

# Alterations in the Nervous System

## CHAPTER

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The nervous system, in coordination with the endocrine system, provides the means by which cell and tissue functions are integrated into a solitary, surviving organism. It controls skeletal muscle movement and helps to regulate cardiac and visceral smooth muscle activity. The nervous system enables the reception, integration, and perception of sensory information; it provides the substratum necessary for intelligence, anticipation, and judgment; and it facilitates adjustment to an ever-changing external environment.

### NERVOUS TISSUE CELLS

The nervous system can be divided into two parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and spinal cord, which is

protected by the skull and vertebral column. The PNS is found outside these structures. Inherent in the basic design of the nervous system is the provision for the concentration of computational and control functions in the CNS. In this design, the PNS functions as an input-output system for relaying input to the CNS and for transmitting output messages that control effector organs, such as muscles and glands.

Nervous tissue contains two types of cells: neurons and supporting cells. The neurons are the functional cells of the nervous system. They exhibit membrane excitability and conductivity and secrete neurotransmitters and hormones, such as epinephrine and antidiuretic hormone. The supporting cells, such as Schwann cells in the PNS and the glial cells in the CNS, protect the nervous system and provide metabolic support for the neurons.

## Neurons

The functioning cells of the nervous system are called *neurons*. Neurons have three distinct parts: the soma or cell body and its cytoplasm-filled processes, the dendrites and axons (Fig. 36-1). These processes form the functional connections, or synapses, with other nerve cells, with receptor cells, or with effector cells. Axonal processes are particularly designed for rapid communication with other neurons and the many body structures innervated by the nervous system. Afferent, or sensory, neurons transmit information from the PNS to the CNS. Efferent neurons, or motoneurons, carry information away from the CNS (Fig. 36-1). Interspersed between the afferent and efferent neurons is a network of interconnecting neurons (interneurons or internuncial neurons) that modulate and control the body's response to changes in the internal and external environments.

The cell body of a neuron contains a large, vesicular nucleus with one or more distinct nucleoli and a well-developed rough endoplasmic reticulum. A neuron's nucleus has the same DNA

and genetic code content that is present in other cells of the body, and its nucleolus, which is composed of portions of several chromosomes, produces RNA associated with protein synthesis. The cytoplasm contains large masses of ribosomes that are prominent in most neurons. These acidic RNA masses, which are involved in protein synthesis, stain as dark Nissl bodies with basic histologic stains (see Fig. 36-1).

The dendrites (*i.e.*, "treelike") are multiple, branched extensions of the nerve cell body; they conduct information toward the cell body and are the main source of information for the neuron. The dendrites and cell body are studded with synaptic terminals that communicate with axons and dendrites of other neurons.

Axons are long efferent processes that project from the cell body and carry impulses away from the cell. Most neurons have only one axon; however, axons may exhibit multiple branching that results in many axonal terminals. The cytoplasm of the cell body extends to fill the dendrites and the axon. The proteins and other materials used by the axon are synthesized in the cell body and then flow down the axon through its cytoplasm.

The cell body of the neuron is equipped for a high level of metabolic activity. This is necessary because the cell body must synthesize the cytoplasmic and membrane constituents required to maintain the function of the axon and its terminals. Some of these axons extend for a distance of 1 to 1.5 m and have a volume that is 200 to 500 times greater than the cell body itself. Two axonal transport systems, one slow and one rapid, move molecules from the cell body through the cytoplasm of the axon to its terminals. Replacement proteins and nutrients slowly diffuse from the cell body, where they are synthesized, down the axon, moving at the rate of approximately 1 mm/day. Other molecules, such as some neurosecretory granules (*e.g.*, neurotransmitters, neuromodulators, and neurohormones) or their precursors, are conveyed by a rapid, energy-dependent active transport system, moving at the rate of approximately 400 mm/day. For example, antidiuretic hormone and oxytocin, which is synthesized by neurons in the hypothalamus, is carried by rapid axonal transport to the posterior pituitary, where the hormones are released into the blood. A reverse rapid (*i.e.*, retrograde) axonal transport system moves materials, including target cell messenger molecules, from axonal terminals back to the cell body.

