Brain Facts

A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

SOCIETY FOR NEUROSCIENCE

The Society for Neuroscience is the world's largest organization of scientists and physicians dedicated to understanding the brain, spinal cord, and peripheral nervous system.

Neuroscientists investigate the molecular and cellular levels of the nervous system; the neuronal systems responsible for sensory and motor function; and the basis of higher order processes, such as cognition and emotion. This research provides the basis for understanding the medical fields that are concerned with treating nervous system disorders. These medical specialties include neurology, neurosurgery, psychiatry, and ophthalmology.

Founded in 1969, the Society has grown from 500 charter members to more than 36,000 members. While a predominantly North American organization, SfN also has many members who live in Europe, Asia, Latin America, and Australia/Oceania. The Society has more than 100 regional chapters. With activities ranging from lectures to networking events and information sharing, SfN chapters enable individual members to engage their colleagues at the local level.

The mission of the Society is to:

- Advance the understanding of the brain and the nervous system by bringing together scientists of diverse backgrounds, by facilitating the integration of research directed at all levels of biological organization, and by encouraging translational research and the application of new scientific knowledge to develop improved disease treatments and cures.

- Provide professional development activities, information, and educational resources for neuroscientists at all stages of their careers, including undergraduates, graduates, and postdoctoral fellows, and increase participation of scientists from a diversity of cultural and ethnic backgrounds.

- Promote public information and general education about the nature of scientific discovery and the results and implications of the latest neuroscience research. Support active and continuing discussions on ethical issues relating to the conduct and outcomes of neuroscience research.

- Inform legislators and other policymakers about new scientific knowledge and recent developments in neuroscience research and their implications for public policy, societal benefit, and continued scientific progress.

The exchange of scientific information occurs at an annual fall meeting where more than 16,000 reports of new scientific findings are presented and more than 30,000 people attend. This meeting, the largest of its kind in the world, is *the* arena for the presentation of new results in neuroscience.

The Society's weekly journal, *The Journal of Neuroscience*, contains articles spanning the entire range of neuroscience research and has subscribers worldwide. The Society's ongoing education and professional development efforts reach teachers and help promote the education of Society members. Print and electronic publications inform members about Society activities.

A major goal of the Society is to inform the public about the progress and benefits of neuroscience research. The Society accomplishes this goal by providing information about neuroscience to schoolteachers and encouraging its members to speak to young people about the human brain and nervous system.

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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 all 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 a trillion 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 $400 billion. In addition, mental disorders, excluding drug and alcohol problems, strike 44 million adults a year at a cost of some $148 billion.

However, during the congressionally designated Decade of the Brain, which ended in 2000, neuroscience made significant discoveries in these areas:

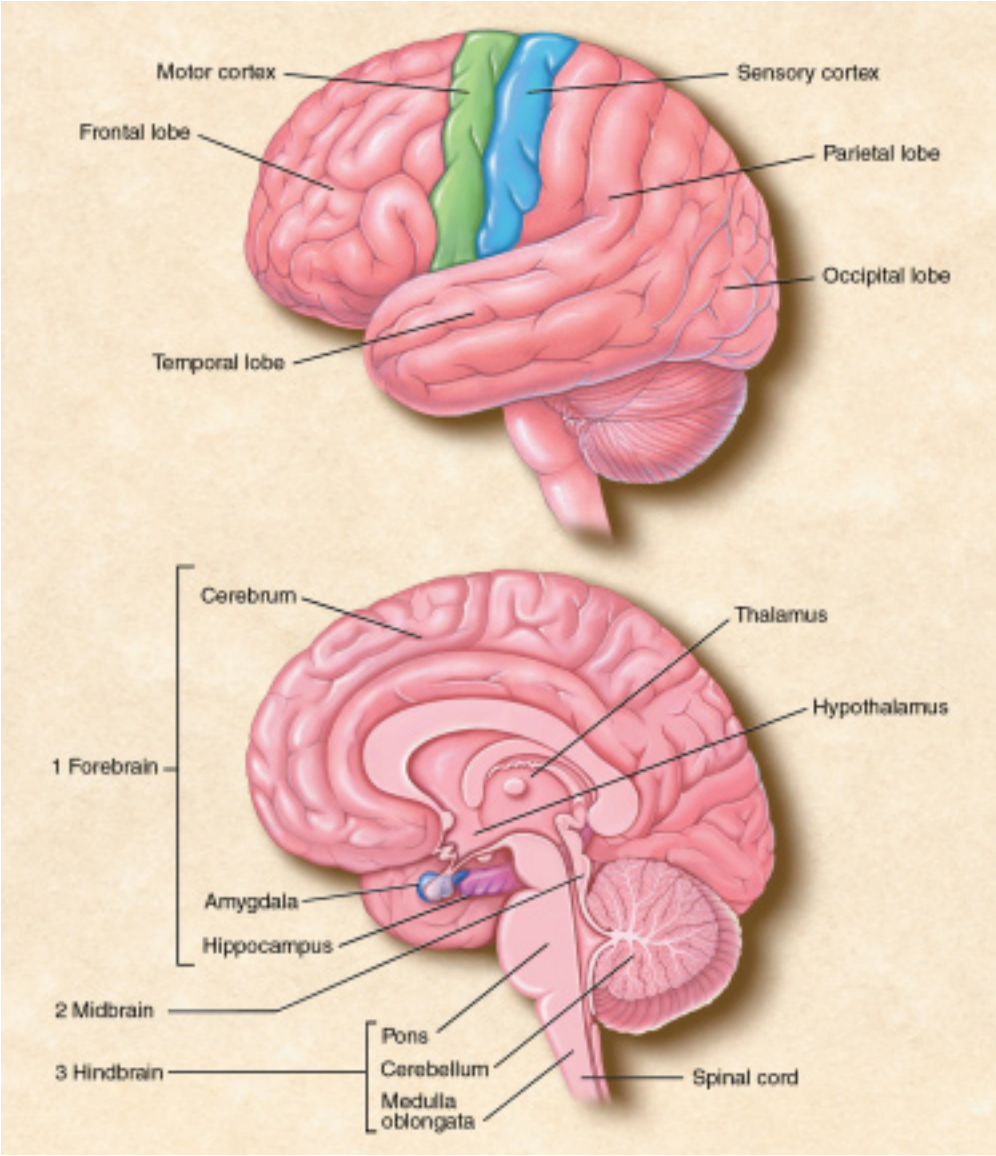
- **Genetics.** Disease genes were identified that are key to several neurodegenerative disorders—including Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis. This has provided new insights into underlying disease mechanisms and is beginning to suggest new treatments.

With the mapping of the human genome, neuroscientists will be able to make more rapid progress in identifying genes that either contribute to human neurological disease or that directly cause disease. Mapping animal genomes will aid the search for genes that regulate and control many complex behaviors.

- **Brain Plasticity.** Scientists began to uncover the molecular basis of neural 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 gained new insights into the mechanisms of molecular neuropharmacology, which provides a new understanding of the mechanisms of addiction. These advances also have led to new treatments for depression and obsessive compulsive disorder.
- **Imaging.** Revolutionary imaging techniques, including magnetic resonance imaging and positron emission tomography, now reveal brain systems underlying attention, memory, and emotions and indicate dynamic changes that occur in schizophrenia.
- **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 should vastly expand our knowledge of the brain in the years ahead.

This book only provides 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 (above). 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 (below). 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 of 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*

Condition	*Total Cases*	*Costs Per Year*
Hearing Loss	28 million	$ 56 billion
All Depressive Disorders	20.5 million	44 billion
Alzheimer's Disease	4.5 million	100 billion
Huntington's Disease	30,000	2 billion
Stroke	4.7 million	51 billion
Schizophrenia	2 million	32.5 billion
Parkinson's Disease	1 million	5.6 billion
Traumatic Head Injury	5 million	56.3 billion
Multiple Sclerosis	2.5 million	9.5 billion
Spinal Cord Injury	250,000	10 billion

** Estimates provided by the 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. It contains between one billion and one trillion neurons, depending on the species.

The neuron consists of a *cell body* containing the nucleus, cytoplasm, and an electrically excitable output fiber, the *axon*. Most axons also give rise to many smaller branches before ending at *nerve terminals*. *Synapses*, from the Greek word meaning "to clasp together," are the contact points where one neuron communicates with another. Other structures, *dendrites*, Greek for "tree branches," extend from the neuron cell body and receive messages from other neurons. The dendrites and cell body are covered with synapses formed by the ends of axons of 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 or more feet. Many axons are covered with a layered insulating *myelin* sheath, made of specialized cells called oligodendrocytes in the brain and Schwann cells in the peripheral nervous system, which speeds the transmission of electrical signals along the axon.

Nerve impulses involve the opening and closing of *ion channels*, 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 membrane.

The ability of a neuron to fire — that is, to become sufficiently activated by incoming synapses to discharge and communicate to its own synaptic target neurons — depends on a small difference in electrical charge between the inside and outside of the cell. When a nerve impulse begins, a dramatic reversal occurs at one point on the cell's membrane. 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 scores of 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 ending terminals, diffuse across the intrasynaptic space, and bind to receptors on the surface of the target neuron.

These receptors act as on and off switches for the next cell. Each receptor has a distinctly shaped part that selectively recognizes a particular chemical messenger. A neurotransmitter fits into this region in much the same way as a key fits into a lock. And when the transmitter is in place, this alters the neuron's outer membrane potential (or excitability) and triggers a change, such as the contraction of a muscle or increased activity of an enzyme in the cell.

Knowledge of neurotransmitters in the brain and the action of drugs on these chemicals — gained largely through the study of animals — is 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 the biological basis of mental illness is.

Neurotransmitters

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 terminal, the electrically charged calcium ion rushes in, and ACh is released into the synapse and attaches to ACh receptors. In voluntary muscles, this opens sodium channels and causes the muscle to contract. ACh is then broken down and resynthesized in the nerve terminal. Antibodies that block the receptor for ACh cause *myasthenia gravis*, a disease characterized by fatigue and muscle weakness.

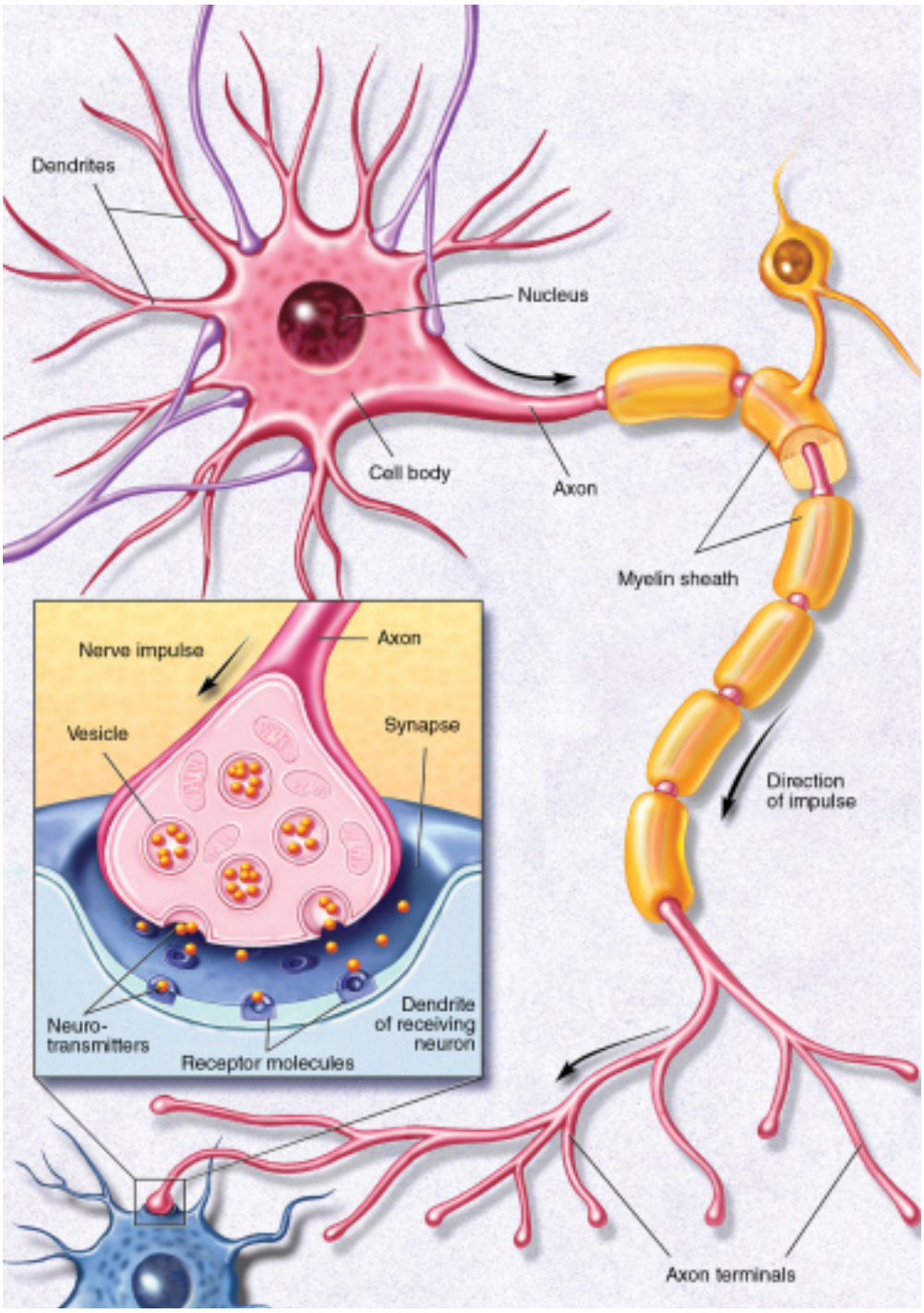
Much less is known about ACh in the brain. Recent discoveries suggest, however, that it may be critical for normal attention, memory, and sleep. Since ACh-releasing neurons die in Alzheimer's patients, finding ways to restore this neurotransmitter is one goal of current research.

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 *glutamate* and *aspartate* act as excitatory signals. *Glycine* and *gamma-aminobutyric acid* (GABA) inhibit the firing of neurons. The activity of GABA is increased by *benzodiazepine* (Valium) and by anticonvulsant drugs. In Huntington's disease, a hereditary disorder that begins during midlife, the GABA-producing neurons in the brain centers coordinating movement degenerate, thereby causing uncontrollable movements.

Glutamate or aspartate activates *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. 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 this receptor's precise structure, regulation, location, and function. For example, developing drugs to block or stimulate activity at NMDA receptors holds promise



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 that are present on the surfaces of adjacent neurons. The point of virtual contact is known as the synapse.

for improving brain function and treating neurological disorders. But this work is still in the early stage.

Catecholamines *Dopamine* and *norepinephrine* are widely present in the brain and peripheral nervous system. Dopamine, which is present in three circuits in the brain, controls movement, causes psychiatric symptoms such as psychosis, and regulates hormonal responses.

The dopamine circuit that regulates movement has been directly linked to disease. The brains of people with *Parkinson's disease* — with symptoms of muscle tremors, rigidity, and difficulty in moving — have practically no dopamine. Thus, medical scientists 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 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 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. It 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.

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.

Serotonin This neurotransmitter is present in many tissues, particularly blood platelets, the lining of the digestive tract, and the brain. Serotonin was first thought to be involved in high blood pressure because it is present in blood and induces a very powerful contraction of smooth muscles. 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* (Prozac), have relieved symptoms of depression and obsessive-compulsive disorder.

Peptides These are chains of amino acids linked together. Brain peptides called *endorphins* act like opium to kill pain or cause sleepiness. (Peptides differ from proteins, which are much larger and 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, the endorphins — another type of opioid peptide, whose name comes from endogenous morphine — were discovered.

The precise role of the opioid peptides in the body is unclear. A plausible guess 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.

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, released locally in the brain, and bind to receptors expressed by specific neurons. Researchers have also 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 After the nervous system, the *endocrine system* is the second great communication system of the body. The pancreas, kidneys, heart, adrenal glands, gonads, thyroid, 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 endorphins are released from the pituitary gland into the bloodstream, they might also function as endocrine hormones. Hormones activate specific receptors in target organs that release other hormones into the blood, which then act on other tissues, the pituitary itself, and the brain. 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 such as growth, 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 both the thyroid hormone and the six classes of steroid hormones — *estrogens, androgens,*

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 the DNA genetic material and regulate the action of genes. This can result in long-lasting changes in cellular structure and function.

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 can also alter brain function, including learning. Severe and prolonged stress can cause permanent brain damage.

Reproduction is a good example of a regular, cyclic process driven by circulating hormones: The hypothalamus produces *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 into the bloodstream. In females, FSH and LH act on the ovaries and cause the release of the female hormones estrogen and progesterone. 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 also induce changes in cell structure and chemistry that lead to an increased capacity to engage in sexual behavior.

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. Some functions can be attributed to these sex differences, but much more must be learned in terms of perception, memory, and cognitive ability. Although differences exist, the brains of men and women are more similar than they are different.

Recently, several teams of researchers have found anatomical differences 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.

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.

Gases Very recently, scientists identified a new class of neurotransmitters that are gases. These molecules — *nitric oxide* and *carbon monoxide* — do not obey the "laws" governing neurotransmitter behavior. Being gases, they cannot be stored in any structure, certainly not in synaptic storage structures. Instead, they are made by enzymes as they are needed. They are released from neurons by diffusion. And rather than acting at receptor sites, they simply diffuse into adjacent neurons and act upon chemical targets, which may be enzymes.

Though only recently characterized, nitric oxide has already been shown to play important roles. For example, nitric oxide neurotransmission governs erection in neurons of 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. Exact functions for carbon monoxide have not yet been shown.

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 cell. For example, when norepinephrine binds to its receptors on the surface of the neuron, the activated receptor binds G proteins 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 on 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. cAMP is called a second messenger because it acts after the first messenger, the transmitter chemical, has crossed the synaptic space and attached itself to a receptor.

Second messengers also are thought to play a role in the manufacture and release of neurotransmitters, intracellular movements, carbohydrate metabolism in the *cerebrum* — the largest part of the brain, consisting of two hemispheres — and the processes of growth and development. Direct effects of these substances on the genetic material of cells may lead to long-term alterations of behavior.

Brain development

Three to four weeks after conception, one of the two cell layers of the gelatinlike human embryo, now about one-tenth of an inch long, starts to thicken and build up along the middle. As 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 then the hemispheres of the brain appear later.

