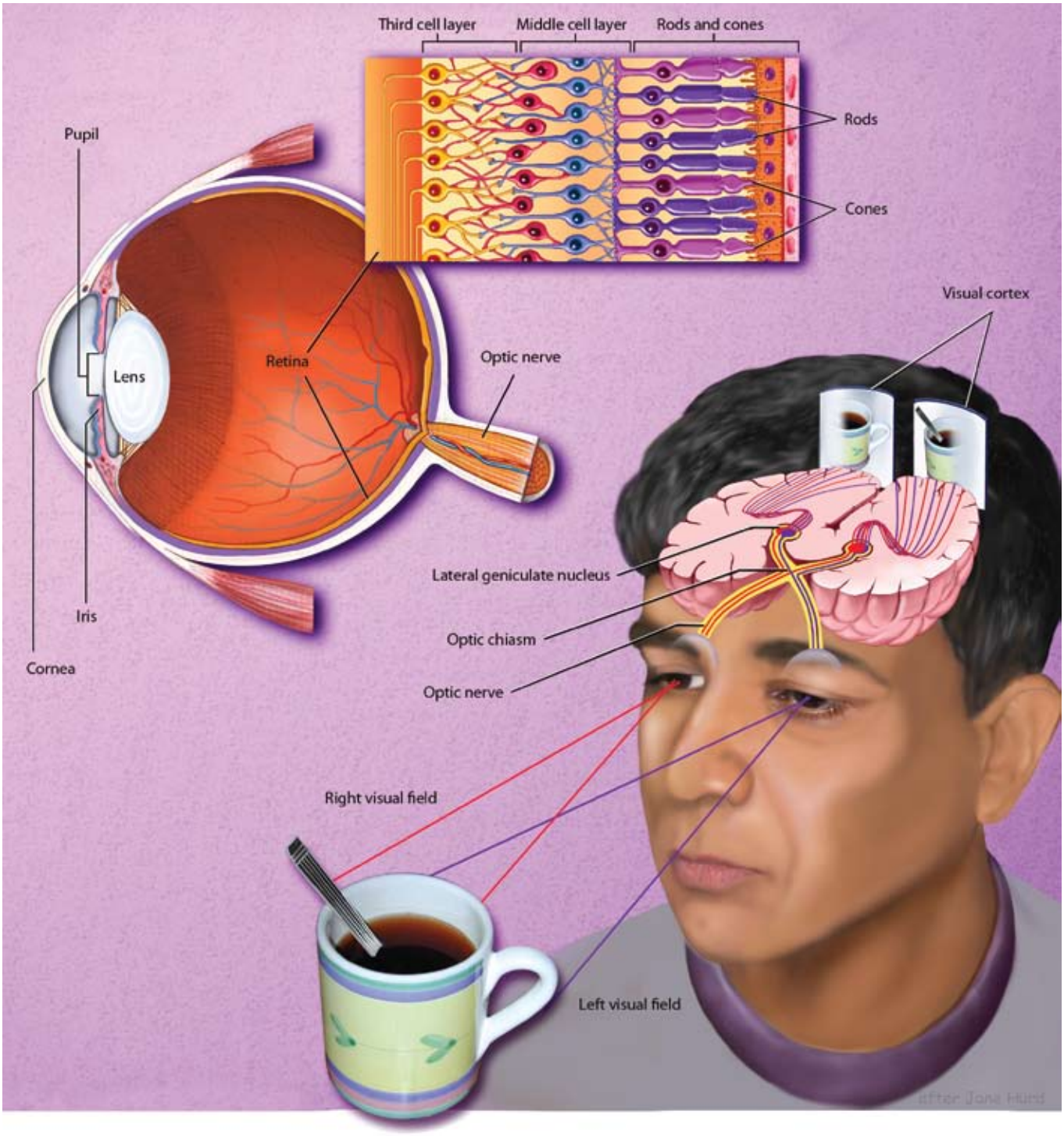
The result is that the left half of the scene you are watching registers in your right hemisphere. Conversely, the right half of the scene registers in your left hemisphere. A similar arrangement applies to movement and touch: Each half of the cerebrum is responsible for the opposite half of the body and external world.

Scientists know much about the way cells encode visual information in the retina, the *lateral geniculate nucleus* — an intermediate way station between the retina and visual cortex — and the visual cortex. These studies give us the best knowledge so far about how the brain analyzes and processes sensory information.

The retina contains three stages of neurons. The first, the layer of rods and cones, sends its signals to the middle layer, which relays signals to the third layer, which consists of the ganglion cells whose axons form the optic nerve. Each cell in the middle and third layer typically receives input from many cells in the previous layer, but the number of inputs varies widely across the retina. Near the center of the gaze, where visual acuity is highest, each cell in the third layer receives inputs — via the middle layer — from one cone or, at most, a few, allowing us to resolve very fine details. Near the margins of the retina, each cell in the third layer receives signals from a cluster of many rods and cones, explaining why we cannot see fine details off to either side. Whether large or small, the region of visual space providing input to a visual neuron is called its *receptive field*.

About 55 years ago, scientists discovered that the receptive field of a vision cell is activated when light hits a tiny region in its receptive field center and is inhibited when light hits the part of the receptive field surrounding the center. If light covers the entire receptive field, the cell responds weakly. Thus, the visual process begins by comparing the amount of light striking any small region of the retina with the amount of surrounding light.

Visual information from the retina is relayed through the lateral geniculate nucleus of the thalamus to the primary visual cortex — a thin sheet of tissue (less than one-tenth of an inch thick) a bit larger than a half-dollar that is located in the occipital lobe in the back of the brain. The primary visual cortex is densely packed with cells in many layers. In its middle layer, which receives messages from the lateral geniculate nucleus, scientists have found responses similar to those observed in the retina and in lateral geniculate cells. Cells above and below this layer respond differently. They prefer stimuli in the shape of bars or edges and those at a particular angle (orientation). Further studies have shown that different cells prefer edges at different angles or edges moving in a particular direction.



VISION. The cornea and lens help produce a clear image of the visual world on the retina, the sheet of photoreceptors and neurons lining the back of the eye. As in a camera, the image on the retina is reversed: Objects to the right of the center project images to the left part of the retina and vice versa. The eye's 125 million visual receptors — composed of rods and cones — turn light into electrical signals. Rods are most sensitive to dim light and do not convey the sense of color; cones work in bright light and are responsible for acute detail, black-and-white vision, and color vision. The human eye contains three types of cones that are sensitive to red, green, and blue but, in combination, convey information about all visible colors. Rods and cones connect with a middle cell layer and third cell layer (see inset, above). Light passes through these two layers before reaching the rods and cones. The two layers then receive signals from rods and cones before transmitting the signals onto the optic nerve, optic chiasm, lateral geniculate nucleus, and, finally, the visual cortex.

Although the process is not yet completely understood, recent findings suggest that visual signals are fed into at least three separate processing systems. One system appears to process information mainly about shape; a second, mainly about color; and a third, movement, location, and spatial organization. These findings of separate processing systems come from anatomical and physiological studies in monkeys. They are supported by human psychological studies showing that the perception of movement, depth, perspective, the relative size of objects, the relative movement of objects, shading, and gradations in texture all depend primarily on contrasts in light intensity rather than on color.

Why movement and depth perception should be emphasized by one processing system may be explained by a school of thought called Gestalt psychology. Perception requires various elements to be organized so that related ones are grouped together. This stems from the brain's ability to group the parts of an image together and also to separate images from one another and from their individual backgrounds.

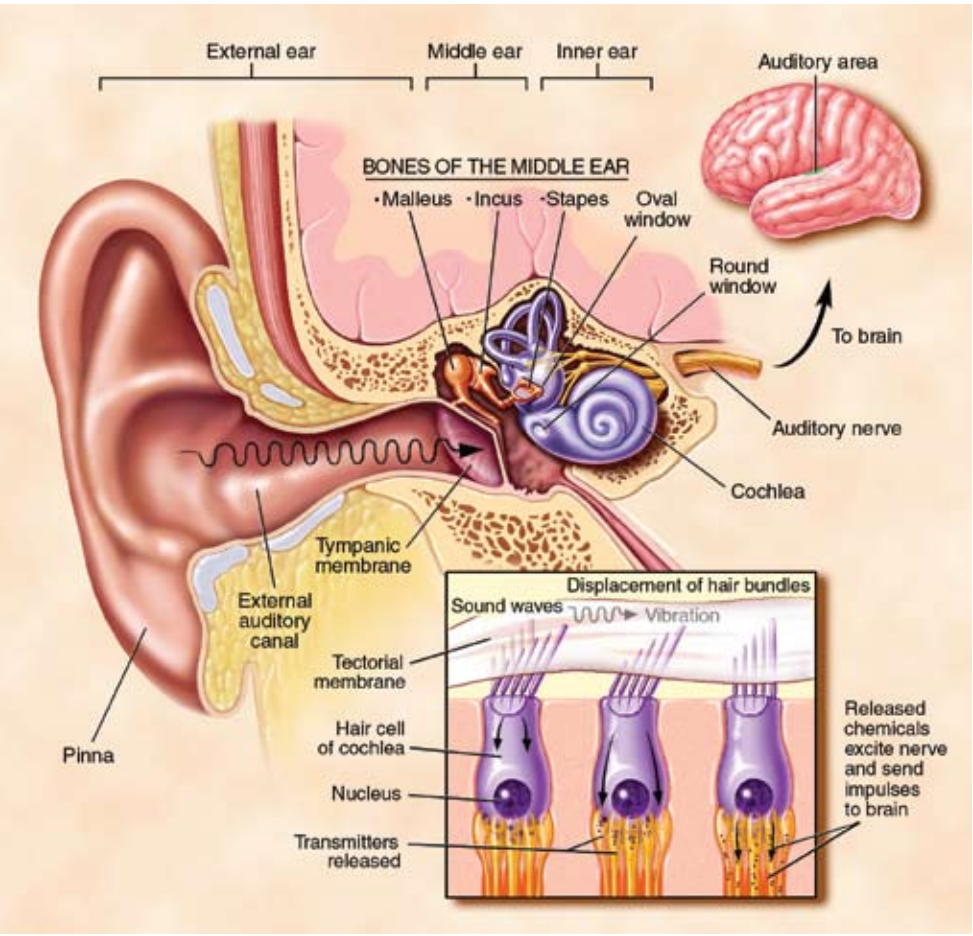
How do all these systems combine to produce the vivid images of solid objects that we perceive? This involves extracting biologically relevant information at each stage and associating firing patterns of neuronal populations with past experience.

Vision studies also have led to better treatment for visual disorders. Information from research in cats and monkeys has improved the therapy for *strabismus*, or *squint*, a term for cross-eye or walleye. Children with strabismus initially have good vision in each eye. But because they cannot fuse the images in the two eyes, they tend to favor one eye and often lose useful vision in the other. Vision can be restored in such cases, but only during infancy or early childhood. Beyond the age of 6 or so, the blindness in one eye becomes permanent. Until a few decades ago, ophthalmologists waited until children reached the age of 4 before operating to align the eyes or prescribing exercises or an eye patch. Now strabismus is corrected very early in life — before age 4, when normal vision can still be restored.

Hearing

Often considered the most important sense for humans, hearing allows us to communicate with each other by receiving sounds and interpreting speech. It also gives us information vital to survival; for instance, by alerting us to an approaching car.

Like the visual system, our hearing system distinguishes several qualities in the signals it detects. Our hearing system, however,



HEARING. From the chirping of crickets to the roar of a rocket engine, sound waves are collected by the external ear — the pinna and the external auditory canal — and funneled to the tympanic membrane (eardrum) to make it vibrate. Attached to the tympanic membrane, the malleus (hammer) transmits the vibration to the incus (anvil), which passes vibration on to the stapes (stirrup). The stapes pushes on the oval window, which separates the air-filled middle ear from the fluid-filled inner ear, to produce pressure waves in the snail-shaped cochlea of the inner ear. Hair cells in the cochlea, riding on the vibrating basilar membrane, have "hair bundles" of microscopic stereocilia that are deflected by the overlying tectorial membrane. Hair cells convert the mechanical vibration to an electrical signal; they, in turn, release chemicals to excite the 30,000 fibers of the auditory nerve that carry the signals to the brainstem. Auditory information is analyzed by multiple brain centers as it flows to the temporal gyrus or auditory cortex, the part of the brain involved in perceiving sound.

does not blend different sounds, as the visual system does when two different wavelengths of light are mixed to produce color. Instead, it separates complex sounds into their component tones or frequencies so that we can follow different voices or instruments as we listen to conversations or to music.

Whether from the chirping of crickets or the roar of a rocket engine, sound waves are collected by the external ear — the pinna and the external auditory canal — and funneled to the tympanic membrane (eardrum) to make it vibrate. Attached to the tympanic membrane, the malleus (hammer) transmits the vibration to the incus (anvil), which passes vibration on to the stapes (stirrup). The stapes pushes on the oval window, which separates the air-filled middle ear from the fluid-filled inner ear, to produce pressure waves in the snail-shaped cochlea of the inner ear. The separation of frequencies occurs in the cochlea, which is tuned along its length to different frequencies, so that a high note causes one region of the cochlea's basilar membrane to vibrate and a lower note causes a different region to vibrate.

Hair cells in the cochlea, riding on the basilar membrane, have *hair bundles* of microscopic hairlike stereocilia that are deflected by the overlying tectorial membrane. Hair cells convert the mechanical vibration to an electrical signal; they in turn excite the 30,000 fibers of the auditory nerve that carry the signals to the brainstem. Because each hair cell rides on a different part of the basilar membrane, each is best excited by a different frequency, and so each nerve fiber carries information about a different frequency to the brain. Auditory information is analyzed by multiple brain centers as it flows to the temporal gyrus or auditory cortex, the part of the brain involved in perceiving sound.

In the auditory cortex, adjacent neurons tend to respond to tones of similar frequency. However, they specialize in different combinations of tones. Some respond to pure tones like a flute, and some to complex sounds like a violin. Some respond to long sounds and some to short, and some to sounds that rise or fall in frequency. Other neurons might combine information from these specialist neurons to recognize a word or an instrument.

Sound is processed in the auditory cortex on both sides of the brain. However the left side in most people is specialized for perceiving and producing speech. Damage to the left auditory cortex, such as from a stroke, can leave someone able to hear but unable to understand language.

Taste and smell

Although different, the two sensory experiences of taste and smell are intimately entwined. They are separate senses with their own receptor organs. However, these two senses act together to allow us to distinguish thousands of different flavors. Alone, taste is a relatively focused sense concerned with distinguishing among sweet, salty, sour, bitter, and umami (Japanese for "savory"). The interaction between taste and smell explains why loss of the sense of smell causes a serious reduction in the overall taste experience, which we call flavor.

Taste is detected within *taste buds*, special structures embedded within *papillae*, or protuberances, located mainly on the tongue. Others are found in the back of the mouth and on the palate. Every person has between 5,000 and 10,000 taste buds. Taste substances stimulate specialized sensory cells, and each taste bud consists of 50 to 100 of these cells.

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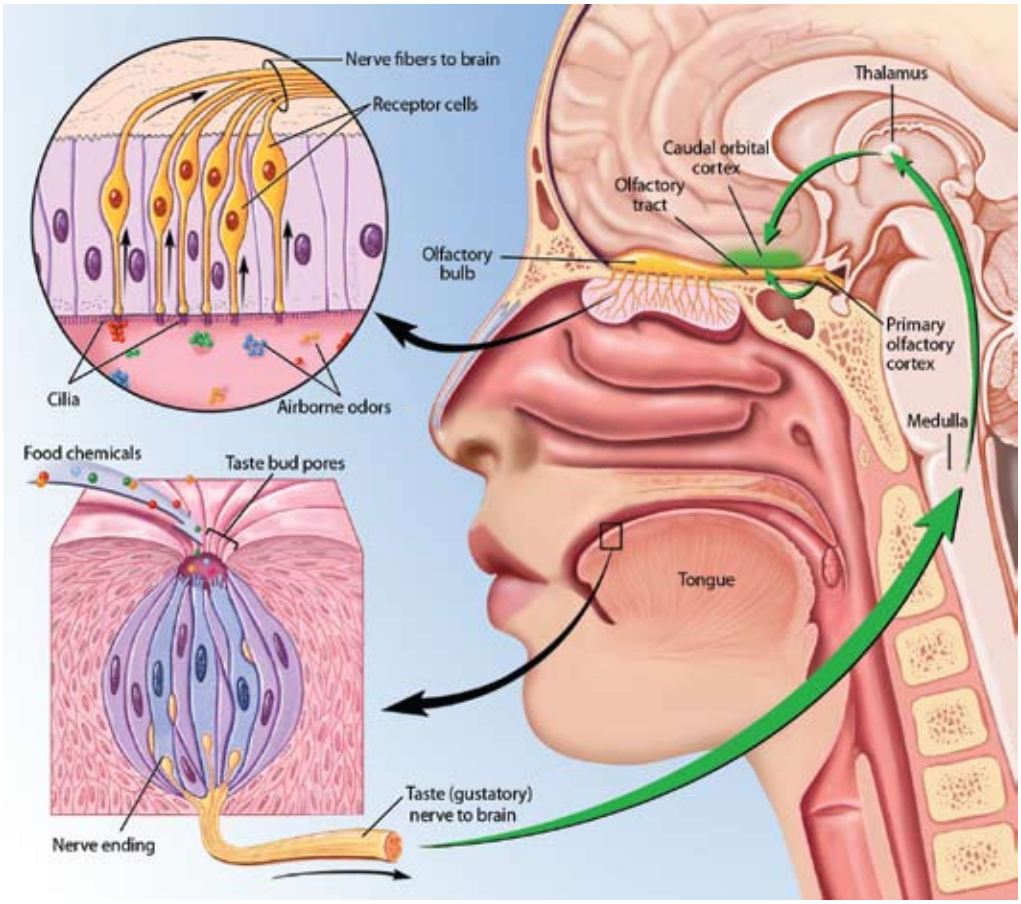
Taste signals in the sensory cells are transferred to the ends of nerve fibers, which send impulses along cranial nerves to taste regions in the brainstem. From here, the impulses are relayed to the thalamus and on to the cerebral cortex for conscious perception of taste.

Specialized olfactory receptor cells are located in a small patch of mucous membrane lining the roof of the nose. Axons of these sensory cells pass through perforations in the overlying bone and enter two elongated *olfactory bulbs* lying on top of the bone. The portion of the sensory cell that is exposed to odors possesses hairlike cilia. These cilia contain the receptor sites that are stimulated by airborne odor molecules. These molecules dissolve in the mucous lining in order to stimulate receptor proteins in the cilia to start the smell response. An odorant acts on many receptors to different degrees. Similarly, a receptor interacts with many different odorants to varying degrees.

The pattern of activity set up in the receptor cells is projected to the olfactory bulb, where neurons are activated to form a spatial



"image" of the odor. Impulses created by this stimulation pass to the primary olfactory cortex at the back of the underside (or orbital) part of the frontal lobe. Olfactory information then passes to adjacent parts of the orbital cortex where it is combined with taste information to form flavor.

Touch and pain

Touch is the sense by which we determine the characteristics of objects: size, shape, and texture. We do this through touch receptors in the skin. In hairy skin areas, some receptors consist of webs of sensory nerve cell endings wrapped around the base of hairs. The nerve endings are remarkably sensitive, being triggered by slight movement of the hairs.

Signals from touch receptors pass via sensory nerves to the spinal cord, where they synapse (make contact) with other nerve cells, which in turn send the information to the thalamus and sensory cortex. The transmission of this information is highly topographic, meaning that the body is represented in an orderly fashion at different levels of the nervous system. Larger areas of the cortex are devoted to sensations from the hands and lips; much smaller cortical regions represent less sensitive parts of the body.

Different parts of the body vary in their sensitivity to tactile and painful stimuli according to the number and distribution of receptors. The cornea is several hundred times more sensitive to painful stimuli than are the soles of the feet. The fingertips are good at touch discrimination, but the torso is not: You don't try to figure out what coin is in your pocket by rubbing it on your back.

Neurologists measure sensitivity by determining the patient's *two-point threshold*. This method involves touching the skin with calipers at two points. The two-point threshold is the distance between the two points that is necessary for the individual to distinguish two distinct stimuli from one. Not sur-

TASTE AND SMELL. Specialized receptors for smell are located in a patch of mucous membrane lining the roof of the nose. Each cell has several fine hairlike cilia containing receptor proteins, which are stimulated by odor molecules in the air, and a long fiber (axon), which passes through perforations in the overlying bone to enter the olfactory bulb. Stimulated cells give rise to impulses in the fibers, which set up patterns in the olfactory bulb that are relayed to the primary olfactory cortex at the back of the brain's frontal lobe to give rise to smell perception, and to the limbic system to elicit emotional responses. Tastes are detected by special structures, taste buds, of which every human has some 5,000 to 10,000. Taste buds are embedded within papillae (protuberances) mainly on the tongue, with a few located in the back of the mouth and on the palate. Each taste bud consists of about 100 receptors that respond to stimuli — sweet, salty, sour, bitter, and umami — from which all tastes are formed. A substance is tasted when chemicals in foods dissolve in saliva, enter the pores on the tongue, and come in contact with taste buds. Here they stimulate hairs projecting from the receptor cells and cause signals to be sent from the cells, via synapses, to cranial nerves and taste centers in the brain. Taste and smell information come together to form flavor in the caudal (back) part of the orbital cortex.

prisingly, acuity is greatest in the most densely nerve-packed areas of the body. The threshold is lowest on the fingers and lips.

Until recently, pain was thought to represent a simple message resulting from neurons sending electrical impulses from a site of injury directly to the brain. We now know that the process is far more complicated. Nerve impulses from sites of injury can persist for hours, days, or longer. Moreover, persistent injury can lead to changes in the nervous system that amplify and prolong the "pain" signal. The result is a state of hypersensitivity in which pain persists and can even be evoked by normally innocuous stimuli. Persistent pain is in many respects a disease of the nervous system, not merely a symptom of some other disease process.

The sensory fibers that respond to stimuli that damage tissue and can cause pain are called *nociceptors*. Different nociceptor subsets express molecules that are responsible for the response to noxious (i.e., painful) thermal, mechanical, or chemical stimulation. Interestingly, these same molecules respond to plant-derived chemicals that can produce pain, such as capsaicin, garlic, and wasabi. Tissue injury also causes the release of numerous chemicals at the site of damage and inflammation. For example, *prostaglandins* enhance the sensitivity of receptors to tissue damage and ultimately can induce more intense pain sensations. Prostaglandins also contribute to the clinical condition of *allodynia*, in which innocuous stimuli can produce pain (as with sunburned skin).

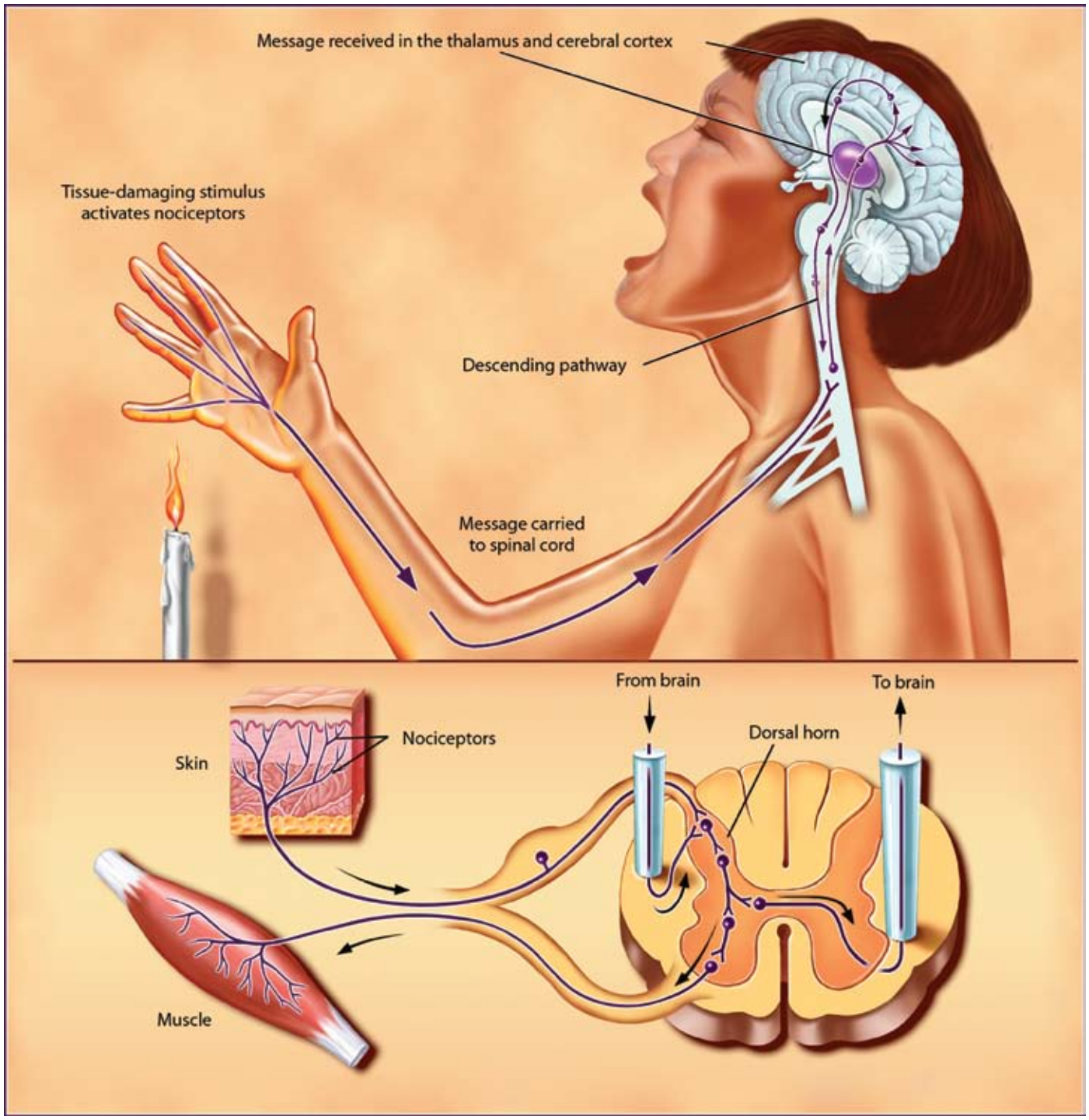
Until recently, pain was thought to represent a simple message resulting from neurons sending electrical impulses from a site of injury directly to the brain. We now know that the process is far more complicated.

Pain messages are transmitted to the spinal cord via small, myelinated fibers and C fibers — very small unmyelinated fibers. The small, myelinated, pain-sensitive nerve fibers probably evoke the sharp, fast pain that is produced by, for example, a pinprick. C fiber-induced pain, by contrast, is generally slower in onset, dull, and more diffuse.