## Supporting Cells

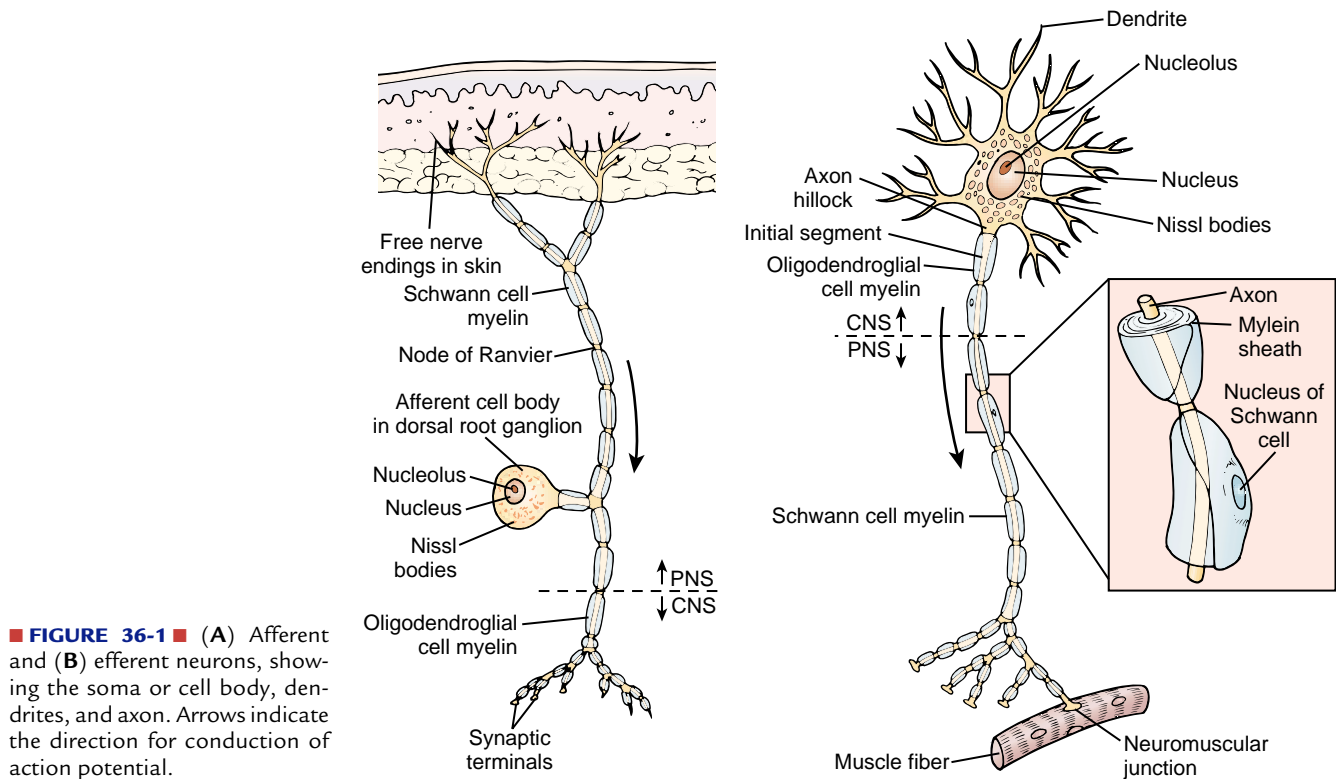
Supporting cells of the nervous system, the Schwann and satellite cells of the PNS and the several types of glial cells of the CNS, give the neurons protection and metabolic support. The supporting cells segregate the neurons into isolated metabolic compartments, which are required for normal neural function. Astrocytes, together with the tightly joined endothelial cells of the capillaries in the CNS, contribute to what is called the *blood-brain barrier*. This term is used to emphasize the impermeability of the nervous system to large or potentially harmful molecules.

The many-layered myelin wrappings of Schwann cells of the PNS and the oligodendroglia of the CNS produce the myelin sheaths that serve to increase the velocity of nerve impulse conduction in axons. Myelin has a high lipid content, which gives

### KEY CONCEPTS

#### THE STRUCTURAL ORGANIZATION OF THE NERVOUS SYSTEM

- The nervous system is divided into two parts: the CNS, which consists of the brain and spinal cord, and the PNS, which contains the input and output neurons that lie outside the CNS.
- The neurons, which are functioning cells of the nervous system, consist of a cell body with cytoplasm-filled processes, the dendrites, and the axons, which form the functional connections with other nerve or effector cells.
- There are two types of neurons: afferent neurons or sensory neurons, which carry information to the CNS, and efferent neurons or motoneurons, which carry information from the CNS to the effector organs.