How does all this happen? Although many of the mechanisms of human brain development remain secrets, neuroscientists are beginning to uncover some of these complex steps through studies of the roundworm, fruit fly, frog, zebrafish, mouse, rat, chicken, cat, and monkey.

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

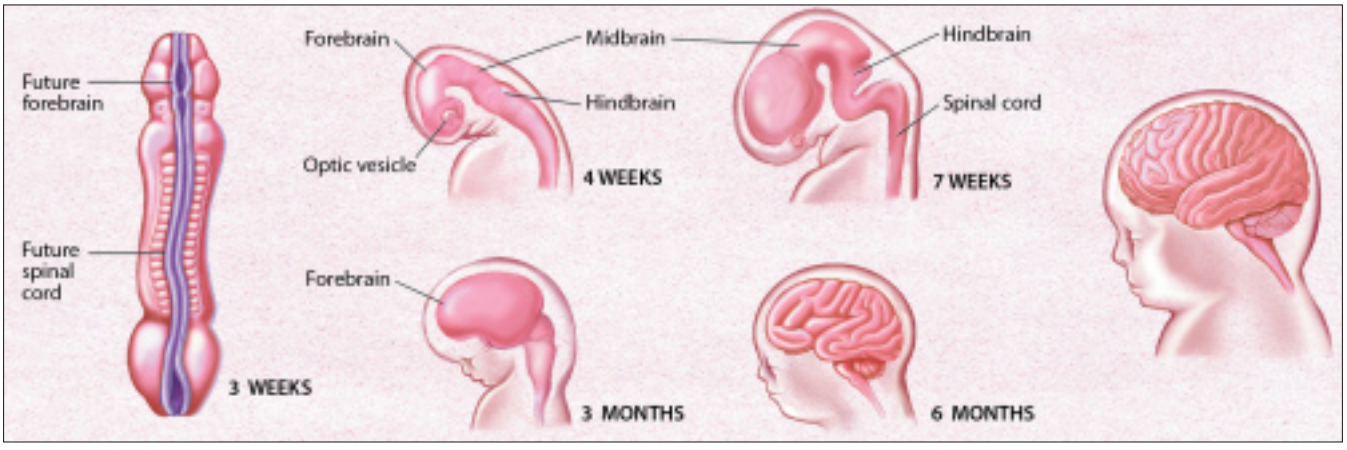
Neurons are initially produced along the central canal in the neural tube. These neurons then migrate from their birthplace to a final destination in the brain. They collect together to form each of the various brain structures and acquire specific ways of transmitting nerve messages. Their axons grow 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.

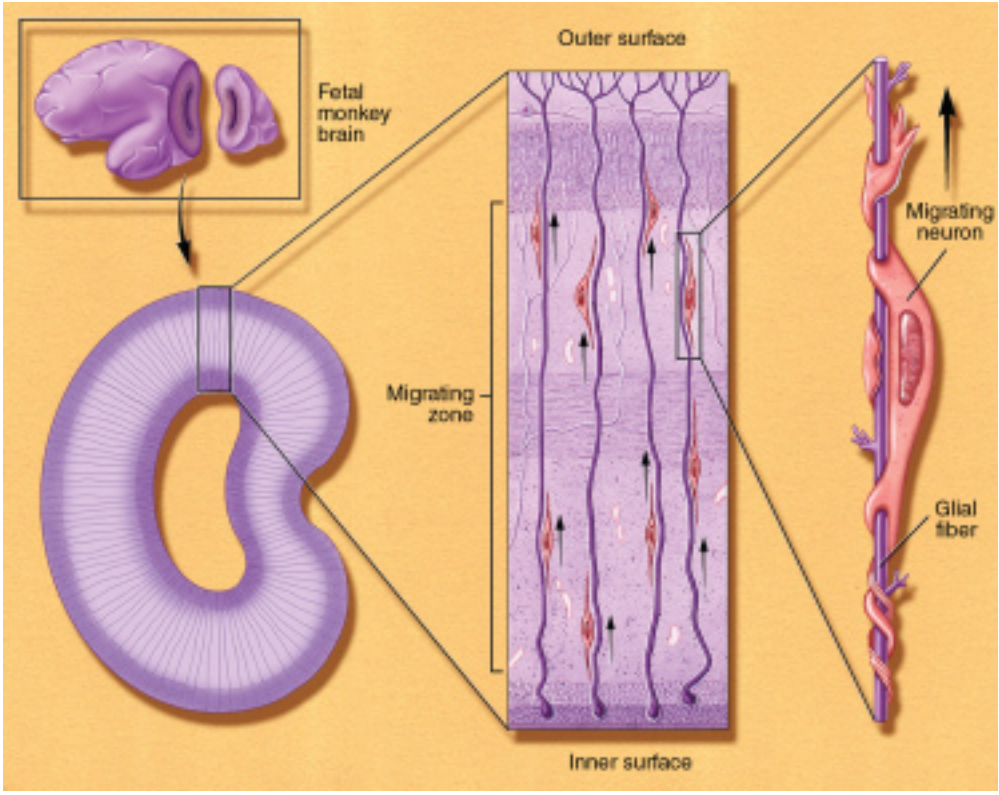
Knowing how the brain is put together is essential for understanding its ability to reorganize in response to external influences or injury. Such studies also shed light on brain functions such as learning and memory. Brain diseases such as schizophrenia and mental retardation are thought to result from a failure to construct proper connections during development. Neuroscientists are beginning to discover some general principles to understand the processes of development, many of which overlap in time.

Birth of neurons and brain wiring

The embryo has three layers that undergo many interactions in order to grow into organ, bone, muscle, skin, or neural tissue.

BRAIN DEVELOPMENT. The human brain and nervous system begin to develop at about three weeks' gestation with the closing of the neural tube (left). 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.

Skin and neural tissue arise from one layer, the *ectoderm*, in response to signals provided by the next 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 molecules that inhibit the activity of various proteins. If nothing interrupts the activity of such proteins, the tissue becomes skin. If other molecules, which are secreted from the mesoderm, block protein signaling, then the tissue becomes neural.

Once the ectodermal tissue has acquired its neural fate, more signaling interactions determine the type of neural cell to which it gives rise. 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 factors, including position, 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 young neural cells that are directly adjacent 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 that 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, such as motor neurons, the type of neurotransmitter is fixed, but for others it is a matter of choice. Scientists found that when certain neurons are maintained in a dish with no other cell type, they produce the neurotransmitter norepinephrine. In contrast, if the same neurons are maintained with other cells, such as cardiac or heart tissue cells, they produce the neurotransmitter acetylcholine. Since all neurons have genes containing the information for the production of 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.

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 sur-

face, along nonneuronal 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 such mechanism for long-distance migration is the movement of neurons along elongated fibers that form transient scaffolding in the fetal 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 recently 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, such as vision or hearing, to occur. They do this through their axons. These wirelike 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 opposite sides 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 destinations. 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 molecules include proteins with names such as cadherin, netrin, semaphorin, ephrin, neuropilin, and plexin. In most cases, these are families of related molecules; for example, there are 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 family is smaller in flies or worms than in mice or people, but their functions are quite similar. It has therefore been possible to use the simpler animals to gain knowledge that can be directly applied 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. Worm receptors for netrins were then found and proved invaluable in finding the corresponding, and again 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. Few of these molecules have been identified. There has been more success, however, in identifying the ways in which the synapse forms 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 opposed to each other so that transmission can be fast and efficient.

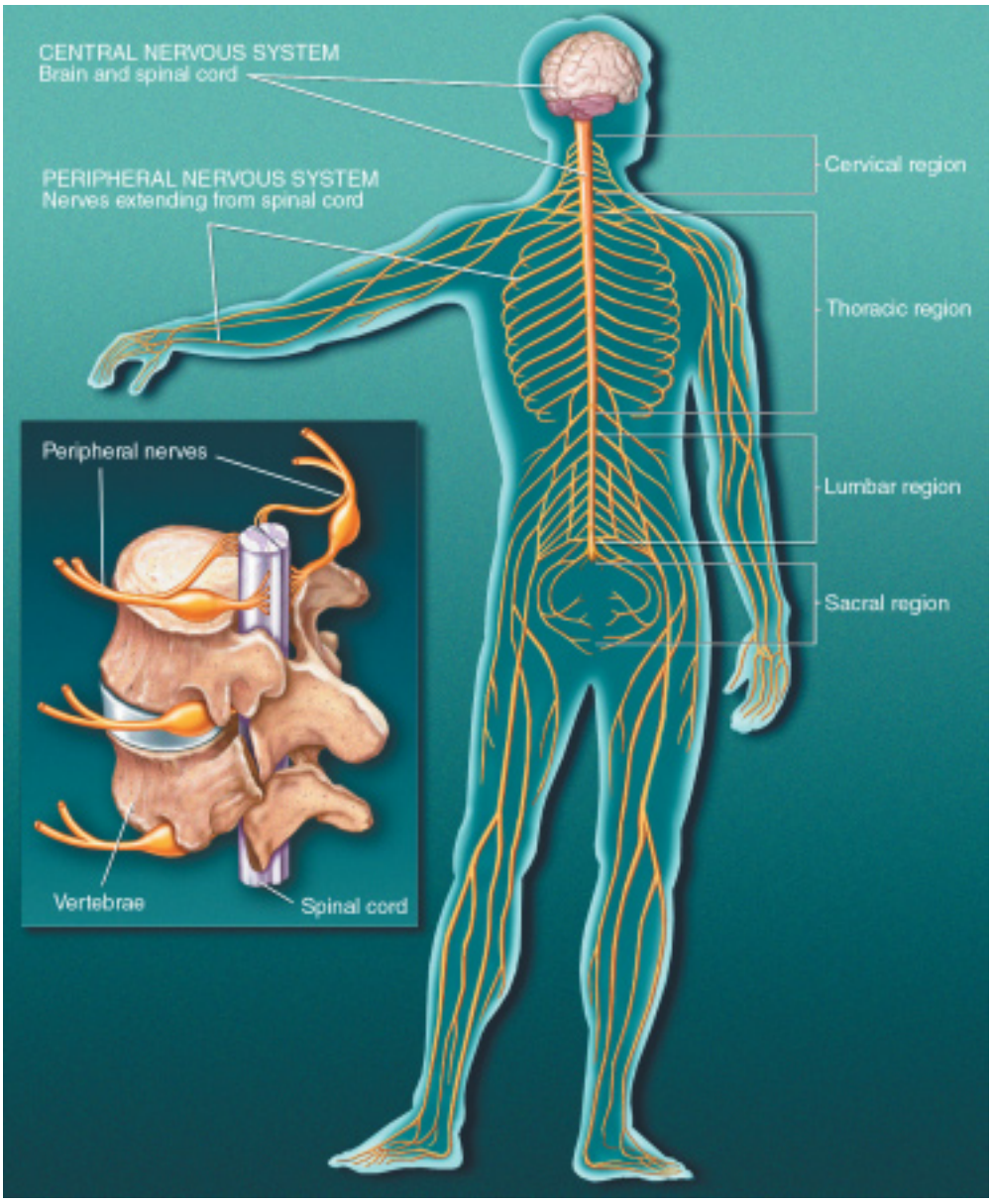
Paring back

After growth, the network is pared back to create a more sturdy system. Only about half the neurons generated during development survive to function in the adult. Entire populations of neurons are removed through internal suicide programs initiated in the cells. The programs are activated if a neuron loses its battle with other neurons to receive life-sustaining nutrients 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. It has recently become clear that the internal suicide program 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 inevitably 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 only to one eye or the other. Furthermore, in the young primate cerebral cortex, the connections between neurons are greater in number and twice as dense as those in an adult primate. Communication 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

The brain's refining and building of the network in mammals, including humans, continues after birth. An organism's interac-



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.

tions with its surroundings fine-tune connections.

Changes occur during critical periods. 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.

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 sensory or social deprivation 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.

In one example, 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 during postnatal life. 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.

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

Sensation and perception

Vision. This wonderful sense allows us to image 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 the most delicate and complicated senses. It is also the most studied. About one-fourth of the 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 the *cornea*, which does about three-quarters of the focusing, and then the *lens*, which varies the focus. Both help produce a clear image of the visual world on the *retina* — the sheet of *photoreceptors* that process vision, and 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, and objects above the center project to the lower part and vice versa. The shape of the lens is altered by the muscles of the *iris* so that near or far objects can be brought into focus on the retina.

Visual receptors, about 125 million in each 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 that are sensitive to red, green, and blue, but working together they convey information about all visible colors.

Primates, including humans, have well-developed vision using two eyes. 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 effect 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.

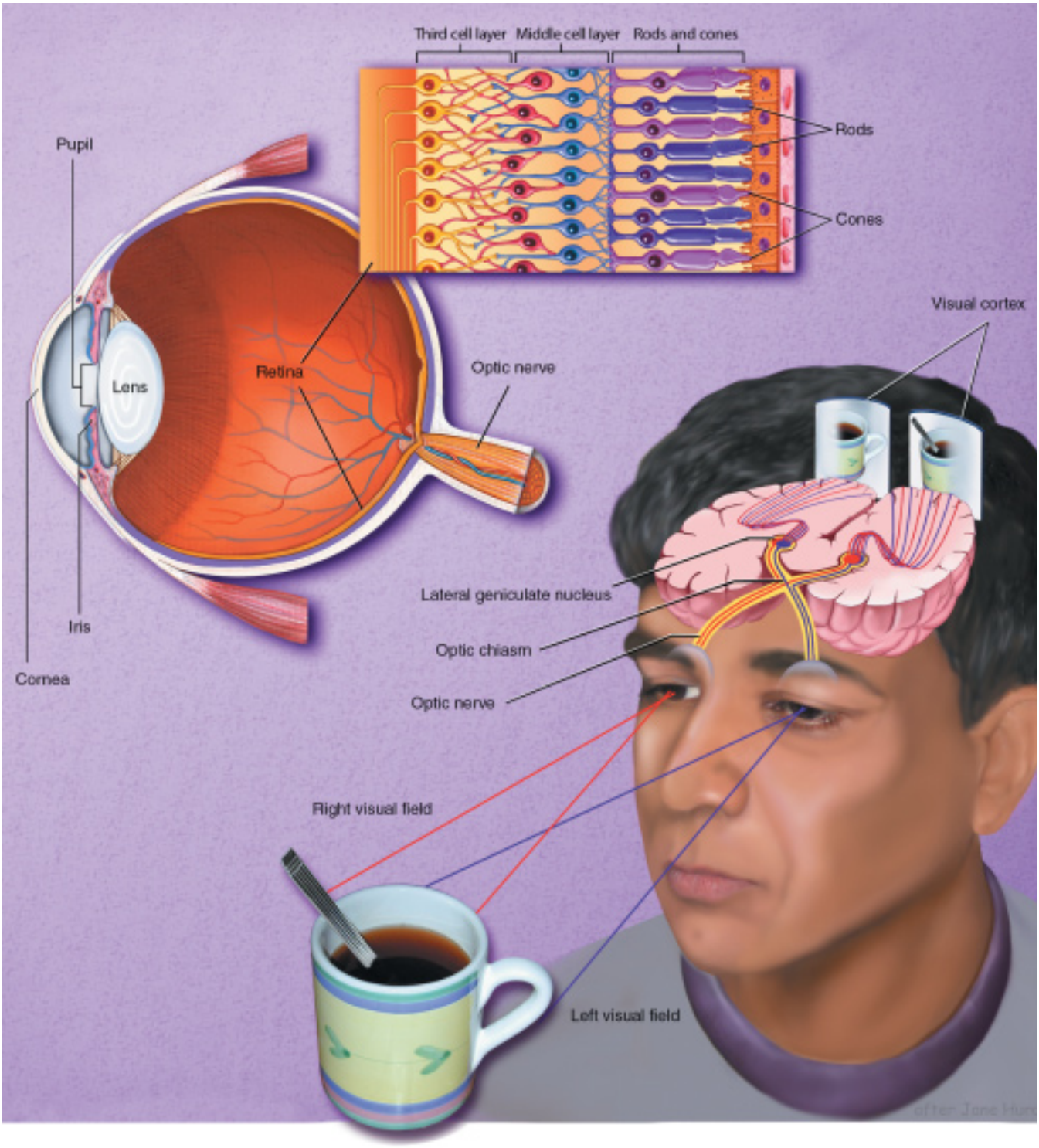
Scientists know much about the way cells encode visual information in the retina, the *lateral geniculate nucleus* — an intermediate point between the retina and visual cortex — and the visual cortex. These studies give us the best knowledge so far about how the brain analyzes and processes information.

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. Nerve fibers from the third layer assemble to form the optic nerve. Each cell in the middle or 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 gaze, where visual acuity is highest, each cell in the third layer receives inputs — via the middle layer — from one or a few cones, thus 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 rods and cones, explaining why we cannot see fine details off to either side. Whether large or small, this region of visual space is called the *receptive field* of the third-layer cell.

About 55 years ago, scientists discovered that the receptive field of such a 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 reacts only weakly and perhaps not at all.

Thus, the visual process begins with a comparison of the amount of light striking any small region of the retina and the amount of light around it. Located in the occipital lobe, the primary visual cortex — two millimeters thick (a bit larger than a half-dollar) and densely packed with cells in many layers — receives messages from the lateral geniculate. In the middle layer, which also receives input from the lateral geniculate, scientists found patterns of responsiveness similar to those observed in the retina and lateral geniculate cells. Cells above and below this layer responded differently. They preferred stimuli in the shape of bars or edges. Further studies showed that different cells preferred edges at particular angles, edges that moved, or edges moving in a particular direction.

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 about shape; a second, color; and a third, movement,



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.

location, and spatial organization. These findings of separate processing systems come from monkey anatomical and physiological data. They are verified 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 in color.

Why movement and depth perception should be carried out by only 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 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 wall-eye. 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 becomes permanent. But 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 example, the sound of an oncoming train tells us to stay clear of the railroad track.

Like the visual system, our hearing system distinguishes several qualities in the signal it detects. However, our hearing system does not blend different sounds, as the visual system does when two different wavelengths of light are mixed to produce color. We can follow the separate melodic lines of several instruments as we listen to an orchestra or rock band.