In the *ascending system*, impulses are relayed from the spinal cord to several brain structures, including the thalamus and cerebral cortex, which is involved in the process by which pain messages become a conscious experience. The experience of pain is not just a function of the magnitude of the injury or even the intensity of the impulse activity generated by the injury. The setting in which the injury occurs (e.g., the pain of childbirth or that produced in a car accident) and the emotional component of the experience are also major contributors to the overall experience.

Pain messages can be suppressed by systems of neurons that originate within the gray matter in the brainstem. These *descending systems* suppress the transmission of pain signals from the dorsal horn of the spinal cord to higher brain centers. Some of these descending systems use naturally occurring chemicals, the endogenous opioids, or endorphins, which are functionally similar to morphine. The endorphins act at multiple opioid receptors in the brain and spinal cord, a discovery that has had important implications for pain therapy. For example, scientists began studying the spinal delivery of opioids when they discovered a dense distribution of opioid receptors in the spinal cord horn. Such treatments were begun in humans after the method was successfully used in animals; the technique is now common in treating pain after surgery.

Modern imaging tools are now used to monitor brain activity when pain is experienced. One finding is that no single area in the brain generates pain; rather, emotional and sensory components together constitute a mosaic of activity leading to pain. Interestingly, when people are hypnotized so that a painful stimulus is not experienced as unpleasant, activity in only some areas of the brain is suppressed. The stimulus is still experienced, but it doesn't hurt anymore. As such techniques for brain study improve, it should be possible to better monitor the changes in the brain that occur in people with persistent pain and to better evaluate the different painkilling drugs being developed.



PAIN. Messages about tissue damage are picked up by receptors and transmitted to the spinal cord via small myelinated fibers and very small unmyelinated fibers. From the spinal cord, the impulses are carried to the brainstem, thalamus, and cerebral cortex and ultimately perceived as pain. These messages can be suppressed by a system of neurons that originates in the gray matter of the midbrain. This descending pathway sends messages to the spinal cord where it suppresses the transmission of tissue damage signals to the higher brain centers. Some of these descending pathways use naturally occurring, opiatelike chemicals called endorphins.

Learning, Memory, and Language

LEARNING AND MEMORY.

A major breakthrough in understanding how the brain accomplishes learning and memory began with the study of a person known by his initials, H.M. As a child, H.M. developed a severe and intractable epilepsy, and an experimental surgical treatment involving removal of the medial regions of his temporal lobes greatly alleviated the seizures. However, the surgery left H.M. with severe amnesia. He can remember recent events for only a few minutes and is unable to form explicit memories of new experiences. Talk with him awhile, and then leave the room. When you return, he has no recollection of ever having seen you.

Despite his inability to remember new information, H.M. remembers his childhood very well. From these observations, researchers concluded that the parts of H.M.'s medial temporal lobe that were removed, including the hippocampus and *parahippocampal region*, play critical roles in converting memories of experiences from short-term memories to long-term, permanent memories. The fact that H.M. retains some memories for events that occurred long before his surgery indicates that the medial temporal region is not the site of permanent storage but instead plays a role in the organization and permanent storage of memories elsewhere in the brain.

The medial temporal region is richly connected to widespread areas of the cerebral cortex, including the regions responsible for thinking and language. Whereas the medial temporal region is important for forming, organizing, consolidating, and retrieving memory, cortical areas are important for the long-term storage of knowledge about facts and events and for how this knowledge is used in everyday situations.

Our ability to learn and consciously remember everyday facts and events is called *declarative memory*. Studies using functional brain imaging have identified a large network of areas in the cerebral cortex that work together to support declarative memory. These cortical areas play a distinct role in complex aspects of perception, movement, emotion, and cognition.

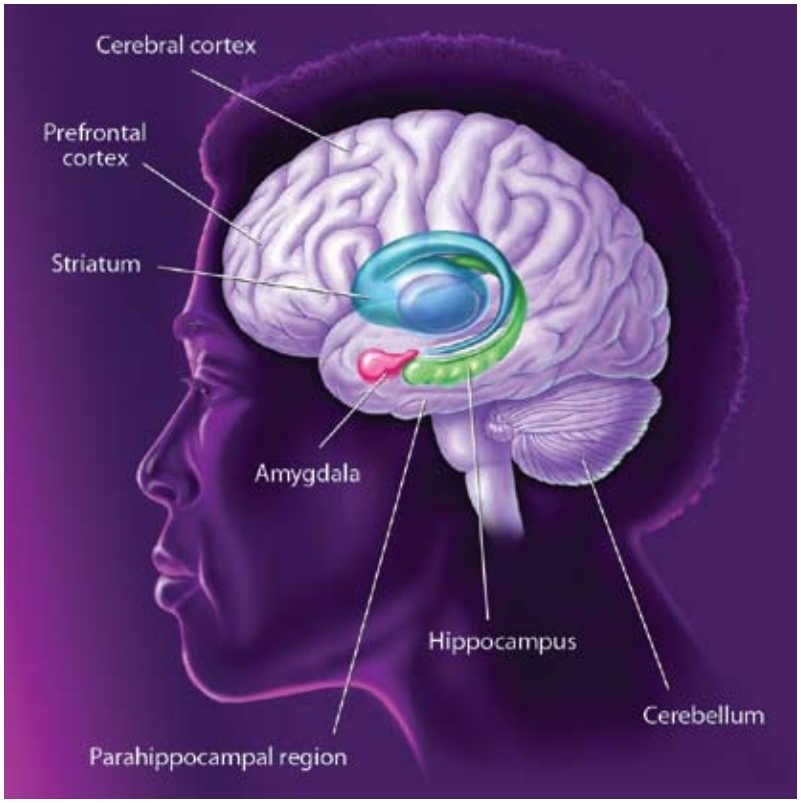
When we have new experiences, information initially enters *working memory*, a transient form of declarative memory. Working memory depends on the prefrontal cortex as well as other cerebral cortical areas. Studies on animals have shown that neurons in the *prefrontal cortex* maintain relevant information during working memory and can combine different kinds of sensory information when required. In humans, the prefrontal cortex is highly activated when people maintain and manipulate memories.

Distinct areas within the prefrontal cortex support *executive functions*, such as selection, rehearsal, and monitoring of information being retrieved from long-term memory. To serve these functions, the prefrontal cortex also interacts with a large network of posterior cortical areas that encode, maintain, and retrieve specific types of information, such as visual images, sounds, and words, as well as where important events occurred and much more.

Semantic memory is a form of declarative knowledge that includes general facts and data. Although scientists are just beginning to understand the nature and organization of cortical areas involved in semantic memory, it appears that different cortical networks are specialized for processing particular kinds of information, such as faces, houses, tools, actions, language, and many other categories of knowledge. Studies using functional imaging of normal humans have revealed zones within a large cortical expanse that selectively process different categories of information, such as animals, faces, or words.

Our memories of specific personal experiences that happened at a particular place and time are called *episodic memories*. It is generally believed that the medial temporal lobe areas serve a critical role in the initial processing and storage of these memories. Studies have shown that different parts of the parahippocampal region play distinct roles in processing "what," "where," and "when" information about specific events. The hippocampus links these elements of an episodic memory. The linkages are then integrated back into the various cortical areas that represent the details of each type of information.

How exactly are memories stored in brain cells? After years of study, much evidence supports the idea that memory involves a persistent change in synapses, the connections between neurons.



LEARNING AND MEMORY. Different brain areas and systems mediate distinct forms of memory. The hippocampus, parahippocampal region, and areas of the cerebral cortex (including prefrontal cortex) compose a system that supports declarative, or cognitive, memory. Different forms of nondeclarative, or behavioral, memory are supported by the amygdala, striatum, and cerebellum.

The fact that H.M. and other people with amnesia show deficits in some types of memories and not others indicates that the brain has multiple memory systems supported by distinct brain regions. *Nondeclarative knowledge*, the knowledge of how to do something, is expressed in skilled behavior and learned habits and requires processing by the basal ganglia and cerebellum. The cerebellum is specifically involved in motor tasks that are time-dependent. The amygdala appears to play an important role in emotional aspects of memory attaching emotional significance to otherwise neutral stimuli and events. The expression of emotional memories involves the hypothalamus and sympathetic nervous system, which support emotional reactions and feelings. Thus, the brain appears to process different kinds of information in separate ways.

How exactly are memories stored in brain cells? After years of study, much evidence supports the idea that memory involves a persistent change in synapses, the connections between neurons. In animal studies, researchers found that this occurs in the short term through biochemical events that affect the strength of the relevant synapses. Turning on certain genes may lead to modifications within neurons that change the strength and number of synapses, stabilizing new memories. Researchers studying the sea slug *Aplysia californica*, for example, can correlate specific chemical and structural changes in relevant cells with several simple forms of memory that the animal shows.

Another important model for the study of memory is the phenomenon of *long-term potentiation* (LTP), a long-lasting increase in the strength of a synaptic response following stimulation. LTP occurs prominently in the hippocampus, as well as in the cerebral cortex and other brain areas involved in various forms of memory. LTP occurs through changes in the strength of synapses at contacts involving N-methyl-d-aspartate (NMDA) receptors.

Subsequently, a series of molecular reactions plays a vital role in stabilizing the changes in synaptic function that occur in LTP. These molecular events begin with the entry of calcium ions into the synapse, which activates the cyclic adenosine monophosphate (cAMP) molecule. This molecule activates several kinds of enzymes, some of which increase the number of synaptic receptors, making the synapse more sensitive to neurotransmitters. In addition, cAMP activates another molecule, called cAMP-response element binding protein (CREB). CREB operates within the nucleus of the neuron to activate a series of genes, many of which direct protein synthesis. Among the proteins produced are neurotrophins, which activate growth of the synapse and increase the neuron's responsiveness to stimulation.

Many studies have shown that the molecular cascade leading to protein synthesis is not essential to initial learning or to maintaining short-term memory; however, this cascade is essential

for long-term memory. In addition, studies using genetically modified mice have shown that alterations in specific genes for NMDA receptors or CREB can dramatically affect the capacity for LTP in particular brain areas, and the same studies have shown that these molecules are critical to memory.

The many kinds of studies of human and animal memory have led scientists to conclude that no single brain center stores memory. It most likely is stored in distributed collections of cortical processing systems that are also involved in the perception, processing, and analysis of the material being learned. In short, each part of the brain most likely contributes differently to permanent memory storage.

Language

One of the most prominent human abilities is language, a complex system involving many components, including sensory-motor functions and memory systems. Although the neural basis of language is not fully understood, scientists have learned a great deal about this function of the brain from studies of patients who have lost speech and language abilities owing to stroke, and from brain imaging studies of normal people.

It has long been known that damage to different regions within the left hemisphere produce different kinds of language disorders, or aphasias. Damage to the left frontal lobe can produce nonfluent aphasias, such as *Broca's aphasia*, a syndrome in which speech production abilities are impaired. Speech output is slow and halting, requires effort, and often lacks complexity in word or sentence structure. By comparison, comprehension of heard speech is spared, although structurally complex sentences may be poorly understood.

Damage to the left temporal lobe can produce fluent aphasia, such as *Wernicke's aphasia*, in which comprehension of heard speech is impaired. Speech output, although of normal fluency and speed, is often riddled with errors in sound and word selection and tends to be unintelligible gibberish.

Damage to the superior temporal lobes in both hemispheres can produce *word deafness*, a profound inability to comprehend auditory speech on any level. Whereas Wernicke's aphasics can often comprehend bits and pieces of a spoken utterance and can comprehend isolated words, patients with word deafness are functionally deaf for speech, lacking the ability to comprehend even single words, despite being able to hear sound and even identify the emotional quality of speech or the gender of the speaker.

Research on aphasia has led to several conclusions regarding the neural basis of language. Researchers once believed that all aspects of language ability were governed only by the left hemisphere. Recognition of speech sounds and words, however, involves both left and right temporal lobes. In contrast, speech production is a strongly left-dominant function that relies on frontal lobe areas but also involves posterior brain regions in the left temporal lobe. These appear to be important for accessing appropriate words and speech sounds.

Recently, functional imaging methods have identified new structures involved in language. For example, systems involved in accessing the meaning of words appear to be located (in part) in the middle and inferior portions of the temporal lobe. In addition, the anterior temporal lobe is under intense investigation as a site that may participate in some aspect of sentence-level comprehension.

Recent work has also identified a sensory-motor circuit for speech in the left posterior temporal lobe, which is thought to translate between speech recognition and speech production systems. This circuit is involved in speech development and is thought to support verbal short-term memory.

Although the understanding of how language is implemented in the brain is far from complete, there are now several techniques that may be used to gain important insights into this critical aspect of brain function.

Movement

FROM THE STANDS, WE MARVEL at the perfectly placed serves of professional tennis players and the lightning-fast double plays executed by big league baseball infielders. But in fact, each of us in our daily activities performs a host of complex, skilled movements — such as walking upright, speaking, and writing — that are just as remarkable. This is made possible by a finely tuned and highly complex central nervous system, which controls the actions of hundreds of muscles. Through learning, the nervous system can adapt to changing movement requirements to accomplish these everyday marvels and to perform them more skillfully with practice.

To understand how the nervous system performs such tricks, we have to start with the muscles, for these are the body parts that produce movement under the control of the brain and spinal cord.

Most muscles attach to points on the skeleton and cross one or more joints, so they are called *skeletal muscles*. Activation of a given muscle can open or close the joints that it spans, depending upon whether it is a joint *flexor* (closer) or *extensor* (opener).

In addition, if flexors and extensors at the same joint are activated together, they can "stiffen" a joint, thus maintaining limb position in the face of unpredictable external forces that would otherwise displace the limb. Muscles that move a joint in an intended direction are called *agonists*, and those that oppose this direction of movement are antagonists. Skilled movements at high speed are started by agonists and stopped by *antagonists*, thus placing the joint or limb at a desired position.

Some muscles act on soft tissue, such as the muscles that move the eyes and tongue and those that control facial expression. These muscles also are under control of the central nervous system, and their principles of operation are similar to those that attach to bone.

Each skeletal muscle is made up of thousands of individual muscle fibers, and each muscle fiber is controlled by one *alpha motor neuron* in either the brain or the spinal cord. On the other hand, each single alpha motor neuron controls many muscle fibers (ranging from a few to 100 or more); an alpha motor neuron and all the muscle fibers it contains form a functional unit referred to as a *motor unit*. These motor units are the critical link between the brain and muscles. If the motor neurons die, which can happen in certain diseases, a person is no longer able to move, either voluntarily or through reflexes.

Perhaps the simplest and most fundamental movements are reflexes. These are relatively fixed, automatic muscle responses to particular stimuli, such as the sudden withdrawal of the foot when you step on a sharp object or the slight extension of the leg when a physician taps your knee with a small rubber hammer. All reflexes involve the activation of small sensory receptors in the skin, the joints, or even in the muscles themselves. For example, the knee movement referred to above is produced by a slight stretch of the knee extensor muscles when the physician taps the muscle tendon at the knee. This slight muscle stretch is "sensed" by receptors in the muscle called *muscle spindles*. Innervated by sensory fibers, the spindles send information to the spinal cord and brain about the length and speed of the shortening or lengthening of a muscle. This information is used in reflex control of the joint at which the muscle acts and also for control of voluntary movements.

A sudden muscle stretch sends a barrage of impulses into the spinal cord along the muscle spindle sensory fibers. In turn, these fibers activate motor neurons in the stretched muscle, causing a contraction called the *stretch reflex*. The same sensory stimulus causes inactivation, or inhibition, of the motor neurons of the antagonist muscles through connecting neurons, called *inhibitory interneurons*, within the spinal cord. Thus, even the simplest of reflexes involves a coordination of activity across motor neurons that control agonist and antagonist muscles.

The brain can control not only the actions of motor neurons and muscles but, even more amazing, the nature of the feedback that it receives from sensory receptors in the muscles as movements occur. For example, the sensitivity of the muscle spindle organs is controlled by the brain through a separate set of *gamma motor neurons* that control the specialized muscle fibers and allow the brain to fine-tune the system for different movement tasks.

In addition to such exquisite sensing and control of muscle length by muscle spindles, other specialized sense organs in muscle tendons — the *golgi tendon organs* — detect the force applied by a contracting muscle, allowing the brain to sense and control the muscular force exerted during movement.

We now know that these complex systems are coordinated and organized to respond differently for tasks that require precise control of position, such as holding a full teacup, than for those requiring rapid, strong movement, such as throwing a ball. You can experience such changes in motor strategy when you compare walking down an illuminated staircase with the same task done in the dark.

Another useful reflex is the *flexion withdrawal* that occurs if your bare foot encounters a sharp object. Your leg is immediately

lifted from the source of potential injury (flexion), but the opposite leg responds with increased extension in order to maintain your balance. The latter event is called the *crossed extension reflex*.

These responses occur very rapidly and without your attention because they are built into systems of neurons that are located within the spinal cord itself. It seems likely that the same systems of spinal neurons also participate in controlling the alternating action of the legs during normal walking. In fact, the basic patterns of muscle activation that produce coordinated walking can be generated in four-footed animals within the spinal cord itself. These spinal mechanisms, which evolved in primitive vertebrates, are likely still present in the human spinal cord.

The most complex movements that we perform, including voluntary ones that require conscious planning, involve control of these basic spinal mechanisms by the brain. Scientists are only beginning to understand the complex interactions that take place among different brain regions during voluntary movements, mostly through careful experiments on animals.

One important brain area in the control of voluntary movement is the *motor cortex*, which exerts powerful control over the spinal cord, in part through direct control of its alpha motor neurons. Some neurons in the motor cortex appear to specify the coordinated action of many muscles to produce the organized movement of a limb to a particular place in space. Others appear to control only two or three functionally related muscles, such as those of the hand or arm, that are important for finely tuned, skilled movement.

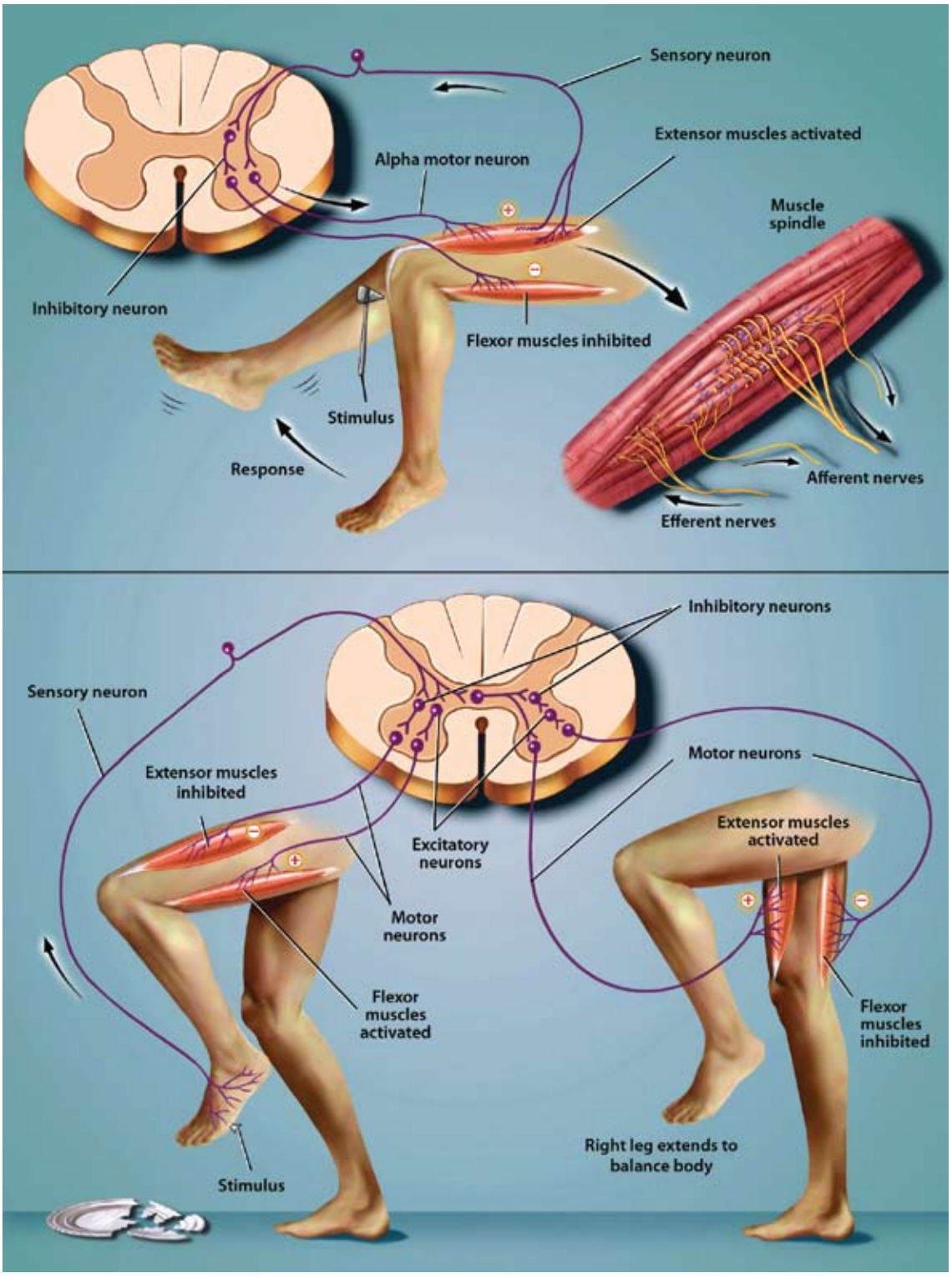
Scientists are only beginning to understand the complex interactions that take place among different brain regions during voluntary movements, mostly through careful experiments on animals.

In addition to the motor cortex, movement control involves the interaction of many other brain regions, including the *basal ganglia*, thalamus, *cerebellum*, and a large number of neuron groups located within the midbrain and brainstem — regions that send axons to the spinal cord. Scientists know that the basal ganglia and thalamus have widespread connections with motor and sensory areas of the cerebral cortex.

Dysfunction of the basal ganglia can lead to serious movement disorders. For example, the depletion of the neurotransmitter dopamine from specific portions of the basal ganglia results in the tremor, rigidity, and akinesia of Parkinson's disease. Dopamine is supplied to the basal ganglia by the axons of neurons located in the *substantia nigra*, a midbrain cell group. Dopamine is depleted during Parkinson's disease because of the degeneration of the nigral neurons.

Another brain region that is crucial for coordinating and adjusting skilled movement is the cerebellum. A disturbance of cerebellar function leads to poor coordination of muscle control, disorders of balance and reaching, and even difficulties in speech, one of the most intricate forms of movement control.

The cerebellum receives direct and powerful information from all the sensory receptors in the head and the limbs and from most areas of the cerebral cortex. The cerebellum apparently acts to integrate all this information to ensure smooth coordination of muscle action, enabling us to perform skilled movements more or less automatically. Considerable evidence indicates that the cerebellum helps us adjust motor output to deal with changing conditions, such as growth, disability, changes in weight, and aging. It tunes motor output to be appropriate to the specific requirements of each new task: Our ability to adjust when picking up a cup of coffee that is empty or full depends on the cerebellum. Evidence suggests that as we learn to walk, speak, or play a musical instrument, the necessary, detailed control information is stored within the cerebellum, where it can be called upon by commands from the cerebral cortex.



MOVEMENT. The stretch reflex (top) occurs when a doctor taps a muscle tendon to test your reflexes. This sends a barrage of impulses into the spinal cord along muscle spindle sensory fibers and activates motor neurons to the stretched muscle to cause contraction (stretch reflex). The same sensory stimulus causes inactivation, or inhibition, of the motor neurons to the antagonist muscles through connection neurons, called inhibitory neurons, within the spinal cord. Afferent nerves carry messages from sense organs to the spinal cord; efferent nerves carry motor commands from the spinal cord to muscles. Flexion withdrawal (bottom) can occur when your bare foot encounters a sharp object. Your leg is immediately lifted (flexion) from the source of potential injury, but the opposite leg responds with increased extension in order to maintain your balance. The latter event is called the crossed extension reflex. These responses occur very rapidly and without your attention because they are built into systems of neurons located within the spinal cord itself.

Sleep

Sleep remains one of the great

mysteries of modern neuroscience. We spend nearly one-third of our lives asleep, but the function of sleep still is not known. Fortunately, over the past few years, researchers have made great headway in understanding some of the brain circuitry that controls wake-sleep states.

Scientists now recognize that sleep consists of several different stages; that the choreography of a night's sleep involves the interplay of these stages, a process that depends upon a complex switching mechanism; and that the sleep stages are accompanied by daily rhythms in hormones, body temperature, and other functions.

Sleep is crucial for concentration, memory, and coordination. Without enough sleep, people have trouble focusing and responding quickly — in fact, sleep loss can have as big an effect on performance as drinking alcohol. It is also important for our emotional health. And growing evidence suggests that a lack of sleep increases the risk of a variety of health problems, including diabetes, cardiovascular disease and heart attacks, stroke, depression, high blood pressure, obesity, and infections.

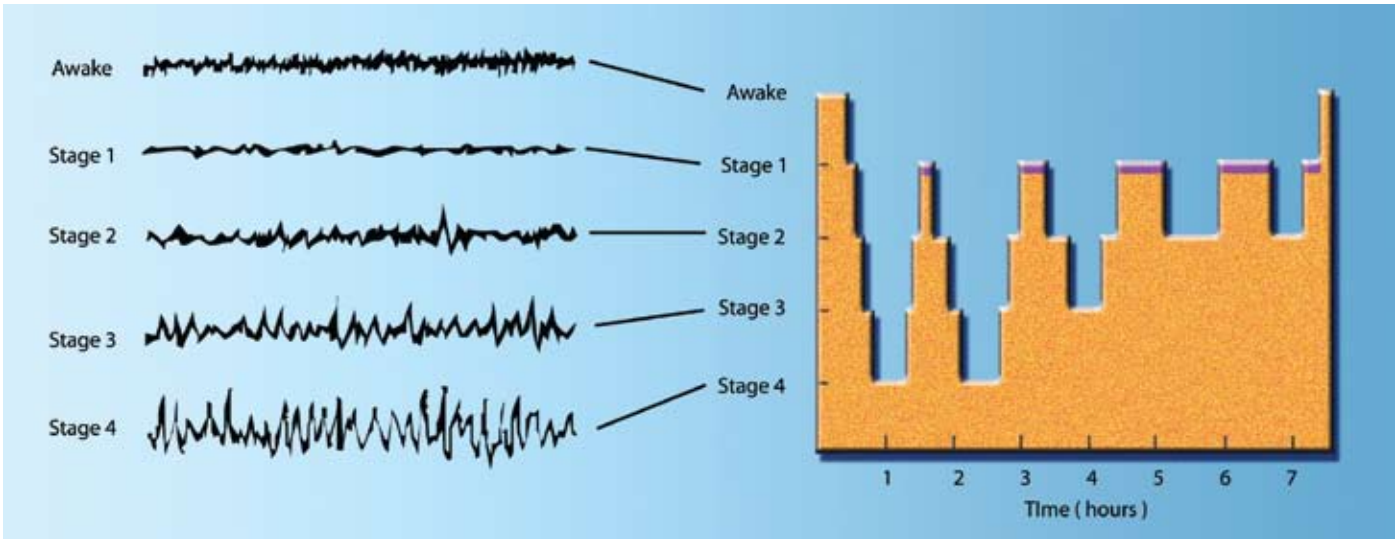
Disorders of sleep are among the nation's most common health problems, affecting up to 70 million people, most of whom are undiagnosed and untreated. These disorders are one of the least recognized sources of disease, disability, and even death, costing an estimated $100 billion annually in lost productivity, medical bills, and industrial accidents. Research holds promise for devising new treatments to allow millions of people to get a good night's sleep.