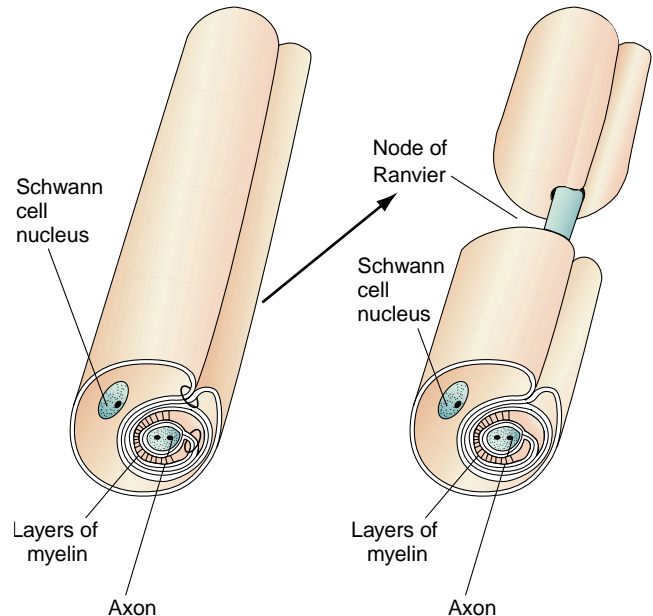


it a whitish color, and the name white matter is given to the masses of myelinated fibers of the spinal cord and brain. Besides its role in increasing conduction velocity, the myelin sheath is essential for the survival of larger neuronal processes, perhaps by the secretion of neurotrophic compounds. In some pathologic conditions, such as multiple sclerosis in the CNS and Guillain-Barré syndrome in the PNS, the myelin may degenerate or be destroyed, leaving a section of the axonal process without myelin while leaving the nearby Schwann or oligodendroglial cells intact. Unless remyelination takes place, the axon eventually dies.

### Supporting Cells of the Peripheral Nervous System

Schwann cells and satellite cells are the two types of supporting cells in the PNS. Normally, the nerve cell bodies in the PNS are collected into ganglia, such as the dorsal root and autonomic ganglia. The cell bodies and processes of the peripheral nerves are separated from the connective tissue framework of the ganglion by a single layer of flattened capsular cells called *satellite cells*. Satellite cells secrete a basement membrane that protects the cell body from the diffusion of large molecules.

The processes of larger afferent and efferent neurons are surrounded by the cell membrane and cytoplasm of Schwann cells, which are close relatives of the satellite cells. During myelination, the Schwann cell wraps around the nerve process many times in a “jelly roll” fashion (Fig. 36-2). Schwann cells line up along the neuronal process, and each of these cells forms its own discrete myelin segment. The end of each myelin segment attaches to the cell membrane of the axon by means



**FIGURE 36-2** The Schwann cell forms a myelin sheath around the larger nerve fibers in the peripheral nervous system. During myelination, the Schwann cell wraps around the nerve process many times in a “jelly roll” fashion. The end of each myelin segment attaches to the cell membrane of the axon by means of intercellular junctions. Successive Schwann cells are separated by short extracellular fluid gaps called the *nodes of Ranvier*, where the myelin is missing and the voltage-gated sodium channels are concentrated.

of intercellular junctions. Successive Schwann cells are separated by short extracellular fluid gaps called the *nodes of Ranvier*, where the myelin is missing and voltage-gated sodium channels are concentrated. The nodes of Ranvier increase nerve conduction by allowing the impulse to jump from node to node through the extracellular fluid in a process called *saltatory conduction* (from the Latin *saltare*, "to jump"). In this way, the impulse can travel more rapidly than it could if it were required to move systematically along the entire nerve process. This increased conduction velocity greatly reduces reaction time, or time between the application of a stimulus and the subsequent motor response. The short reaction time is of particular importance in peripheral nerves with long distances (sometimes 1 to 1.5 m) for conduction between the CNS and distal effector organs.

Each of the Schwann cells along a peripheral nerve is enclosed in a continuous tube of basement membrane, which in turn is surrounded by a multilayered sheath of loose connective tissue known as the *endoneurium* (Fig. 36-3). The endoneurial sheath, which is essential to the regeneration of injured peripheral nerves, provides a collagenous tube through which a regenerating axon can again reach its former target. The endoneurial sheath does not penetrate the CNS. The absence of the endoneurial sheath is thought to be a major factor in the limited axonal regeneration of CNS nerves compared with those of the PNS.

The endoneurial sheaths are bundled with blood vessels into small bundles or clusters of nerves called *fascicles*. In the nerve, the fascicles consisting of bundles of nerve fibers are surrounded by another protective covering called the *perineurium*. Usually, several fascicles are further surrounded by the heavy, protective *epineurial sheath* of the peripheral nerve. The protective layers that surround the peripheral nerve processes are continuous with the connective tissue capsule of the sensory nerve endings and the connective tissue that surrounds the effector