From the chirping of crickets to the roar of a rocket engine, most of the sounds processed by the ear are heard by a mechanism known as *air conduction*. In this process, sound waves are first funneled through the externally visible part of the ear, the pinna (or external ear) and the *external auditory canal*, to the *tympanic membrane* (eardrum), which vibrates at different speeds. The *malleus* (hammer), which is attached to the tympanic membrane, transmits the vibrations to the *incus* (anvil). This structure passes them onto the *stapes* (stirrup), which delivers them, through the oval window, to the *inner ear*.

The fluid-filled spiral passages of each cochlea contain 16,000 hair cells, whose microscopic, hairlike projections respond to the vibrations produced by sound. The hair cells, in turn, excite the 28,000 fibers of the auditory nerve, which terminate in the medulla of the brain. Auditory information flows via the thalamus to the *temporal gyrus*, the part of the cerebral cortex involved in receiving and perceiving sound.

The brain's analysis of auditory information follows a pattern similar to that of the visual system. Adjacent neurons respond to tones of similar frequency. Some neurons respond to only a small range of frequencies, others react to a wide range; some react only to the beginning of a sound, others only respond to the end.

Speech sounds, however, may be processed differently than others. Our auditory system processes all the signals that it receives in the same way until they reach the primary auditory cortex in the temporal lobe of the brain. When speech sound is perceived, the neural signal is funneled to the left hemisphere for processing in language centers.

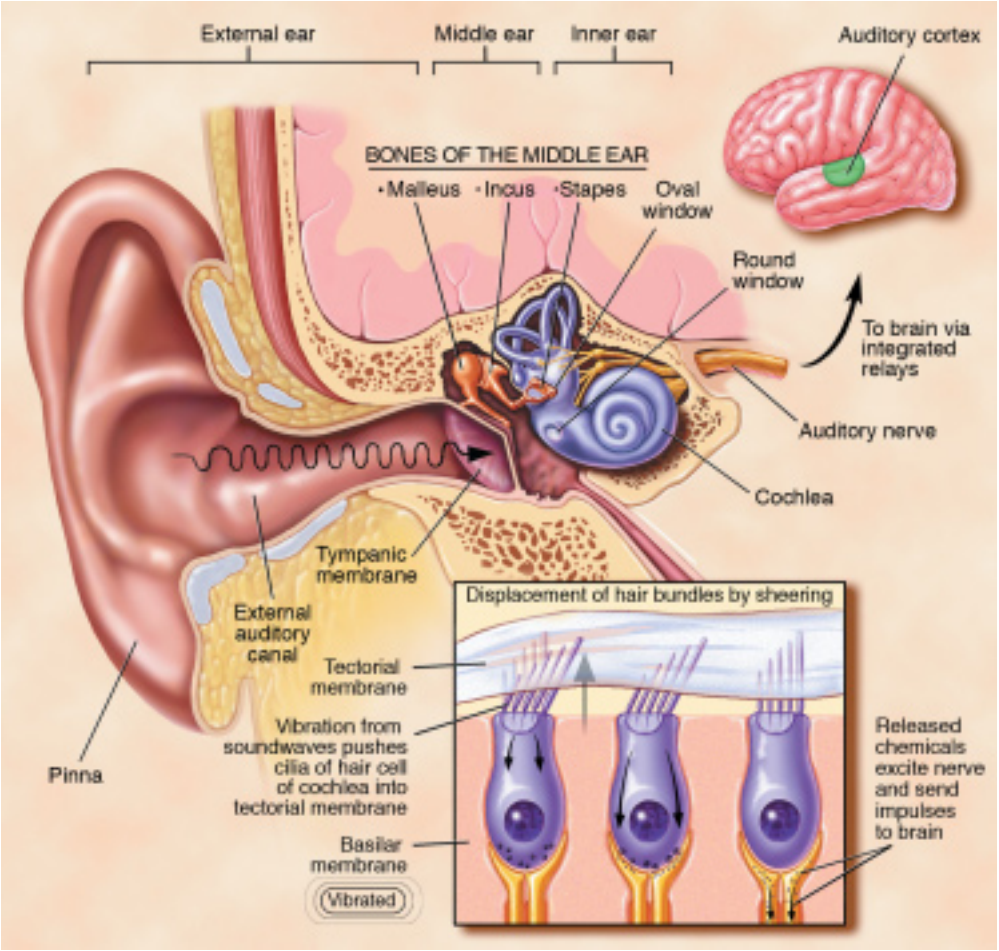
Taste and smell

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 apparently causes a serious reduction in the overall taste experience, which we call flavor.

Tastes are detected within *taste buds,* special structures of which every human has some 5,000 to 10,000. Taste buds are embedded within *papillae*, or protuberances, located mainly on the tongue, with others found in the back of the mouth and on the palate. Taste substances stimulate specialized sensory cells. Each taste bud consists of 50 to 100 of these cells, which respond to salts, acidity, sweet substances, bitter compounds, and monosodium glutamate and related amino acids.

Taste signals in the sensory cells are transferred by synapses to the ends of nerve fibers, which send impulses along cranial nerves to taste regions in the brain. From here, the impulses are relayed to other brainstem centers responsible for the basic responses of acceptance or rejection of the tastes, and to the thalamus and on to the cerebral cortex for conscious perception of taste.

Specialized smell receptor cells are located in a small patch of mucus 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 odorants carried by airborne molecules. These dissolve in the



HEARING. From the chirping of crickets to the roar of a rocket engine, almost all of the thousands of single tones processed by the human ear are heard by a mechanism known as air conduction. In this process, sound waves are first funneled through the external ear — the pinna and the external auditory canal — to the middle ear — the tympanic membrane (eardrum) — that vibrates at different speeds. The malleus (hammer), which is attached to the tympanic membrane, transmits the vibrations to the incus (anvil). The vibrations are then passed onto the stapes (stirrup) and oval window that, in turn, pass them onto the inner ear. In the inner ear, the fluid-filled spiral passage of the cochlea contains cells with microscopic, hairlike projections that respond to the vibrations produced by sound. The hair cells, in turn, excite the 28,000 fibers of the auditory nerve that end in the medulla in the brain. Auditory information flows via the thalamus to the temporal gyrus, the part of the cerebral cortex involved in receiving and perceiving sound.

mucus 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 it forms a spatial image of the odor. Impulses created by this stimulation pass to other smell regions, giving rise to conscious perceptions of odor in the frontal lobe and emotional responses in the limbic system of the brain.

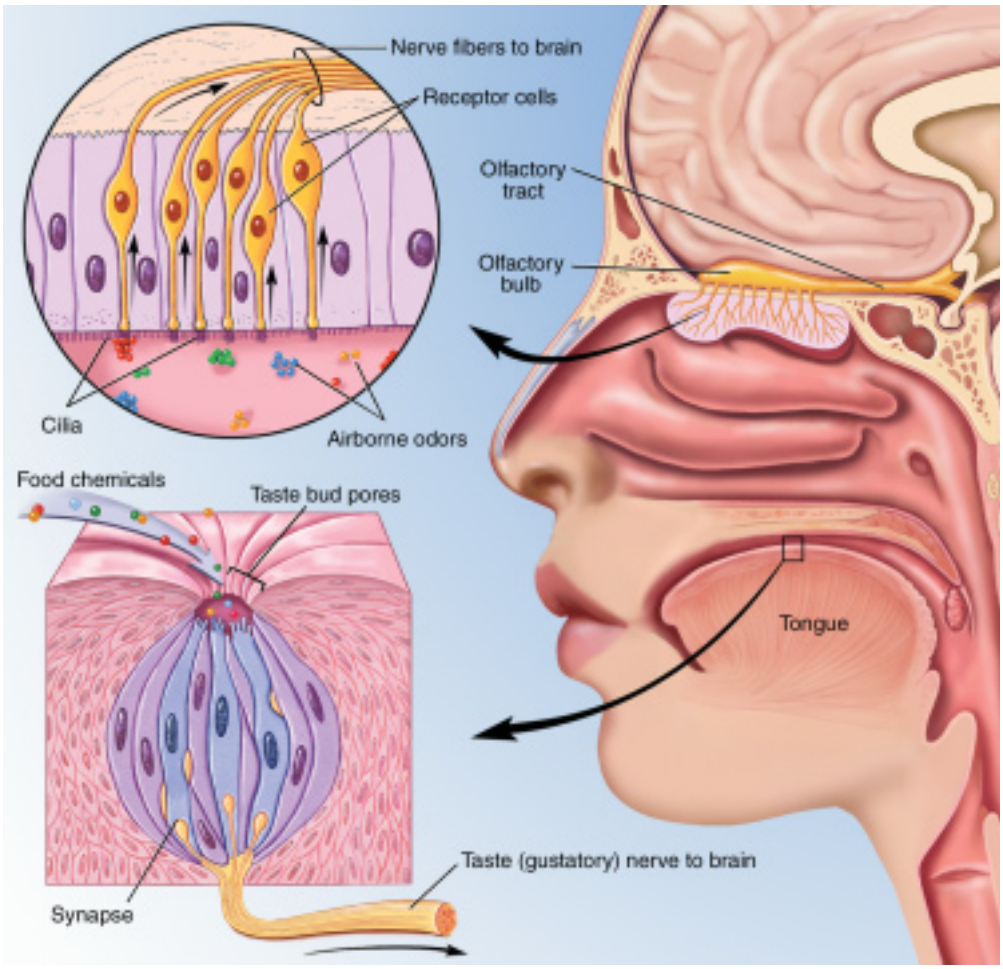
Touch and pain

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. Other receptors are more common in nonhairy areas, such as the lips and fingertips, and consist of nerve cell endings that may be free or surrounded by bulblike structures.

Signals from touch receptors pass via sensory nerves to the spinal cord, where they *synapse* (make contact) and then travel 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 touch discrimination 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 chest and back are less sensitive.

TASTE AND SMELL . Specialized receptors for smell are located in a patch of mucus 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 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 the four types of stimuli — sweet, salty, sour, and bitter — 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.



Not surprisingly, acuity is greatest in the most densely nerve-packed areas of the body. This feature, in fact, is used to test clinically for the integrity of these somatosensory pathways. For example, neurologists can run tests by using a *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.

Until recently, pain was thought to be a simple message by which neurons sent electrical impulses from the site of injury directly to the brain. We now know that the process is far more complicated. Nerve impulses from sites of injury that persist for hours, days, or longer lead to changes in the nervous system that result in an amplification and increased duration of the pain. These changes involve dozens of chemical messengers and receptors. 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 injure tissue and can cause pain are called *nociceptors*, special receptors that respond to tissue-damaging stimuli. In addition to directly activating the nociceptor and evoking a pain sensation, tissue injury causes the release of numerous chemicals at the site of damage and inflammation. One such family of chemicals includes the *prostaglandins*, which enhance the sensitivity of receptors to tissue damage and ultimately can induce more intense pain sensations. Prostaglandins also contribute to the clinical condition in which innocuous stimuli can produce pain (such as in sunburned skin) because the threshold of the nociceptor is significantly reduced. This phenomenon is called *allodynia*.

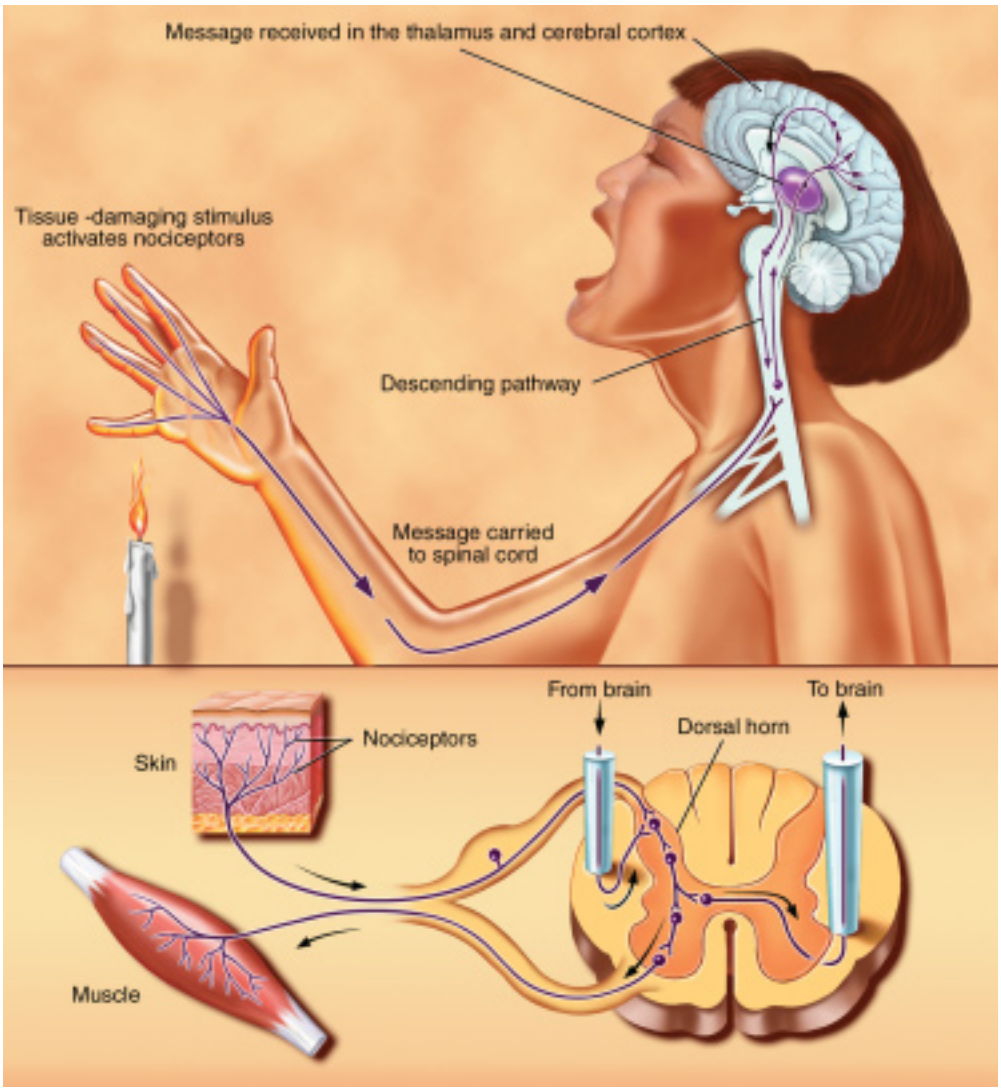
Pain messages are transmitted to the spinal cord via small myelinated fibers and C fibers — very small unmyelinated fibers. *Myelin* is a covering sheath around nerve fibers that helps them send their messages more rapidly. The small myelinated pain-sensitive nerve fibers probably evoke the sharp, fast pain that is produced by, for example, a pin prick. C fiber-induced pain, by contrast, is generally

slower in onset, dull, and more diffuse.

In the *ascending system*, the impulses are relayed from the spinal cord to several brain structures, including the thalamus and cerebral cortex, that are involved in the process by which "pain" messages become 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 contributes (e.g., the pain of childbirth or that produced in a car accident). The emotional component of the experience is a major contributor to the overall pain.

Pain messages can also be suppressed by a system of neurons that originate within the gray matter in the brainstem. This *descending system* sends messages to the dorsal horn of the spinal cord, where it suppresses the transmission of pain signals to the higher brain centers. Some of these descending systems use naturally occurring chemicals similar to opioids. The three major families of opioid peptides identified in the brain — enkephalins, beta-endorphins, and dynorphins — originate from three precursor proteins encoded by three different genes. They act at multiple opioid receptors in the brain and spinal cord. Knowledge of the way pain messages are transmitted has led to new treatments for pain. 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. Because the spinal opioid does not interact at all levels of the nervous system, this technique bypasses many potentially negative opioid side effects.

Many new insights into the pain experience are coming from studies in which modern imaging tools are used to monitor brain activity when pain is experienced. One finding is that there is no single area in the brain where pain is generated; rather, there are both emotional and sensory components. 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. 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 analgesic 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, opiate-like chemicals called endorphins.

Learning, memory, and language

The conscious memory of a patient known as H.M. is limited almost entirely to events that occurred years before his surgery, in which part of the medial temporal lobe of his brain was removed to relieve epilepsy. H.M. can remember recent events for only a few minutes. Talk with him awhile and then leave the room. When you return, he has no recollection of ever having seen you.

The medial temporal lobe, which includes the hippocampus and adjacent brain areas, seems to play a role in converting memory from a short-term to a long-term, permanent form. The fact that H.M. retains memories for events that are remote to his surgery is evidence that the medial temporal region is not the site of permanent storage but that it plays a role in the formation of new memories. Other patients like H.M. have also been described.

Additional evidence comes from patients undergoing *electroconvulsive therapy* (ECT) for depression. ECT is thought to temporarily disrupt the function of the hippocampus and related structures. These patients typically have difficulty with new learning and have amnesia for events that occurred during the several years before treatment. Memory of earlier events is unimpaired. As time passes after treatment, much of the lost part of memory becomes available once again.

The hippocampus and the medial temporal region are connected to widespread areas of the cerebral cortex, especially the vast regions responsible for thinking and language. Whereas the medial temporal region is important for forming and organizing 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.

Working memory, a type of transient, "online" memory that enables us to retain what someone has said just long enough to reply, depends in part on the prefrontal cortex. Researchers discovered that certain neurons in this area are influenced by neurons releasing dopamine and other neurons releasing glutamate.

Although much remains to be discovered about learning and memory, scientists have already put together important pieces of the puzzle. For example, the brain appears to process different kinds of information in separate ways and then store it differently.

Declarative knowledge requires processing in the medial temporal region and parts of the thalamus and can be grouped into working memory, episodic memory, and semantic memory. Working memory allows us to keep and use information in our minds and is mediated by a network of areas in the cerebral cortex. Episodic memory lets us store and replay events in our minds and depends on the hippocampus. Semantic memory includes raw facts and data and is stored throughout the cerebral cortex. The hippocampus may play a role in integrating new episodic memories into the semantic memory storehouse.