Brain activity during sleep

Although sleep appears to be a passive and restful time, it actually involves a highly active and well-scripted interplay of brain circuits to produce its various stages.

The stages of sleep were discovered in the 1950s in experiments using electroencephalography (EEG) to examine human brain waves during sleep. Researchers also measured movements of the eyes and the limbs. They found that over the course of the first hour or so of sleep each night, the brain progresses through a series of stages during which the brain waves slow down. This period of *slow wave sleep* is accompanied by relaxation of the muscles and the eyes. Heart rate, blood pressure, and body temperature all fall. If awakened at this time, most people recall only fragmented thoughts, not an active dream.

Over the next half hour or so, brain activity alters drastically from deep slow wave sleep to generate neocortical EEG waves that



SLEEP PATTERNS. During a night of sleep, the brain waves of a young adult recorded by the electroencephalogram (EEG) gradually slow down and become larger as the individual passes into deeper stages of slow wave sleep. After about an hour, the brain re-emerges through the same series of stages, and there is usually a brief period of REM sleep (on dark areas of graph), during which the EEG is similar to wakefulness. The body is completely relaxed; the person is deeply unresponsive and usually is dreaming. The cycle repeats over the course of the night, with more REM sleep, and less time spent in the deeper stages of slow wave sleep as the night progresses.

are similar to those observed during waking. Paradoxically, the fast, waking-like EEG activity is accompanied by *atonia*, or paralysis of the body's muscles (only the muscles that allow breathing and control eye movements remain active). This state is often called *rapid eye movement* (REM) sleep. During REM sleep, there is active dreaming. Heart rate, blood pressure, and body temperature become much more variable. Men often have erections during this stage of sleep. The first REM period usually lasts 10 to 15 minutes.

During the night, these cycles of slow wave and REM sleep alternate, with the slow wave sleep becoming less deep and the REM periods more prolonged until waking occurs. Over the course of a lifetime, the pattern of sleep cycles changes. Infants sleep up to 18 hours per day, and they spend much more time in deep slow wave sleep. As children mature, they spend less time asleep and less time in deep slow wave sleep. Older adults may sleep only six to seven hours per night, often complain of early waking that they cannot avoid, and spend very little time in slow wave sleep.

Sleep disorders

The most common sleep disorder, and the one most people are familiar with, is *insomnia*. Some people have difficulty falling asleep initially, but other people fall asleep and then awaken partway through the night and cannot fall asleep again. Although a variety of short-acting sedatives and sedating antidepressant drugs are available to help, none produces a truly natural and restful sleep state because they tend to suppress the deeper stages of slow wave sleep.

Excessive daytime sleepiness may have many causes. The most common are disorders that disrupt sleep and result in inadequate amounts of sleep, particularly of the deeper stages.

In *obstructive sleep apnea*, as sleep deepens, the airway muscles in the throat relax to the point of collapse, closing the airway. This prevents breathing, which causes arousal from sleep and prevents the sufferer from entering the deeper stages of slow wave sleep. This condition also can cause high blood pressure and may increase the risk of heart attack. Increased daytime sleepiness leads to an increased risk of daytime accidents, especially automobile accidents. Treatment may include a variety of attempts to reduce airway collapse during sleep. Whereas simple things like losing weight, avoiding alcohol and sedating drugs prior to sleep, and avoiding sleeping on one's back can sometimes help, most people with sleep apnea require devices that induce continuous positive airway pressure to keep the airway open. This can be accomplished by fitting a small mask over the nose that provides an airstream under pressure during sleep. In some cases, surgery is needed to correct the airway anatomy.

Periodic limb movements of sleep are intermittent jerks of the legs or arms that occur as the individual enters slow wave sleep and can cause arousal from sleep. Other people have episodes in which their muscles fail to become paralyzed during REM sleep, and they act out their dreams. This *REM behavior disorder* also can be very disruptive to a normal night's sleep. Both disorders are more common in people with Parkinson's disease, and both can be treated with drugs for Parkinson's or with a benzodiazepine called clonazepam.

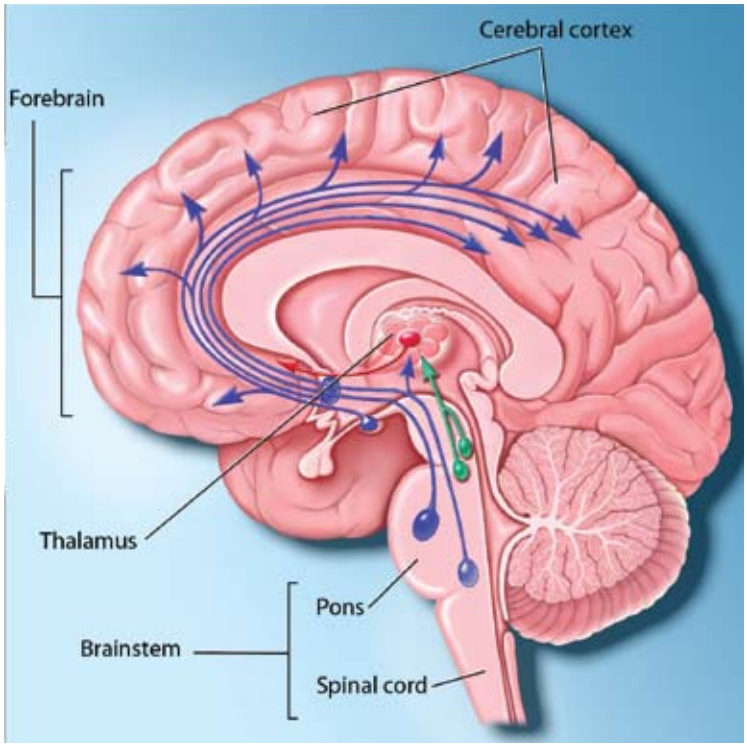
Narcolepsy is a relatively uncommon condition — only one case per 2,500 people — in which the switching mechanisms controlling the transitions into sleep, particularly REM sleep, do not work properly. This problem is due to the loss of nerve cells in the lateral hypothalamus containing the neurotransmitter orexin (also known as hypocretin). Narcoleptics have sleep attacks during the day, in which they suddenly fall asleep. This is socially disruptive, as well as dangerous — for example, if it strikes while they are driving. They tend to enter REM sleep very quickly as well and may even enter a dreaming state while still partially awake, a condition known as *hypnagogic hallucination*. They also have attacks during which they lose muscle tone — similar to what occurs during REM sleep but while they are awake. These attacks of paralysis, known as *cataplexy*, can be triggered by emotional experiences, even by hearing a funny joke.

Recently, studies into the mechanism of narcolepsy have given researchers major insight into the processes that control these mysterious transitions between waking, slow wave sleep, and REM sleep states.

How is sleep regulated?

During wakefulness, the brain is kept in an active or aroused state by the actions of two major systems of nerve cells that use either acetylcholine or monoamines, such as norepinephrine, serotonin, dopamine, and histamine, as their neurotransmitters. Nerve cells in the upper part of the pons and in the midbrain that mainly contain acetylcholine send inputs to activate the thalamus. When the thalamus is activated, it in turn provides information from the sensory systems about the world around us to the cerebral cortex. Other nerve cells in the upper brainstem, largely containing norepinephrine, serotonin, and dopamine, send their outputs directly to the hypothalamus, the basal forebrain, and the cerebral cortex. They are joined by nerve cells in the hypothalamus containing the neurotransmitter orexin and another group containing histamine, and neurons in the basal forebrain containing acetylcholine or GABA, all of which also send outputs directly to the cortex. This activates the cerebral cortex so that input from the thalamus is interpreted accurately during wakefulness.

During REM sleep, the cholinergic nerve cells activate the thalamus, producing an EEG pattern that is similar to wakefulness,



THE WAKING AND SLEEPING BRAIN. Wakefulness is maintained by activity in two systems of neurons. Neurons that make the neurotransmitter acetylcholine are located in two main arousal centers, one in the brainstem (green pathways) and one in the forebrain (red pathway). The brainstem arousal center supplies the acetylcholine for the thalamus and brainstem, and the forebrain arousal center supplies that for the cerebral cortex. Activation of these centers alone can create rapid eye movement sleep. Activation of other neurons that make monoamine neurotransmitters such as norepinephrine, serotonin, and histamine (blue pathways) is needed for waking.

but the monoamine pathway from the upper brainstem directly to the cerebral cortex is quiet. As a result, the input from the thalamus to the cerebral cortex is perceived as dreams. When the nerve cells containing the monoamine neurotransmitters are active, they suppress the occurrence of REM sleep.

The brainstem cell groups that control arousal from sleep are, in turn, influenced by two groups of nerve cells in the hypothalamus, the part of the brain that controls basic body cycles. One group of nerve cells, in the ventrolateral preoptic nucleus, contains the inhibitory neurotransmitters galanin and GABA. When the ventrolateral preoptic neurons fire, they are thought to turn off the arousal systems, causing sleep. Damage to the ventrolateral preoptic nucleus produces irreversible insomnia.

A second group of nerve cells in the lateral hypothalamus promotes wakefulness and suppresses REM sleep. They contain the neurotransmitter orexin, which provides an excitatory signal to the arousal system, particularly to the monoamine neurons. In experiments in which the gene for the neurotransmitter orexin was experimentally removed in mice, the animals became narcoleptic. Similarly, in two dog species with naturally occurring narcolepsy, an abnormality was discovered in the gene for the type 2 orexin receptor. Although humans with narcolepsy rarely have genetic defects in orexin signaling, most develop the disorder in their teens or 20s because of the loss of orexin nerve cells. Recent studies show that in humans with narcolepsy, the orexin levels in the brain and spinal fluid are abnormally low. Thus, orexin appears to play a critical role in activating the monoamine system and in preventing abnormal transitions, particularly into REM sleep.

Two main signals control our need for sleep and its circuitry. First is homeostasis, or the body's need to seek a natural equilibrium of wakefulness followed by rest and sleep. Several mechanisms for the signal of accumulating sleep have been suggested. Evidence suggests that levels of a chemical called adenosine, which is linked to brain energy and activity homeostasis, increase in the brain during prolonged wakefulness and that these levels modulate sleep homeostasis. Interestingly, the drug caffeine, which is widely used to prevent sleepiness, acts as an adenosine blocker.

If an individual does not get enough sleep, the sleep debt progressively accumulates and leads to a degradation of mental function. When the opportunity to sleep comes again, the individual will sleep much more, to "repay" the debt. The slow wave sleep debt is usually "paid off" first.

The other major influence on sleep cycles is the brain's circadian timing system. The suprachiasmatic nucleus is a small group of nerve cells in the hypothalamus that acts as a master clock. These cells express clock proteins, which go through a biochemical cycle of about 24 hours, setting the pace for daily cycles of activity, sleep, hormone release, and other bodily functions. The suprachiasmatic nucleus also receives input directly from the retina, and the clock can be reset by light so that it remains linked to the outside world's day-night cycle. The suprachiasmatic nucleus provides signals to an adjacent brain area, called the subparaventricular nucleus, which in turn contacts the dorsomedial nucleus of the hypothalamus. The dorsomedial nucleus in turn contacts the ventrolateral preoptic nucleus and the orexin neurons that directly regulate sleep and arousal.

Stress

THE ABILITY TO REACT in response to threatening events has been with us since the time of our ancient ancestors. In response to impending danger, muscles are primed, attention is focused, and nerves are readied for action — "fight or flight." In today's complex and fast-paced world, stressors are more consistently psychological or socially based, and we face them with less reprieve. The continued stimulation of the systems that respond to threat or danger may contribute to heart disease, obesity, arthritis, and depression, as well as accelerating the aging process.

Nearly two-thirds of ailments seen in doctors' offices are adversely affected by stress; indeed, stress can both cause diseases and exacerbate existing ones. Surveys indicate that 60 percent of Americans feel they are under a great deal of stress at least once a week. Costs due to stress from absenteeism, medical expenses, and lost productivity are estimated at $300 billion annually.

Stress is difficult to define because its effects vary with each individual. Specialists now define stress as any external stimulus that threatens homeostasis — the normal equilibrium of body function. Stress also can be induced by the belief that homeostasis might soon be disrupted. Among the most powerful stressors are psychological and psychosocial stressors that exist between members of the same species. Lack or loss of control is a particularly important feature of severe psychological stress that can have physiological consequences. Most harmful are the chronic aspects of stress.

During the past several decades, researchers have found that stress both helps and harms the body. When confronted with a crucial physical challenge, properly controlled stress responses can provide the extra strength and energy needed to cope. Moreover, the acute physiological response to stress protects the body and brain and helps to re-establish or maintain homeostasis. But stress that continues for prolonged periods can repeatedly elevate physiological stress responses or fail to shut them off when they are not needed. When this occurs, the same physiological mechanisms can badly upset the body's biochemical balance and accelerate disease.

Scientists also believe that the individual variation in responding to stress is somewhat dependent on a person's perception of external events. This perception ultimately shapes his or her internal physiological response. Thus, by controlling your perception of events, you can do much to avoid the harmful consequences of the sorts of mild to moderate stressors that typically afflict modern humans.

The immediate response

A stressful situation activates three major communication systems in the brain that regulate bodily functions. Scientists have come to understand these complex systems through experiments primarily with rats, mice, and nonhuman primates, such as monkeys. Scientists then verified the action of these systems in humans.

The first of these systems is the *voluntary nervous system*, which sends messages to muscles so that we may respond to sensory information. For example, the sight of a shark in the water may prompt you to run from the beach as quickly as possible.

The second communication system is the *autonomic nervous system*. It combines the *sympathetic* branch and the *parasympathetic* branch. The sympathetic nervous system gets us going in emergencies, while the parasympathetic nervous system keeps the body's maintenance systems, such as digestion, in order and calms the body's responses to the emergency branch.

Each of these systems has a specific task. The sympathetic branch causes arteries supplying blood to the muscles to relax in order to deliver more blood, allowing greater capacity to act. At the same time, blood flow to the skin, kidneys, and digestive tract is reduced, and supply to the muscles increases. In contrast, the parasympathetic branch helps to regulate bodily functions and soothe the body once the stressor has passed, preventing the body from remaining too long in a state of mobilization. If these functions are left mobilized and unchecked, disease can develop. Some actions of the calming branch appear to reduce the harmful effects of the emergency branch's response to stress.

The brain's third major communication process is the *neuroendocrine system*, which also maintains the body's internal functioning. Various stress hormones travel through the blood and stimulate the release of other hormones, which affect bodily processes such as metabolic rate and sexual function.

The major stress hormones are *epinephrine* (also known as adrenaline) and *cortisol*. When the body is exposed to stressors, epinephrine, which combines elements of hormones and neurotransmitters, is quickly released into the bloodstream to put the body into a general state of arousal and enable it to cope with a challenge.

The adrenal glands secrete *glucocorticoids*, which are hormones that produce an array of effects in response to stress. These include mobilizing energy into the bloodstream from storage sites in the body, increasing cardiovascular tone, and delaying long-term processes in the body that are not essential during a crisis, such as

feeding, digestion, growth, and reproduction. In primates, the main glucocorticoid is cortisol (hydrocortisone), whereas in rodents, it is corticosterone. Some of the actions of glucocorticoids help to mediate the stress response, while some of the other, slower actions counteract the primary response to stress and help re-establish homeostasis. Over the short run, epinephrine mobilizes energy and delivers it to muscles for the body's response. Cortisol promotes energy replenishment and efficient cardiovascular function.

Glucocorticoids also affect food intake during the sleep-wake cycle. Cortisol levels, which vary naturally over a 24-hour period, peak in the body in the early-morning hours just before waking. This hormone acts as a wake-up signal and helps turn on appetite and physical activity. This effect of glucocorticoids may help to explain disorders such as jet lag, which results when the light-dark cycle is altered by travel over long distances, causing the body's biological clock to reset itself more slowly. Until that clock is reset, cortisol secretion and hunger, as well as sleepiness and wakefulness, occur at inappropriate times of day in the new location.

Acute stress also enhances memory of threatening situations and events, increases activity of the immune system, and helps protect the body from pathogens. Cortisol and epinephrine facilitate the movement of immune cells from the bloodstream and storage organs such as the spleen into tissue where they are needed to defend against infection.

Glucocorticoids do more than help the body respond to stress. In fact, they are an integral part of daily life and the adaptation to environmental change. The adrenal glands help protect us from stress and are essential for survival.

Chronic stress

When glucocorticoids or epinephrine are secreted in response to the prolonged psychological stress commonly encountered by modern humans, the results are not ideal. Normally, bodily systems gear up under stress and release hormones to improve memory, increase immune function, enhance muscular activity, and restore homeostasis. If you are not fighting or fleeing but standing frustrated in a supermarket checkout line or sitting in a traffic jam, you are not engaging in muscular exercise. Yet these systems continue to be stimulated, and when they are stimulated chronically, the consequences are different: Memory is impaired, immune function is suppressed, and energy is stored as fat.

Overexposure to cortisol also can lead to weakened muscles and can chip away at the mechanisms that keep our body systems in a healthy balance. Elevated epinephrine release increases blood pressure. Together, elevated cortisol and epinephrine can contribute to chronic hypertension (high blood pressure), abdominal obesity, and atherosclerosis (hardening of the arteries). Epinephrine also increases the activity of body chemicals that contribute to inflammation, and these chemicals add to the burden of chronic stress, potentially leading to arthritis and possibly aging of the brain.

Stress also can contribute to sleep loss. Elevated levels of glucocorticoids can delay the onset of sleep, and sleep deprivation raises glucocorticoid levels, setting off a vicious cycle.

Scientists have identified a variety of stress-related disorders, including colitis, high blood pressure, clogged arteries, impotency and loss of sex drive in males, irregular menstrual cycles in females, and adult-onset diabetes. Aging rats show impairment of neuronal function in the hippocampus — an area of the brain important for learning, memory, and emotion — as a result of glucocorticoid secretion throughout their lifetimes.

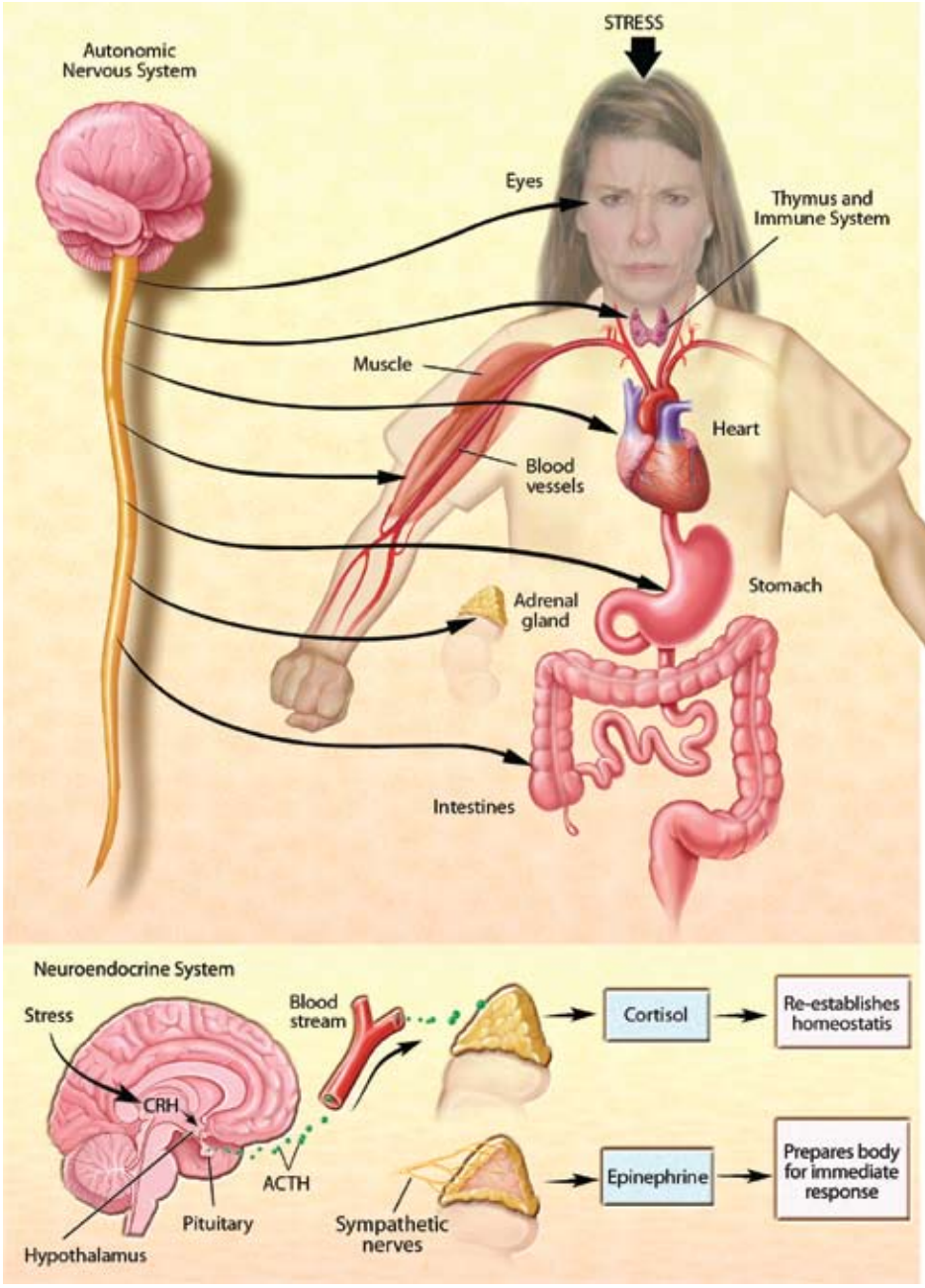
Overexposure to glucocorticoids also increases the number of neurons damaged by stroke. Moreover, prolonged exposure before or immediately after birth can cause a decrease in the normal number of brain neurons and smaller brain size.

The *immune system*, which receives messages from the nervous system, also is sensitive to many of the circulating hormones of the body, including stress hormones. Although acute elevations of stress hormones actually facilitate immune function, sustained exposure to moderate to high levels of glucocorticoids acts to suppress immune function.

While acute, stress-induced immunoenhancement can be protective against disease pathogens, glucocorticoid-induced immunosuppression also can be beneficial. Normally, the glucocorticoids help reverse the immunoenhancement brought about by stress. Without this reversal, there is an increased chance of diseases of overactive immunity and inflammation, such as *autoimmune disorders*, which occur when the body's immune defenses turn against body tissue. Synthetic glucocorticoids like hydrocortisone and prednisone suppress the immune system and therefore are used often to treat autoimmune and inflammatory diseases.

One important determinant of resistance or susceptibility to disease may be a person's sense of control as opposed to a feeling of helplessness. This phenomenon may help explain large individual variations in response to disease. Scientists are trying to identify how the perception of control or helplessness influences physiological responses to stress, including the regulation of immune function.

The cardiovascular system receives many messages from the autonomic nervous system, and stressful experiences have an immediate and direct effect on heart rate and blood pressure. In the short run, these changes help in response to stressors. But when stressors are chronic and psychological, the effect can be harmful and result in accelerated atherosclerosis and increased risk for heart attack.



THE STRESS REACTION. When stress occurs, the sympathetic nervous system is triggered. Norepinephrine is released by nerves, and epinephrine is secreted by the adrenal glands. By activating receptors in blood vessels and other structures, these substances ready the heart and working muscles for action. Acetylcholine is released in the parasympathetic nervous system, producing calming effects. The digestive tract is stimulated to digest a meal, the heart rate slows, and the pupils of the eyes become smaller. The neuroendocrine system also maintains the body's normal internal functioning. Corticotrophin-releasing hormone (CRH), a peptide formed by chains of amino acids, is released from the hypothalamus, a collection of cells at the base of the brain that acts as a control center for the neuroendocrine system. CRH travels to the pituitary gland, where it triggers the release of adrenocorticotropic hormone (ACTH). ACTH travels in the blood to the adrenal glands, where it stimulates the release of cortisol.

Research supports the idea that people holding jobs that carry high demands and low control, such as telephone operators, waiters, and cashiers, have higher rates of heart disease than people who can dictate the pace and style of their working lives.

Behavioral type affects a person's susceptibility to heart attack. People at greatest risk are hostile, irritated by trivial things, and exhibit signs of struggle against time and other challenges. Researchers found that two groups of men — one with high hostility scores and the other with low hostility scores — exhibited similar increases in blood pressure and muscle blood flow when performing a lab test. This finding confirmed that hostility scores do not predict the biological response to simple mental tasks.

Then the researchers added harassment to the test by leading the subjects to believe that their performances were being unfairly criticized. Men with high hostility scores showed much larger increases in muscle blood flow and blood pressure and showed slower recovery than those with low hostility scores. Scientists found that harassed men with high hostility scores had larger increases in levels of stress hormones. Thus, if you have personality traits of hostility, learning to reduce or avoid anger could be important to avoid cardiovascular damage.

Aging

NEUROSCIENTISTS BELIEVE that the brain can remain relatively healthy and fully functioning as it ages and that diseases cause the most severe decline in memory, intelligence, verbal fluency, and other tasks. Researchers are investigating both the abnormal and normal changes that occur over time and their effect on reasoning and other intellectual activities.

The effects of age on brain function are subtle and very selective. Almost everyone gets a bit forgetful in old age, particularly in forming memories of recent events. For example, once you reach your 70s, you may start to forget names, phone numbers, or where you parked your car, or you might respond more slowly to conflicting information. This is not disease. Some individuals, however, develop *senile dementia*, the progressive and severe impairment in mental function that interferes with daily living. The senile dementias include Alzheimer's and cerebrovascular diseases and affect about 1 percent of people younger than age 65, with the incidence possibly increasing to nearly 50 percent in those older than 85. In a small, third group, mental functioning seems relatively unaffected by age. Many people do well throughout life and continue to do well even when old, at least until shortly before death. The wisdom and experience of older people often make up for deficits in performance. The oldest human, Jeanne Calment, kept her wits throughout her 122-year life span.

The belief that pronounced and progressive mental decline is inevitable was and still is popular for several reasons. For one, until the 20th century, few people lived past 65. In 1900, when average life expectancy was about 47 years, 3 million people, or 4 percent of the population, were older than age 65 and typically were ill. In 2003, when life expectancy was more than 77 years, nearly 36 million people, or more than 12 percent of the population, were older than age 65. A generation ago, frailty was seen among people in their 60s; today it is more typical among those in their 80s. Moreover, few people challenged the notion that aging meant inevitable brain decline because scientists knew little about the brain or the aging process. Today's understanding of how the normal brain ages comes from studies of the nervous system that began decades ago and are just now bearing results. Modern technologies now make it possible to explore the structure and function of the brain in more depth than ever before and to ask questions about what actually happens in its aging cells.