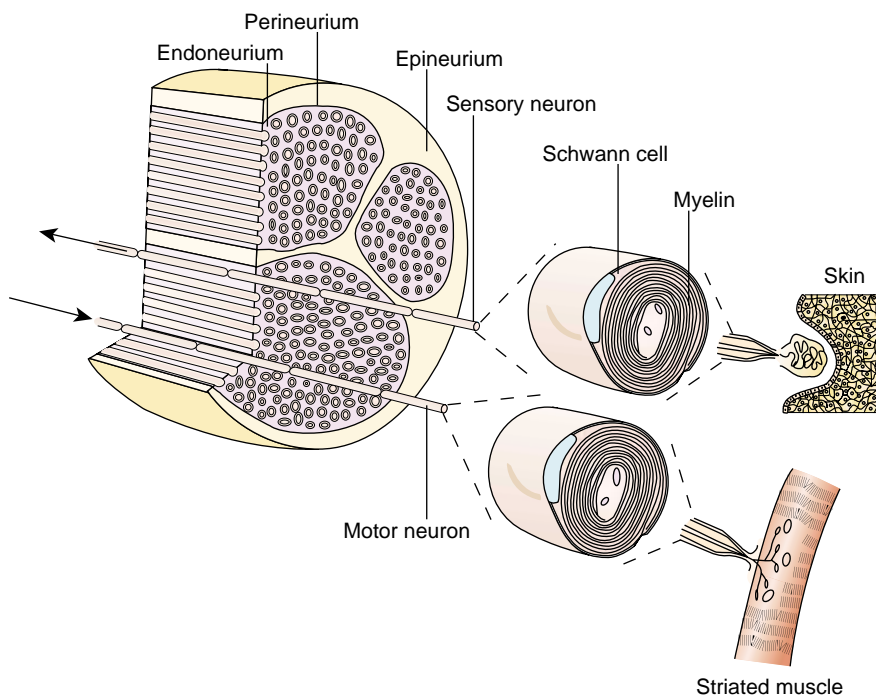
structures, such as the skeletal muscle cell. Centrally, the connective tissue layers continue along the dorsal and ventral roots of the nerve and fuse with the meninges that surround the spinal cord and brain.

### Supporting Cells of the Central Nervous System

Supporting cells of the CNS consist of the oligodendroglia, astroglia, microglia, and ependymal cells (Fig. 36-4). The *oligodendroglial* cells form the myelin in the CNS. Instead of forming a myelin covering for a single axon, these cells reach out with several processes, each wrapping around and forming a multilayered myelin segment around several different axons. The coverings of axons in the CNS function in increasing the velocity of nerve conduction, similar to the peripheral myelinated fibers.

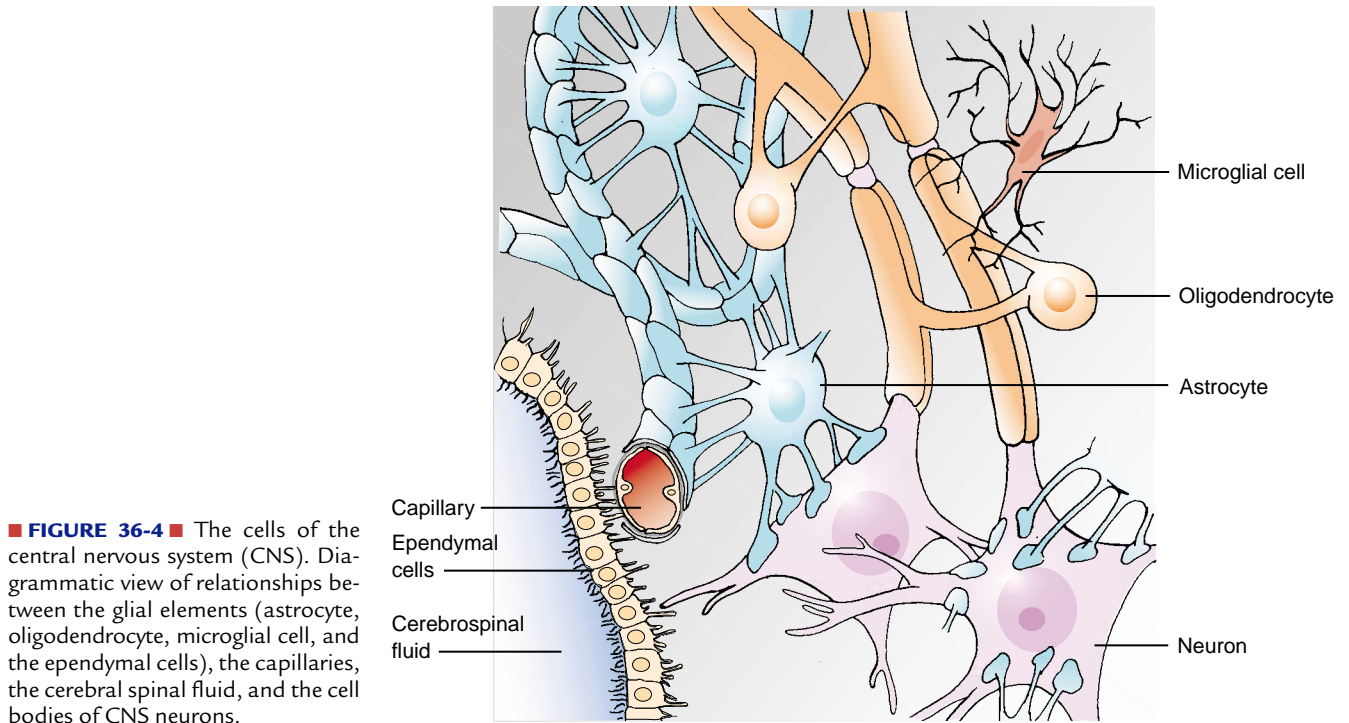
A second type of glial cell, the *astroglia*, is particularly prominent in the gray matter of the CNS. These large cells have many processes, some reaching to the surface of the capillaries, others reaching to the surface of the nerve cells, and still others filling most of the intercellular space of the CNS. The astrocytic linkage between the blood vessels and the neurons may provide a transport mechanism for the exchange of oxygen, carbon dioxide, and metabolites. The astrocytes also have an important role in sequestering cations such as calcium and potassium from the intercellular fluid. Astrocytes can fill their cytoplasm with microfibrils (*i.e.*, fibrous astrocytes), and masses of these cells form the special type of scar tissue called *gliosis* that develops in the CNS when tissue is destroyed.