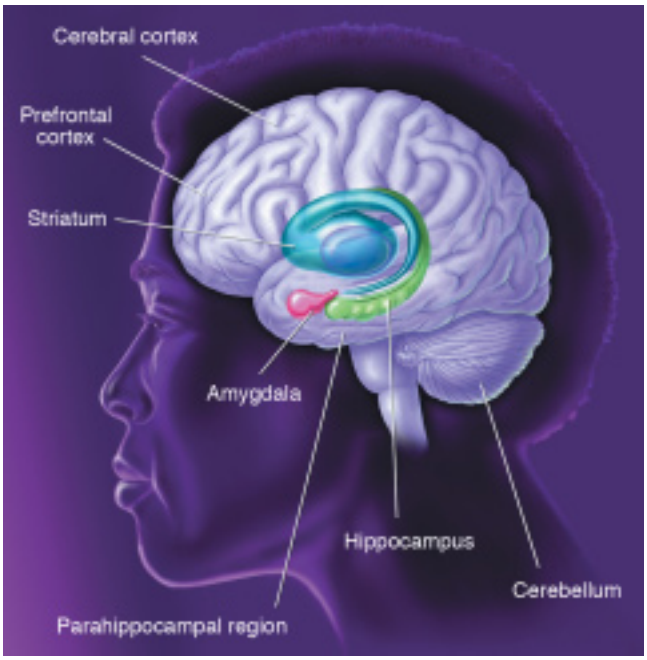
In contrast, *nondeclarative knowledge*, the knowledge of how to do something, is expressed in skilled behavior and learned habits and requires processing by the basal ganglia.

The amygdala appears to play an important role in the emotional aspects of memory. An important factor that influences what is stored and how strongly it is stored is whether the action is followed by reward, punishment, or highly emotional consequences. These consequences help determine what behaviors an organism will learn and remember.

Memory of motor learning tasks in which precise timing is involved depends on the cerebellum.

How exactly does memory occur? After years of study, there is much support for the idea that memory involves a persistent change in the connection between neurons. In animal studies, scientists found that this occurs in the short term through two biochemical events that affect the strength of the relevant synapses. The stability of long-term memory is conferred by turning on genes that may lead to modifications within neurons that change the strength and number of synapses. For example, researchers can correlate specific chemical and structural changes in the relevant cells with several simple forms of memory exhibited by the sea slug *Aplysia californica*.

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 other brain areas. Studies of rats suggest that LTP occurs through changes in synaptic strength at contacts involving NMDA receptors. It is now possible to study LTP and learning in genetically modified mice that have alterations in specific



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.

genes. Examples of these modified genes can be limited both to particular brain areas and to specific times, such as during learning.

Much of what we have learned about memory comes from studies of amnesia due to damage to the hippocampus and cortical areas — called the *parahippocampal region* — in the medial part of the temporal lobe. Patients with damage in these areas can remember recent events only while actively engaged in the material — yet they often retain childhood memories quite well. This pattern suggests that the temporal lobe is critical in integrating early memories into a permanent storehouse that can be accessed whenever needed.

Several types of memory are spared in amnesia. Reports indicate that the sense of familiarity one has with a face or a scene is spared, even though the specific context of the experience may be lost. The emotional association one might develop with a given item is also commonly spared in amnesia.

Scientists believe 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.

One of the most prominent intellectual activities dependent on memory is language. 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 due to stroke, and from behavioral and functional neuroimaging studies of normal people.

A prominent and influential model, based on studies of these patients, proposes that the underlying structure of speech comprehension arises in part of the left hemisphere of the brain, called *Wernicke's area.* This temporal lobe region is connected with another region, *Broca's area,* in the frontal lobe, where a program for vocal expression is created. This program is then transmitted to a nearby area of the motor cortex that activates the mouth, tongue, and larynx.

This same model proposes that, when we read a word, the information is transmitted from the primary visual cortex to the *angular gyrus,* where the message is somehow matched with the words when they are spoken. The auditory form of the word is then processed for comprehension in Wernicke's area as if the word had been heard. Writing in response to an oral instruction requires information to be passed along the same pathways in the opposite direction — from the auditory cortex to Wernicke's area to the angular gyrus. This model accounts for much of the data from patients and is the most widely used for clinical diagnosis and prognosis. Some refinements to this model may be necessary, however, because of both recent studies with patients and functional neuroimaging studies in healthy people.

For example, using an imaging technique called *positron emission tomography* (PET), scientists have demonstrated that some reading tasks performed by normal people do not activate Wernicke's area or the angular gyrus. These results suggest that, at least under some conditions, there is a direct reading route that does not involve speech-sound recoding of the visual stimulus before the processing of either meaning or speaking. Other studies with patients also have indicated that it is likely that familiar words need not be recoded into sound before they can be understood.

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 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 that 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 it. 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 are also under control of the central nervous system, and their principles of operation are similar to those that attach to bone.

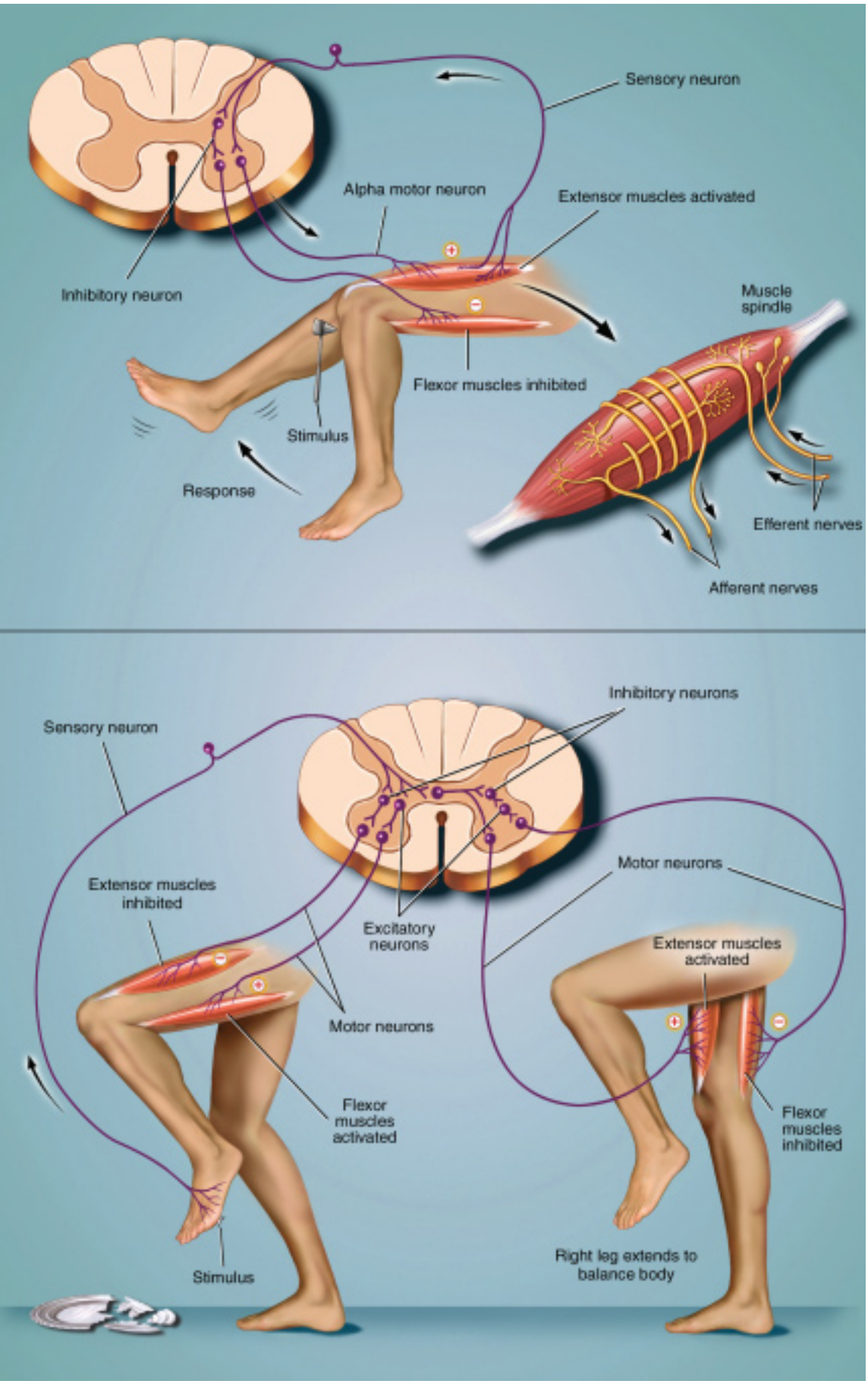
Each skeletal muscle is made up of thousands of individual muscle fibers, and each of these is controlled by one *alpha motor neuron* in either the brain or the spinal cord. On the other hand, each single alpha motor neuron controls many muscle fibers (ranging from a few to a hundred or more), forming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

Perhaps the simplest and most fundamental of movements are reflexes. These are relatively fixed, automatic muscle responses to particular stimuli, such as 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 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 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.

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

Even more amazing is the fact that the brain can control not only the actions of motor neurons and muscles, but also 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 also sense and control the muscular force exerted during movement.



MOVEMENT. The stretch reflex (above) 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 (below) 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.

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, and 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 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.

In addition to the motor cortex, movement control also 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 connect cerebral hemispheres with the spinal cord. The brain regions devoted to such control are large, containing millions of intricately interconnected neurons.

Scientists know that the basal ganglia and thalamus have widespread connections with sensory and motor areas of the cerebral cortex. Loss of regulation of the basal ganglia by dopamine depletion can cause serious movement disorders, such as Parkinson's disease. Loss of dopamine neurons in the substantia nigra of the midbrain, which connects with the basal ganglia, is a major factor in Parkinson's disease.

We now know that complex systems are coordinated and organized to respond differently for tasks that require precise control of position, such as holding a teacup, and for those requiring rapid, strong movement, such as throwing a ball.

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

The cerebellum receives direct and powerful sensory information from the muscle receptors and the sense organs of the inner ear, which signal head position and movement, and signals from 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. There is evidence 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.

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 bodily hormones, body temperature, and other functions.

Sleep disorders 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.

The stuff of 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) that examined human brain waves during sleep. Researchers also measured movements of the eyes and the limbs during sleep. 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 progressively 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 the deep slow wave sleep to generate neocortical EEG waves that are indistinguishable from 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 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 there are a variety of short-acting sedatives and sedating antidepressant drugs available to help, none of these 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. These are usually diagnosed in the sleep laboratory, where the EEG, eye movements, and muscle tone are monitored electrically as the individual sleeps. In addition, the heart, breathing, and oxygen content of the blood can be monitored.

Obstructive sleep apnea causes the airway muscles in the throat to collapse as sleep deepens. This prevents breathing, which causes arousal from sleep, and prevents the sufferer from entering the deeper stages of slow wave sleep. This condition can also cause high blood pressure and may increase the risk of heart attack. The 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 provided by fitting a small mask over the nose that provides an air stream 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 be paralyzed during REM sleep, and they act out their dreams. This *REM behavior disorder* can also 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 that treat Parkinson's or with a drug called clonazepam.

Narcolepsy is a relatively uncommon condition — only one case per 2,500 people — in which the switching mechanism for REM sleep does not work properly. Narcoleptics have sleep attacks during the day, in which they suddenly fall asleep. This is socially disruptive, as well as dangerous, for example, if 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 major insights into the processes that control these mysterious transitions between waking, slow wave, and REM sleep states.

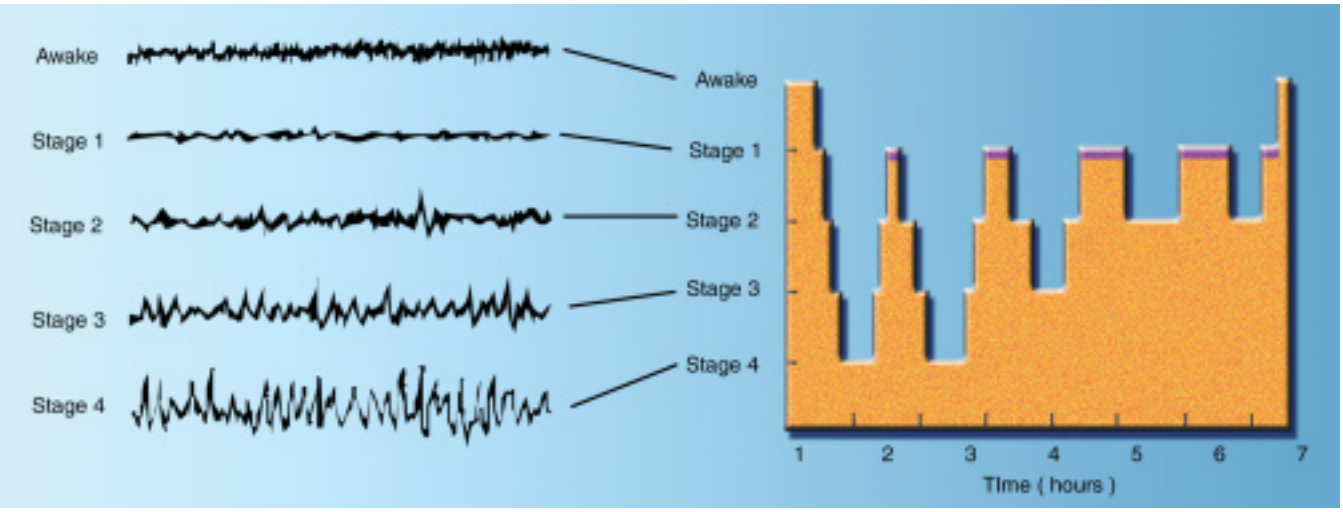
How is sleep regulated?

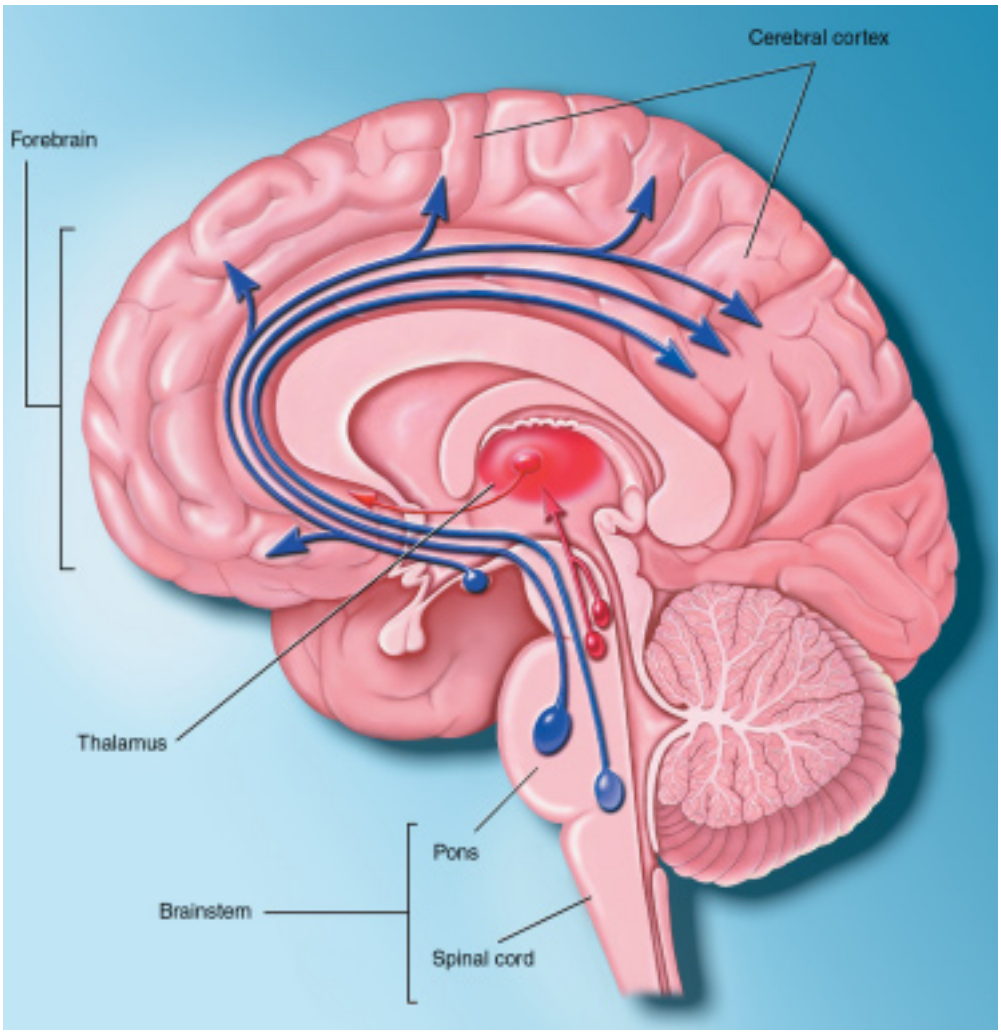
During wakefulness, the brain is kept in an alert state by the interactions of two major systems of nerve cells. Nerve cells in the upper part of the pons and in the midbrain, which produce acetylcholine, send inputs to activate the thalamus. When the thalamus is activated, it in turn activates the cerebral cortex and produces a waking EEG pattern. Another important wakefulness center is in the basal forebrain, whose neurons project directly to the cerebral cortex. In addition to acetylcholine, other neurotransmitters promote wakefulness, including norepinephrine, serotonin, histamine, and glutamate.

During REM sleep, the cholinergic nerve cells and the thalamus and cortex are in a condition similar to wakefulness, but the brain is not very responsive to external stimuli. The difference is in the activity of three sets of monoamine nerve cells: the brainstem nerve cells in the locus coeruleus that use the neurotransmitter norepinephrine; the dorsal and median raphe groups that contain serotonin; and, in the hypothalamus, the tuberomammillary cell group that uses histamine. These monoamine neurons fire most rapidly during wakefulness, but they slow down during slow wave sleep and stop during REM sleep. These monoamine neurons act to 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, part of the brain that controls basic body cycles. One group

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.





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 and one in the forebrain (red pathways). 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.

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 influences 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. 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, there is homeostasis, or the body's need to seek a natural equilibrium of rest and sleep followed by wakefulness. Several mechanisms for the signal of accumulating sleep have been suggested. There is evidence that a chemical called adenosine, which is linked to brain energy depletion, accumulates in the brain during prolonged wakefulness and that it may drive 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 again comes, 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 body's circadian clock, the suprachiasmatic nucleus. This small group of nerve cells in the hypothalamus contains clock genes, which go through a biochemical cycle of about 24 hours, setting the pace for daily cycles of activity, sleep, hormones, 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 the brain areas regulating 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." But in today's complex and fast-paced world, this response to stress is not enough, and 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 commonly thought to be stress induced; 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 last six decades, researchers using animals 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 reestablish or maintain homeostasis. But stress that continues for prolonged periods can repeatedly elevate the physiological stress responses or fail to shut them off when not needed. When this occurs, these 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 Westernized humans.