Thus, neuroscientists are increasingly able to distinguish between the processes of normal aging and disease. Although some changes do occur in normal aging, they are not as severe as scientists once thought and certainly do not include widespread cell loss.

All human behavior is determined by how well the brain's communication systems work. Often a failure in the cascade of one of these systems results in a disturbance of normal function. Such a failure may be caused by an abnormal biochemical process or a loss of connections between neurons.

The cause of normal brain aging remains a mystery. Dozens of theories abound. One says that specific "aging genes" are switched on at a certain time of life. Another points to genetic mutations or deletions. Other theories implicate hormonal influences, an immune system gone awry, and the accumulation of damage caused by free radicals, cell byproducts that destroy fats and proteins vital to normal cell function.

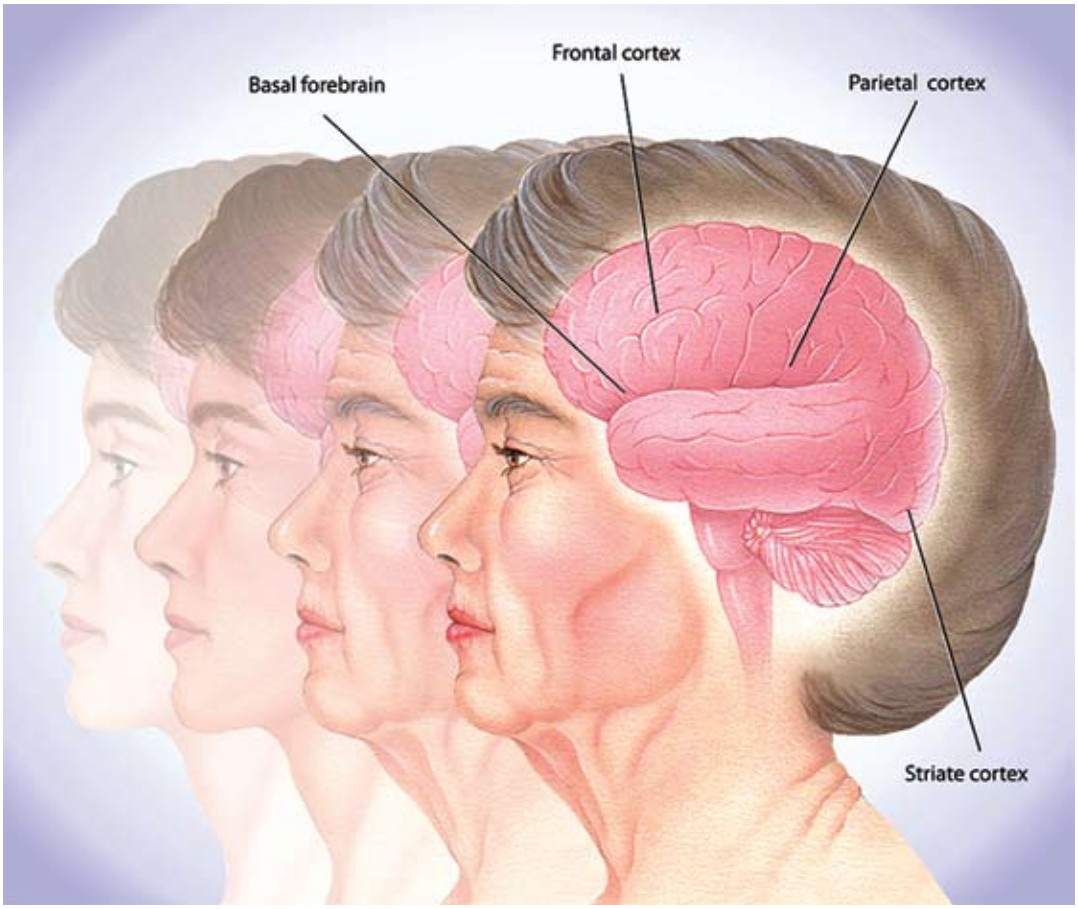
Aging neurons

The brain reaches its maximum weight near age 20; subtle changes in the chemistry and structure of the brain begin at midlife for most people. During a lifetime, the brain is at risk for losing some of its neurons, but normal aging does not result in widespread neuron loss as occurs in Alzheimer's disease or after a stroke. Brain tissue can respond to damage or loss of neurons by expanding dendrites and fine-tuning connections between neurons. A damaged brain neuron can readjust to damage only if its cell body remains intact. If it does, regrowth can occur in dendrites and axons. When neurons are destroyed, nearby surviving neurons can compensate, in part, by growing new dendrites and connections. Physical exercise also can improve neuronal functions at later ages.

Intellectual capacity

From the first large studies to monitor the same group of healthy humans for many years, scientists have uncovered unexpected results. They report declines in some mental functions and improvements in others. In several studies, the speed of carrying out certain tasks becomes slower, but vocabulary improves. Other findings demonstrate less severe declines in the type of intelligence relying on learned or stored information compared with the type that uses the ability to deal with new information.

This research is supported by animal studies in which scientists find that changes in mental function are subtle. For example, in rodents and primates in which only minor brain abnormalities can be detected, certain spatial tasks, such as navigating to find food, tend to become more difficult with age.



THE AGING BRAIN.
Studies of people who have died contradict the popular belief that adults lose an enormous number of neurons every day. In fact, many areas of the brain, primarily in the cortex, maintain most of their neurons. Examples include the parietal cortex, which plays a role in sensory processes and language, and the striate cortex, which processes visual information. The connectivity between neurons changes with aging, so that the brain is constantly capable of being modified or improved.

The aging brain is only as resilient as its circuitry. Scientists debate whether this circuitry is changed only by neuron atrophy or whether some neuron loss over time also is inevitable. In any event, when the circuitry begins to break down, remaining neurons can adapt by expanding their roles, and larger portions of the brain can be recruited in older people to accomplish performance levels similar to those of younger adults.

Learning conditions may dictate what happens to brain cells. Studies of rats shed light on some of the changes that occur in brain cells when the animals live in challenging and stimulating environments. Middle-aged rats exposed to such environments formed more and longer dendrite branches in the cerebral cortex than did rats housed in isolated conditions. In response to enriched environments, older rats tend to form new dendrite outgrowths and synapses, just as younger animals do. But the response is more sluggish and not as large. Compared with younger rats, older rats have less growth of the new blood vessels that nourish neurons.

Another study showed that brain cells in rats given acrobatic training had more synapses per cell than rats given only physical exercise or rats that were inactive. The scientists concluded that motor learning generates new synapses. Physical exercise, however, improved blood circulation in the brain. Aerobic exercise can also improve cognitive performance in humans.

Although much has been learned about the aging brain, many questions remain. For instance, does the production of proteins decline with age in all brain neurons? In a given neuron, does atrophy lead to a higher likelihood of death? How does aging affect gene expression in the brain — the organ with the greatest number of active genes? Do hormonal changes at menopause contribute to gender differences in brain aging?

Neuroscientists speculate that certain genes may be linked to events leading to cell death in the nervous system. By understanding the biology of the proteins produced by genes, scientists hope to be able to influence the survival and function of neurons.

Neural Disorders: Advances and Challenges

In this Chapter —

Addiction

Drug abuse is one of the nation's most serious health problems. Indeed, 9 percent of Americans, more than 22 million people, abuse drugs on a regular basis. Recent estimates show that the abuse of drugs, including alcohol and nicotine, costs the nation more than $276 billion each year.

If continued long enough, *drug abuse* — often defined as harmful drug use — can eventually alter the very structure and chemical makeup of the brain, producing a true brain disorder. This disorder is called *drug addiction* or *drug dependence*. Drug addiction is characterized by a pathological desire for drugs, such that drug-seeking and drug-taking behaviors occupy an inordinate amount of an individual's time and thoughts, at the expense of other activities, and these behaviors persist despite many adverse consequences. Addiction is also characterized by difficulty controlling frequency of use and terminating use, despite a stated desire to do so.

People initially experiment with drugs for many different reasons, one of which is that most drugs of abuse produce feelings of pleasure or remove feelings of stress and emotional pain. Neuroscientists have found that almost all abused drugs produce pleasure by activating a specific network of neurons called the *brain reward system*. The circuit is normally involved in an important type of learning that helps us to stay alive. It evolved to mediate the pleasurable and motivating effects of natural rewards, such as eating when we are hungry or drinking when we are thirsty. Indeed, when a reward produces feelings of pleasure, we learn to repeat the actions that got us the reward in the first place. Drugs can activate this same system and therefore can also promote continued drug use.

Neuroscientists have learned a great deal about how drugs of abuse affect neurons to exert their influence. Abused drugs alter the ways neurotransmitters carry their messages from neuron to neuron. Some drugs mimic neurotransmitters, whereas others block them. Still others alter the way neurotransmitters are released or inactivated. Ultimately, in all cases, the brain reward system is activated inappropriately because drugs alter the chemical messages sent among neurons in this circuit.

Finally, neuroscientists have learned that addiction requires more than the activation of the brain reward system. Over the past 20 years or so, research has indicated that the drugs themselves change the brain of susceptible individuals in complex ways, leading

to symptoms of addiction. The brain regions that are changed by drugs include the brain reward system as well as brain regions involved in executive functions and judgment. These latter brain systems are important in inhibiting behavior and in decision-making.

The process of becoming addicted is influenced by many factors that scientists are only beginning to understand. Motivation for drug use is an important one. For example, people who take opioids to get high may get addicted, but people who use them properly to relieve pain rarely do. Genetic susceptibility and environmental factors, such as stress, also alter the way that people respond to drugs. The characteristics of the drugs themselves, such as how quickly they enter the brain, also play a role in addiction. In addition, the development of *tolerance* — the progressive need for a higher drug dose to achieve the same effect — varies in different people, as does *drug dependence* — the adaptive physiological state that results in withdrawal symptoms when drug use stops. Tolerance and dependence are standard responses of the brain and body to the presence of drugs. However, addiction requires that these occur while a *motivational form of dependence* — the feeling that a person can't live without a drug — also is developing.

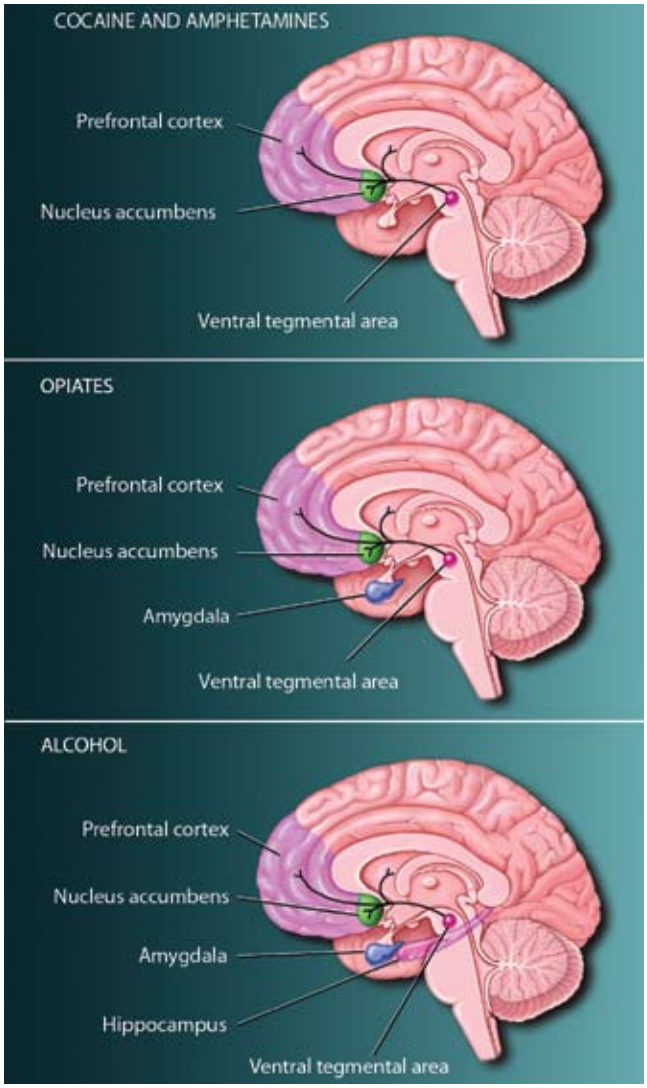
An important question for addiction research is to understand how these many factors interact to predispose individuals to addiction and, conversely, how to protect them. The knowledge and insight into abuse and addiction arising from this research will lead to new therapies.

Alcohol Although legal, alcohol is addictive. Alcohol abuse and alcohol addiction — sometimes referred to as alcoholism or alcohol dependence — together are one of the nation's major health problems.

Nearly 14 million people abuse alcohol or are alcoholic. *Fetal alcohol syndrome*, affecting about 0.5 to 3 of every 1,000 babies born in the United States, is the leading preventable cause of mental retardation. Cirrhosis, the main chronic health problem associated with alcohol addiction, and other chronic liver diseases are responsible for more than 25,000 deaths each year. The annual cost of alcohol abuse and addiction is estimated at $185 billion.

Genetic and environmental factors contribute to alcoholism, but no single factor or combination of factors enables doctors to predict who will become an alcoholic.

Alcohol activates the endogenous opioid system so that susceptible individuals may feel an opioidlike euphoria from their own endorphins when they drink. Based on animal research showing that opiate receptors were involved in the dopamine-reward activation of alcohol, naltrexone, a medication developed for heroin addiction, was used to treat alcoholics. Clinical trials began in 1983, and in 1995, naltrexone was approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcoholism.



BRAIN DRUG REWARD SYSTEMS. Scientists are not certain about all the structures involved in the human brain reward system. However, studies of rat and monkey brains, and brain imaging studies in humans, have provided many clues. These illustrations show what areas are most likely part of the reward systems in the human brain. A central group of structures is common to the actions of all drugs. These structures include a collection of dopamine-containing neurons found in the ventral tegmental area. These neurons are connected to the nucleus accumbens and other areas, such as the prefrontal cortex. Cocaine exerts its effects mainly through this system. Opiates act in this system and many other brain regions, including the amygdala, that normally use opioid peptides. Opioids are naturally occurring brain chemicals that induce the same actions as drugs, such as heroin and morphine. Alcohol activates the core reward system and additional structures throughout the brain because it acts where GABA and glutamate are used as neurotransmitters. GABA and glutamate are widely distributed in the brain, including in the cortex, hippocampus, amygdala, and nucleus accumbens.

Ethanol, the active ingredient in alcoholic beverages, reduces anxiety, tension, and inhibitions. In low doses, it may act as a stimulant, whereas at higher doses, it acts as a depressant. In both cases, it significantly alters mood and behavior. It can also cause heat loss and dehydration.

The drug, which is easily absorbed into the bloodstream and the brain, affects several neurotransmitter systems. For example, alcohol's interaction with the gamma-aminobutyric acid (GABA) receptor can calm anxiety, impair muscle control, and delay reaction time. At higher doses, alcohol also decreases the function of N-methyl-d-aspartate (NMDA) receptors that recognize the neurotransmitter glutamate. This interaction can cloud thinking and eventually lead to coma.

Club drugs Ecstasy, herbal ecstasy, Rohypnol ("roofies"), GHB (gamma hydroxy-butyrate), and ketamine are among the drugs used by some teens and young adults as part of raves and trances. These drugs are rumored to increase stamina and to produce intoxicating highs that are said to deepen the rave or trance experience. Recent research, however, is uncovering the serious damage that can occur in several parts of the brain from use of some of these drugs.

MDMA, called "Adam," "ecstasy," or "XTC" on the street, is a synthetic psychoactive drug with hallucinogenic and amphetamine-like properties. Users encounter problems similar to those found with the use of amphetamines and cocaine. Recent research also links chronic ecstasy use to long-term changes in those parts of the brain critical to thought, memory, and pleasure.

Rohypnol, GHB, and ketamine are predominantly central nervous system depressants. Because they are often colorless, tasteless, and odorless, they can be added easily to beverages and ingested unknowingly. These drugs have emerged as the so-called *date-rape drugs*. When mixed with alcohol, Rohypnol can incapacitate victims and prevent them from resisting sexual assault. Rohypnol may be lethal when mixed with alcohol and other depressants. Since about 1990 in the United States, GHB has been abused for its euphoric, sedative, and anabolic (body-building) effects. It, too, has been associated with sexual assault. Ketamine is another central nervous system depressant abused as a date-rape drug. Ketamine, or "Special K," is a fast-acting general anesthetic. It has sedative, hypnotic, analgesic, and hallucinogenic properties. It is marketed in the United States and a number of foreign countries as a general anesthetic — a drug that brings about a reversible loss of consciousness — in both human and veterinary medical practice.

Many users tend to experiment with a variety of club drugs in combination. This practice creates a larger problem, because combinations of any of these drugs, particularly with alcohol, can lead to unexpected adverse reactions and even death after high doses. Physical exhaustion also can enhance some toxicities and problems.

Marijuana This drug distorts perception and alters the sense of time, space, and self. In certain situations, marijuana can produce intense anxiety.

In radioactive tracing studies, scientists found that *tetrahydrocannabinol* (THC), the active ingredient in marijuana, binds to specific receptors, many of which coordinate movement. This may explain why people who drive after they smoke marijuana are impaired. The hippocampus, a structure involved with memory storage and learning, also contains many receptors for THC. This may explain why heavy users or those intoxicated on marijuana have poor short-term memory and problems processing complex information. Scientists recently discovered that these receptors normally bind to natural internal chemicals termed endocannabinoids, one of which is called *anandamide*. A large effort is now addressing the development of medications that target the endogenous cannabinoid system, with the hope that these will prove beneficial in treating a number of different brain disorders, including addiction, anxiety, and depression.

Nicotine In 2003, more than 70 million people smoked, at least occasionally, making nicotine one of the most widely abused substances. Tobacco kills more than 430,000 U.S. citizens each year — more than alcohol, cocaine, heroin, homicide, suicide, car accidents, fire, and AIDS combined. Tobacco use is the leading preventable cause of death in the United States. Smoking is responsible for approximately 7 percent of total U.S. health-care costs, an estimated $80 billion each year. The direct and indirect costs of smoking are estimated at more than $138 billion per year.

Nicotine, the addicting substance in tobacco, acts through the well-known cholinergic nicotinic receptor. This drug can act as both a stimulant and a sedative. Nicotine stimulates the adrenal glands, and the resulting discharge of epinephrine causes a "kick": a sudden release of glucose paired with an increase in blood pressure, respiration, and heart rate. Nicotine also suppresses insulin output from the pancreas, which means that smokers are always slightly hyperglycemic. In addition, nicotine releases dopamine in the brain regions that control motivation, which is one reason that people continue to smoke.

Much better understanding of addiction, coupled with the identification of nicotine as an addictive drug, has been instrumental in the development of treatments. Nicotine gum, the transdermal patch, nasal spray, and inhalers are equally effective in treating the more than one million people addicted to nicotine. These techniques are used to relieve withdrawal symptoms and produce less severe physiological alterations than tobacco-based systems.

They generally provide users with lower overall nicotine levels than they receive with tobacco and totally eliminate exposure to smoke and its deadly contents. The first non-nicotine prescription drug, bupropion, an antidepressant, has been approved for use as a pharmacological treatment for nicotine addiction. An exciting advance is the use of varenicline for smoking cessation, which directly interacts with the cholinergic nicotinic receptor in a key component of the brain's reward circuitry and prevents nicotine from activating this circuit. The development of varenicline is a prime example of how basic science research can lead to the production of novel medications. Behavioral treatments also are important in helping an individual learn coping skills for both short- and long-term prevention of relapse.

Tobacco kills more than 430,000 U.S. citizens each year — more than alcohol, cocaine, heroin, homicide, suicide, car accidents, fire, and AIDS combined.

Opiates Humans have used opiate drugs, such as morphine, for thousands of years. Monkeys and rats readily self-administer heroin or morphine and, like humans, will become tolerant and physically dependent with unlimited access. Withdrawal symptoms range from mild, flulike discomfort to severe muscle pain, stomach cramps, diarrhea, and unpleasant mood.

Opiates increase the amount of dopamine released in the brain reward system and mimic the effects of endogenous opioids. Heroin injected into a vein reaches the brain in 15 to 20 seconds and binds to opiate receptors found in many brain regions, including the reward system. Activation of the receptors in the reward circuits causes a brief rush of intense euphoria, followed by a couple of hours of a relaxed, contented state.

Opiates create effects like those elicited by the naturally occurring opioid peptides. They relieve pain, depress breathing, cause nausea and vomiting, and stop diarrhea — important medical uses. In large doses, heroin can make breathing shallow or stop altogether — the cause of death in thousands of people who have died of heroin overdose.

A standard treatment for opiate addiction involves *methadone*, a long-acting oral opioid that helps keep craving, withdrawal, and relapse under control. Methadone helps opiate addicts rehabilitate themselves by preventing withdrawal symptoms that can motivate continued drug use. Naloxone and naltrexone are available medications that act as antagonists at opioid receptors; in other words, they can curb the allure of opiates by blocking the opiate receptors so that opiates produce no pleasurable effects when they are taken. The blockers alone are sometimes useful for addicts who are highly motivated to quit. In addition, scientists are developing a long-lasting version of naltrexone that needs to be taken only once a month.

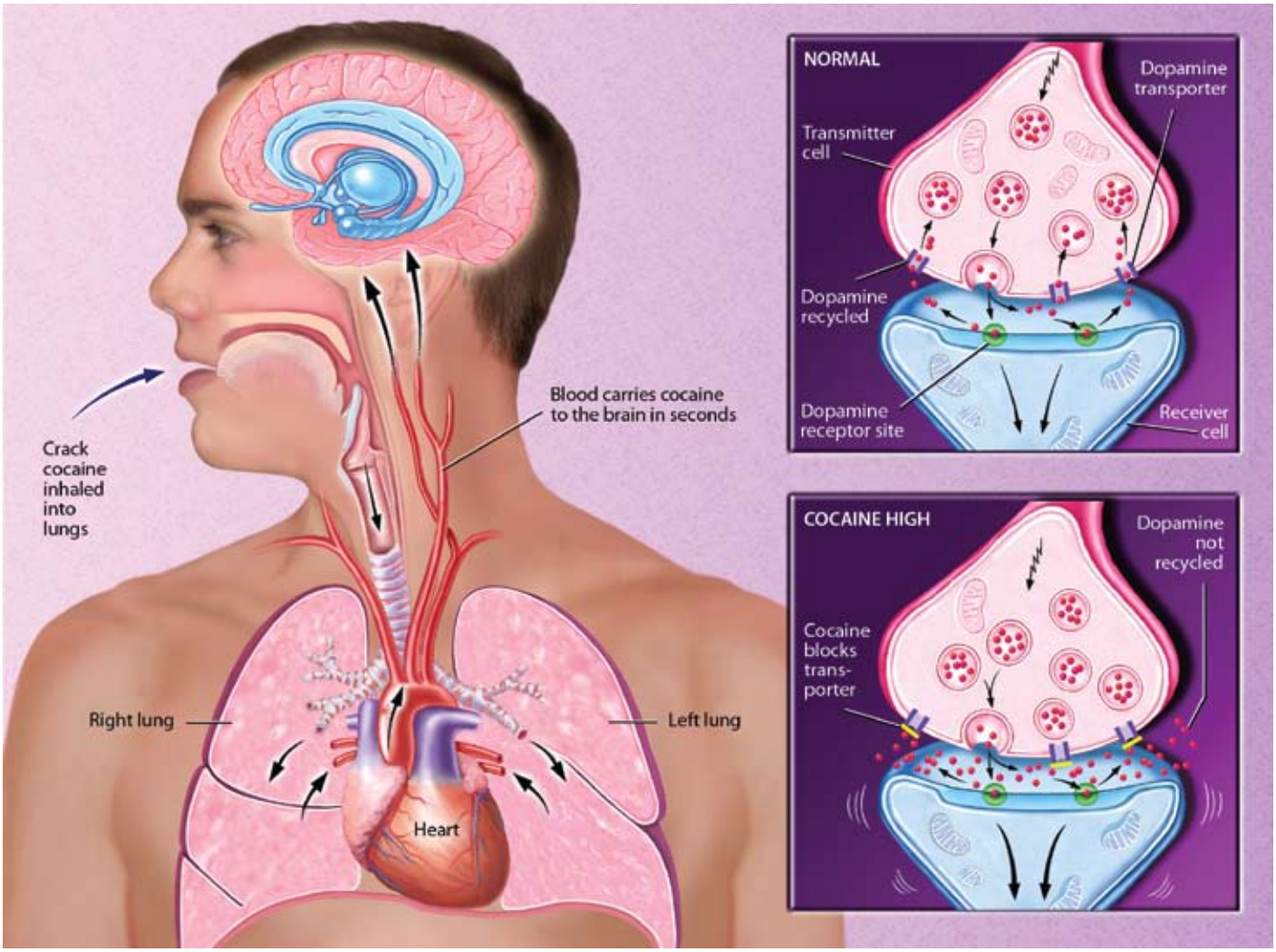
Another medication to treat heroin addiction, buprenorphine, causes a weaker effect on the receptors than methadone and creates only a limited high, which deters an addict from abusing the medication itself. Buprenorphine has been prescribed for over 500,000 patients in the United States.

Psychostimulants This class of drugs includes cocaine and amphetamines. In 2003, there were an estimated 2.3 million chronic cocaine users and 5.9 million occasional cocaine users in the United States. A popular, chemically altered form of cocaine, crack, is smoked. It enters the brain in seconds, producing a rush of euphoria and feelings of power and self-confidence. A smokable form of methamphetamine, "crystal meth," also has become popular. The key biochemical factor that underlies the reinforcing effects of psychostimulant drugs is their ability to greatly elevate the brain chemical dopamine in specific brain regions, such as the *nucleus accumbens*, and repeated use of these drugs progressively increases their ability to activate brain dopamine systems. This is thought to result in a progressively increasing motivation to take the drugs, eventually leading to addiction.

Cocaine users often go on binges, consuming a large amount of the drug in just a few days. A *crash* occurs after this period of intense drug-taking and includes symptoms of emotional and physical exhaustion and depression. These symptoms may result from an actual crash in dopamine and serotonin function as well as an increased response of the brain systems that react to stress. Vaccines to produce antibodies to cocaine in the bloodstream are in clinical trials.

Alzheimer's disease

One of the most frightening and devastating of all neurological disorders is the dementia that occurs in the elderly. The most common cause of this illness is Alzheimer's disease (AD). Rare before age 60 but increasingly prevalent in each decade thereafter, AD affects more than 40 percent of those age 85 and over and nearly



HOW CRACK COCAINE AFFECTS THE BRAIN. Crack cocaine takes the same route as nicotine by entering the bloodstream through the lungs. Within seconds, it is carried by the blood to the brain. The basis for increased pleasure occurs at the gap where the impulses that represent neural messages are passed from one neuron to another. This gap is called a synapse. Dopamine-containing neurons normally relay their signals by releasing dopamine into many synapses. Dopamine crosses the synapse and fits into receptors on the surface of the receiving cell. This triggers an electrical signal that is relayed through the receiver. Then, to end the signal, dopamine molecules break away from the receptors and are pumped back into the nerve terminals that released them. Cocaine molecules block the pump or "transporter," causing more dopamine to accumulate in the synapse. Pleasure circuits are stimulated again and again, producing euphoria.