A third type of glial cell, the *microglia*, is a small phagocytic cell that is available for cleaning up debris after cellular damage, infection, or cell death. The fourth type of cell, the *ependymal* cell, forms the lining of the neural tube cavity, the ventricular system. In some areas, these cells combine with a rich vascular network to form the *choroid plexus*, where production of the cerebrospinal fluid (CSF) takes place.



■ **FIGURE 36-3** ■ Section of a peripheral nerve containing axons of both afferent (sensory) and efferent (motor) neurons. (Modified from Cormack D.H. [1987]. *Ham's histology* [9th ed., p. 374]. Philadelphia: J.B. Lippincott)





■ **FIGURE 36-4** ■ The cells of the central nervous system (CNS). Diagrammatic view of relationships between the glial elements (astrocyte, oligodendrocyte, microglial cell, and the ependymal cells), the capillaries, the cerebral spinal fluid, and the cell bodies of CNS neurons.

## Metabolic Requirements of Nervous Tissue

Nervous tissue has a high rate of metabolism. Although the brain comprises only 2% of the body's weight, it receives approximately 15% of the resting cardiac output and consumes 20% of its oxygen. Despite its substantial energy requirements, the brain can neither store oxygen nor engage in anaerobic metabolism. An interruption in the blood or oxygen supply to the brain rapidly leads to clinically observable signs and symptoms. Without oxygen, brain cells continue to function for approximately 10 seconds. Unconsciousness occurs almost simultaneously with cardiac arrest, and the death of brain cells begins within 4 to 6 minutes. Interruption of blood flow also leads to the accumulation of metabolic by-products that are toxic to neural tissue.

Glucose is the major fuel source for the nervous system, but neurons have no provision for storing glucose. Ketones can provide for limited temporary energy requirements; however, these sources are rapidly depleted. Unlike muscle cells, neurons have no glycogen stores and must rely on glucose from the blood or the glycogen stores of supporting glial cells. Persons receiving insulin for diabetes may experience signs of neural dysfunction and unconsciousness (*i.e.*, insulin reaction or shock) when blood glucose drops because of insulin excess (see Chapter 32).

**In summary,** nervous tissue is composed of two types of cells: neurons and supporting cells. Neurons are composed of three parts: a cell body, which controls cell activity; the dendrites, which conduct information toward the cell body; and the axon, which carries impulses from the cell body. The supporting cells consist of Schwann and satellite cells of the PNS and the glial cells of the CNS. Supporting cells protect and

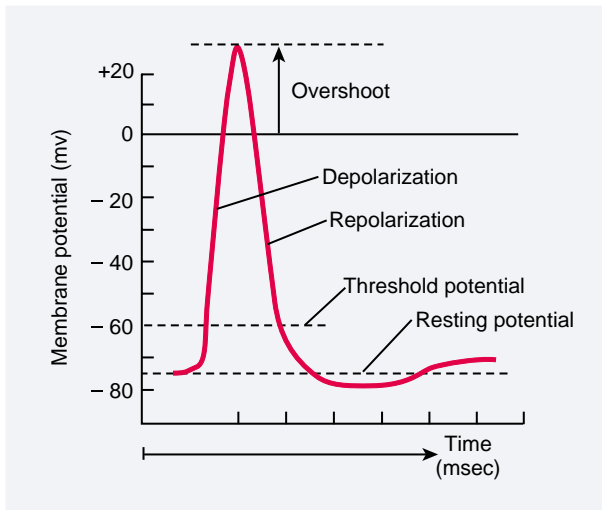
provide metabolic support for the neurons and aid in segregating them into isolated compartments, which is necessary for normal neuronal function. The Schwann cells of the PNS and the oligodendroglial cells of the CNS form the myelin sheath that allows for rapid conduction of impulses. The nervous system has a high level of metabolic activity, requiring a continuous supply of oxygen and glucose. Although the brain comprises only 2% of the body's weight, it receives approximately 15% of the resting cardiac output and consumes 20% of its oxygen.