The immediate response

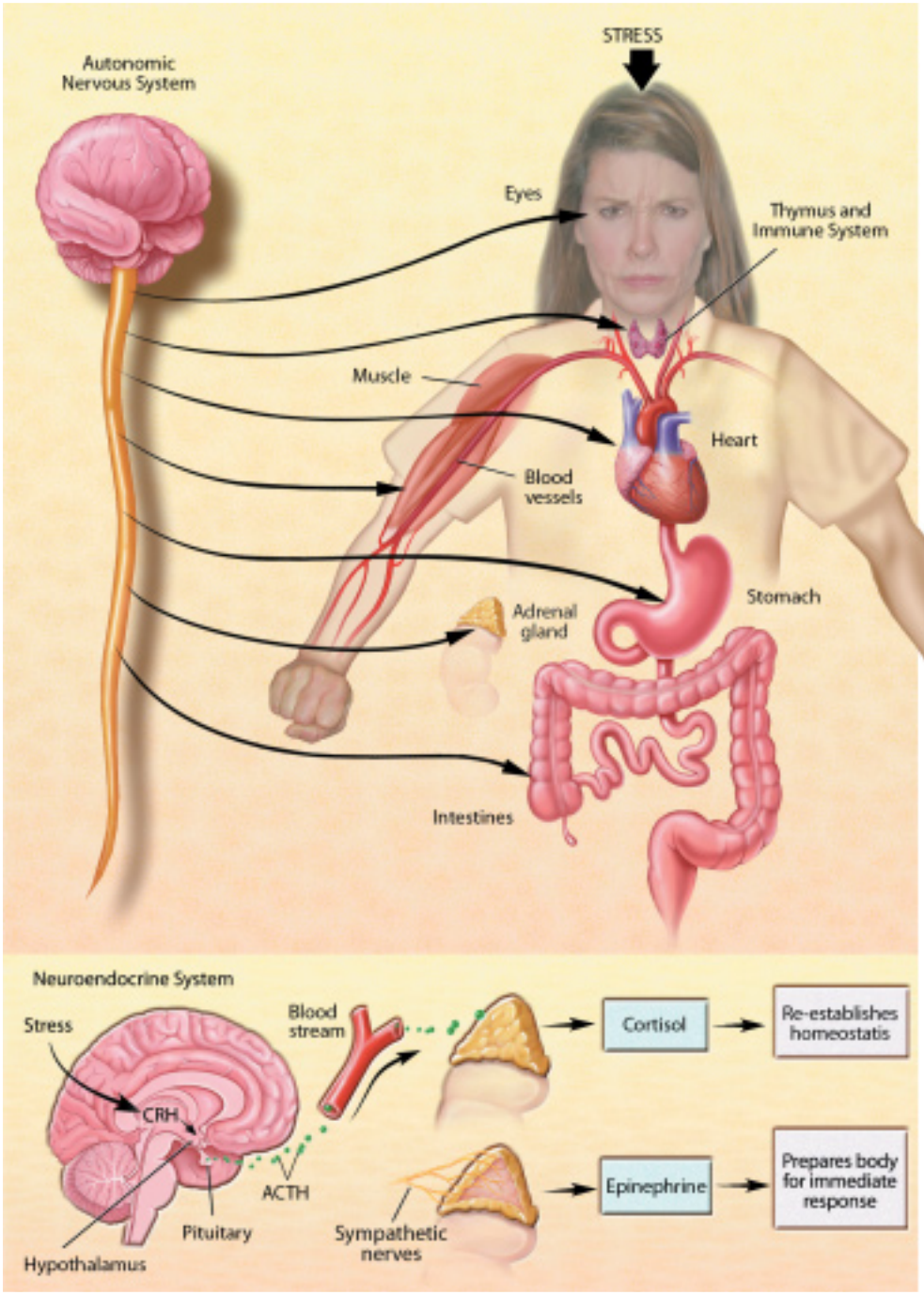
A stressful situation activates three major communication systems in the brain that regulate bodily functions. Scientists have come to understand these complex systems through experiments primarily with rats, mice, and nonhuman primates, such as monkeys. Scientists then verified the action of these systems 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 growling bear on a trail in Yellowstone National Park prompts you to run as quickly as possible.

The second communication system is the *autonomic nervous system*. It combines the *sympathetic* or emergency branch, which gets us going in emergencies, and the *parasympathetic* or calming branch, which 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 emergency 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, the emergency system reduces blood flow to the skin, kidneys, and digestive tract and increases blood flow to the muscles. In contrast, the calming 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. Left mobilized and unchecked, these body functions could lead to disease. 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



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.

processes such as metabolic rate and sexual functions.

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 the nervous system, 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 affecting glucose metabolism. 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 reestablish homeostasis. Over the short run, adrenaline mobilizes energy and delivers it to muscles for the body's response. With prolonged exposure, cortisol enhances feeding and helps the body recover from energy mobilization. Cortisol also raises blood pressure and increases the risk of adult-onset diabetes, immunosuppression, reproductive impairments, and depression, among other difficulties.

Acute stress enhances memory of threatening situations and events, increases activity of the immune system, and helps pro-

tect the body from pathogens. The two major stress hormones, cortisol and adrenaline, 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 also affect food intake during the sleep-wake cycle. Cortisol levels peak in the body in the early morning hours just before waking. This hormone acts as a wake-up signal and helps to 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.

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 adrenaline are secreted in response to the prolonged psychological stress commonly encountered by 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, there are different consequences: Memory is impaired, immune function is suppressed, and energy is stored as fat.

Overexposure to cortisol also can lead to weakened muscles and the suppression of major bodily systems. Elevated epinephrine production increases blood pressure. Together, elevated cortisol and epinephrine can contribute to chronic hypertension (high blood pressure), abdominal obesity, and atherosclerosis (hardening of the arteries). Adrenaline also increases the activity of body chemicals that contribute to inflammation, and these chemicals add to the burden of chronic stress, potentially leading to atherosclerosis, arthritis, and possibly also aging of the brain.

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, adult-onset diabetes, and possibly cancer. 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 cortisol 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. Moderate to high levels of glucocorticoids act to suppress immune function, although acute elevations of stress hormones actually facilitate immune function.

Although acute stress-induced immunoenhancement can be protective against disease pathogens, the glucocorticoid-induced immunosuppression can also be beneficial. It reduces inflammation and counteracts allergic reactions and *autoimmune responses*, which occur when the body's defenses turn against body tissue. Synthetic glucocorticoids like hydrocortisone and prednisone are used often to decrease inflammation and autoimmunity. But glucocorticoids may be harmful in the case of increased tumor growth associated with stress in experiments on animals — an area of intense research yet to yield any final conclusions.

One important determinant of the immune system's 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 processes that regulate 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. 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 the normal changes that occur over time and their effect on reasoning and other intellectual activities.

It appears that the effects of age on brain function vary widely. 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 or phone numbers or respond more slowly to conflicting information. This is not disease. However, other individuals 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 increasing to nearly 50 percent in those older than 85. In a small, third group, mental functioning seems unaffected by age. Many people do well throughout life and continue to do well even when old. The oldest human, Jeanne Calment, kept her wits throughout her 122-year lifespan.

It's important to understand that scientific studies measure trends and reflect what happens to the norm — they don't tell what happens to everybody. Some people in their 70s and 80s function as well as those in their 30s and 40s. The wisdom and experience of older people often make up for deficits in performance.

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 were typically 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.

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 neurons.

The cause of brain aging still 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.

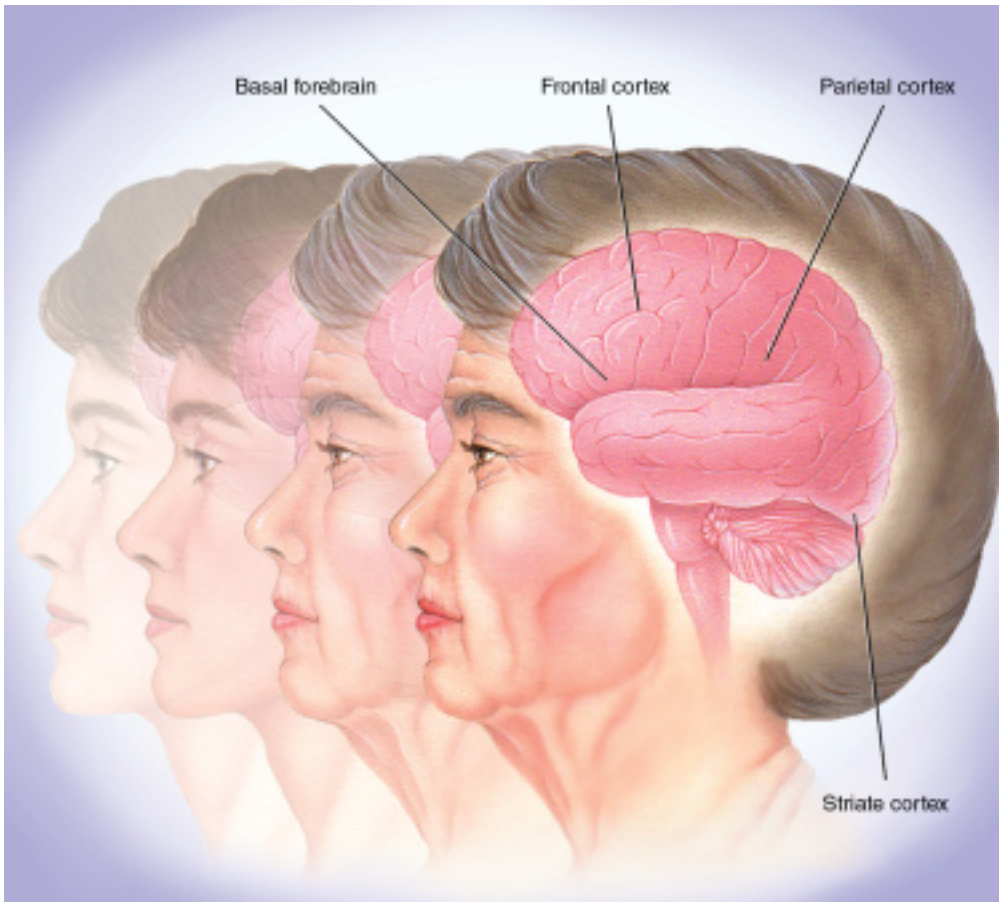
Aging neurons

The brain reaches its maximum weight near age 20 and slowly loses about 10 percent of its weight over a lifetime. 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 widespread neuron loss is not a normal process of aging. Brain tissue can respond to damage or loss of neurons in Alzheimer's disease or after stroke 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.

Intellectual capacity

From the first large studies to monitor the same group of healthy humans for many years, scientists have uncovered unexpected

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.



results. They report declines in some mental functions and improvements in others. In several studies, the speed of carrying out certain tasks became slower, but vocabulary improved. Several studies found 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 found 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 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.

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. In tests of middle-aged rats exposed to such environments, researchers found that dendrites in the cerebral cortex developed more and longer branches than did rats housed in isolated conditions. 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 human cognitive performance.

Other scientists report that rats reared in a stimulating environment made significantly fewer errors in a maze test than did similar rats kept in an isolated environment. Moreover, the stimulated rats showed an increase in brain weight and cortical thickness compared with animals in the control group.

In response to enriched environments, older rats tend to form new dendrites 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.

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 cause a higher likelihood of death? How does aging affect gene expression in the brain — the organ with the greatest number of active genes? Are there gender differences in brain aging that may be due to hormonal changes at menopause?

Neuroscientists speculate that certain genes may be linked to events leading to 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.

Advances

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 affects 1.2 percent of Americans age 18 or older annually, 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. Because 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, like lithium, 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.

Epilepsy

Epilepsy, a chronic neurological disorder characterized by sudden, disorderly discharge of brain cells, is marked by recurrent, unprovoked seizures that temporarily alter one or more brain functions. The disorder affects approximately 1 percent of the population.

Many different types of epilepsy have been recognized. Epilepsy can start at any age and can be idiopathic (having an uncertain cause) or symptomatic. Most idiopathic epilepsies are likely due to inheriting a mutant gene, more than a dozen of which have been identified during the last decade. Symptomatic epilepsies result from a wide variety of brain diseases or injuries, including birth trauma, brain infection such as abscess or meningitis, brain tumors, and stroke.

Seizures are of two types, generalized and partial. Generalized seizures, which typically result in loss of consciousness, can cause several behavioral changes, including convulsions or sudden changes in muscle tone, and arise when there is simultaneous excessive electrical activity over a wide area of the brain. Partial seizures may 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 a limited area of the brain.

There are more than a dozen antiseizure medications, approximately half of which have been introduced in the last several years, available to prevent seizures. The principal targets of antiseizure drugs are voltage-gated ion channels permeable to sodium or calcium and synapses using the transmitter GABA, a naturally occurring substance in the brain that acts to inhibit electrical discharge. Identification of the mutant genes underlying human epilepsy may provide new targets for the next generation of antiseizure drugs. In many instances, epilepsy can be controlled with a single antiseizure drug that lessens the frequency of seizures, but sometimes a combination of drugs is necessary. Complete control of seizures can be achieved in more than 50 percent of patients, and another 25 percent can be improved significantly. It is hoped that the newly available antiseizure drugs will provide complete control in additional patients.

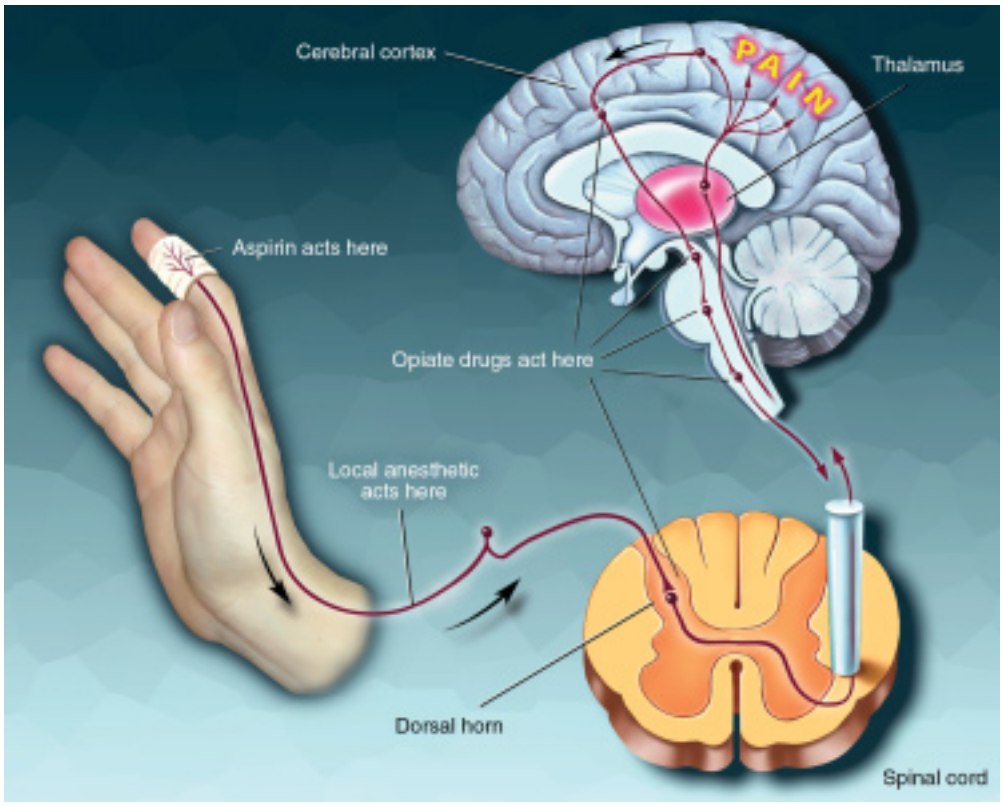
Surgery, considered for patients who do not respond to antiseizure drugs, should be performed only at specialized medical centers qualified to evaluate patients and perform epilepsy surgery. Epilepsy surgery requires precise location and removal of the area of the brain where the seizures originate. After surgery, about 90 percent of properly selected patients experience striking improvement or complete remission of seizures.

A new form of epilepsy treatment, electrical stimulation therapy, was introduced during the mid-1990s as another option for hard-to-control seizures. The implantable pacemaker-like device delivers small bursts of electrical energy to the brain via the vagus nerve on the side of the neck.

Major depression

This condition, with its harrowing feelings of sadness, hopelessness, pessimism, loss of interest in life, and reduced emotional

HOW PAIN KILLERS 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.



well-being, is one of the most common and debilitating mental disorders and one of the leading causes of morbidity worldwide. 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 (EEGs) 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, such as imipramine, primarily block the reabsorption 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. MAOIs available for use include isocarboxazid, phenelzine, and tranylcypromine.

The popular medication fluoxetine (Prozac) is the first of a class of drugs called selective serotonin reuptake inhibitors, or SSRIs. SSRIs block the reabsorption 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. There are also several newer antidepressants available, such as bupropion, that are also very effective but seem to have a different and as yet unknown mechanism of action.

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.

Until the mid-19th century, pain relief during surgery relied on natural substances, such as opium, alcohol, and cannabis. All were inadequate and short-lived. Not until 1846 did doctors dis-

cover the anesthetic properties of ether, first in animals and then in humans. Soon, the usefulness of chloroform and nitrous oxide became known and heralded a new era in surgery. The dozens of drugs used today during surgery abolish pain, relax muscles, and induce unconsciousness. Other agents reverse these effects.

Local anesthesia is used in a limited area of a person's body to prevent pain during examinations, diagnostic procedures, treatments, and surgical operations. The most famous of these agents, which temporarily interrupt the action of pain-carrying nerve fibers, is Novocain, which dentists used as a local anesthetic for many years; lidocaine is more popular today. Very recently, lidocaine has been used in a slow-release patch to provide long-lasting pain in localized, specific parts of the body.

Analgesia refers to loss of pain sensation without loss of sensitivity to touch. The two main types of analgesics are *nonopioids* (aspirin and related nonsteroidal anti-inflammatory drugs [NSAIDs] such as ibuprofen, naproxen, and acetaminophen) and *opioids* (morphine, codeine). Nonopioid analgesics are useful for treating mild or moderate pain, such as headache or toothache. Because NSAIDs are anti-inflammatory, they are effective for treating such inflammatory conditions as arthritis. Moderate pain also can be treated by combining a mild opioid, such as codeine, with aspirin. Opioids are the most potent painkillers and are used for severe pain, such as that occurring after major chest or abdominal surgery.