20 percent of those ages 75 to 84. As many as 5 million Americans have AD. The disease is predicted to affect approximately 14 million individuals in the United States by the year 2040.

The earliest symptoms of AD include forgetfulness; disorientation to time or place; and difficulty with concentration, calculation, language, and judgment. As the disease progresses, some patients have severe behavioral disturbances and may even become psychotic. In the final stages, the affected individual is incapable of self-care and becomes bed-bound. Patients usually die from pneumonia or some other complication of immobility. AD, which in 2005 was reported to have killed 72,000 Americans, is the seventh leading cause of death in the United States.

In the earliest stages, the clinical diagnosis of possible or probable AD can be made with greater than 80 percent accuracy. As the course of the disease progresses, the accuracy of diagnosis at Alzheimer's research centers exceeds 90 percent. The diagnosis depends on medical history, physical and neurological examinations, psychological testing, laboratory tests, and brain imaging studies. New brain imaging strategies promise to enable doctors to visualize AD neuropathology during life. At present, however, final

confirmation of the diagnosis requires examination of brain tissue, usually obtained at autopsy.

The causes and mechanisms of the brain abnormalities underlying AD are not yet fully understood, but great progress has been made through genetics, biochemistry, cell biology, and experimental treatments. Reductions occur in levels of markers for many neurotransmitters, including acetylcholine, somatostatin, monoamines, and glutamate, that allow cells to communicate with one another. Damage to these neural systems, which are critical for attention, memory, learning, and higher cognitive abilities, is believed to cause the clinical symptoms.

Microscopic examination of AD brain tissue shows abnormal accumulations of a small fibrillar peptide, termed *beta amyloid*, in the spaces around synapses (*neuritic plaques*) and abnormal accumulations of a modified form of the protein tau in the cell bodies of neurons (*neurofibrillary tangles*). In all forms of AD, plaques and tangles mostly develop in brain regions important for memory and intellectual functions. New brain imaging strategies show amyloid plaques and tau tangles labeled by a mildly radioactive chemical marker in living people.

Early-onset AD is a rare, dominantly inherited form of the disease. Recently, scientists have identified AD-associated mutations. The gene encoding the *amyloid precursor protein* (APP) is on chromosome 21. In other families with early-onset AD, mutations have been identified in the presenilin 1 and 2 genes. Genes that cause dominant Alzheimer's appear to do so by causing beta amyloid plaques to accumulate. *Apolipoprotein* E (apoE), which influences susceptibility in late life, exists in three forms. The variant known as *APOE epsilon 4* is clearly associated with enhanced risk.

Currently approved treatments do not modify the course of the disease and offer only temporary mitigation of some symptoms of AD, such as agitation, anxiety, unpredictable behavior, sleep disturbances, and depression. Five drugs have been approved by the FDA to treat AD. Four prevent the breakdown of acetylcholine, a brain chemical important for memory and thinking. The fifth regulates glutamate, a brain chemical that may cause brain cell death when produced in large amounts. These agents improve memory deficits temporarily and provide some symptomatic relief but do not prevent progression of the disease. Several other approaches, such as antioxidants, are being tested.

An exciting area of research is the introduction of AD-causing genes in mice. These mice, carrying mutant genes linked to inherited AD, develop behavioral abnormalities and some of the microscopic changes in tissue structure that occur in humans. It is hoped that these mouse models will prove useful for studying the mechanisms of AD and testing novel therapies, although appropriate caution must be taken. Experimental therapies in models of other neurodegenerative diseases — amyotrophic lateral sclerosis, for example — have been effective in mice but not in humans with the disease.

Researchers have begun to modulate the actions of genes that play critical roles in the production of amyloid in animal models. These genes encode the amyloid-producing enzymes beta and gamma secretases, which cleave amyloid peptide from the precursor. The amyloid peptide is then released from the neuron into the extracellular space, where it can accumulate and form AD plaques. Amyloid-destroying enzymes, known as alpha secretases, break up the amyloid peptide, preventing amyloid accumulation. Anti-amyloid therapies for AD aim either to remove existing amyloid or decrease production of new amyloid.

Within the past three to five years, greater appreciation has developed for the surprisingly important roles that diet and lifestyle play in determining risk for AD. Cognitive activity, physical activity, and heart-healthy diets lower the risk for AD, while obesity, high blood pressure, high cholesterol, metabolic syndrome, and diabetes raise the risk. Some evidence indicates that successful management of these cardiovascular risks can delay the onset or slow the progression of dementia.

Amyotrophic lateral sclerosis

This progressive disorder strikes more than 5,000 Americans annually, with an average survival time of just three to five years from symptom onset. It is the most common disorder within a group of diseases affecting motor neurons and costs Americans some $300 million annually.

Commonly known as Lou Gehrig's disease, amyotrophic lateral sclerosis (ALS) affects neurons that control voluntary muscle movements such as walking. For reasons that are not completely understood, motor neurons in the brain and spinal cord begin to disintegrate. Because signals from the brain are not carried by these damaged nerves to the body, the muscles begin to weaken and deteriorate from the lack of stimulation and resulting disuse.

The first signs of progressive paralysis are usually seen in the hands and feet. They include weakness in the legs, difficulty walking, and clumsiness of the hands when washing and dressing. Eventually, almost all muscles under voluntary control, including those of the respiratory system, are affected. Despite the paralysis, however, the mind and the senses remain intact. Death is usually caused by respiratory failure or pneumonia.

No specific test identifies ALS, but muscle biopsies, blood studies, electrical tests of muscle activity, computed tomography (CT) and magnetic resonance imaging (MRI) scans, and X-rays

of the spinal cord help identify the disease and rule out other disorders. Still, diagnosis is often difficult because the causes of ALS remain unknown. Potential causes or contributors to the disease include glutamate toxicity, oxidative stress, environmental factors, and an autoimmune response in which the body's defenses turn against body tissue.

In more than 90 percent of cases, ALS is sporadic, arising in individuals with no known family history of the disorder. In the other 5 to 10 percent of cases, ALS is *familial* — transmitted to family members because of a gene defect.

Scientists have now identified several genes that are responsible for some forms of ALS. The most common and well studied of these are mutations in the gene that codes for *superoxide dismutase*. Scientists believe that whatever they learn from studying this gene and others will have relevance for understanding the more common sporadic form of motor neuron disease.

Once ALS is diagnosed, physical therapy and rehabilitation methods can help strengthen unused muscles. Various drugs can ease specific problems, such as twitching and muscle weakness, but there is no cure. An anti-glutamate drug moderately slows the disease. Additional drugs are now under study. Protecting or regenerating motor neurons using nerve growth factors, other more potent drugs, and stem cells may someday provide additional hope for patients.

Anxiety disorders

The most widespread mental illnesses, anxiety disorders annually affect an estimated 12.6 percent of the adult population, or 24.8 million Americans. They include obsessive-compulsive disorder (OCD); panic disorder; phobias, such as fear of heights, agoraphobia (fear of open spaces), and social anxiety disorder; generalized anxiety disorder; and post-traumatic stress disorder (PTSD). Some can keep people completely housebound. Anxiety disorders often occur together with depression, and individuals doubly afflicted are at a high risk of suicide.

In OCD, people become trapped, often for many years, in repetitive thoughts and behaviors, which they recognize as groundless but cannot stop. Such behavior includes repeatedly washing hands or checking that doors are locked or stoves turned off. The illness is estimated to affect 5 to 6 million Americans annually. Environmental factors and genetics probably play a role in the development of the disorder. Positron emission tomography (PET) scans reveal abnormalities in both cortical and deep areas of the brain, implicating central nervous system changes in OCD patients.

Scientists have recently discovered that certain breeds of large dogs that develop *acral lick syndrome*, severely sore paws from compulsive licking, respond to the serotonergic antidepressant clomipramine, which was the first effective treatment developed for OCD in people. This and other serotonergic antidepressants and the selective serotonin reuptake inhibitors (SSRIs), such as sertraline and paroxetine, are effective in treating OCD. A specialized type of behavioral intervention, *exposure and response prevention*, also is effective in many patients.

Panic disorder, with a lifetime prevalence rate of 1.7 to 3.5 percent in the United States, usually starts "out of the blue." Patients experience an overwhelming sense of impending doom, accompanied by sweating, weakness, dizziness, and shortness of breath. With repeated attacks, patients may develop anxiety in anticipation of another attack and avoid public settings where attacks might occur. If these patients are untreated, they may develop *agoraphobia* and become virtually housebound. Antidepressants, including SSRIs, are effective, as is cognitive behavioral therapy.

Phobia is an intense, irrational fear of a particular object or situation. Individuals can develop phobias of almost anything, including dogs, dating, blood, snakes, spiders, or driving over bridges. Exposure to the feared object or situation can trigger an extreme fear reaction that may include a pounding heart, shortness of breath, and sweating. Cognitive behavioral therapy is an effective treatment.

Extreme stressors such as trauma in combat, being a victim of assault or sexual abuse, or experiencing or witnessing a crime can lead to a form of stress that can last a lifetime. Termed PTSD, the lifetime prevalence rate in the United States for this disorder is 6.8 percent (9.7 percent in women and 1.8 percent in men). It is characterized by intense fear, helplessness or horror, intrusive recollections of the traumatic event, avoidance and numbing, and hyperarousal. In addition, PTSD is associated with dysregulation of the hypothalamic-pituitary-adrenal axis, disordered sleep, and major depressive disorder. Military personnel are at elevated risk for exposure to trauma and not surprisingly have higher prevalence rates when compared to the general population.

Scientists have learned that very high levels of norepinephrine are released in the brain during stress and that patients with PTSD have heightened levels of this chemical long after the traumatic event has passed. High levels of norepinephrine strengthen the primitive emotional reactions of the amygdala, the fear center of the brain, while weakening the rational functions of the prefrontal cortex, which quiets the amygdala. Very high levels of norepinephrine release can strengthen the consolidation of emotional memories and strengthen fear responses through the stimulation of alpha-1 and beta receptors in the amygdala. In contrast, stimulation of alpha-1 receptors in the prefrontal cortex takes this higher brain region "offline." The prefrontal cortex normally allows us to suppress troubling memories and thoughts, and inhibits

the amygdala to let us know that we are safe (the extinction of the fear response). Imaging studies show that patients with PTSD have weaker prefrontal function and stronger amygdala activation, consistent with their symptoms.

New successful medications for PTSD have arisen from this basic research. The alpha-1 blocker, prazosin, a drug used to lower blood pressure for more than 20 years, is now used to treat nightmares experienced with PTSD; those treated with prazosin include people with very long-standing illness, such as Holocaust survivors. Beta-blockers such as propranolol also are being tested in individuals exposed to trauma, but these agents must be administered close in time after the trauma, before PTSD has been established, which brings up complex ethical issues.

The discovery of brain receptors for the benzodiazepine antianxiety drugs has sparked research to identify the brain's own antianxiety chemical messengers. The benzodiazepine receptors are a component of the GABA receptor and enhance the responsiveness to endogenous GABA, the major inhibitory neurotransmitter in the brain. Indeed, recent studies have revealed alterations in certain GABA receptors in the central nervous system of patients with PTSD. This finding may lead to ways to regulate this brain system and correct its possible defects in anxiety disorders.

PTSD also is treated with antidepressant and atypical antipsychotic medications and with psychotherapies such as cognitive behavioral therapy or eye movement desensitization and reprocessing therapy.

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) was first described more than 100 years ago. Characterized by excessively inattentive, hyperactive, or impulsive behaviors, ADHD affects an estimated 2 million children in the United States, or 3 to 5 percent of children. Studies show that 30 percent to 70 percent of these children will continue to experience ADHD symptoms as adults.

By definition, symptoms of ADHD appear before age 7, last for six months or longer, and impair normal functioning in at least two types of settings — at school, among friends, at home, or at work, in the case of adults. Currently, no objective diagnostic test for ADHD exists. Diagnosis requires a comprehensive evaluation, including a clinical interview, parent and teacher ratings, and, sometimes, learning disorder or psychological testing. Multiple evaluation techniques are required because healthy children occasionally show similar behavior, and other conditions, disorders, or environmental triggers — such as stress — may be associated with the same behaviors.

Twin and family studies show that ADHD has a strong genetic influence, and genes encoding components of dopamine and norepinephrine transmission have been implicated. Studies increasingly are finding correlations between ADHD and differences in brain volume or function. Smaller volume and reduced activity are often observed in prefrontal cortical-striatal-cerebellar circuits, particularly in the right hemisphere. Recent studies show a delay in cortical development in some children with ADHD, speculated to represent the subgroup who "grow out" of the disorder.

Recent imaging studies are consistent with reduced catecholamine transmission in at least some patients with this disorder.

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As prefrontal circuits require an optimal level of catecholamine stimulation, reduced catecholamine transmission could lead to weakened prefrontal cortical regulation of attention and behavior and symptoms of ADHD.

ADHD is commonly treated with medications such as stimulants (e.g., methylphenidate) and newer, nonstimulant drugs. These agents all act by enhancing catecholamine transmission in the prefrontal cortex. Despite the widespread use of stimulants, concerns about their risks linger. Thus, parents and clinicians have to balance the benefits of a child with better attention and behavioral regulation on one hand, and the uncertainty about the risks of exposing children to psychotropic drugs on the other.

Autism

An autism spectrum disorder (ASD) is diagnosed in 1 of every 150 babies born in the United States (approximately 1.7 million Americans), an incidence far greater than in the 1970s owing mainly to changes in diagnostic criteria, grouping of multiple disorders into one spectrum, and enhanced clinician referral based on greater awareness. ASD is characterized by communication difficulties; absent, delayed, or abnormal language; impaired social skills; and narrow, obsessive interests or repetitive behaviors. Common associated symptoms include mental retardation, seizures, and behavioral abnormalities.

Currently, ASD is diagnosed in 3- to 5-year-olds based on behavioral symptoms. New research indicates that very sensitive measures of social engagement and interaction can detect differences in the first year of life, a time when many affected children exhibit accelerated growth of the brain. This abnormal growth is a potential marker for early evaluation that may also indicate that development has gone awry.

Studies of brain neurophysiology, tissue, and imaging indicate that ASD is a disorder that disrupts basic developmental processes that occur both before and after birth, potentially including neural cell proliferation, migration, survival, axon and dendrite extension, and synapse formation. Specific brain regions involved in language, cognition, and social communication, or the connections among them, may be formed abnormally. Research also indicates that genetic factors are major contributors to ASD (10 to 20 percent of cases have identified genetic causes), with potential involvement of environmental factors.

Although no cure exists, many affected children respond well to highly structured environments and specialized education and language programs, with earlier interventions leading to better outcomes. Associated symptoms respond to medications.

Knowledge of specific functional deficits in social and cognitive circuits is leading to distinct clinical training to improve brain activity and behavioral outcomes, whereas genetic findings may allow new targeted therapies at the molecular level. One day, genetic tests may complement behavioral indicators to allow earlier diagnosis and intervention as well as the means to overcome and possibly prevent ASD symptoms.

Bipolar disorder

Patients with bipolar disorder, previously known as manic-depressive illness, usually experience episodes of deep depression and manic highs, with a return to relatively normal functioning in between. They also have an increased risk of suicide. Bipolar disorder annually affects 1.2 percent of Americans age 18 or older, or 2.2 million individuals. Approximately equal numbers of men and women suffer from this disorder.

Bipolar disorder tends to be chronic, and episodes can become more frequent without treatment. As bipolar disorder runs in families, efforts are underway to identify the responsible gene or genes.

Bipolar patients can benefit from a broad array of treatments. One of these is lithium. During the 1940s, researchers showed that lithium injections into guinea pigs made them placid, which implied mood-stabilizing effects. When given to manic patients, lithium calmed them and enabled them to return to work and live relatively normal lives. Regarded as both safe and effective, lithium is often used to prevent recurrent episodes.

Other useful medications include certain anticonvulsants, such as valproate or carbamazepine, which can have mood-stabilizing effects and may be especially useful for difficult-to-treat bipolar episodes. Newer anticonvulsant medications are being studied to determine how well they work in stabilizing mood cycles.

Brain tumors

Although brain tumors are not always *malignant* — a condition that spreads and becomes potentially lethal — these growths always are serious because they can interfere with normal brain activity.

Primary brain tumors arise within the brain, whereas metastatic (also called secondary) brain tumors spread from other parts of the body through the bloodstream. The incidence of primary brain tumors is about 15 per population of 100,000. About 44,000 new cases occur in the United States annually.

Symptoms vary according to location and size, but seizures and headache are among the most common. To expand, *gliomas*, typically malignant brain tumors, release the neurotransmitter glutamate at toxic concentrations. This kills off neurons in their vicinity, making room for the tumor's expansion. The released glutamate explains seizures originating from tissue surrounding the tumor. An expanding tumor can increase pressure within the skull, causing headache, vomiting, visual disturbances, and impaired mental functioning. Brain tumors are diagnosed with MRI and CT scanning.

Treatment options for primary brain tumors are limited. Surgery is generally the first step if the tumor is accessible and vital structures will not be disturbed. Radiation is used to stop a tumor's growth or cause it to shrink. Chemotherapy destroys tumor cells that may remain after surgery and radiation but is not very effective for gliomas. Steroid drugs relieve brain swelling, and antiepileptic drugs control seizures.

New therapies for brain tumors are developed in organized studies called clinical trials. Many of these trials focus on targeted therapy — treatment aimed at biologic characteristics of tumors. Targeted therapies include vaccines created from the patient's own tumor combined with substances that boost the immune system or kill tumor cells; *monoclonal* antibodies, which home in on receptors on the surface of the tumor cells; *anti-angiogenic* therapy, in which the tumor's blood supply is restricted; *immunotherapy*, which uses the body's own immune system against the tumor; *gene therapy*, in which bioengineered genes are delivered to the cancer cells to kill them; and several approaches for a targeted delivery of antibodies, toxins, or growth-inhibiting molecules that attach specifically to the tumor cells and interfere with their growth. A scorpion-derived toxin called chlorotoxin that interferes with tumor spread has shown promise in clinical studies where it extended life expectancy significantly.

Researchers are exploring the role of stem cells in the origin of brain tumors. *Epidemiologists*, or scientists studying disease in human populations, also are looking into tumor genetics and patients' lifestyle, environment, occupation, and medical history for clues as to the causes of these tumors. International efforts are underway to increase awareness of brain tumors, encourage research collaboration, and explore new and innovative therapies.

Down syndrome

Down syndrome, the most frequently occurring chromosomal condition, appears in 1 of every 732 babies. It typically occurs when an extra copy of chromosome 21 — or part of its long arm — is present in the egg or, less commonly, in the sperm, at the time of conception. It is not known why this error occurs, and the error has not been linked to any environmental or behavioral factors, either before or during pregnancy, but the risk is markedly increased with the age of the mother. At age 35, the risk is about 1 in 365 births; at age 40, it is 1 in 110. Because of higher fertility rates in younger women, 80 percent of children with Down syndrome are born to women under 35 years of age. Prenatal screening tests, such as the Triple and Quadruple Screens, can accurately detect Down syndrome in about 70 percent of fetuses. Definitive prenatal diagnoses can be obtained with either chorionic villus sampling or amniocentesis.

Down syndrome is associated with approximately 50 physical and developmental characteristics. An individual with Down syndrome is likely to possess, to various degrees, some of these characteristics: mild to moderate intellectual disabilities; low muscle tone; an upward slant to the eyes; a flat facial profile; an enlarged tongue; and an increased risk of congenital heart defects, respiratory problems, and digestive tract obstruction. Nearly all people with Down syndrome show some neuropathological changes like those seen in Alzheimer's disease by age 40, and most show cognitive decline by age 60.

Babies with Down syndrome develop much as typical children do but at a somewhat slower rate. They learn to sit, walk, talk, and toilet train, just like their peers. Early intervention programs can begin shortly after birth and can help foster an infant's development.

Thanks to medical advances and a greater understanding of the potential of those with this condition, people with Down syndrome have been able to have longer and fuller lives. They are being educated in their neighborhood schools, participating in community activities, and finding rewarding employment and relationships.

Although there is no cure for or means of preventing Down syndrome, scientists are moving closer to understanding the role that the genes on chromosome 21 play in a person's development. Once this mystery is understood, they hope to decode the biochemical processes that occur in Down syndrome and learn to treat or cure this disorder.

Dyslexia

An estimated 15 to 20 percent of the population, as many as 60 million Americans, has some form of learning disability involving difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These challenges often occur in people with normal or even high intelligence.

Dyslexia, or specific reading disability, is the most common and most carefully studied of the learning disabilities. It affects 80 percent of all those identified as learning-disabled. Dyslexia is characterized by an unexpected difficulty in reading in children and adults who otherwise possess the intelligence, motivation, and schooling considered necessary for accurate and fluent reading. Studies indicate that although there can be improvement, dyslexia is a persistent, chronic condition.

There is now a strong consensus that the central difficulty in most forms of dyslexia reflects a deficit within the language system

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— and more specifically, in a component of the language system called phonology. This results in difficulty transforming the letters on the page to the sounds of language.

As children approach adolescence, one manifestation of dyslexia may be a very slow reading rate. Children may learn to read words accurately, but their reading will not be fluent or automatic,

reflecting the lingering effects of a phonologic deficit. Because they can read words accurately — albeit very slowly — dyslexic adolescents and young adults may mistakenly be assumed to have "outgrown" their dyslexia. The ability to read aloud accurately, rapidly, and with good expression, as well as facility with spelling, may be most useful clinically in distinguishing students who are average from those who are poor readers. In some languages that are more consistent in the relationship between letters and sounds, for instance Finnish and Italian, slow reading may be the only manifestation of dyslexia at any age.

A range of investigations indicates that there are differences in brain regions between dyslexic and nonimpaired readers involving three important left hemisphere neural systems, two posteriorly (parieto-temporal, occipito-temporal) and one anteriorly around the left inferior frontal region (Broca's area). Converging evidence using functional brain imaging indicates that dyslexic readers demonstrate a functional disruption in an extensive system in the posterior portion of the brain. The disruption occurs within the neural systems linking visual representations of letters to the phonologic structures they represent, and the resulting brain images are referred to as the neural signature of dyslexia.

It is clear that dyslexia runs in families, and research has advanced understanding of its genetic basis. Following the gradual identification over the past 20 years of sites on the human genome that are associated with an increased risk for developing dyslexia, in the past four years, six candidate dyslexia susceptibility genes have been reported, and multiple studies have confirmed some of these candidates. These *risk alleles*, the term given to gene variants that increase the risk of developing a condition or illness, have been shown to play important roles in the development of the brain during fetal life, and some of them may eventually be confirmed to play a role in dyslexia.

Interventions to help children with dyslexia focus on teaching the child that words can be segmented into smaller units of sound and that these sounds are linked with specific letter patterns. In addition, children with dyslexia require practice in reading stories, both to allow them to apply their newly acquired decoding skills to reading words in context and to experience reading for meaning and enjoyment.

Huntington's disease

Affecting some 30,000 Americans and placing 200,000 more at risk, Huntington's disease (HD) is now considered one of the most common hereditary brain disorders. The disease, which killed folk singer Woody Guthrie in 1967, progresses slowly over a 10- to 20-year period and eventually robs the affected individual of the ability to walk, talk, think, and reason. HD usually appears between the ages of 30 and 50. It affects both the basal ganglia, which control coordination, and the brain cortex, which serves as the center for thought, perception, and memory.

The most recognizable symptoms include involuntary jerking movements of the limbs, torso, and facial muscles. These are often accompanied by mood swings, depression, irritability, slurred speech, and clumsiness. As the disease progresses, common symptoms include difficulty swallowing, unsteady gait, loss of balance, impaired reasoning, and memory problems. Eventually, the individual becomes totally dependent on others for care, with death often due to pneumonia, heart failure, or another complication.

Diagnosis consists of a detailed clinical examination and family history. Brain scans may be helpful. The identification in 1993 of the gene that causes HD has simplified genetic testing, which can be used to help confirm a diagnosis. HD researchers and genetic counselors, however, have established specific protocols for predictive testing to ensure that the psychological and social consequences of a positive or negative result are understood. Predictive testing is available only for adults, though children under 18 may be tested to confirm a diagnosis of juvenile-onset HD. Prenatal testing may be performed. The ethical issues of testing must be considered, and the individual must be adequately informed, because there is no effective treatment or cure.

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The HD mutation is an expanded triplet repeat in the HD gene — a kind of molecular stutter in the DNA. This abnormal gene codes for an abnormal version of the protein called Huntingtin. The Huntingtin protein, whose normal function is still unknown, is widely distributed in the brain and appears to be associated with proteins involved in transcription, protein turnover, and energy production. The cause of HD probably involves the gain

of a new and toxic function. Cell and animal models can replicate many features of the disease and are now being used to test new theories and therapies. Although currently no effective treatments for slowing disease progression exist, clinical and observational trials are being conducted. Any of these may yield an effective treatment that would slow the progression or delay onset of the disease while researchers continue working toward a cure.

Major depression

This condition, with its harrowing feelings of sadness, hopelessness, pessimism, loss of interest in life, and reduced emotional well-being, is one of the most common and debilitating mental disorders. Depression is as disabling as heart disease or arthritis. Depressed individuals are 18 times more likely to attempt suicide than people with no mental illness.

Annually, major depression affects 5 percent of the population, or 9.8 million Americans, aged 18 years and older. Fortunately, 80 percent of patients respond to drugs, psychotherapy, or a combination of the two. Some severely depressed patients can be helped with electroconvulsive therapy.

Depression arises from many causes: biological (including genetic), psychological, environmental, or a combination of these. Stroke, hormonal disorders, antihypertensives, and birth control pills also can play a part.

Physical symptoms — disturbances of sleep, sex drive, energy level, appetite, and digestion — are common. Some of these symptoms may reflect the fact that the disorder affects the delicate hormonal feedback system linking the hypothalamus, the pituitary gland, and the adrenal glands. For example, many depressed patients secrete excess cortisol, a stress hormone, and do not respond appropriately to a hormone that should counter cortisol secretion. When tested in sleep laboratories, depressed patients' electroencephalograms often exhibit abnormalities in their sleep patterns.

The modern era of drug treatment for depression began in the late 1950s. Most antidepressants affect norepinephrine or serotonin in the brain, apparently by correcting the abnormal signals that control mood, thoughts, and other sensations. The *tricyclic antidepressants* primarily block the reuptake and inactivation of serotonin and norepinephrine to varying degrees. Another class of antidepressant medications is the *monoamine oxidase inhibitors* (MAOIs). These agents inhibit monoamine oxidase, an enzyme that breaks down serotonin and norepinephrine, allowing these chemicals to remain active.