## NERVE CELL COMMUNICATION

Neurons are characterized by the ability to communicate with other neurons and body cells through pulsed electrical signals called *impulses*. An impulse, or action potential (discussed in Chapter 1), represents the movement of electrical charge along the axon membrane. This phenomenon, sometimes called *conductance*, is based on the rapid flow of charged ions through the plasma membrane. In excitable tissue, ions such as sodium, potassium, and calcium move through the membrane channels and carry the electrical charges involved in the initiation and transmission of such impulses.

## Action Potentials

Nerve signals are transmitted by action potentials, which are abrupt, pulsatile changes in the membrane potential that last a few ten thousandths to a few thousandths of a second. Action potentials can be divided into three phases: the resting or polarized state, depolarization, and repolarization (Fig. 36-5).



■ **FIGURE 36-5** ■ Time course of the action potential recorded at one point of an axon with one electrode inside and one on the outside of the plasma membrane.

The *resting membrane potential* represents the undisturbed period of the action potential during which the nerve is not transmitting impulses. During this time the inside of the membrane is negatively charged with respect to the outside, and the membrane is said to be *polarized*. The resting phase of the membrane potential continues until some event causes the membrane to increase its permeability to sodium. The *threshold potential* represents the membrane potential at which neurons or other excitable tissues are stimulated to fire. When the threshold potential is reached, the gatelike structures in the ion channels open. The gates are either fully open or fully closed (all-or-none). Under ordinary circumstances, the threshold stimulus is sufficient to open large numbers of ion channels, triggering massive depolarization of the membrane (the action potential).

*Depolarization* is characterized by the flow of electrically charged ions and the reversal of the membrane potential. During the depolarization phase, the membrane suddenly becomes permeable to sodium ions. The rapid inflow of sodium ions produces local currents that travel through the adjacent cell membrane, causing the sodium channels in this part of the membrane to open. Thus, the impulse moves longitudinally along the nerve, moving from one part of the axon to another. Repolarization is the phase during which the polarity of the resting membrane potential is re-established. This is accomplished with closure of the sodium channels and opening of the potassium channels. The outflow of positively charged potassium ions across the cell membrane returns the membrane potential to negativity. The sodium-potassium pump gradually re-establishes the resting ionic concentrations on each side of the membrane.

The excitability of neurons can be affected by conditions that alter the resting membrane potential, moving it either closer to or further from the threshold potential. *Hypopolarization* increases the excitability of the postsynaptic neuron by bringing the membrane potential closer to the threshold potential so that a smaller subsequent stimulus is needed to cause the neuron to fire. *Hyperpolarization* brings the membrane potential further from threshold and has the opposite effect. It

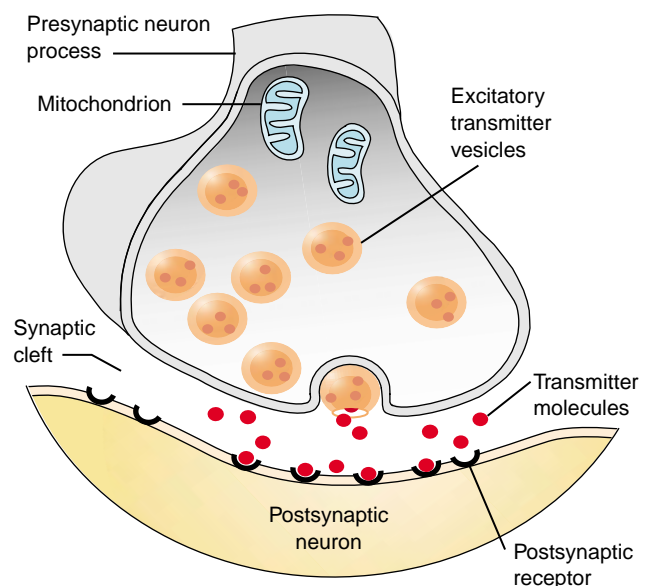
has an inhibitory effect and decreases the likelihood that an action potential will be generated.

## Synaptic Transmission

Neurons communicate with each other through structures known as synapses. Two types of synapses are found in the nervous system: electrical and chemical. *Electrical synapses* permit the passage of current-carrying ions through small openings called *gap junctions* that penetrate the cell junction of adjoining cells and allow current to travel in either direction. The gap junctions allow an action potential to pass directly and quickly from one neuron to another. They may link neurons having close functional relationships into circuits.