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 (targets) through which opioids exert their effects. These findings led to the use of injections of morphine and endorphins, 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. This technique is now commonly used in humans to treat pain after surgery and is a mainstay for pain relief after caesarean section.

Although NSAIDs and opioids are quite effective for pain produced by tissue injury, they are much less effective when the pain results from injury to the nervous system. These so-called neuropathic pains include the pain of diabetic neuropathy, postherapeutic neuralgia, phantom limb pain, and post-stroke pain. For these pains, anticonvulsants are more effective, and some patients can be helped with low doses of antidepressants.

New targets, however, are on the horizon. Molecular biology has identified many molecules (ion channels and receptors) that are predominantly, if not exclusively, expressed by the *nociceptor*, which is the first-order nerve fiber in the pain pathway. 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 new targets are glutamate receptors, vanilloid receptors (which are targeted by capsaicin, the active ingredient in hot peppers), and a variety of acid-sensing 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 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, that act directly on dopamine receptors.

Genetic studies have demonstrated several heritable gene abnormalities in certain families, but almost all cases of Parkinson's occur sporadically. It is believed 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 heroin-like compound. MPTP was found to be converted in the brain to a substance that destroys dopamine neurons. Parkinson's is now being intensively studied in primate MPTP models.

In the past several decades, scientists have shown in primate models of Parkinson's that specific regions in the basal ganglia, collections of cell bodies deep in the brain, are abnormally overactive. Most importantly, they found that surgical 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.

Challenges

Addiction. Drug abuse is one of the nation's most serious health problems. Indeed, 6 percent of Americans, roughly 15 million people, abuse drugs on a regular basis. Recent estimates show that the abuse of drugs, including alcohol and nicotine from tobacco, 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 defined as having lost control over drug taking, even in the face of adverse physical, personal, or social consequences.

People abuse drugs for a simple reason: Drugs 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 is activated when we fulfill survival functions, such as eating when we are hungry or drinking when we are thirsty. In turn, our brain rewards us with pleasurable feelings that teach us to repeat the task. Because drugs inappropriately turn on this reward circuit, people want to repeat drug use.

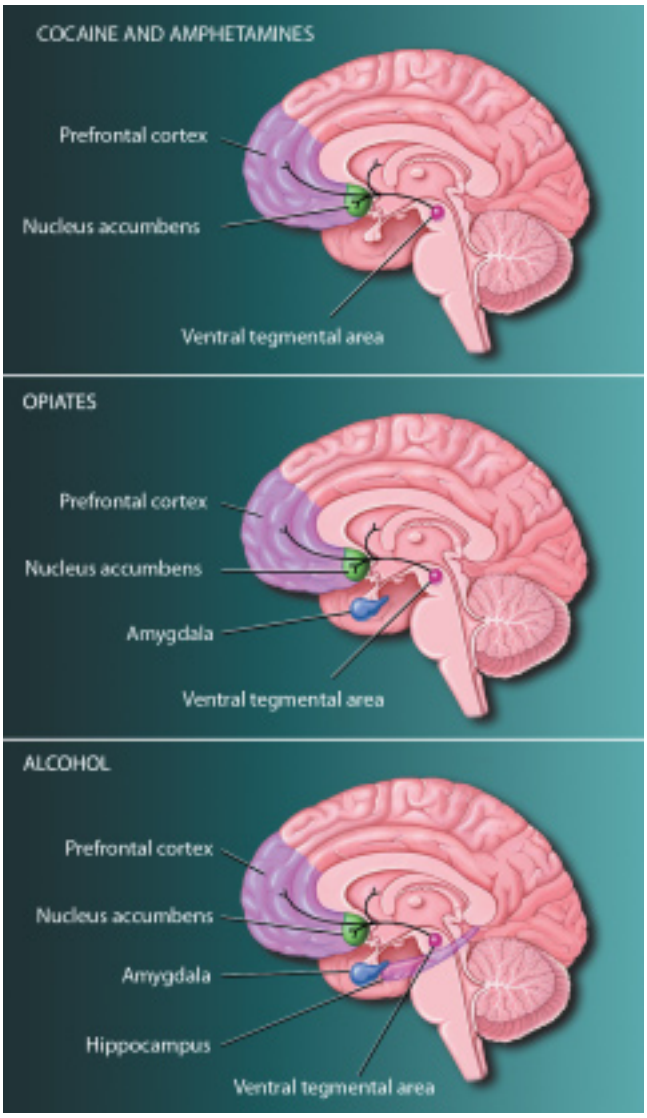
Neuroscientists also have learned specifically how drugs affect neurons to exert their influence. Neurons release special chemicals, called *neurotransmitters*, to communicate with each other. Abused drugs alter the ways neurotransmitters carry their messages from neuron to neuron. Some drugs mimic neurotransmitters, whereas others block them. Still others alter the way that the neurotransmitters are released or inactivated. The brain reward system is inappropriately activated because drugs alter the chemical messages sent among neurons in this circuit.

Finally, neuroscientists also have learned that addiction requires more than the activation of the brain reward system. The process of becoming addicted appears to be influenced by many factors. Motivation for drug use is an important one. For example, people who take drugs to get high may get addicted, but people who use them properly as medicine rarely do. Genetic susceptibility or environmental factors, such as stress, may also alter the way that people respond to drugs. In addition, the development of *tolerance*—the progressive need that accompanies chronic use 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, accompanied by negative affective states—is also developing. Together, these insights on abuse and addiction are leading to new therapies.

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. Immediately after exposure to nicotine, there is a "kick" caused in part by the drug's stimulation of the adrenal glands and resulting discharge of epinephrine. The rush of adrenaline stimulates the body and causes a sudden release of glucose as well as 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 pleasure and motivation. This mechanism is thought to underlie the pleasurable sensations experienced by many smokers.

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 all appear to be equally effective in treating more than 1 million people addicted to nicotine. These techniques are used to relieve withdrawal



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 the cortex, hippocampus, amygdala, and nucleus accumbens.

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, as well as totally eliminating exposure to smoke and its deadly contents. The first non-nicotine prescription drug, bupropion, an antidepressant marketed as Zyban, has been approved for use as a pharmacological treatment for nicotine addiction. Behavioral treatments are important for helping an individual learn coping skills for both short- and long-term prevention of relapse.

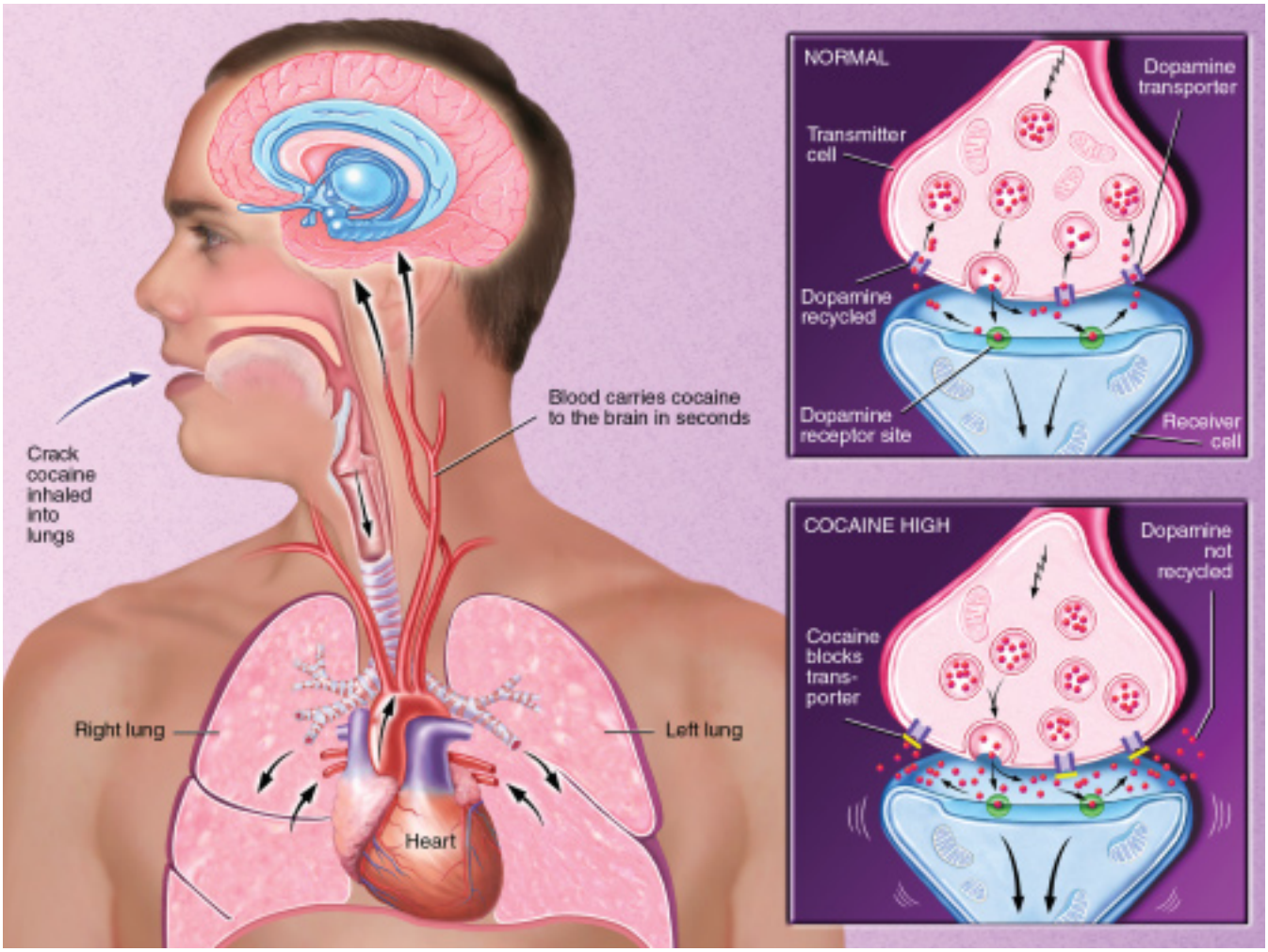
Psychostimulants In 2003, there were an estimated 2.3 million chronic cocaine users and 5.9 million occasional cocaine users in the United States. A popular chemically altered form of cocaine, crack, is smoked. It enters the brain in seconds, producing a rush of euphoria and feelings of power and self-confidence. The key biochemical factor that underlies the reinforcing effects of psychostimulants is the brain chemical dopamine. We feel pleasure when dopamine-containing neurons release dopamine into specific brain areas that include a special portion of the *nucleus accumbens.* Cocaine and amphetamines produce intense feelings of euphoria by increasing the amount of dopamine that is available to send messages within the brain reward system.

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 function and the activity of another brain chemical, serotonin, 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.

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 flu-like discomfort to major physical ailments, including severe muscle pain, stomach cramps, diarrhea, and unpleasant mood.

Opiates, like psychostimulants, increase the amount of dopamine released in the brain reward system and mimic the effects of endogenous opioids such as opioid peptides. 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.



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.

A standard treatment for opiate addiction involves *methadone*, a long-acting oral opiate that helps keep craving, withdrawal, and relapse under control. Methadone helps opiate addicts rehabilitate themselves by preventing withdrawal symptoms that are powerful motivators of drug use. A synthetic opiate, known as LAAM, can exert its effects on heroin for up to 72 hours with minimal side effects when taken orally. In 1993, the Food and Drug Administration approved the use of LAAM for treating patients addicted to heroin. Its long duration of action permits dosing just three times per week, eliminating the need for daily dosing. LAAM will be increasingly available in clinics that already dispense methadone. Naloxone and naltrexone are medications that also block the effects of morphine, heroin, and other opiates. As antagonists, they are especially useful as antidotes. Another medication to treat heroin addiction, buprenorphine, causes weaker opiate effects and is less likely to cause overdose problems. Buprenorphine is expected to become an important treatment.

Alcohol Although legal, alcohol is highly addictive. Alcohol abuse and alcohol addiction — sometimes referred to as alcoholism or alcohol dependence — are the nation's major drug problem, with some people being more susceptible than others. 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. Chronic liver diseases, including cirrhosis — the main

chronic health problem associated with alcohol addiction — 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.

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 GABA receptor can calm anxiety, impair muscle control, and delay reaction time. At higher doses, alcohol also decreases the function of NMDA receptors that recognize the neurotransmitter glutamate. This interaction can cloud thinking and eventually lead to coma.

Attention deficit hyperactivity disorder (ADHD) was first described more than 100 years ago. Today it is the focus of hundreds of studies.

Researchers are developing treatments that interfere with molecules, such as the opioid peptides, that trigger alcohol's positive reinforcing effects. One such drug, naltrexone, recently has been approved for treating alcoholism.

Marijuana This drug can distort perception and alter 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 THC receptors. 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 a natural internal chemical called *anandamide*, and they are now working to see how this chemical affects brain function.

Club Drugs Ecstasy, herbal ecstasy, rohypnol ("roofies"), GHB, and ketamine are among the drugs used by some teens and young adults as part of rave and trance events, which are generally night-long dances, often held in warehouses. The drugs are rumored to increase stamina and to produce intoxicating highs that are said to deepen the rave or trance experience. Recent hard science, however, is uncovering the serious damage that can occur in several parts of the brain from use of some of these drugs.

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.

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 may link ecstasy use to long-term damage to those parts of the brain critical to thought, memory, and pleasure.

Rohypnol, GHB (gamma hydroxy-butyrate), and ketamine are predominantly central nervous system depressants. Because they are often colorless, tasteless, and odorless, they can be easily added 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. Also, rohypnol may be lethal when mixed with alcohol and other depressants. Since about 1990, GHB has been abused in the United States for 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 for use as a general anesthetic in both human and veterinary medical practice.

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) was first described more than 100 years ago. Today it is the focus of hundreds of studies. Characterized by excessively inattentive, hyperactive, or impulsive behaviors, ADHD affects an estimated 2 million children in the United States, or 3 percent 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 areas of a child's life — at school, among friends, or at home, for example. Adults must show impairment at home and at work. Normal children sometimes show similar behavior, and other conditions, disorders, or environmental triggers — such as novelty — may also be present with ADHD children; therefore, diagnosis requires a comprehensive evaluation, using parent and teacher rating scales, a clinical interview, and testing. Currently, ADHD is diagnosed solely on the basis of behavioral symptoms.

Some studies show a correlation between ADHD and changes

in brain structure, suggesting the possibility of using neuroimaging techniques in the future to help identify targets for treatment or to help distinguish ADHD symptoms from those stemming from a learning disability. ADHD also is thought to have a strong genetic influence.

In addition to behavioral therapy, ADHD is commonly treated with medication—largely stimulants. Ritalin, one brand name under which the stimulant methylphenidate is sold, is one of the most widely prescribed drugs for treating ADHD. Its use is controversial. Debate about treatment with Ritalin centers on the benefits of a more focused child, on the one hand, and doubts about the long-term risks of exposing children to psychotropic drugs, on the other.

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 an estimated 4 to 5 million Americans. By the year 2040, it is predicted to affect approximately 14 million individuals in the United States.

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.

The earliest symptoms are forgetfulness and memory loss; disorientation to time or place; and difficulty with concentration, calculation, language, and judgment. Some patients have severe behavioral disturbances and may even become psychotic. The illness is progressive. In the final stages, the affected individual is incapable of self-care. Unfortunately, no effective treatments exist, and patients usually die from pneumonia or some other complication. AD, which kills 100,000 people a year, is one of the leading causes 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. At present, final confirmation of the diagnosis requires examination of brain tissue, usually obtained at autopsy.

The causes and mechanisms of the brain abnormalities are not yet fully understood, but great progress has been made through genetics, biochemistry, cell biology, and experimental treatments. Microscopic examination of AD brain tissue shows abnormal accumulations of a small fibrillar peptide, termed a *beta amyloid*, in the spaces around synapses (*neuritic plaques*) and by abnormal accumulations of a modified form of the protein tau in the cell bodies of neurons (*neurofibrillary tangles*). The plaques and tangles are mostly in brain regions important for memory and intellectual functions.

In cases of AD, reductions occur in levels of markers for several neurotransmitters, including acetylcholine, somatostatin, monoamine, 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.

Rare individuals with AD have a dominantly inherited form of the disease. These patients often have early-onset illness. Recently, scientists have identified mutations in AD-linked genes on three chromosomes. The gene encoding the *amyloid precursor protein* is on chromosome 21. In other families with early-onset AD, mutations have been identified in the presenilin 1 and 2 genes, which are on chromosomes 14 and 1, respectively. *Apolipoprotein* E (apoE), a chromosome 19 gene, which influences susceptibility in late life, exists in three forms, with apoE4 clearly associated with enhanced risk.

Treatments are available mostly only for some symptoms of AD, such as agitation, anxiety, unpredictable behavior, sleep disturbances, and depression. Three drugs treat cognitive symptoms in patients with mild to moderate Alzheimer's. These agents improve memory deficits temporarily. Several other approaches, such as antioxidants, are being tested.

An exciting area of research is the use of approaches in which genes are introduced in mice. These transgenic mice carrying mutant genes linked to inherited AD develop behavioral abnormalities and some of the cellular changes that occur in humans. It is anticipated that these mice models will prove very useful for studying the mechanisms of AD and testing novel therapies.

Moreover, researchers have begun to knock out genes playing critical roles in the production of amyloid. These enzymes, termed beta and gamma secretase, which cleave the amyloid peptide from the precursor, are clearly targets for development of drugs to block amyloid.

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, CT and MRI scans, and X-rays of the spinal cord help identify the disease and rule out other disorders. Still, diagnosis is often difficult because its causes 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 5–10 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*, located on chromosome 21, that were linked to the presence of this disorder. 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 diagnosed, physical therapy and rehabilitation methods 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 significant 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 phobias such as fear of heights, agoraphobia, and social anxiety disorder; generalized anxiety disorder; post-traumatic stress disorder; panic disorder; and obsessive-compulsive disorder (OCD). Some can keep people completely housebound or, as in the case of panic disorder, contribute to suicide. Many of these disorders occur with depression, and individuals so afflicted are at 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 as repeatedly washing hands, or checking that doors are locked or stoves turned off. The illness is estimated to affect 3.8 million Americans annually. Social learning and genetics likely play a role in developing the disorder. Positron emission tomography (PET) scans reveal abnormalities in both cortical and deep areas of the brain, suggesting central nervous system changes in OCD patients.