The popular medication fluoxetine is the first of a class of drugs called *selective serotonin reuptake inhibitors*, or SSRIs. SSRIs block the reuptake and inactivation of serotonin and keep it active in certain brain circuits. Hence, they are functionally similar to the tricyclic antidepressants but act selectively on the serotonin system and have much less toxicity. Several newer antidepressants, such as bupropion, are also very effective but may affect the synaptic levels of dopamine.

Multiple sclerosis

The most common central nervous system disease of young adults after epilepsy, multiple sclerosis (MS) is a lifelong ailment of unknown origin that affects more than 400,000 Americans. MS is diagnosed mainly in individuals between the ages of 20 and 50, with 2 of 3 cases occurring in women. The disease results in earning losses of about $10.6 billion annually for U.S. families with MS.

Although a cause has yet to be found, MS is thought to be an autoimmune disease in which the body's natural defenses act against the myelin and nerve fibers in the central nervous system as though they were foreign tissue. Some nerve fibers are actually cut in association with the loss of myelin. In MS, when brain tissue is destroyed, it is either repaired or replaced by scars of hardened sclerotic patches of tissue. Areas of disease activity are called lesions or *plaques* and appear in multiple places within the central nervous system. These effects are comparable to the loss of insulating material around an electrical wire, or cutting of the wire itself, which interferes with the transmission of signals.

Siblings of people with MS are 10 to 15 times more likely than the general population to be diagnosed with the disorder, whereas the risk for disease concordance for identical twins is about 30 percent. In addition, the disease is as much as five times more prevalent in temperate zones, such as the northern United States and northern Europe, than it is in the tropics. Caucasians are more susceptible than other races. Women are at a higher risk than men. Thus, both genetic and environmental factors are probably involved in the cause. Previous studies had suggested that MS susceptibility peaked before age 15; more recent, larger studies suggest that there is no exact age cutoff.

The most common symptoms of MS are numbness, fatigue, blurred vision, and clumsiness. These can occur singly or in combination, vary in intensity, and last from several weeks to months or may remain permanent symptoms. In some patients, symptoms include slurred speech, weakness, loss of coordination, pain, uncontrollable tremors, loss of bladder control, memory and other cognitive problems, depression, and paralysis (rarely). Muscle spasticity can affect balance and coordination, causing stiffness and involuntary jerking movement — and, if untreated, can create *contractures*, or the "freezing" of a joint that prevents movement.

MS cannot be cured at present, but several medications help control forms of MS where attacks or relapses occur. A wide range

of medications and therapies are available to control symptoms such as spasticity, pain, fatigue, and mood swings, as well as bladder, bowel, or sexual dysfunctions. Steroids, which have been used to treat MS for more than three decades, may effectively shorten attacks and speed recovery from MS-related acute attacks. Many promising new agents to control MS or to alleviate its symptoms are in clinical trials. Treatments given early in the disease are the most effective.

Neurological AIDS

In 2007, about 2.5 million people worldwide became infected with *human immunodeficiency virus* (HIV); 33 million are now living with HIV. Advanced HIV infection is known as acquired *immunodeficiency syndrome*, or AIDS. The epidemic is still the most intense in sub-Saharan Africa but is gaining speed in Asia and Eastern Europe. The impact of AIDS in the United States has been muted because of life-prolonging drugs, but in developing countries only 2 million of the 6 million people who need therapy are receiving such treatment. Women now represent half of all cases worldwide.

Although the principal target of HIV is the immune system, the nervous system may be profoundly affected. Some 20 to 40 percent of untreated patients with full-blown AIDS also develop clinically significant dementia that includes movement impairment, with a smaller percentage still suffering from an overt dementia. Those affected have mental problems ranging from mild difficulty with concentration or coordination to progressive, fatal dementia.

Despite advances in treating other aspects of the disease, AIDS dementia remains incompletely understood. Most current hypotheses center on an *indirect* effect of HIV infection related to secreted viral products or cell-coded signal molecules called *cytokines*. Convincing evidence also exists that some proteins of the virus itself are neurotoxic and may play a role in the ongoing damage that occurs during infection. The viral Tat, released by infected cells, has been among the proteins suspected of neurotoxicity. In any case, HIV infection appears to be the prime mover in this disorder because antiviral treatment may prevent or reverse this condition in many patients.

Experts believe that serious neurologic symptoms are uncommon early in HIV infection. Later, however, patients develop difficulty with concentration and memory and experience general slowing of their mental processes. At the same time, patients may develop leg weakness and a loss of balance. Imaging techniques, such as CT and MRI, show that the brains in these patients have undergone some shrinkage. The examination of brain cells under a microscope suggests that abnormalities are present principally in subcortical areas. Neurons in the cortex also may be altered or lost.

Recent studies indicate that highly active combination antiretroviral treatment — *cocktails* of three or more drugs active against HIV — is effective in reducing the incidence of AIDS dementia. Such treatment also can effectively reverse but not eliminate the cognitive abnormalities attributed to brain HIV infection.

Peripheral neuropathy, nerve death in extremities that causes severe pain, is also a major neurological problem commonly seen in HIV patients. It is believed that the virus triggers a distal sensory neuropathy through neurotoxic mechanisms. This has often been unmasked or exacerbated by certain antiretroviral drugs that have mitochondrial toxicity and tend to make the neuropathies more frequent and serious. More than half of advanced patients have neuropathy, making it a major area for preventive and symptomatic therapeutic trials.

Despite remarkable advances toward new therapies, some patients develop these neurological problems and fail to respond to treatment, thus requiring additional approaches to prevention and treatment of the symptoms. In addition, because of immunodeficiency in HIV patients, otherwise rare opportunistic infections and malignancies are relatively common.

Neurological trauma

Some 1.4 million people suffer traumatic head injuries each year in the United States, of whom roughly 50,000 die. Those who survive face a lifetime of disability, and economic costs approach $60 billion annually.

No magic bullet has yet been found, but doctors have discovered several methods to stave off severe neurological damage caused by head and spinal cord injuries and to improve neurological function following trauma. These treatments include better imaging techniques, methods to understand and improve the brain's ability to regenerate and repair itself, and improved rehabilitation techniques.

Greater access to and use of CT and MRI offer physicians the opportunity to diagnose the extent of trauma and to avoid secondary injury related to *edema*, or swelling, and a reduction in blood flow to the brain (*ischemia*).

In general, patients who arrive in the emergency room and are diagnosed with a severe head injury are monitored for pressure on the brain from bleeding or swelling. Treatments for increases in intracranial pressure include the removal of cerebrospinal fluid, moderate hyperventilation to decrease blood volume, and the administration of drugs to reduce cellular metabolism or to remove water from the injured tissue. No drug for improving outcomes of traumatic brain injury has yet been approved. A recent pilot

clinical trial for patients with moderate to severe closed head injury found that the hormone progesterone cut the number of deaths in severely injured patients by 50 percent, and those in the moderately injured group had improved functional recovery 30 days after injury. Treatments for the injury-induced reduction of cerebral blood flow include the administration of drugs that increase mean arterial blood pressure. In combination with the reduction in intracranial pressure, this results in an increase in blood flow, allowing more blood to reach vital areas.

In addition to helping the physician avoid cerebral edema and reductions in cerebral blood flow following traumatic brain injury, imaging can reveal mass lesions produced by the initial injury. These mass lesions can consist of bleeding on the surface or within the brain as well as the formation of contusions (bruises). Once blood leaks from vessels and comes into direct contact with brain tissue, it can add focal pressure, thereby reducing cerebral blood flow, or can by itself be toxic to brain cells. As a consequence, it may be removed surgically. Contusions can be troubling because they can increase pressure as well as contribute to the development of post-traumatic epilepsy. As a last resort to reduce increased intracranial pressure, part of the skull may be removed to allow the brain to swell, a procedure known as a *craniotomy*.

An estimated 250,000 individuals are living with spinal cord injury in the United States. Some 11,000 new injuries are reported annually and are caused mostly by motor vehicle accidents, sports injuries, violence, and falls. Economic costs approach $10 billion a year.

Researchers have found that people who suffer spinal cord injuries may become less severely impaired if they receive high intravenous doses of a commonly used steroid drug, *methylprednisolone*, within eight hours of the injury. Building on these clues and insight into precisely how and why spinal cord cells die after injury, researchers hope to develop new therapies to reduce the extent of spinal cord damage after trauma.

Scientists have known that, after a spinal cord injury, animals can regain the ability to bear their weight and walk at various speeds on a treadmill belt. More recently, scientists have recognized that the level of this recovery depends to a large degree on whether these tasks are practiced — that is, trained for — after injury. People with spinal cord injury also respond to training interventions.

Scientists have discovered that new nerve cells can be born in the adult brain, but these new cells do not seem capable of helping the injured brain regenerate. Studies are underway to determine how to "jump-start" the pathway that stimulates *neurogenesis*, the birth of new nerve cells. Researchers are trying to decipher how certain environmental cues can be used or overcome to attract these new cells — or transplanted stem or progenitor cells — to areas of brain injury to facilitate regeneration and repair.

These and other recent discoveries are pointing the way toward new therapies to promote nerve regeneration after brain and spinal cord injury. Although these new therapies have not yet reached the clinic, several approaches are on the path to clinical trials.

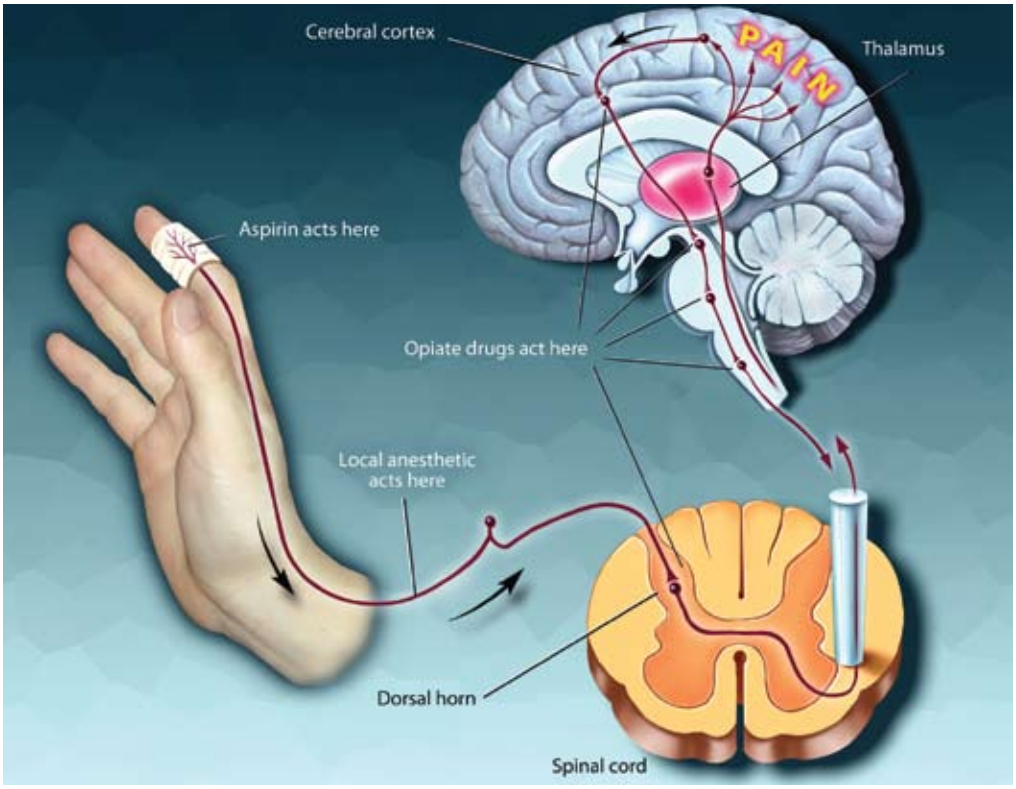
Pain

If there is a universal experience, pain is it. Each year, more than 97 million Americans suffer chronic, debilitating headaches or a bout with a bad back or the pain of arthritis — all at a total cost of some $100 billion. But it need not be that way. New discoveries about how chemicals in the body transmit and regulate pain messages have paved the way for new treatments for both chronic and acute pain.

Local anesthesia, or loss of sensation in a limited area of a person's body, is used to prevent pain during diagnostic procedures, labor, and surgical operations. Local anesthetics temporarily interrupt the action of all nerve fibers, including pain-carrying ones, by interfering with the actions of sodium channels. Historically, the most familiar of these agents was Novocain, which was used by dentists. Lidocaine is more popular today.

Analgesia refers to the loss of pain sensation. The four main types of analgesics are *nonopioids* (aspirin and related nonsteroidal anti-inflammatory drugs, or NSAIDs, such as ibuprofen and naproxen), *opioids* (morphine, codeine), antiepileptic agents (gabapentin, pregabalin), and antidepressants (amitriptyline). NSAIDs are useful for treating mild or moderate pain, such as headache, sprains, or toothache. Because NSAIDs are anti-inflammatory, they also are useful in treating injuries or conditions such as arthritis. NSAIDS inhibit the cyclo-oxygenase (COX) enzymes that make the inflammatory and pain-producing chemical prostaglandin. Acetaminophen has analgesic properties but does not reduce inflammation. Often moderate pain is treated by combining a mild opioid, such as codeine, with aspirin or an NSAID. Opioids are the most potent painkillers and are used for severe pain. Opioids, however, have a high abuse potential and can affect breathing.

The antiepileptic and antidepressant drugs are useful primarily for *neuropathic pain*, pain due to injury to the nervous system, which includes the pain of diabetic neuropathy, post-herpetic neuralgia, phantom limb pain, and post-stroke pain. The best results have been reported with antidepressants that regulate both serotonin and norepinephrine. Interestingly, SSRIs are not effective for neuropathic pain. Topical lidocaine may be effective for the treatment of some neuropathic pain conditions where light touch of the skin can produce severe pain.



HOW PAINKILLERS WORK. At the site of injury, the body produces prostaglandins that increase pain sensitivity. Aspirin, which acts primarily in the periphery, prevents the production of prostaglandins. Acetaminophen is believed to block pain impulses in the brain itself. Local anesthetics intercept pain signals traveling up the nerve. Opiate drugs, which act primarily in the central nervous system, block the transfer of pain signals from the spinal cord to the brain.

Studies of the body's own pain-control system not only demonstrated the existence of naturally occurring opioids (the endorphins) but also identified the receptors through which opioids exert their effects. The finding that opiate receptors are concentrated in the spinal cord led to the use of injections of morphine and other opioids into the cerebrospinal fluid (in which the spinal cord is bathed) without causing paralysis, numbness, or other severe side effects. This technique came about through experiments with animals that first showed that injecting opioids into the spinal cord could produce profound pain control. It is now commonly used in humans to treat pain after surgery and in some patients to treat chronic pain using an implanted pump.

New targets are on the horizon. Molecular biology and genetic approaches have identified many molecules (ion channels and receptors) that are predominantly, if not exclusively, expressed by the *nociceptor*, the peripheral nerve fiber that initially responds to the injury stimulus. Because adverse side effects of drugs arise from the widespread location of the molecules targeted by analgesics (e.g., constipation results from morphine's action on opioid receptors in the gut), new analgesics that target only the nociceptor may have a better side-effect profile. Among the many nociceptor targets are specialized receptor channels (one of which is activated by capsaicin, the pungent ingredient in hot peppers, and another by mustard oil) and a variety of acid-sensing sodium and calcium ion channels.

Blocking the activity of many of these molecules has proven effective in animal studies, suggesting that the development of drugs that target these molecules in humans may have great value for the treatment of acute and persistent pain.

However, it should be emphasized that pain experience is the product of brain function. The pain is in the brain, not in the nociceptors that respond to the injury. In addition to the sensory-discriminative aspects, pain involves emotional factors and the meaning of previous painful experiences, which need to be addressed concurrently in order to treat pain. The fact that placebos and hypnosis can significantly reduce pain clearly illustrates the importance of these psychological factors. New targets for the treatment of pain also include approaches that identify molecules in the brain associated with the elaboration of persistent pain.

Parkinson's disease

This neurologic disorder afflicts 1 million individuals in the United States, most of whom are older than 50. Parkinson's disease is characterized by symptoms of slowness of movement, muscular rigidity, tremor, and postural instability.

The discovery in the late 1950s that the level of dopamine was decreased in the brains of Parkinson's patients was followed in the 1960s by the successful treatment of this disorder by administration of the drug levodopa, which is converted to dopamine in the brain. The successful treatment of Parkinson's by replacement therapy is one of the greatest success stories in neurology.

Levodopa is now combined with another drug, carbidopa, that reduces the peripheral breakdown of levodopa, thus allowing greater levels to reach the brain and reducing side effects. Also playing an important role are newer drugs, such as inhibitors of dopamine breakdown and dopamine agonists.

Genetic studies have demonstrated several heritable gene abnormalities in certain families, but most cases of Parkinson's occur sporadically. It is believed, however, that hereditary factors may render some individuals more vulnerable to environmental factors, such as pesticides. The discovery in the late 1970s that a chemical substance, MPTP, can cause parkinsonism in drug addicts stimulated intensive research on the causes of the disorder. MPTP was accidentally synthesized by illicit drug designers seeking to produce a heroinlike compound. MPTP was found to be converted in the brain to a substance that destroys dopamine neurons. Parkinson's continues to be studied intensively in both rodent and primate MPTP models.

In the past several decades, scientists have shown in primate models of Parkinson's that specific regions in the basal ganglia, a group of cellular structures deep in the brain, are abnormally overactive. Most important, they found that surgical deactivation or destruction of these overactive nuclei — the pallidum and subthalamic nucleus — can greatly reduce symptoms of Parkinson's disease.

The past decade has witnessed a resurgence in this surgical procedure, pallidotomy, and more recently chronic deep-brain stimulation. These techniques are highly successful for treating patients who have experienced significant worsening of symptoms and are troubled by the development of drug-related involuntary movements. The past decade has also seen further attempts to treat such patients with surgical implantation of cells, such as fetal cells, capable of producing dopamine. Replacement therapy with stem cells also is being explored. More recently, gene transfer of trophic factors has been studied in animal models and is being tested in clinical trials. Lastly, four clinical trials are currently underway testing the hypothesis that gene therapy can provide symptomatic (in some cases) or neuroprotective (in others) benefit to patients with Parkinson's.

Schizophrenia

Marked by disturbances in thinking, emotional reactions, and social behavior, schizophrenia usually results in chronic illness and personality change. Delusions, hallucinations, and thought disorder are common.

Affecting about 1 percent of the population, or 2 million Americans each year, schizophrenia is disabling and costly. On a given day, these patients occupy up to 100,000 hospital beds. Annual costs total about $32.5 billion.

Schizophrenia is thought to reflect changes in the brain, possibly caused by disruption of neurodevelopment through genetic predisposition, which may be exacerbated by environmental factors such as maternal infections or direct brain trauma. Brain scans and postmortem studies show abnormalities in some people with schizophrenia, such as enlarged ventricles (fluid-filled spaces) and reduced size of certain brain regions. Functional neuroimaging scans such as PET and functional magnetic resonance imaging (fMRI) taken while individuals perform cognitive tasks, particularly those involving memory and attention, show abnormal functioning in specific brain areas of people with this illness. Brain systems using the chemicals dopamine, glutamate, and GABA appear to be particularly involved in the pathogenesis of the disorder. Recently, several genes involved in controlling nerve cell communication have been identified that appear to increase the risk of developing schizophrenia.

Schizophrenia is thought to reflect changes in the brain, possibly caused by disruption of neurodevelopment through genetic predisposition, which may be exacerbated by environmental factors such as maternal infections or direct brain trauma.

The disorder usually is diagnosed between the ages of 15 and 25. Few patients recover fully following treatment, and most continue to have moderate or severe symptoms that may be exacerbated by life stressors. About 15 percent of patients return to a productive life after a single episode, 60 percent will have intermittent episodes throughout their lives, and an additional 25 percent will not recover their ability to live as independent adults. Deficits in cognition are frequent, lifelong manifestations in most patients, even those who show good recovery from more acute positive symptoms. The negative symptoms may be the most debilitating in terms of leading a productive life and generally are resistant to drug treatment.

The first antipsychotic drug, *chlorpromazine*, serendipitously was discovered to reduce symptoms of schizophrenia in the 1950s. Clinical trials demonstrated that chlorpromazine was more effective than placebo or a sedative. Subsequently, more than 20 effective antipsychotic drugs were developed. Antipsychotics act by blocking certain dopamine receptors. This action accounts for the high prevalence of parkinsonian side effects associated with the use of the first generation of antipsychotics and the risk of developing an irreversible movement disorder, tardive dyskinesia.

The second generation of antipsychotic medications, developed to be more effective in treating the positive symptoms of schizophrenia, can lead to debilitating side effects such as very large weight gain, blood disorders, and muscle pain and dysfunction. Safer drugs are being sought.

Seizures and epilepsy

Seizures are due to sudden, disorderly discharges of interconnected neurons in the brain that temporarily alter one or more brain functions. Epilepsy is a chronic neurological disorder characterized by the occurrence of unprovoked seizures. In developed countries, epilepsy affects approximately 50 of every 100,000 people. It affects three to four times that number in developing countries.

Many different types of epilepsy have been recognized. Epilepsy can start at any age and can be idiopathic (having an uncertain cause) or symptomatic (having a known or presumed cause). Most idiopathic epilepsies probably are due to the inheritance of one or more mutant genes, often a mutant ion channel gene. Symptomatic epilepsies result from a wide variety of brain diseases or injuries, including birth trauma, head injury, neurodegenerative disease, brain infection, brain tumor, or stroke.

Epilepsies are of two types, generalized and partial. *Generalized seizures* typically result in loss of consciousness and can cause a range of behavioral changes, including convulsions or sudden changes in muscle tone. They arise when there is simultaneous excessive electrical activity over a wide area of the brain, often involving the thalamus and cerebral cortex. In *partial epilepsies*, seizures typically occur with maintained consciousness or with altered awareness and behavioral changes. Partial seizures can produce localized visual, auditory, and skin sensory disturbances; repetitive uncontrolled movements; or confused, automatic behaviors. Such seizures arise from excessive electrical activity in one area of the brain, such as a restricted cortical or hippocampal area.

Many antiepileptic drugs are available. Their principal targets are either ion channels or neurotransmitter receptors. Generalized epilepsies often are readily controlled by antiepileptic drugs, with up to 80 percent of patients seizure-free with treatment. Unfortunately, partial epilepsies are generally more difficult to treat. Often, they can be controlled with a single antiepileptic that prevents seizures or lessens their frequency, but sometimes a combination of these drugs is necessary. Identification of the mutated genes underlying epilepsy may provide new targets for the next generation of antiseizure drugs.

Surgery is an excellent option for patients with specific types of partial seizures who do not respond to antiepileptic drugs. Surgery requires the precise location and removal of the brain area from which the partial seizures originate. After surgery, most properly selected patients experience improvement or complete remission of seizures for at least several years.

A new form of epilepsy treatment, electrical stimulation therapy, was introduced as another option for hard-to-control partial seizures. An implantable pacemakerlike device delivers small bursts of electrical energy to the brain via the vagus nerve on the side of the neck. While not curative, vagal nerve stimulation has been shown to reduce the frequency of partial seizures in many patients.

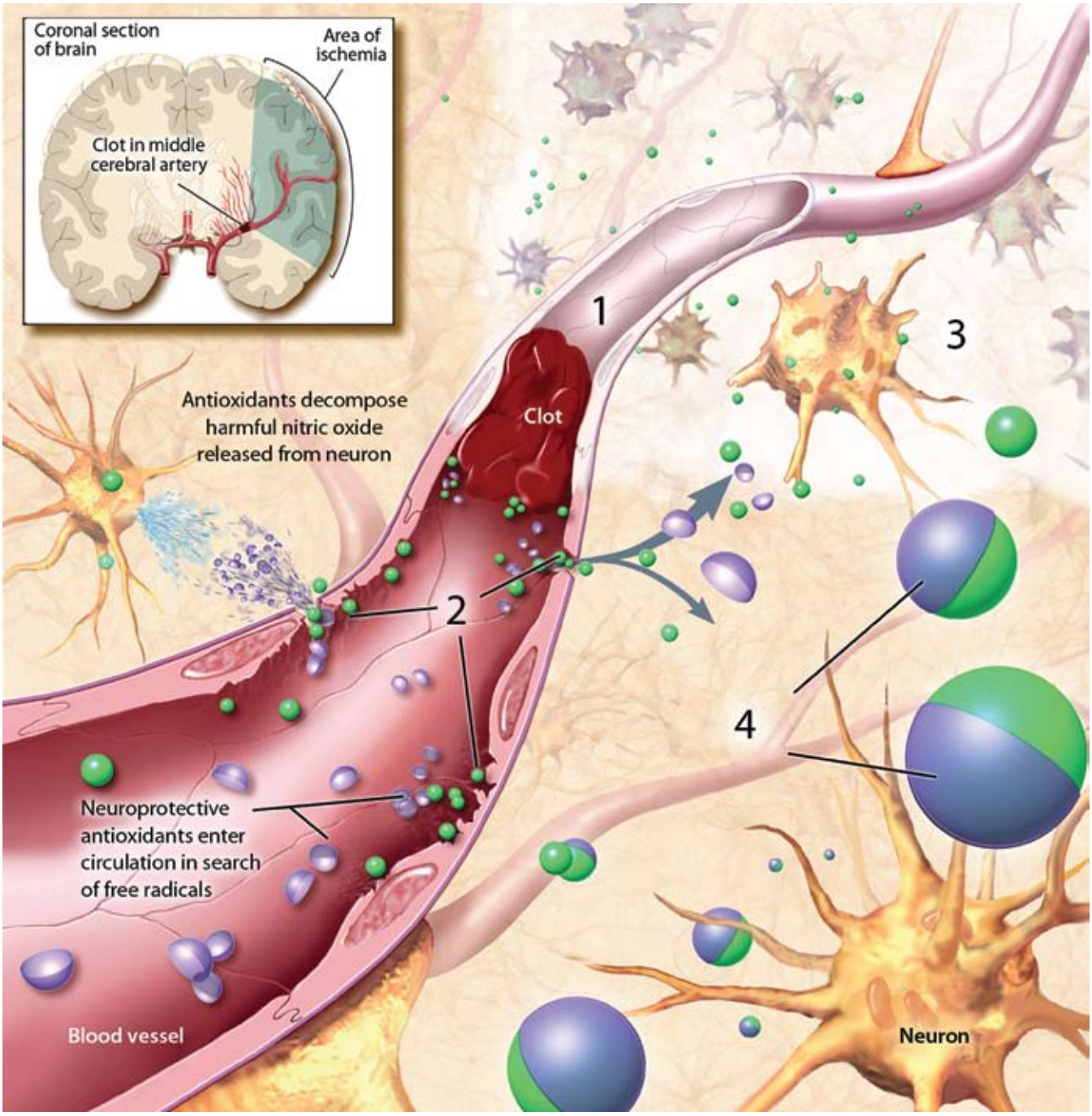
Stroke

A stroke occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is clogged by a blood clot or some other particle. This deprives the brain of blood, causing the death of neurons within minutes. Depending on its location, a stroke can cause many permanent disorders, such as paralysis on one side of the body and loss of speech.