The most common type of synapse is the *chemical synapse*. Chemical synapses involve special presynaptic and postsynaptic membrane structures, separated by a synaptic cleft (Fig. 36-6). The presynaptic terminal secretes one and often several chemical transmitter molecules (*i.e.*, neurotransmitters or neuromodulators) into the synaptic cleft. The neurotransmitters diffuse into the synaptic cleft and unite with receptors on the postsynaptic membrane. In contrast to an electrical synapse, a chemical synapse serves as a rectifier, permitting only one-way communication. One-way conduction is a particularly important characteristic of chemical synapses. Chemical synapses are divided into two types: excitatory and inhibitory. In excitatory synapses, binding of the neurotransmitter to the receptor produces depolarization of the postsynaptic membrane. Binding of the neurotransmitter to the receptor in an inhibitory synapse reduces the postsynaptic neuron's ability to generate an action potential. Most inhibitory neurotransmitters induce hyperpolarization of the postsynaptic membrane by making the membrane more permeable to potassium or chloride, or both (see Chapter 6).

Chemical synapses are the slowest component in progressive communication through a sequence of neurons, such as in



■ **FIGURE 36-6** ■ A chemical synapse showing the synaptic vesicles in the presynaptic neuron, release of the transmitter, and binding of the transmitter to the receptors on the membrane surface of the postsynaptic neuron.

a spinal reflex. In contrast to the conduction of electrical action potentials, each successive event at the chemical synapse—transmitter secretion, diffusion across the synaptic cleft, interaction with postsynaptic receptors, and generation of a subsequent action potential in the postsynaptic neuron—consumes time. On average, conduction across a chemical synapse requires approximately 0.3 milliseconds.

A neuron's cell body and dendrites are covered by thousands of synapses, any or many of which can be active at any moment. Because of the interaction of this rich synaptic input, each neuron resembles a little integrator, in which circuits of many neurons interact with one another. It is the complexity of these interactions and the subtle integrations involved in producing behavioral responses that gives the system its intelligence.

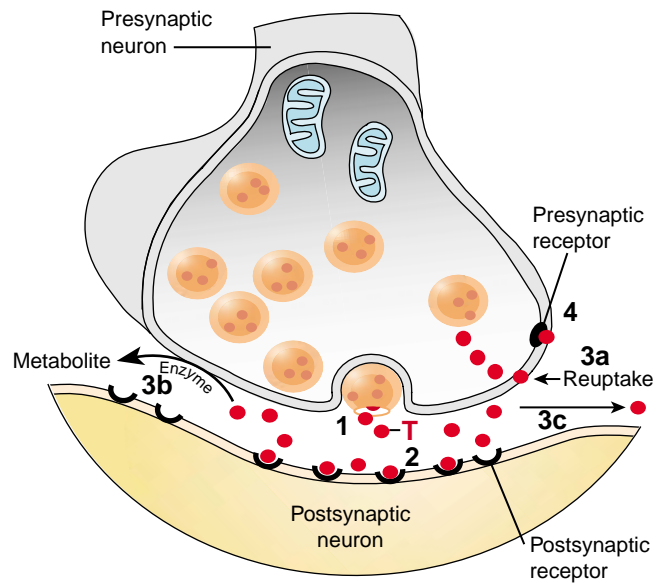
## Messenger Molecules

Neurotransmitters are the chemical messenger molecules of the nervous system. The messenger molecules of the nervous system include the neurotransmitters, neurohumoral mediators such as epinephrine, neuromodulators, and neurotrophic or nerve growth factors.

Neurotransmitters are small molecules that incorporate a positively charged nitrogen atom; they include several amino acids, peptides, and monoamines. Amino acids are the building blocks of proteins and are present in body fluids. Peptides are low-molecular-weight molecules that are made up of two or more amino acids. They include substance P and the endorphins and enkephalins, which are involved in pain sensation and perception (see Chapter 39). A monoamine is an amine molecule containing one amino group ( $\text{NH}_2$ ). Serotonin, dopamine, norepinephrine, and epinephrine are monoamines synthesized from amino acids. Fortunately, the blood-brain barrier protects the nervous system from circulating amino acids and other molecules with potential neurotransmitter activity.

The process of neurotransmission involves the synthesis, storage, and release of a neurotransmitter; the reaction of the neurotransmitter with a receptor; and termination of the receptor action (Fig. 36-7). Neurotransmitters are synthesized in the cytoplasm of the axon terminal. The synthesis of transmitters may require one or more enzyme-catalyzed steps (*e.g.*, one for acetylcholine and three for norepinephrine). Neurons are limited as to the type of transmitter they can synthesize by their enzyme systems. After synthesis, the neurotransmitter molecules are stored in the axon terminal in tiny, membrane-bound sacs called *synaptic vesicles*. There may be thousands of vesicles in a single terminal, each containing 10,000 to 100,000 transmitter molecules. The vesicle protects the neurotransmitters from enzyme destruction in the nerve terminal. The arrival of an impulse at a nerve terminal causes the vesicles to move to the cell membrane and release their transmitter molecules into the synaptic space.