The most widespread mental illnesses, anxiety disorders annually affect an estimated 12.6 percent of the adult population, or 24.8 million Americans.

Scientists 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.

Serotonergic antidepressants — especially the tricyclics, such as clomipramine, and the selective serotonin reuptake inhibitors (SSRIs), such as sertraline (Zoloft) and paroxetine (Paxil) — are effective in treating OCD. A specialized type of behavioral intervention, *exposure and response prevention*, is also effective in many patients.

Panic disorder, which affects 2.4 million Americans annually, 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, their lives may constrict until they develop *agoraphobia*, becoming virtually housebound.

Phobia is an intense, irrational fear of a particular object or situation. Individuals can develop phobias of almost anything, such as dogs, dating, 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.

Experiencing or witnessing a crime or being a victim of sexual abuse can lead to a form of stress that can last a lifetime. Termed post-traumatic stress disorder, the condition afflicts 5.2 million Americans aged 18 to 54 each year.

The recent discovery of brain receptors for the benzodiazepine antianxiety drugs has sparked research to identify the brain's own antianxiety chemical messengers. This finding may lead to ways to regulate this brain system and correct its possible

defects in panic anxiety disorders. PET scans reveal that during such attacks, the tip of the brain's temporal lobe is unusually active compared with controls. When normal people expect to receive a shock to the finger, the same general area is activated.

The SSRIs, the serotonin-norepinephrine reuptake inhibitors (SSRNs), cognitive behavior therapy, or a combination of these are now the first-choice treatments of most anxiety disorders. Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and high-potency benzodiazepines are also effective for many of these disorders.

Autism

Almost one in every 166 babies born in the United States, or about 1.5 million Americans, will develop some form of autism. The numbers are staggering, considering that in the 1970s, the estimates were just a few in 10,000 births. The rapid rise in incidence is a key mystery to be solved.

Characterized by communication difficulties, delayed development of language, impaired social skills, communication difficulties, and narrow, obsessive interests or repetitive behaviors, autism is extremely isolating. There is no cure, but children with autism respond well to a highly structured environment and specialized education and language intervention programs. The earlier the interventions begin, the better the outcome.

Currently, autism is diagnosed on the basis of behavioral symptoms. New research shows that brain imaging data is 95 percent accurate in identifying how the brains of individuals with autism differ from those of typically developing young children.

Research has also revealed that genetic factors contribute to the development of autism. Success in identifying the so-called "vulnerability" genes for autism may allow scientists to develop an improved diagnostic technique that combines the detection of behavioral indicators with biological abnormalities to better identify infants and toddlers at risk for autism.

A clear understanding of the biological abnormalities that alter brain development in autism could guide the formulation of new therapies that target the disorder on a molecular level. These research efforts will mean that health-care practitioners will be better armed with the necessary tools for early diagnosis and more effective interventions.

Brain tumors

Although brain tumors are not always *malignant*—a condition that spreads and becomes potentially lethal—these growths are always serious because they can cause pressure in the brain and compression of nearby structures, interfering with normal brain activity.

Primary brain tumors arise within the brain, whereas secondary brain tumors spread from other parts of the body through the bloodstream. For tumors starting in the brain, about 60 percent of which are malignant, the cause is unknown. Tumors that begin as cancer elsewhere and then spread to the brain are always malignant.

The incidence of primary brain tumors is about 12 per 100,000 population. About 36,000 new cases occur in the United States annually. Because of difficulties in diagnosing and classifying brain tumors, exact statistics on secondary tumors are unknown.

Symptoms vary according to location and size. The compression of brain tissue or nerve tracts, as well as expansion of the tumor, can cause symptoms such as seizures, headaches, muscle weakness, loss of vision or other sensory problems, and speech difficulties. An expanding tumor can increase pressure within the skull, causing headache, vomiting, visual disturbances, and impaired mental functioning. Brain tumors are diagnosed with MRI (magnetic resonance imaging) and CT (computed tomography) scanning.

Surgery is a common treatment 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. Steroid drugs relieve swelling and other symptoms.

Available treatments are primarily palliative and at best prolong life by a few weeks. A number of promising experimental therapies, however, are currently being explored. These include *antiangiogenic 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 cancer cells and kill them.

Down syndrome

Down syndrome, the most frequently occurring chromosomal abnormality, appears in one of every 800 to 1,000 babies. It 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 it is not 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 one in 365 births; at age 40, it is one in 110. It is important to note, however, that the average age of women who give birth to children with Down syndrome is 28, because younger women give birth more often. Prenatal screening tests, such as the Triple Screen and Alpha-fetaprotein Plus, can accurately detect Down syndrome in about 60 percent of fetuses.

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 mental retardation; 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. All people with Down syndrome show the neuropathological changes of Alzheimer's disease by age 40, and most show cognitive decline by age 60.

Babies with Down syndrome develop much like typical children, but at a somewhat slower rate. They will 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. Individuals with Down syndrome 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.

Huntington's disease

Affecting some 30,000 Americans and placing another 200,000 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. However, HD researchers and genetic counselors 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.

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 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. But the cause of HD probably involves the gain of a new and toxic function. Cell and transgenic animal models can replicate many features of the disease and are now being used to test new theories and therapies. Clinical and observational trials are being conducted. Any of these may yield an effective treatment that would slow the progression of or delay onset of the disease while researchers continue working toward a cure.

Affecting some 30,000 Americans and placing another 200,000 at risk, Huntington's disease is now considered one of the most common hereditary brain disorders.

Learning disorders

An estimated 10 percent of the population, as many as 25 million Americans, have 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 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 of 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 dyslexia is a persistent, chronic condition. It does not represent a transient "developmental lag."

There is now a strong consensus that the central difficulty in most forms of dyslexia reflects a deficit within the language system — and more specifically, in a component of the language system called phonology. This is illustrated in difficulty transforming the letters on the page to the sounds of language. A current debate exists as to whether this difficulty reflects a general sound-processing deficit or a problem specific to sounds of language, phonemes, and conscious awareness of these sounds.

As children approach adolescence, one manifestation of dyslexia may be a very slow reading rate. Children may learn to read words accurately, but they 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.

A range of investigations indicates that there are differences in brain regions between dyslexic and nonimpaired readers, especially the temporo-parieto-occipital and frontal opercular regions. Recent data using functional brain imaging indicate 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 the letters to the phonologic structures they represent. The specific cause of the disruption of neural systems in dyslexia is thought to result from developmental missteps relating to neuronal migration to the cerebral cortex. It is clear that dyslexia runs in families, and active research aims to identify what appear to be several dyslexia-susceptibility genes.

An estimated 10 percent of the population, as many as 25 million Americans, have some form of learning disability involving difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities.

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.

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 two of three cases occurring in women. MS results in earning losses of about $2 billion annually for 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 replaced by scars of hardened *sclerotic* patches of tissue. Such lesions are called *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, which interferes with the transmission of signals.

Siblings of people with MS are 10 to 15 times more likely than others 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. Thus, both genetic and environmental factors are probably involved in the cause. An infection acquired during the first 15 years of life may be responsible for triggering the disease in a genetically susceptible individual.

The most common symptoms are blurred vision, awkward gait, numbness, and fatigue. These can occur singly or in combination, vary in intensity, and last from several weeks to months. In some patients, symptoms include slurred speech, weakness, loss of coordination, uncontrollable tremors, loss of bladder control, memory problems, depression, and paralysis. Muscle spasticity can affect balance and coordination, causing pain 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 control relapsing forms of MS. 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. Promising new agents to control MS or to alleviate its symptoms are in clinical trials.

Neurological AIDS

In 2003, about 4.8 million people became infected with *human immunodeficiency virus* (HIV), the largest number since the onset of the AIDS epidemic; 38 million are now living with HIV. 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 400,000 of 6 million people are receiving such treatment. Women now represent nearly half of all worldwide cases.

Although the principal target of HIV is the immune system, the nervous system also may be profoundly affected. Some 20

percent to 40 percent of 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*. Nonetheless, HIV infection appears to be the prime mover in this disorder because antiviral treatment may prevent or reverse this condition in some patients.

Experts believe that serious neurologic symptoms are uncommon early in HIV/AIDS 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 computed tomography (CT) and magnetic resonance imaging (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, however.

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 the cognitive abnormalities attributed to brain HIV infection.

Peripheral neuropathy is also a major neurological problem seen commonly 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 of the antiretroviral drugs that have mitochondrial toxicity and tend to make the neuropathies more frequent and serious. In current cohorts of advanced patients, more than half have neuropathy, making it a major area for preventive and symptomatic therapeutic trials.

Despite remarkable progress in developing therapy, some patients develop these problems and fail to respond to treatment, thus requiring additional approaches to prevention and treatment of these symptoms. In addition, because of immunodeficiency in HIV patients, encountering otherwise rare opportunistic infections and malignancies is still relatively common.

Neurological trauma

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. These treatments include better imaging techniques, methods to understand and improve the brain's ability to regenerate and repair itself, and improved rehabilitation techniques.

Some 750,000 people suffer traumatic head injuries requiring hospitalization each year, and roughly 100,000 die — many before reaching the hospital. Economic costs approach $25 billion annually.

Greater access to and use of computed tomography (CT) and magnetic resonance imaging (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 have a pressure-monitoring device inserted into their brain, usually within the lateral ventricle. As swelling progresses, the CT or MRI images of the brain show the surface of the brain being pressed against the inside of the skull. This pressure inside the skull increases and can become life-threatening. Patients so injured are not allowed to lie flat on their backs in bed. Rather, they are positioned in a modified sitting position, which raises the head to reduce pressure effects within the skull.

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. 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. Once blood leaves its respective vessels and comes into direct contact with brain tissue, it can add focal pressure, thereby reducing cerebral blood flow, or it can by itself be toxic to brain cells. As a consequence, once detected, it is usually surgically removed. Contusions can also be troubling, because they can increase pressure as well as contribute to the development of post-traumatic epilepsy. Depending on the location and type, they are also candidates for surgical removal.

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, violence, and falls. Economic costs approach $10 billion a year.

Researchers have found that people who suffer spinal cord injuries 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 this knowledge, researchers hope to decipher the precise order of chemical reactions that lead to damage and to develop new therapies to block these reactions.

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. It appears that humans with spinal cord injury also respond to training interventions.

Recently, 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 "jumpstart" the pathway that stimulates *neurogenesis*, the birth of new nerve cells. Researchers are also 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.

Schizophrenia is thought to reflect changes in the brain, possibly caused by disease or injury at the time of birth, and a genetic disposition that may be exacerbated by environmental stress.

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 disease or injury at the time of birth, and a genetic disposition that may be exacerbated by environmental stress. Recently, several genes have been identified that appear to increase the risk of developing schizophrenia. Brain systems using the chemicals dopamine, glutamate, and GABA appear to be particularly involved in the pathogenesis of the disorder. 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 positron emission tomography (PET) and *functional magnetic resonance imaging* (fMRI) taken during intellectual tasks show abnormal functioning in specific brain areas of people with this illness.

The disorder usually begins between the ages of 15 and 25. Some patients fully recover following treatment, but most continue to have moderate or severe symptoms, particularly in response to stress. About 15 percent of patients return to normal life after a single episode, 60 percent will have intermittent episodes throughout their lives, and another 25 percent will not recover their ability to live as independent adults. Deficits in cognition, particularly involving attention and memory, are frequent, lifelong manifestations in most patients, even in those who show good recovery from acute symptoms.

After a long search for an effective antipsychotic medication, scientists synthesized the drug *chlorpromazine* during the late 1940s. By the 1950s, it was found to be useful in treating psychotic states and later became a mainstay of drug treatment.

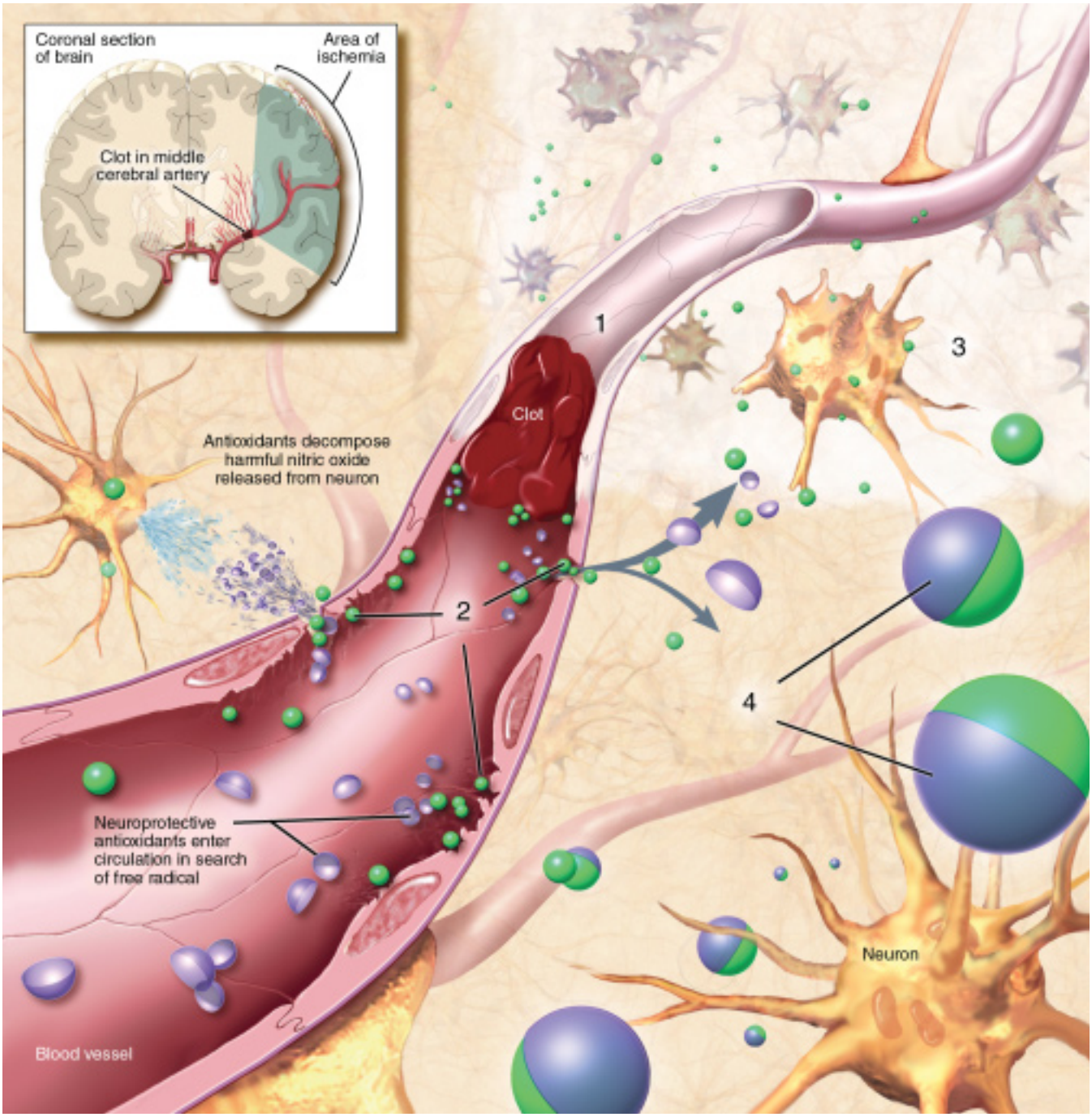
Since that time, many agents similar to chlorpromazine have been developed. When given as long-acting injections, these drugs reduce some symptoms and aid patients' readiness for adjustment back into their communities. Chronic use of the drugs, however, may cause abnormal muscle movements and tremors in some patients. Safer treatments are being sought.

Thus far, most drugs are successful in treating hallucinations and thought disorder. *Clozapine* acts somewhat differently from other antipsychotic drugs. It treats the approximately 30 percent of patients who are not helped by conventional medications. The drug can, however, induce a potentially fatal blood disorder, *agranulocytosis*, in about 1 percent of patients. To prevent this disorder, patients must take regular weekly to biweekly blood tests, a precaution that makes using the drug very costly. Several new antipsychotics — *risperidone, olanzapine, quetiapine, ziprasadone*, and *aripiprazole* — offer some of the benefits of clozapine without risk of angranulocytosis, but their long-term side effect profiles are not fully known.

Stroke

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 understandings of the mechanisms that lead to the death of neurons following stroke and devising ways to protect these neurons.



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.

Stroke affects roughly 700,000 Americans a year—150,000 of whom die; total annual costs are estimated at $51.2 billion.

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.

Stroke often occurs in individuals over 65 years of age, yet a third are younger. Stroke tends to occur more in males and blacks and in those with diabetes, high blood pressure, heart disease, obesity, high cholesterol, and a family history of stroke.

In addition to tPA, increased use of preventive measures is battling the disorder. Controlling risk factors such as obesity, blood pressure, diabetes, and high cholesterol can help prevent stroke. Other specific treatments involving surgery can clear clogs in the arteries of the neck region and help prevent a cutoff of blood supply.

Treatments that target the heart's blood flow can prevent stroke. Surgery can help repair damaged heart valves. Anticoagulant drugs can reduce the chance 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.

Another promising possibility is 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 an estimated one in 500 Americans, roughly 200,000 people. Males are affected three to four times as often as females.

Symptoms usually appear between the ages of four and eight, 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. Generally, this disorder lasts a lifetime, but one-third of patients may experience a remission or decrease in symptoms as they get older. Most people with TS do not require medication; their symptoms are mild and do not affect functioning.

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

The disorder seems to result from a hypersensitivity of dopamine receptors. Another neurotransmitter, serotonin, also has been implicated. The most effective drugs for control of movements, such as *haloperidol,* act by blocking the overactive system. Other symptoms, such as obsessive-compulsive traits and attention deficit disorder, often require treatment with other classes of drugs that act on serotonin.

The neuroleptic drugs haloperidol and *pimozide* have been the mainstays of treatment for the movements and vocalizations, but not for the associated conditions that so many people with TS experience. The neuroleptics are not perfect medications and are prescribed only when the movements are fairly severe and interfere with functioning. They can cause disturbing side effects—abnormal involuntary movements, stiffness of the face and limbs, or sedation and weight gain—in some patients. Recently, newer medications, such as low doses of selective serotonin reuptake inhibitors like risperidone, have been found effective in some patients. Other classes of medications are prescribed to reduce the symptoms of the comorbid conditions.