Until recently, if you or a loved one had a stroke, your doctor would tell your family there was no treatment. In all likelihood, the patient would live out the remaining months or years with severe neurological impairment.

This dismal scenario is now brightening. For one, use of the clot-dissolving bioengineered drug, tissue plasminogen activator (tPA), is now a standard treatment in many hospitals. This approach rapidly opens blocked vessels to restore circulation before oxygen loss causes permanent damage. Given within three hours of a stroke, it often can help in limiting the ensuing brain damage. Also, attitudes about the nation's third leading cause of death are changing rapidly. Much of this has come from new and better understanding of the mechanisms that lead to the death of neurons following stroke and from devising ways to protect these neurons.

Stroke affects roughly 700,000 Americans a year — 150,000 of whom die; total annual costs are estimated at $51.2 billion. Stroke often occurs in individuals over 65 years of age, yet a third are younger. Stroke tends to occur more in males and African Americans and in those with risk factors such as diabetes, high blood pressure, heart disease, obesity, high cholesterol, and a family history of stroke.



STROKE. A stroke occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is clogged by a blood clot (1). This lack of blood leads to a cascade of neurochemical abnormalities that can cause cell death within minutes. Free radicals are released, causing damage to endothelial cells (2) and the mitochondria (3) of neurons. Normally the body readily disarms free radicals (4), but in stroke, endothelial cell damage allows many more than can be controlled to move into brain tissue. Depending on its location, a stroke can have different symptoms such as paralysis on one side of the body or a loss of speech.

Controlling risk factors with diet, exercise, and certain drugs can help prevent stroke. Other specific treatments involving surgery or arterial stents can clear clogs in the arteries of the neck region; these and treatments targeting heart disease can help prevent a cutoff of blood supply. Anticoagulant drugs can reduce the likelihood of clots forming, traveling to the brain, and causing a stroke. Other experimental therapies under investigation may lead to even bigger payoffs for patients in the future. Some strategies target mechanisms inside the neuron. In this way, the vicious cycle of local damage followed by a widening fringe of biochemical-induced neuronal death can be slowed. A number of classes of drugs have been shown to be effective in animal studies.

Emerging clinical evidence suggests that, following a stroke affecting movement in one arm, encouraging use of the weakened arm by temporarily restricting use of the unaffected arm can aid functional recovery. Another promising possibility for improving recovery after stroke is through the use of neural stem cells. Some animal studies have shown that an injection of stem cells aids recovery even if administered several days after the injury. Administration of growth factors may further enhance the benefits of stem cell transplantation.

Tourette syndrome

One of the most common and least understood neurobiological disorders, Tourette syndrome (TS) is an inherited disorder that affects about 1 in 200 Americans. Males are affected three to four times as often as females.

Symptoms usually appear between the ages of 4 and 8, but in rare cases may emerge in the late teenage years. The symptoms include motor and vocal *tics* — repetitive, involuntary movements or utterances that are rapid and sudden and persist for more than one year. The types of *tics* may change frequently and increase or decrease in severity over time. In roughly one-half of individuals, this disorder lasts a lifetime, but the remaining patients may experience a remission or decrease in symptoms as they get older.

A high percentage of people with TS also have associated conditions such as problems with learning, difficulties with attention, and obsessive thoughts and compulsive rituals. Often these manifestations are more troublesome to individuals than the tics themselves, so physicians must consider them when choosing a treatment regimen.

TS is inherited and seems to result from abnormal activity in a brain system called the basal ganglia. Research suggests that genes associated with TS, perhaps together with in utero or early environmental conditions, cause abnormalities in basal ganglia development or excesses in certain chemicals, including the neuro-transmitter dopamine.

The majority of people with TS are not significantly disabled by symptoms, and therefore do not require medication. However, antipsychotics and SSRIs, as well as drugs to control tics, nausea, high blood pressure, seizures, or anxiety, are available to help control symptoms when they interfere with functioning. Stimulant medications, such as methylphenidate and dextroamphetamine, that are prescribed for attention deficit hyperactivity disorder (ADHD) have been reported to improve attention and decrease tics in TS. For obsessive-compulsive symptoms that interfere significantly with daily functioning, SSRIs, antidepressants, and related medications may be prescribed.

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Medication dosages that achieve maximum control of symptoms vary for each patient and must be gauged carefully by a doctor. The medicine is administered in small doses with gradual increases to the point where there is maximum alleviation of symptoms with minimal side effects. Some of the undesirable reactions to medications are weight gain, muscular rigidity, fatigue, motor restlessness, and social withdrawal, most of which can be reduced with specific medications. Some side effects such as depression and cognitive impairment can be alleviated with dosage reduction or a change of medication.

Other types of therapy also may be helpful. Psychotherapy and counseling can assist people with TS and help their families cope, and some behavior therapies can be very effective in reducing the severity of both tics and compulsions.

New Diagnostic Methods

MANY OF THE RECENT ADVANCES

in understanding the brain are due to the development of techniques that allow scientists to directly monitor neurons throughout the body.

Electrophysiological recordings, for example, the recording of auditory brainstem responses to assess hearing function in infants, trace brain electrical activity in response to a specific external stimulus. In this method, electrodes placed in specific parts of the brain — which vary depending on which sensory system is being tested — make recordings that are then processed by a computer. The computer makes an analysis based on the time lapse between stimulus and response. It then extracts this information from background activity.

Following the discovery that material is transported within neurons, methods have been developed to visualize activity and precisely track fiber connections within the nervous system. This can be done by injecting a radioactive amino acid into the brain of an experimental animal; the animal is sacrificed a few hours later, and then the presence of radioactive cells is visualized on film. In another technique, the enzyme horseradish peroxidase is injected and taken up by nerve fibers that later can be identified under a microscope.

These and other methods have resulted in many advances in knowledge about the workings of the nervous system and are still useful today. New methods, safely applicable to humans, promise to give even more precise information.

Imaging techniques

Positron emission tomography (PET) PET is one of the most important techniques for measuring blood flow or energy consumption in the brain. This method of measuring brain function is based on the detection of radioactivity emitted when positrons, positively charged particles, undergo radioactive decay in the brain. Small amounts of a radioisotope are introduced into the blood, which is then taken up into different brain areas in proportion to how hard the neurons are working. Computers build three-dimensional images of the changes in blood flow based on the amount of radiation emitted in these different brain regions.

PET studies have helped scientists understand more about how drugs affect the brain and what happens during various behaviors, such as learning and using language, and in certain brain disorders — such as stroke, depression, and Parkinson's disease. For example, PET allows scientists to measure changes in the release of some neurotransmitters, which can be used to understand the relationship between a particular neurotransmitter and a behavior or cognitive process. Within the next few years, PET could enable scientists to identify the biochemical nature of neurological and mental disorders and to determine how well therapy is working in patients. For example, PET has revealed marked changes in the depressed brain. Knowing the location of these changes helps researchers understand the causes of depression and monitor the effectiveness of specific treatments.

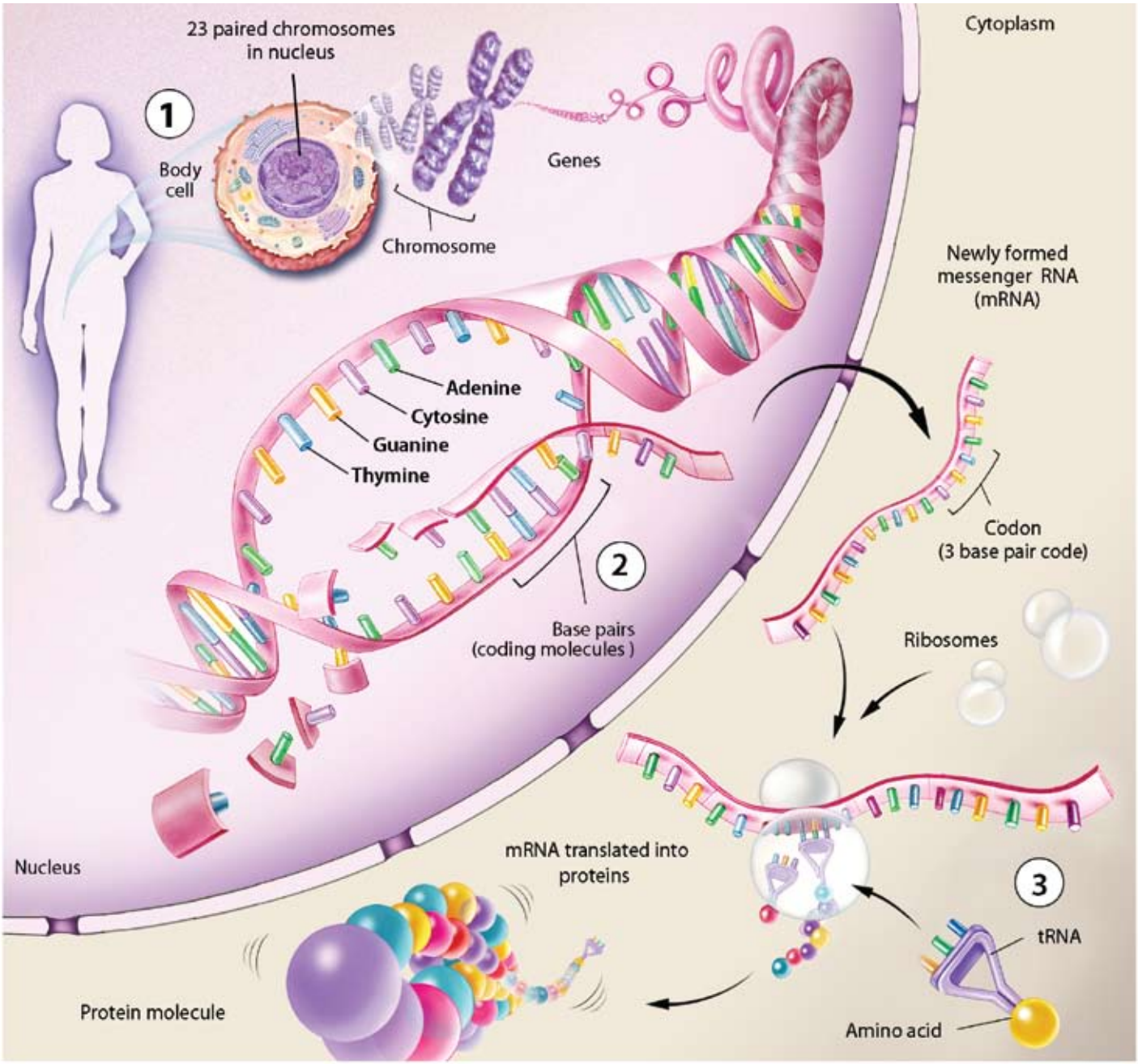
Another technique, *single photon emission computed tomography* (SPECT), is similar to PET, but its pictures are not as detailed. SPECT is much less expensive than PET because the tracers it uses have a longer half-life and do not require a nearby particle accelerator, typical of those used in nuclear physics, to produce them.

Magnetic resonance imaging (MRI) Providing a high-quality, three-dimensional image of organs and structures inside the body without X-rays or other radiation (noninvasive), MRIs are unsurpassed in anatomical detail and may reveal minute changes that occur over time.

MRIs tell scientists when structural abnormalities first appear in the course of a disease, how they affect subsequent development, and precisely how their progression correlates with mental and emotional aspects of a disorder.

During the 15-minute MRI procedure, a patient lies inside a massive, hollow, cylindrical magnet and is exposed to a powerful, steady magnetic field. Different atoms in the brain resonate to different frequencies of magnetic fields. In MRI, a background magnetic field lines up all the atoms in the brain. A second magnetic field, oriented differently from the background field, is turned on and off many times a second; at certain pulse rates, particular atoms resonate and line up with this second field. When the second field is turned off, the atoms that were lined up with it swing back to align with the background field. As they swing back, they create a signal that can be picked up and converted into an image. Tissue that contains a lot of water and fat produces a bright image; tissue that contains little or no water, such as bone, appears black.

A different MRI procedure can also assess the path of fiber tracts in the brain, that is, the connectivity between regions. This technology, referred to as *diffusion tensor imaging*, or DTI, takes advantage of diffusion rates of water, which tend to be higher along fiber tracts, to produce high-resolution images of how areas may connect in the brain.



CHROMOSOMES, GENES, AND PROTEINS. Every trait and chemical process in the body is controlled by a gene or group of genes on 23 paired chromosomes in the nucleus of every cell (1). Each gene is a discrete segment along the two tightly coiled strands of DNA that make up these chromosomes. DNA strands bear four different types of coding molecules — adenine (A), cytosine (C), guanine (G), and thymine (T) — the sequence of which contains the instructions for making all the proteins necessary for life (2). During protein production, a gene uses a molecule called mRNA to send a message with instructions for the amino acids needed to manufacture a protein (3).

MRI images can be constructed in any plane, and the technique is particularly valuable in studying the brain and spinal cord. It reveals the precise extent of tumors rapidly and vividly, and it provides early evidence of potential damage from stroke, allowing physicians to administer proper treatments early.

Magnetic resonance spectroscopy (MRS) MRS, a technique related to MRI, uses the same machinery but measures the concentration of specific chemicals — such as neurotransmitters — in different parts of the brain instead of blood flow. MRS also holds great promise: By measuring the molecular and metabolic changes that occur in the brain, this technique has already provided new information on brain development and aging, Alzheimer's disease, schizophrenia, autism, and stroke. Because it is noninvasive, MRS is ideal for studying the natural course of a disease or its response to treatment.

Functional magnetic resonance imaging (fMRI) Among the most popular neuroimaging techniques today is fMRI. This technique compares brain activity under resting and active conditions. It combines the high-spatial-resolution, noninvasive imaging of brain anatomy offered by standard MRI with a strategy for detecting increases in blood oxygen levels when brain activity brings fresh blood to a particular area of the brain, which is a correlate for neuronal activity. This technique allows for more detailed maps of brain areas underlying human mental activities in health and disease. To date, fMRI has been applied to the study of various functions of the brain, ranging from primary sensory responses to cognitive activities. Given fMRI's temporal and spatial resolution, and its noninvasive nature, this technique is often preferred for studies investigating dynamic cognitive and behavioral changes.

Magnetoencephalography (MEG) MEG is a recently developed technique that reveals the source of weak magnetic fields emitted by neurons. An array of cylinder-shaped sensors monitors the magnetic field pattern near the patient's head to determine the position and strength of activity in various regions of the brain. In contrast with other imaging techniques, MEG can characterize rapidly changing patterns of neural activity — down to millisecond resolution — and can provide a quantitative measure of the strength of this activity in individual subjects. Moreover, by presenting stimuli at various rates, scientists can determine how long neural activation is sustained in the diverse brain areas that respond.

One of the most exciting developments in imaging is the combined use of information from fMRI and MEG. The former provides detailed information about the areas of brain activity in a particular task, whereas MEG tells researchers and physicians when certain areas become active. Together, this information leads to a much more precise understanding of how the brain works in health and disease.

Optical imaging techniques Optical imaging relies on shining weak lasers through the skull to visualize brain activity. These techniques are inexpensive and relatively portable. They are also silent and safe: Because only extremely weak lasers are used, these methods can be used to study even infants. In a technique called *near infrared spectroscopy* (NIRS), technicians shine lasers through the skull at near infrared frequencies, which renders the skull transparent. Blood with oxygen in it absorbs different frequencies of light from blood in which the oxygen has been consumed. By observing how much light is reflected back from the brain at each frequency, researchers can track blood flow. *Diffuse optical tomography* is then used to create maps of brain activity. A similar technique, the *event-related optical signal*, records how light scatters in response to rapid cellular changes that arise when neurons fire and potentially can assess neural activity lasting milliseconds. *Transcranial magnetic stimulation* (TMS) works by inducing electrical impulses in the brain by modulating magnetic fields — an electromagnetic coil that emits powerful magnetic pulses is held against the scalp. Repetitive TMS is being used to investigate the role of specific brain regions during behavior and can be combined with other neuroimaging techniques; for example, with fMRI, to establish a functional correlation between a region and a behavior.

One of the most exciting developments in imaging is the combined use of information from fMRI and MEG. Together, this information leads to a much more precise understanding of how the brain works in health and disease.

Gene diagnosis

The inherited blueprint for all human characteristics, genes consist of short sections of *deoxyribonucleic acid* (DNA) sequence scattered throughout the long, spiraling, double-helix structure found on the 23 pairs of *chromosomes* in the nucleus of every human cell.

New hereditary linkage studies have made it possible to find the chromosomal location of genes responsible for neurologic and psychiatric diseases and to identify structural changes in these genes that are responsible for causing disease. This information is useful for identifying individuals who carry faulty genes and thereby improving diagnosis, for understanding the precise cause of diseases in order to improve methods of prevention and treatment, and for evaluating the malignancy of certain tumors and people's susceptibility to them.

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So far, scientists have found the chromosomal location of defective genes for more than 100 neurological disorders and have identified the defect in up to 50. Prenatal or carrier tests exist for many of the most prevalent of these illnesses.

For example, scientists have tracked down the gene that goes awry in Huntington's patients. The defect is an expansion of a CAG repeat. CAG is the genetic code for the amino acid glutamine, and the expanded repeat results in a long string of glutamines within the protein. This expansion appears to alter the protein's function. Scientists have found that the size of the expanded repeat in an individual is predictive of susceptibility to and severity of Huntington's disease. Several other neurodegenerative disorders have been attributed to expanded CAG repeats in other genes. The mechanisms by which these expansions cause adult-onset neurodegeneration are the focus of intense research.

Sometimes patients with single-gene disorders are found to have a chromosomal abnormality — a deletion or break in the DNA sequence of the gene — that can lead scientists to a more accurate position of the disease gene. This is the case with some abnormalities found on the X chromosome in patients with Duchenne muscular dystrophy and on chromosome 13 in patients with inherited retinoblastoma, a rare, highly malignant childhood eye tumor that can lead to blindness and death.

Gene mapping has led to the localization on chromosome 21 of the gene coding for the beta amyloid precursor protein that is abnormally cut to form the smaller peptide, beta amyloid. It is this peptide that accumulates in the senile plaques that clog the brains of patients with Alzheimer's disease. This discovery shed light on why individuals with Down syndrome with three copies of chromosome 21 (trisomy 21) invariably accumulate amyloid deposits; they make too much amyloid because they have an extra copy of this gene. Mutations in this gene have been shown to underlie Alzheimer's in another subset of these patients.

Gene mapping has enabled doctors to diagnose *fragile X mental retardation*, the most common cause of inherited mental retardation in males. Some scientists have now identified this gene, FMR1, which is found on the X chromosome and is important for neuronal communication. Other groups of scientists are investigating whether genetic components to schizophrenia, bipolar disorder, and alcoholism exist, but their findings are not yet conclusive.

Overall, the characterizations of the structure and function of individual genes causing diseases of the brain and nervous system are in the early stages. Factors that determine variations in the genetic expression of a single-gene abnormality — such as what contributes to the early or late start or severity of a disorder or prevents its occurrence in a mutant gene carrier — are still largely unknown.

Scientists also are studying the genes in *mitochondria*, structures found outside the cell nucleus that have their own DNA and are responsible for the production of energy used by the cell. Recently, mutations in mitochondrial genes were found to cause several rare neurological disorders. Some scientists speculate that an inheritable variation in mitochondrial DNA may play a role in diseases such as Alzheimer's, Parkinson's, and some childhood diseases of the nervous system.

Potential Therapies

NEW DRUGS. Most medicines used today were developed using trial-and-error techniques, which often do not reveal why a drug produces a particular effect. But the expanding knowledge gained from the new methods of molecular biology — the ability to determine the structure of receptors or other proteins — makes it possible to design safer and more effective drugs.

In a test tube, the potency of an agent can be determined by how well it attaches to a receptor or other protein target. A scientist then can vary the drug's structure to enhance its action on the desired target. Thus, subsequent generations of drugs can be designed to interact more selectively with the target or, in many cases, specific subtypes of the target, producing better therapeutic effects and fewer side effects.

While this *rational drug design* holds promise for developing drugs for conditions ranging from stroke and migraine headaches to depression and anxiety, it will take considerable effort to clarify the role of the different potential drug targets in these disorders.

Other promising candidates for drug therapies include trophic factors, antibodies engineered to modify the interactions and toxicity of misfolded proteins, small molecules that take advantage of specific biochemical pathways, interfering RNAs (RNAi) that reduce toxic levels of individual proteins, and stem cells that could replace dead or dying neurons.

Trophic factors

One result of basic neuroscience research is the discovery of numerous growth factors or *trophic factors*, which control the development and survival of specific groups of neurons. Once the specific actions of these molecules and their receptors are identified and their genes cloned, procedures can be developed to modify trophic factor-regulated functions in ways that might be useful in the treatment of neurological disorders.

Once a trophic factor for a particular cell is found, copies of the factor might be genetically targeted to the area of the brain where this type of cell has died. The treatment may not cure a disease but could improve symptoms or delay the disease's progression.

Already, researchers have demonstrated the possible value of at least one of these factors, *nerve growth factor* (NGF). Infused into the brains of rats, NGF prevented cell death and stimulated the regeneration and sprouting of damaged neurons that are known to die in Alzheimer's disease. When aged animals with learning and memory impairments were treated with NGF, scientists found that these animals were able to remember a maze task as well as healthy aged rats. NGF, which slows the destruction of neurons that use acetylcholine, also holds promise for slowing the memory deficits associated with normal aging.

Recently, several new factors have been identified. They are potentially useful for therapy, but scientists must first understand how they may influence neurons. Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) may be treated in the future with trophic factors or their genes.

In an interesting twist on growth factor therapy, researchers demonstrated that neutralization of inhibitory molecules can help repair damaged nerve fiber tracts in the spinal cord. Using antibodies to Nogo-A, a protein that inhibits nerve regeneration, Swiss researchers succeeded in getting some nerves of damaged spinal cords to regrow in rats and monkeys. Treated animals of both species showed large improvements in their ability to walk and use their forepaw digits after spinal cord damage.

This research has been translated to a clinical setting where recently injured spinal cord injury patients are being treated with anti-Nogo-A antibodies in a clinical trial.

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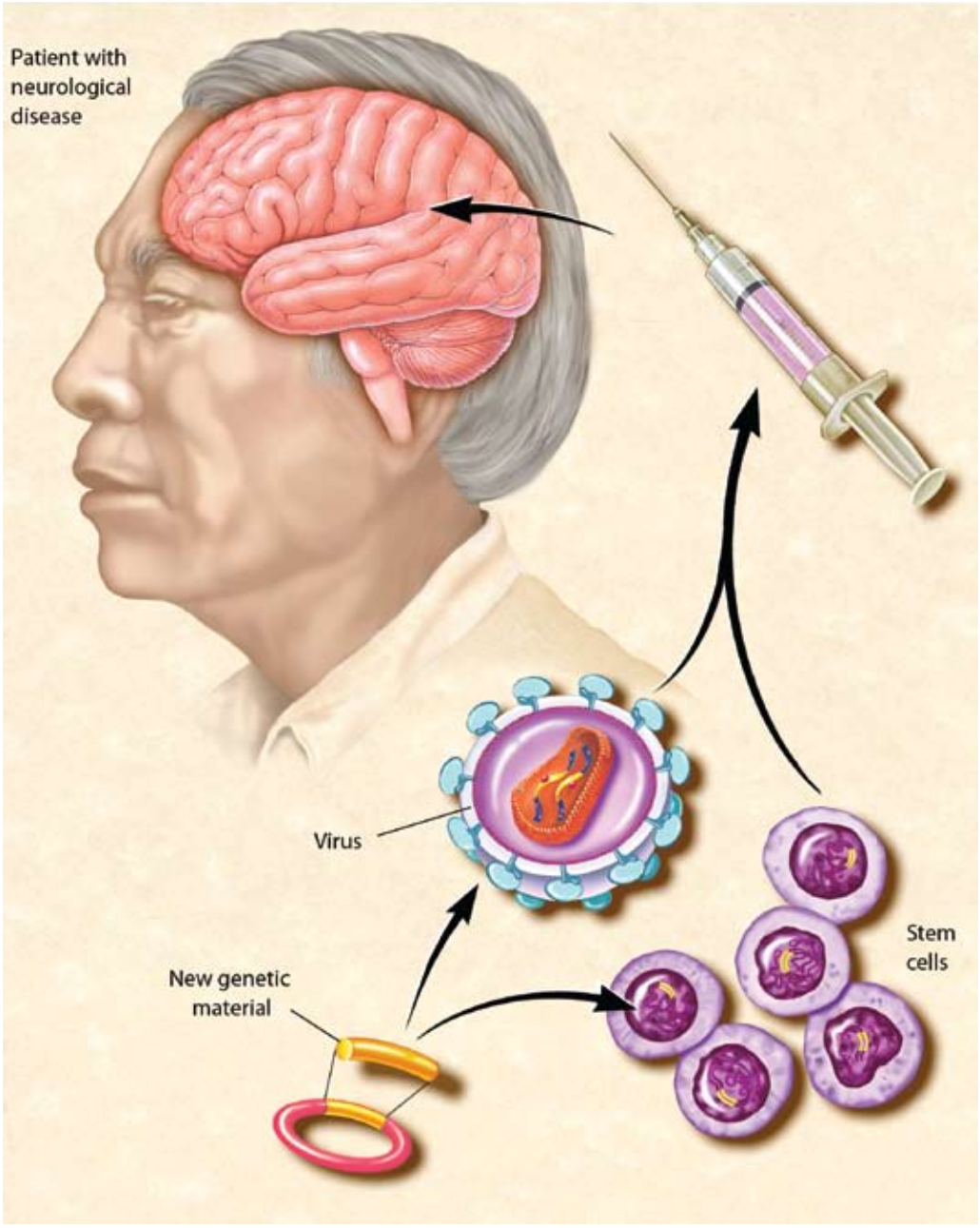
Engineered antibodies

The immune system has evolved to very specifically identify and modify factors both inside and outside of cells. It is sometimes possible to trick the body into attacking proteins that cause neurological diseases by "vaccinating" patients against these proteins.

CELL AND GENE THERAPY.
In potential therapy techniques, scientists plan to insert genetic material for a beneficial neurotransmitter or trophic factor into stem cells or a virus. The cells or virus are then put into a syringe and injected into the patient where they will produce the beneficial molecule and, it is hoped, improve symptoms.



This approach has shown some promise in Alzheimer's disease, although it also carries risks, such as increased inflammation when the brain reacts to the antibodies against its proteins. Another new approach combines genetic engineering with immunology to engineer antibodies or fragments of antibodies that can bind to and alter the disease characteristics of specific proteins. These therapies could be delivered either as proteins or as genes.

Promising preliminary results have been obtained for Huntington's (HD), Parkinson's (PD), and Alzheimer's (AD) diseases and neurodegenerative disorders such as variant Creutzfeld-Jakob disease (vCJD), known as prion diseases. vCJD has been linked to bovine spongiform encephalopathy, or "mad cow" disease. For example, fruit flies (*Drosophila*) that get HD because they have been modified to carry the mutant human gene are generally too weak and uncoordinated to break out of their pupal case the way normal insects do. However, when they also express the gene for an anti-HD antibody, all of them emerge as young adults. Furthermore, these treated flies live longer than the untreated ones that do manage to emerge, and the treated ones show less pathology in their brains.

Small molecules and RNAs

Clarifying the processes that underlie brain damage will open up the potential to use small-molecule drugs to alter these processes. Some success has occurred in developing animal models using approaches based on known mechanisms of drugs. Examples include drugs such as antibiotics and anti-tumor drugs, which appear to reduce the neuronal damage in ALS, HD, and PD. Thousands of small molecule drug candidates can be tested using high-throughput screening to alter a cellular property that represents an important part of a disease process. Because many neurodegenerative diseases involve proteins that misfold and clump abnormally, lasers are used to measure whether proteins are clumped inside cells that have been robotically distributed into tiny wells, along with the small molecules to be tested. A machine then scans the wells and reports whether particular drugs have changed the protein clumping, so that these drugs can be tested further. New leads for drugs to treat AD and prion diseases have recently been described using these methods.

Thousands of small molecule drug candidates can be tested using high-throughput screening to alter a cellular property that represents an important part of a disease process.

Several neurodegenerative diseases are caused by the accumulation of abnormal proteins. If the cells made much less of such proteins to begin with, then presumably the disease would progress much more slowly. A new class of potential drugs is based on removing the RNAs that code for the proteins that are causing damage. Mouse models of HD and ALS appear to have responded positively to such treatments, which are delivered via gene therapies.

Cell and gene therapy

Researchers throughout the world are pursuing a variety of new ways to repair or replace neurons and other cells in the brain. For the most part, these experimental approaches are still being worked out in animals and cannot be considered therapies for humans at this time.

Scientists have identified *embryonic neuronal stem cells* — unspecialized cells that give rise to cells with specific functions — in the brain and spinal cord of embryonic and adult mice. Stem cells can continuously produce all three major cell types of the brain: neurons; *astrocytes*, the cells that nourish and protect neurons; and oligodendrocytes, the cells that surround axons and allow them to conduct their signals efficiently. The production abilities of stem cells may someday be useful for replacing brain cells lost to disease. A more limited type of stem cell also has been discovered in the adult nervous system in various kinds of tissue, raising the possibility that these adult stem cells might be pharmacologically directed to replace damaged neurons.

In other work, researchers are studying a variety of viruses that may ultimately be used as "Trojan horses," carrying therapeutic genes to the brain to correct nervous system diseases. Adeno-associated virus (AAV) and human or equine lentivirus seem to be the safest and most efficient at this time. AAV and equine lentivirus are being used in clinical trials in patients with PD. Herpes simplex virus and adenovirus vectors also have been evaluated in early-stage human trials for treating brain tumors.

NEUROETHICS

BREAKING A CONFIDENCE. Going along to get along. Telling a "white lie" to protect a friend. Everyone faces ethical dilemmas — in school, at home, and nearly everywhere in everyday life. This is no different for neuroscientists. With the tremendous advances in the field, scientists and nonscientists alike have sensed a critical turning point. Advancing knowledge about how the brain enables normal behavior; how injury, drugs, or disease affect it; and how diagnoses and treatments could change brain function raises serious and novel ethical questions.

For example, some recent brain imaging studies have sought to define areas responsible for phenomena such as deception. The post-9/11 era has created much interest in lie detection for security purposes in screening immigrants. How should privacy be balanced with national security? Is the technology accurate enough to provide useful data upon which to base decisions? Pursuing these lines of scientific inquiry in a responsible way requires neuroscientists to examine how what they do affects the world beyond the laboratory or clinic.

This self-examination makes up a field known as *neuroethics*. Scientists and ethicists are beginning to reflect on the implications of neuroscience in areas of behavioral research such as moral reasoning and decision-making, as well as the implications of new neuroscience technologies such as brain scanning, brain stimulation, and pharmaceuticals to manipulate cognition. While many questions and methods within neuroethics are similar to those in biomedical ethics, neuroethics deals with brain-specific issues that touch no other area of science — our sense of self, our personalities, and our behavior. What's more, brain science is developing interventions that can change the way our brains function. Neuroethics links the descriptive science — what *can* we do — with the question of what *should* we do, which is guided by individual and shared value systems.

Neuroethics is the subject of a growing body of literature and an increasing number of meetings and conferences that have attracted a wide range of thinkers, students, basic and clinical neuroscientists, economists, philosophers, journalists, sociologists, lawyers, judges, and others. Some major topics include the subjects listed below.

Personal responsibility and punishment

Neuroscience is teaching us about the neural substrates of human characteristics, such as anger, impulse control, and conscience. It is also giving us insight into the brain mechanisms of conditions such as addiction and other disorders that impair the control of behavior. These discoveries will place traditional questions of personal responsibility in a new light. Our understanding of the brain as the control center for all decisions and actions comes into direct contact with concepts of free will as the basis for personal responsibility. If the brain is the source of all action, when the brain is damaged, do we hold the person less responsible for his or her action? Does antisocial behavior itself provide evidence for a maladapted or miswired brain, or do we need physical evidence of trauma or disease? Neuroscience is interested in these questions about criminal behavior but also in the questions of how "normal" members of society create and enforce the laws that criminals violate. Some commentators think that increasing neuroscience knowledge may seriously challenge fundamental tenets of criminal law, while others foresee incremental changes that may lead to more just, accurate, and fair judgments. Neuroethics can help society think about how knowledge of the brain basis of behavior may affect our ideas of the way society *should* be.

Diagnosis, treatment, and enhancement

Neuroscience already has given rise to drugs and devices, developed for the treatment of illness, that permit healthy people to improve their cognitive performance or alter their emotional states. In the future, drugs may be developed that enhance memory or alter social behaviors. It is critical that scientists engage policy-makers and society at large in discussions about the extension of treatments from the realm of illness to the realm of enhancement. Neuroethical issues in medicine arise where gaps exist between diagnosis and treatment, where treatments may offer tradeoffs in personality or cognitive changes, and where drugs or devices that can help unwell patients also can boost performance of normal people. When diagnostic tests exist for brain-based diseases that have no cure, such as Alzheimer's, how should this capability be used? Should emergency rooms administer memory-altering drugs to patients who have suffered a trauma and may be at risk for post-traumatic stress disorder? If drugs that are effective for treating attention deficit hyperactivity disorder also improve work or classroom performance of normal people, do we need to regulate access, and do we consider such use to be cheating?

Social behavior

The neurobiological basis of social interaction is now an exciting topic of research. While a major goal of such research is the treatment of disabling conditions such as autism spectrum disorders,

the knowledge gleaned may also permit us to delve into other kinds of social behavior. Already it is possible to use brain imaging to observe emotional responses to pictures of minority groups within a society. What are we to make of such information? Will it help us understand prejudice, or could it be used to influence decisions about individuals? It is critical that scientists explain the limitations of current technologies and help formulate policies to minimize the chances of misuse.

Prediction

Neuroimaging and genetic screening may enable us to predict behavior, personality, and disease with greater accuracy than ever before. Neuroimaging technology is also being researched and marketed for lie detection, with consumer targets including national security, employment screening, the legal system, and personal relationships. As individuals and members of groups, people have long been interested in predicting someone else's behavior or detecting whether or not they are truthful. Our approximately 20,000 genes are very distant from our behavior, however, and appear to act in extremely complex combinations in contributing to neural function. Neuroscience technologies that enable more accurate assessment also raise important concerns about privacy and fairness that go beyond those in bioethics. Will we be able to use imaging to measure intelligence? Empathy? Risk for violence? What degree of privacy do we expect to have over our thoughts? If someone has not yet committed a crime but shows brain-based reactions to inappropriate stimuli, such as pictures of children, would we require further monitoring or even preventive detention? The neuroimaging detection of lying has the potential for a major impact on society but will require careful controls and years of research. People lie for different reasons under different circumstances, not all lies cause harm, and even brain correlates of deception will never give us an objective determination of "truth." Predicting individual behavior and determining truthfulness will be major areas of research in neuroimaging and behavioral neuroscience in the coming years, and neuroethics will face many challenges as technologies evolve.

Informed consent in research

Special care must be taken when scientists seek consent to conduct research and throughout experiments, when individuals have thinking or emotional impairments that might affect their decision-making capacity. Consent is an ongoing process that should involve education of the potential research participant and, when appropriate, family members. Researchers are discussing potential needs to exercise greater scrutiny, ensure safeguards, and enhance participants' grasp of a study, including risks and benefits.

Effective and ethical science communication and commercial enterprise

Neuroethics will draw from the experience of bioethics in handling scientific communication with the media and responsible transfer of knowledge from basic science to profit-driven venture. A major concern for neuroethicists is the degree to which the media and the public fascination with neuroscience can lead to overstatements and inaccuracies in media communication. Early studies have shown that neuroscience information and pictures of brain images lend excessive credibility to scientific statements in the media, which may underscore "neurorealism" — the idea that anything neuroscientific must be definitive and true. The powerful allure of neuroscience may also entice commercialization of neurotechnologies before full understandings of the risks, benefits, and limitations of the science are in hand. Neuroethics has a critical role in protecting the integrity of neuroscience by promoting responsible and accurate scientific communication in the media, appropriate oversight of commercialized neurotechnologies including accurate advertising, and proactive communication in the popular media to promote public discussion of ethical, social, and legal issues arising from neuroscience knowledge and technology.

At this stage, the field of neuroethics raises more questions than answers. It poses challenges to scientists, ethicists, lawyers, policy-makers, and the public to work through the social implications of new discoveries. The issues are too broad-based to expect that scientists alone will supply the answers. But neuroscientists are well positioned to help shape and contribute to the debate and discussion.

One of the hallmarks of neuroscience has been the drive toward integrating information from disparate fields and specializations to increase knowledge. Sorting through the complex issues captured under the umbrella of neuroethics provides an important opportunity for informed and rich discussions among scientists and with the public. Continuing study of neuroethics will help all segments of society deal with the challenges posed by emerging technologies that investigate the brain and how it works.

Glossary

ACETYLCHOLINE A neurotransmitter active both in the brain, where it regulates memory, and in the peripheral nervous system, where it controls the actions of skeletal and smooth muscle.

ACTION POTENTIAL An electrical charge that travels along the axon to the neuron's terminal, where it triggers the release of a neurotransmitter. This occurs when a neuron is activated and temporarily reverses the electrical state of its interior membrane from negative to positive.

ADRENAL CORTEX An endocrine organ that secretes steroid hormones for metabolic functions; for example, in response to stress.

ADRENAL MEDULLA An endocrine organ that secretes epinephrine and norepinephrine in concert with the activation of the sympathetic nervous system; for example, in response to stress.

AGONIST 1.) A neurotransmitter, drug, or other molecule that stimulates receptors to produce a desired reaction. 2.) A muscle that moves a joint in an intended direction.

ALZHEIMER'S DISEASE A major cause of dementia in the elderly, this neurodegenerative disorder is characterized by the death of neurons in the hippocampus, cerebral cortex, and other brain regions.

AMINO ACID TRANSMITTERS The most prevalent neurotransmitters in the brain, these include glutamate and aspartate, which have excitatory actions on nerve cells, and glycine and gamma-amino butyric acid (GABA), which have inhibitory actions on nerve cells.

AMYGDALA A structure in the forebrain that is an important component of the limbic system and plays a central role in emotional learning, particularly within the context of fear.

ANDROGENS Sex steroid hormones, including testosterone, found in higher levels in males than females. They are responsible for male sexual maturation.

ANTAGONIST 1.) A drug or other molecule that blocks receptors. Antagonists inhibit the effects of agonists. 2.) A muscle that moves a joint in opposition to an intended direction.

APHASIA Disturbance in language comprehension or production, often as a result of a stroke.

APOPTOSIS Programmed cell death induced by specialized biochemical pathways, often serving a specific purpose in the development of the animal.

AUDITORY NERVE A bundle of nerve fibers extending from the cochlea of the ear to the brain that contains two branches: the cochlear nerve, which transmits sound information, and the vestibular nerve, which relays information related to balance.

AUTONOMIC NERVOUS SYSTEM A part of the peripheral nervous system responsible for regulating the activity of internal organs. It includes the sympathetic and parasympathetic nervous systems.

AXON The fiberlike extension of a neuron by which it sends information to target cells.

BASAL GANGLIA Structures located deep in the brain that play an important role in the initiation of movements. These clusters of neurons include the caudate nucleus, putamen, globus pallidus, and substantia nigra. Cell death in the substantia nigra contributes to Parkinson's disease.

BRAINSTEM The major route by which the forebrain sends information to and receives information from the spinal cord and peripheral nerves. The brainstem controls, among other things, respiration and the regulation of heart rhythms.

BROCA'S AREA The brain region located in the frontal lobe of the left hemisphere that is important for the production of speech.

CATECHOLAMINES The neurotransmitters dopamine, epinephrine, and norepinephrine, which are active in both the brain and the peripheral sympathetic nervous system. These three molecules have certain structural similarities and are part of a larger class of neurotransmitters known as monoamines.

CEREBELLUM A large structure located at the roof of the hindbrain that helps control the coordination of movement by making connections to the pons, medulla, spinal cord, and thalamus. It also may be involved in aspects of motor learning.

CEREBRAL CORTEX The outermost layer of the cerebral hemispheres of the brain. It is largely responsible for all forms of conscious experience, including perception, emotion, thought, and planning.

CEREBRAL HEMISPHERES The two specialized halves of the brain. For example, in right-handed people, the left hemisphere is specialized for speech, writing, language, and calculation; the right hemisphere is specialized for spatial abilities, visual face recognition, and some aspects of music perception and production.

CEREBROSPINAL FLUID A liquid found within the ventricles of the brain and the central canal of the spinal cord.

CIRCADIAN RHYTHM A cycle of behavior or physiological change lasting approximately 24 hours.

CLASSICAL CONDITIONING Learning in which a stimulus that naturally produces a specific response (unconditioned stimulus) is repeatedly paired with a neutral stimulus (conditioned stimulus). As a result, the conditioned stimulus can come to evoke a response similar to that of the unconditioned stimulus.

COCHLEA A snail-shaped, fluid-filled organ of the inner ear responsible for converting sound into electrical potentials to produce an auditory sensation.

COGNITION The process or processes by which an organism gains knowledge or becomes aware of events or objects in its environment and uses that knowledge for comprehension and problem-solving.

CONE A primary receptor cell for vision located in the retina. It is sensitive to color and is used primarily for daytime vision.

CORPUS CALLOSUM The large bundle of nerve fibers linking the left and right cerebral hemispheres.

CORTISOL A hormone manufactured by the adrenal cortex. In humans, cortisol is secreted in the greatest quantities before dawn, readying the body for the activities of the coming day.

CRANIAL NERVE A nerve that carries sensory input and motor output for the head and neck region. There are 12 cranial nerves.

DEPRESSION A mental disorder characterized by sadness, hopelessness, pessimism, loss of interest in life, reduced emotional well-being, and abnormalities in sleep, appetite, and energy level.

DENDRITE A treelike extension of the neuron cell body. The dendrite is the primary site for receiving and integrating information from other neurons.

DOPAMINE A catecholamine neurotransmitter known to have varied functions depending on where it acts. Dopamine-containing neurons in the substantia nigra of the brainstem project to the caudate nucleus and are destroyed in Parkinson's victims. Dopamine is thought to regulate key emotional responses and plays a role in schizophrenia and drug abuse.

DORSAL HORN An area of the spinal cord where many nerve fibers from peripheral sensory receptors meet other ascending and descending nerve fibers.

DRUG ADDICTION Loss of control over drug intake or compulsive seeking and taking of drugs, despite adverse consequences.

ENDOCRINE ORGAN An organ that secretes a hormone directly into the bloodstream to regulate cellular activity of certain other organs.

ENDORPHINS Neurotransmitters produced in the brain that generate cellular and behavioral effects like those of morphine.

EPILEPSY A disorder characterized by repeated seizures, which are caused by abnormal excitation of large groups of neurons in various brain regions. Epilepsy can be treated with many types of anticonvulsant medications.

EPINEPHRINE A hormone, released by the adrenal medulla and specialized sites in the brain, that acts with norepinephrine to affect the sympathetic division of the autonomic nervous system. Sometimes called adrenaline.

ESTROGENS A group of sex hormones found more abundantly in females than males. They are responsible for female sexual maturation and other functions.

EVOKED POTENTIAL A measure of the brain's electrical activity in response to sensory stimuli. This is obtained by placing electrodes on the surface of the scalp (or more rarely, inside the head), repeatedly administering a stimulus, and then using a computer to average the results.

EXCITATION A change in the electrical state of a neuron that is associated with an enhanced probability of action potentials.

FOLLICLE-STIMULATING HORMONE A hormone released by the pituitary gland that stimulates the production of sperm in the male and growth of the follicle (which produces the egg) in the female.

FOREBRAIN The largest part of the brain, which includes the cerebral cortex and basal ganglia. The forebrain is credited with the highest intellectual functions.

FOVEA The centermost part of the eye located in the center of the retina and that contains only cone photoreceptors.

FRONTAL LOBE One of the four subdivisions of the cerebral cortex. The frontal lobe has a role in controlling movement and in the planning and coordinating of behavior.

GAMMA-AMINO BUTYRIC ACID (GABA) An amino acid transmitter in the brain whose primary function is to inhibit the firing of nerve cells.

GLIA Specialized cells that nourish and support neurons.

GLUTAMATE An amino acid neurotransmitter that acts to excite neurons. Glutamate stimulates N-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA). AMPA receptors have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in developing animals. Stimulation of NMDA receptors may promote beneficial changes, whereas overstimulation may be a cause of nerve cell damage or death in neurological trauma and stroke.

GONAD Primary sex gland: testis in the male and ovary in the female.

GROWTH CONE A distinctive structure at the growing end of most axons. It is the site where new material is added to the axon.

HAIR CELLS Sensory receptors in the cochlea that convert mechanical vibration to an electrical signal; they in turn excite the 30,000 fibers of the auditory nerve that carry the signals to the brainstem.

HIPPOCAMPUS A seahorse-shaped structure located within the brain and considered an important part of the limbic system. One of the most studied areas of the brain, it functions in learning, memory, and emotion.

HOMEOSTASIS The normal equilibrium of body function.

HORMONES Chemical messengers secreted by endocrine glands to regulate the activity of target cells. They play a role in sexual development, calcium and bone metabolism, growth, and many other activities.

HUNTINGTON'S DISEASE A movement disorder caused by the death of neurons in the basal ganglia and other brain regions. It is characterized by abnormal movements called chorea — sudden, jerky movements without purpose.

HYPOTHALAMUS A complex brain structure composed of many nuclei with various functions, including regulating the activities of internal organs, monitoring information from the autonomic nervous system, controlling the pituitary gland, and regulating sleep and appetite.

INTERNEURON A neuron that exclusively signals another neuron.

INHIBITION A synaptic message that prevents a recipient neuron from firing.

IONS Electrically charged atoms or molecules.

LIMBIC SYSTEM A group of brain structures — including the amygdala, hippocampus, septum, basal ganglia, and others — that help regulate the expression of emotion and emotional memory.

LONG-TERM MEMORY The final phase of memory, in which information storage may last from hours to a lifetime.

MANIA A mental disorder characterized by excessive excitement, exalted feelings, elevated mood, psychomotor overactivity, and overproduction of ideas. It may be associated with psychosis; for example, delusions of grandeur.

MEMORY CONSOLIDATION The physical and psychological changes that take place as the brain organizes and restructures information to make it a permanent part of memory.

METABOLISM The sum of all physical and chemical changes that take place within an organism and all energy transformations that occur within living cells.

MIDBRAIN The most anterior segment of the brainstem. With the pons and medulla, the midbrain is involved in many functions, including regulation of heart rate, respiration, pain perception, and movement.

MITOCHONDRIA Small cylindrical organelles inside cells that provide energy for the cell by converting sugar and oxygen into special energy molecules, called adenosine triphosphate (ATP).

MONOAMINE OXIDASE (MAO) The brain and liver enzyme that normally breaks down the catecholamines norepinephrine, dopamine, and epinephrine, as well as other monoamines such as serotonin.

MOTOR NEURON A neuron that carries information from the central nervous system to muscle.

MYASTHENIA GRAVIS A disease in which acetylcholine receptors on muscle cells are destroyed so that muscles can no longer respond to the acetylcholine signal to contract. Symptoms include muscular weakness and progressively more common bouts of fatigue. The disease's cause is unknown but is more common in females than in males; it usually strikes between the ages of 20 and 50.

MYELIN Compact fatty material that surrounds and insulates the axons of some neurons.

NMDA RECEPTORS N-methyl-d-aspartate (NMDA) receptors, one of three major classes of glutamate receptors, which have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in a developing animal.

NECROSIS Cell death due to external factors, such as lack of oxygen or physical damage, that disrupt the normal biochemical processes in the cell.

NERVE GROWTH FACTOR A substance whose role is to guide neuronal growth during embryonic development, especially in the peripheral nervous system. Nerve growth factor also probably helps sustain neurons in the adult.

NEURON A nerve cell specialized for the transmission of information and characterized by long, fibrous projections called axons and shorter, branchlike projections called dendrites.

NEUROPLASTICITY A general term used to describe the adaptive changes in the structure or function of nerve cells or groups of nerve cells in response to injuries to the nervous system or alterations in patterns of their use and disuse.

NEUROTRANSMITTER A chemical released by neurons at a synapse for the purpose of relaying information to other neurons via receptors.

NOCICEPTORS In animals, nerve endings that signal the sensation of pain. In humans, they are called pain receptors.

NOREPINEPHRINE A catecholamine neurotransmitter, produced both in the brain and in the peripheral nervous system. Norepinephrine is involved in arousal and in regulation of sleep, mood, and blood pressure.

OCCIPITAL LOBE One of the four subdivisions of the cerebral cortex. The occipital lobe plays a role in processing visual information.

OLFACTORY BULB A round, knoblike structure of the brain responsible for processing the sense of smell. Specialized olfactory receptor cells are located in a small patch of mucous membrane lining the roof of the nose. Axons of these sensory cells pass through perforations in the overlying bone and enter two elongated olfactory bulbs lying on top of the bone.

ORGANELLES Small structures within a cell that maintain the cell and do the cell's work.

PARASYMPATHETIC NERVOUS SYSTEM A branch of the autonomic nervous system concerned with the conservation of the body's energy and resources during relaxed states.

PARIETAL LOBE One of the four subdivisions of the cerebral cortex. The parietal lobe plays a role in sensory processes, attention, and language.

PARKINSON'S DISEASE A movement disorder caused by death of dopamine neurons in the substantia nigra, located in the midbrain. Symptoms include tremor, shuffling gait, and general reduction in movement.

PEPTIDES Chains of amino acids that can function as neurotransmitters or hormones.

PERIPHERAL NERVOUS SYSTEM A division of the nervous system consisting of all nerves that are not part of the brain or spinal cord.

PHOSPHORYLATION Transfer of a phosphate molecule from adenosine triphosphate (ATP) to a protein (ion channel, neurotransmitter receptor, or other regulatory protein), resulting in activation or inactivation of the protein. Phosphorylation is believed to be a necessary step in allowing some neurotransmitters to act and is often the result of second-messenger activity.

PHOTORECEPTOR A nerve ending, cell, or group of cells specialized to sense or receive light.

PITUITARY GLAND An endocrine organ closely linked with the hypothalamus. In humans, the pituitary gland is composed of two lobes and secretes several different hormones that regulate the activity of other endocrine organs throughout the body.

PONS A part of the hindbrain that, with other brain structures, controls respiration and regulates heart rhythms. The pons is a major route by which the forebrain sends information to and receives information from the spinal cord and peripheral nervous system.

PSYCHOSIS A severe symptom of mental disorders characterized by an inability to perceive reality. Psychosis can occur in many conditions, including schizophrenia, mania, depression, and drug-induced states.

RECEPTOR CELL A specialized sensory cell, designed to pick up and transmit sensory information.

RECEPTOR MOLECULE A specific protein on the surface of or inside a cell with a characteristic chemical and physical structure. Many neurotransmitters and hormones exert their effects by binding to receptors on cells.

RETINA A multilayered sensory tissue that lines the back of the eye and contains the receptor cells to detect light.

REUPTAKE A process by which released neurotransmitters are absorbed for later reuse.

ROD A sensory neuron located in the periphery of the retina. The rod is sensitive to light of low intensity and is specialized for nighttime vision.

SCHIZOPHRENIA A chronic mental disorder characterized by psychosis (e.g., hallucinations and delusions), flattened emotions, and impaired cognitive function.

SECOND MESSENGERS Substances that trigger communications among different parts of a neuron. These chemicals play a role in the manufacture and release of neurotransmitters, intracellular movements, carbohydrate metabolism, and processes of growth and development. The messengers' direct effects on the genetic material of cells may lead to long-term alterations of behavior, such as memory and drug addiction.

SEROTONIN A monoamine neurotransmitter believed to play many roles, including but not limited to temperature regulation, sensory perception, and the onset of sleep. Neurons using serotonin as a transmitter are found in the brain and gut. Several antidepressant drugs are targeted to brain serotonin systems.

SHORT-TERM MEMORY A phase of memory in which a limited amount of information may be held for several seconds or minutes.

STEM CELL Unspecialized cells that renew themselves for long periods through cell division.

STIMULUS An environmental event capable of being detected by sensory receptors.

STROKE A block in the brain's blood supply. A stroke can be caused by the rupture of a blood vessel, a clot, or pressure on a blood vessel (as by a tumor). Without oxygen, neurons in the affected area die and the part of the body controlled by those cells cannot function. A stroke can result in loss of consciousness and death.

SYMPATHETIC NERVOUS SYSTEM A branch of the autonomic nervous system responsible for mobilizing the body's energy and resources during times of stress and arousal.

SYNAPSE A physical gap between two neurons that functions as the site of information transfer from one neuron to another.

TASTE BUD A sensory organ found on the tongue.

TEMPORAL LOBE One of the four major subdivisions of each hemisphere of the cerebral cortex. The temporal lobe functions in auditory perception, speech, and complex visual perceptions.

THALAMUS A structure consisting of two egg-shaped masses of nerve tissue, each about the size of a walnut, deep within the brain. The key relay station for sensory information flowing into the brain, the thalamus filters out information of particular importance from the mass of signals entering the brain.

VENTRICLES Comparatively large spaces filled with cerebrospinal fluid. Of the four ventricles, three are located in the forebrain and one in the brainstem. The lateral ventricles, the two largest, are symmetrically placed above the brainstem, one in each hemisphere.

WERNICKE'S AREA A brain region responsible for the comprehension of language and the production of meaningful speech.

WHITE MATTER The part of the brain that contains myelinated nerve fibers. The white matter is white because it is the color of myelin, the insulation covering the nerve fibers.