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 trace brain electrical activity in response to a specific external stimulus. In this method, electrodes placed in specific parts of the brain — depending on which sensory system is being tested — make recordings that are then processed by a computer. The computer makes an anaylsis 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 killed 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 can be later 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 radiation 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 brain based on the amount of radiation emitted in these different areas.

PET studies have helped scientists understand more about how drugs affect the brain and what happens during learning, when using language, and in certain brain disorders — such as stroke, depression, and Parkinson's disease. Within the next few years, PET could enable scientists to identify the biochemical nature of neurological and mental disorders and determine how well therapy is working in patients. 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 an accelerator nearby 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, 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.

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 MRI provides early evidence of potential damage from stroke, allowing physicians to administer proper treatments early.

Magnetic resonance spectroscopy (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 activated 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. 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.

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, they can be used even to study young 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 than 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 related technique, the *event-related optical signal*, records how light is scattered in response to cellular changes that arise when neurons fire and potentially can assess very fast — well under a second — changes in neural activity.

Gene diagnosis

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

New gene diagnosis techniques now make 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 and susceptibility to certain tumors.

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

Scientists have tracked down the gene on chromosome 4 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 Huntington's disease. Other neurodegenerative disorders have been attributed to expanded CAG repeats in other genes. The mechanisms by which these expansions caused adult-onset neurodegeneration is 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.

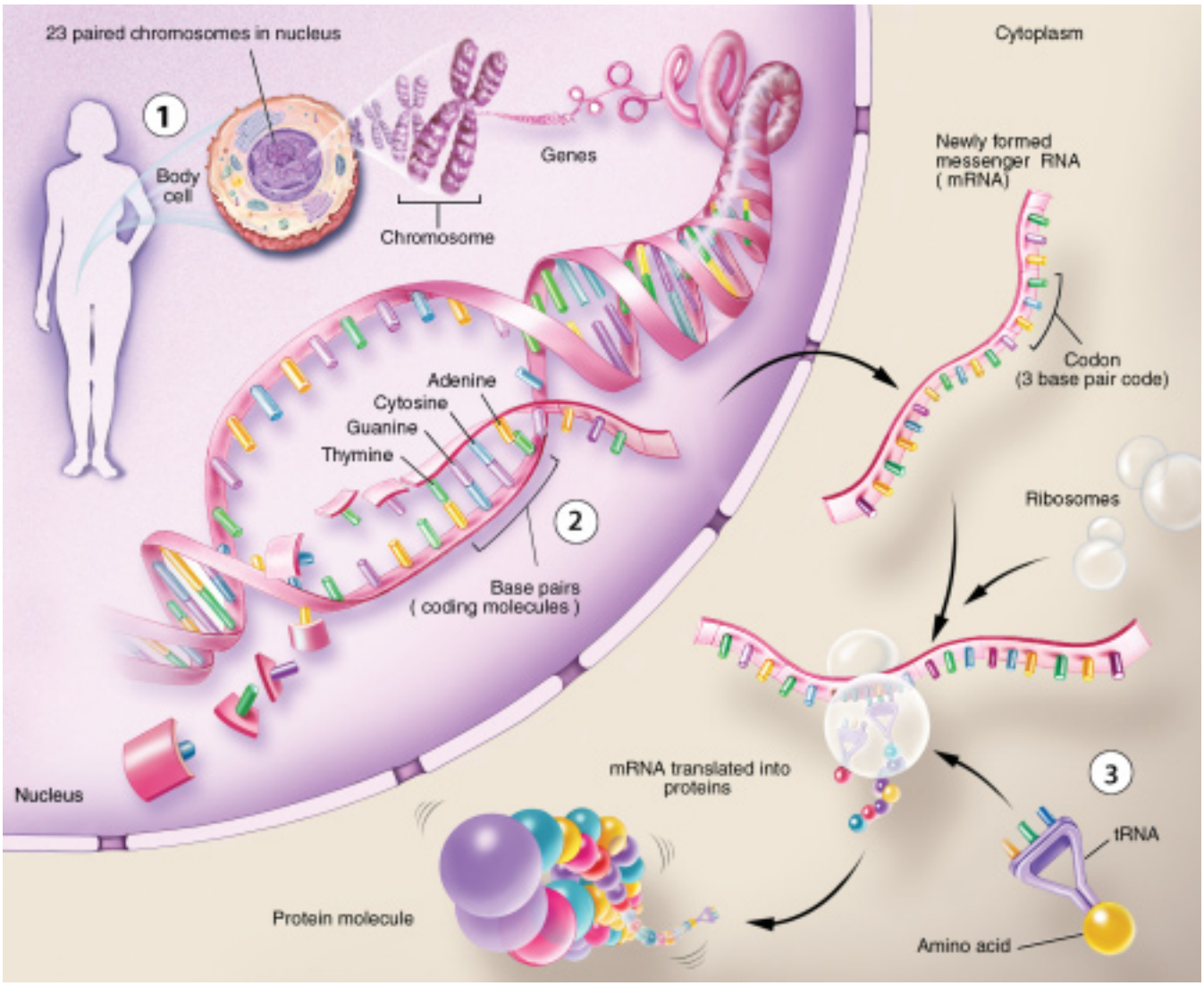
Gene mapping has led to the localization on chromosome 21 of the gene coding for the beta amyloid precursor protein that is abnormally cut to form the smaller peptide, beta amyloid. It is this peptide that accumulates in the senile plaques that clog the brains of patients with Alzheimer's disease. This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

Several other genetic factors have been identified in Alzheimer's disease, including genes for two proteins, presenilin 1 and presenilin 2, located on chromosomes 14 and 1, respectively. A risk factor for late-onset Alzheimer's is the gene for the apolipoprotein E protein located on chromosome 19.

Gene mapping has enabled doctors to diagnose *fragile X mental retardation*, the most common cause of inherited mental retardation. Scientists have now identified this gene, which is important for neuronal communication. Several groups of scientists are investigating whether there are genetic components to schizophrenia, bipolar disorder, and alcoholism, 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 — 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, different 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.



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).

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 specifically 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* in the brain, 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 and delay 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.

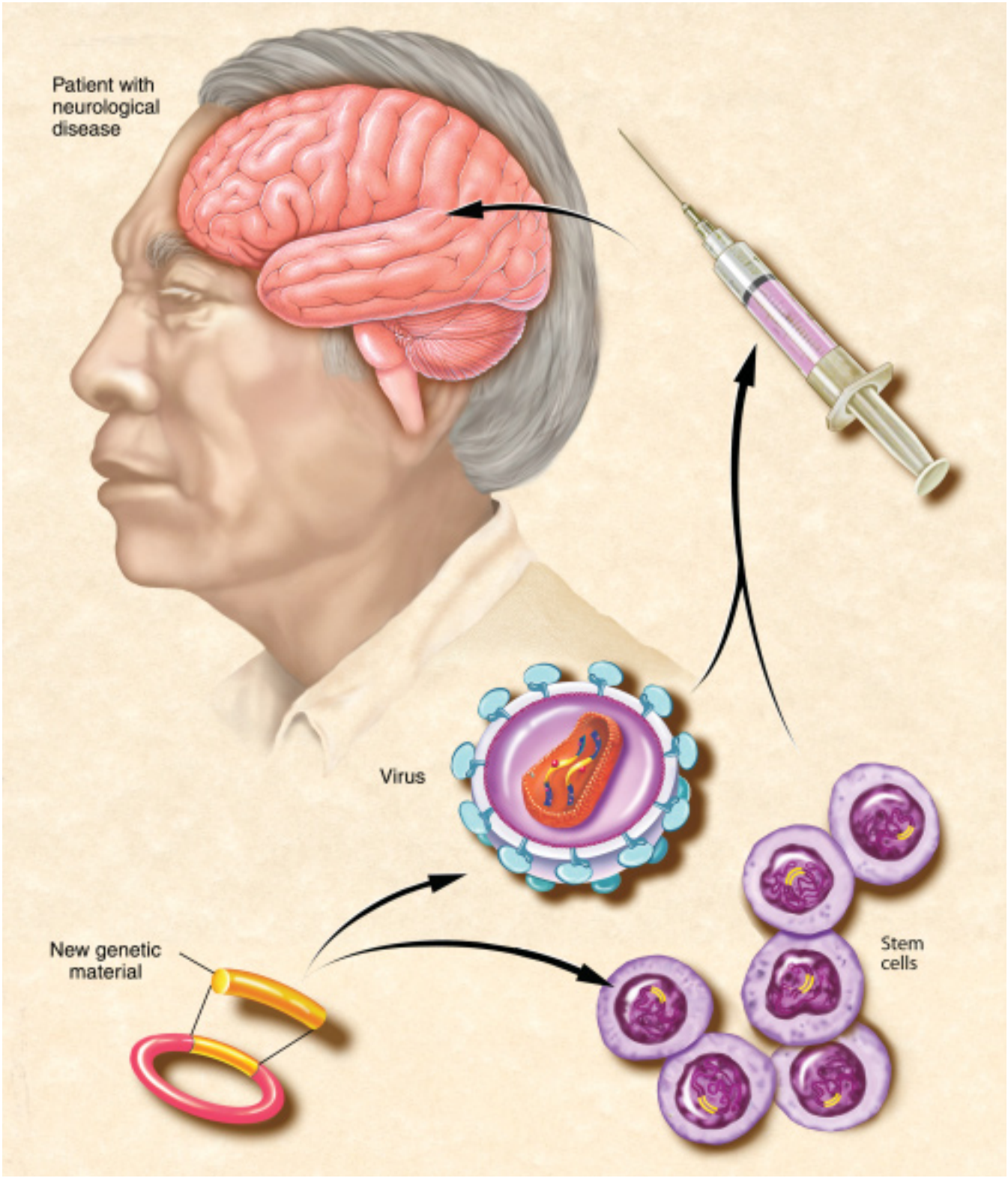
Recently, several new factors have been identified. They are potentially useful for therapy, but scientists must first understand how they may influence neurons. Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) may be treated in the future with trophic factors or their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

In an interesting twist on growth factor therapy, researchers demonstrated that a 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. Treated rats showed large improvements in their ability to walk after spinal cord damage.

In these experiments, scientists cut one of the major groups of nerve fiber tracts in the spinal cord that connect it to the brain. When an antibody directed against the factor Nogo-A was administered to the spinal cords or brains of adult rats, enhanced sprouting of nerve fibers occurred where the spinal cord had been cut. Within two to three weeks, some fibers grew to the lower level of the spinal cord and, in some animals, along its whole length. In untreated spinal cord-injured rats, the maximum distance of nerve regrowth rarely exceeded one-tenth of an inch. This research could eventually have clinical implications for spinal cord- or brain-damaged people.

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. This approach has shown some promise in Alzheimer's disease, although it also carries risks. Another new approach combines



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.

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 can be delivered either as proteins or as genes.

Promising preliminary results have been obtained for Huntington's, Parkinson's, Alzheimer's, and prion diseases. For example, fruit flies (*Drosophila*) that get Huntington's disease (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 can 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 Parkinson's disease. 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 Alzheimer's and prion drugs have recently been described using these methods.

Several neurodegenerative diseases are caused by the accumulation of abnormal proteins. If the cells made much less of such proteins to begin with, then 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.

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.

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. 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 to act as "Trojan horses," carrying therapeutic genes to the brain to correct nervous system diseases. The viruses include *herpes simplex type 1 virus* (HSV), *adenovirus*, *lentivirus*, *adeno-associated virus*, and others naturally attracted to neurons. It has been found that all can be modified to carry new genes to cells in tissue culture and in the rodent central nervous system. HSV and adenovirus vectors have also 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. And this is no different for neuroscientists. With the tremendous advances in the field, many scientists and nonscientists alike have sensed a critical turning point. Researchers are now on the threshold of understanding some fundamental principles of brain function, and are even beginning to develop treatments for some of the most devastating neurological diseases and conditions. At the same time, much of this knowledge and implications for treatments and diagnostics raise 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 such as moral reasoning, decision-making, and behavior. Much discussion will focus on neuroethics in the coming years.

Neuroethics is the part of bioethics that considers the intended and unintended consequences of neuroscience in medical practice, research, and society at large. Neuroethics also deals with issues that touch no other area of science — our sense of self, our personalities, and our behavior. And brain science can change these aspects in significant ways. Neuroethics has been the subject of several conferences that have attracted a wide range of thinkers, basic and clinical neuroscientists, economists, philosophers, journalists, sociologists, lawyers, and others. Some major topics include the subjects listed below.

Need for ethical framework It is very likely that the potential application of new knowledge to human behavior will generate a great deal of ethical and public policy concern. Neuroethics spans fields as diverse as forensic psychiatry, athletics, education, college admissions, corporate hiring, policing, admission to seminaries, and the law. Information about why people, and categories of people, behave as they do will lead those in these fields to eagerly use new knowledge about the human brain. As the brain sciences advance, researchers are working toward developing a paradigm of morals that might help guide the use of the new knowledge.

Morality Learning right from wrong enhances skills in cooperative behavior and helps people know when to modify their social interactions. Discoveries in neuroscience indicate that learning right from wrong may depend on the development of brain tissue during the adolescent years. Given this possibility, researchers are considering the implications of how problems in brain development may affect moral behaviors such as self-control. For example, could some individuals have a biological handicap that impairs their ability to obey the law? Researchers also are investigating the ethical issues related to using drugs that influence behaviors like self-control.

Social behavior Neurobiological factors may play a role in disturbances in social behavior. Patients who have malfunctions caused by disease in selected brain regions exhibit antisocial behav-

ioral change. Because modern neuroscience can investigate the mechanisms behind disturbed behaviors, society must ponder the manner in which it manages individuals who violate its rules by taking into account those with medical conditions. This situation raises questions regarding the punishment and treatment of such individuals.

Social policy Since neuroscience has the potential to transform our understanding of human nature, we may be able to make predictions about an individual's future, including the risk for ill health and cognitive impairment, potential success in school or employment, and violent behavior or addiction to drugs. Of particular concern is the potential role for neuroscience in delineating the boundary between what society views as normal and what is deemed pathological. For example, many boys are being prescribed medicines for hyperactivity, such as Ritalin, for conditions that many worry may not be clear-cut brain diseases. Troubling questions related to this phenomenon include: Who should have access to such agents? If learning can be sped up and attention enhanced through pharmaceuticals, should such drugs be available to all, or should resources be devoted to transforming only the environment of the classroom?

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Genetics Sequencing the human genome — identifying all the approximately 20,000 to 25,000 genes in humans — went hand-in-hand with an investment in studying the ethical, legal, and social implications of human genetics. Neuroethics may play an important role in issues arising from genetics, such as the social consequences of using DNA to predict the future. Should patients with a family history of a neurological or psychiatric disorder be genetically tested even though no treatment is available?

Brain injury Since traumatic brain injury may cause a person to experience significant cognitive, personality, emotional, and behavioral changes, sufferers may become legally incompetent. Traumatic brain injury may excuse or mitigate a person's responsibility for acts that otherwise would be classified as crimes. But the medical profession sometimes can have trouble determining a person's preinjury behavior compared with postinjury behavior. This poses serious problems for clinical evaluators as well as for the legal system.

Neurological disorders With the likelihood of developing effective treatments for disorders such as Alzheimer's disease (AD), in which brain cells die at a progressive rate, it will be important to identify individuals who are at risk in order to prevent brain damage at the earliest stage. Yet there is little precedence for such early intervention. Moreover, AD is a genetically complex disorder with multiple genes and degrees of risk associated with each. Thus, the medical profession faces challenges in ensuring that candidates for treatment understand their risk for severity of AD and evaluating the potential risks and benefits of treatments that may be harmful.

Informed consent in research Special care must be taken in the informed-consent process and throughout the research protocol 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.

Environmental influences Many are concerned about the possible implications of research indicating that most of the brain gets built after birth and that it uses experiences from the outside world to form its circuits. With this as background, scientists are discussing whether society has a moral obligation to ensure that millions of children no longer grow up in violent and impoverished environments that can stunt their brains.

At this stage, the field of neuroethics raises more questions than answers. It poses challenges to scientists and to 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 the field has always 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 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 corticosteroids 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 A neurotransmitter, drug, or other molecule that stimulates receptors to produce a desired reaction.

ALZHEIMER'S DISEASE The major cause of dementia most prevalent in the elderly, it inflicts enormous human financial cost on society. The disease is characterized by 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 also 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 A drug or other molecule that blocks receptors. Antagonists inhibit the effects of agonists.

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 Clusters of neurons, which include the caudate nucleus, putamen, globus pallidus, and substantia nigra, located deep in the brain that play an important role in the initiation of movements. 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.

CHOLECYSTOKININ A hormone released from the lining of the stomach during the early stages of digestion that acts as a powerful suppressant of normal eating. It also is found in the brain.

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 transducing motion into neurotransmission 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.

DEPRESSION A mental disorder characterized by depressed mood and abnormalities in sleep, appetite, and energy level.

DENDRITE A tree-like 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 such as reward and plays a role in schizophrenia and drug abuse.

DORSAL HORN An area of the spinal cord where many nerve fibers from peripheral pain 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 POTENTIALS 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.

FRONTAL LOBE One of the four divisions (the other lobes are the parietal, temporal, and occipital) of each hemisphere 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.

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.

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.

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.

MELATONIN Produced from serotonin, melatonin is released by the pineal gland into the bloodstream. Melatonin affects physiological changes related to time and lighting cycles.

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 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.

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.

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 paucity of 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 A process that modifies the properties of neurons by acting on an ion channel, neurotransmitter receptor, or other regulatory protein. During phosphorylation, a phosphate molecule is placed on a protein and results in the 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.

PINEAL GLAND An endocrine organ found in the brain. In some animals, the pineal gland serves as a light-influenced biological clock.

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.

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.

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

STROKE The third-largest cause of death in the United States, stroke is an impeded blood supply to the brain. Stroke can be caused by a rupture of a blood vessel wall, an obstruction of blood flow caused by a clot or other material, or pressure on a blood vessel (as by a tumor). Deprived of oxygen, which is carried by blood, nerve cells in the affected area cannot function and die. Thus, the part of the body controlled by those cells cannot function either. 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.

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.

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