Neurotransmitters exert their actions through specific proteins, called *receptors*, embedded in the postsynaptic membrane. These receptors are tailored precisely to match the size and shape of the transmitter. In each case, the interaction between a transmitter and receptor results in a specific physiologic response. The action of a transmitter is determined by the type of receptor (excitatory or inhibitory) to which it binds. For example, acetylcholine is excitatory when it is released at a myoneural junction, and it is inhibitory when it is released at the sinoatrial node in the heart. Receptors are named according to the type of



■ **FIGURE 36-7** ■ Schematic illustration of (1) neurotransmitter (T) release; (2) binding of transmitter to postsynaptic receptor; termination of transmitter action by (3a) reuptake of transmitter into the presynaptic terminal, (3b) enzymatic degradation, or (3c) diffusion away from the synapse; and (4) binding of transmitter to presynaptic receptors for feedback regulation of transmitter release.

neurotransmitter with which they interact. For example, a *cholinergic receptor* is a receptor that binds acetylcholine.

Rapid removal of a transmitter, once it has exerted its effects on the postsynaptic membrane, is necessary to maintain precise control of neural transmission. A released transmitter can undergo one of three fates: it can be broken down into inactive substances by enzymes; it can be taken back up into the presynaptic neuron in a process called *reuptake*; or it can diffuse away into the intercellular fluid until its concentration is too low to influence postsynaptic excitability. For example, acetylcholine is rapidly broken down by acetylcholinesterase into acetic acid and choline, with the choline being taken back into the presynaptic neuron for reuse in acetylcholine synthesis. The catecholamines are largely taken back into the neuron in an unchanged form for reuse. Catecholamines also can be degraded by enzymes in the synaptic space or in the nerve terminals.

*Neurohumoral mediators* reach their target cells through the bloodstream and produce an even slower action than do the neuromodulators. Both the nervous system and the endocrine system use chemical molecules as messengers. As more information is obtained about the chemical messengers of these systems, the distinction between them becomes less evident. Many neurons, such as those in the adrenal medulla, secrete transmitters into the bloodstream, and it has been found that other neurons possess receptor sites for hormones. Many hormones have turned out to be neurotransmitters. Vasopressin (also known as *antidiuretic hormone*), a peptide hormone released from the posterior pituitary gland, acts as a hormone in the kidney and as a neurotransmitter for nerve cells in the hypothalamus. More than a dozen of these cell-to-cell and blood-borne messengers can relay signals in the nervous system or the endocrine system.

Other classes of messenger molecules, known as *neuromodulators*, also may be released from axon terminals. Neuro-modulator molecules react with presynaptic or postsynaptic



receptors to alter the release of or response to neurotransmitters. Neuromodulators may act on postsynaptic receptors to produce slower and longer-lasting changes in membrane excitability. This alters the action of the faster-acting neurotransmitter molecules by enhancing or decreasing their effectiveness. By combining with autoreceptors on its own presynaptic membrane, a transmitter can act as a neuromodulator to augment or inhibit further nerve activity. In some nerves, such as the peripheral sympathetic nerves, a messenger molecule can have both transmitter and modulator functions. For example, norepinephrine can activate an  $\alpha_1$ -adrenergic postsynaptic receptor to produce vasoconstriction or stimulate an  $\alpha_2$ -adrenergic presynaptic receptor to inhibit further norepinephrine release.

*Neurotrophic* or *nerve growth factors* are required to maintain the long-term survival of the postsynaptic cell and are secreted by axon terminals independent of action potentials. Examples include neuron-to-neuron trophic factors in the sequential synapses of CNS sensory neurons. Trophic factors from target cells that enter the axon and are necessary for the long-term survival of presynaptic neurons also have been demonstrated. Target cell-to-neuron trophic factors probably have great significance in establishing specific neural connections during normal embryonic development.

**In summary,** neurons are characterized by the ability to communicate with other neurons and body cells through pulsed electrical signals called *action potentials*. The cell membranes of neurons contain ion channels that are responsible for generating action potentials. Action potentials are divided into three parts: (1) the resting membrane potential, during which the membrane is polarized but no electrical activity occurs; the (2) depolarization phase, during which sodium channels open, allowing rapid inflow of the sodium ions that generate the electrical impulse; and (3) the repolarization phase, during which the membrane is permeable to the potassium ion, allowing for the efflux of potassium ions and return to the resting membrane potential.

Synapses are structures that permit communication between neurons. Two types of synapses have been identified: electrical and chemical. Electrical synapses consist of gap junctions between adjacent cells that allow action potentials to move rapidly from one cell to another. Chemical synapses involve special presynaptic and postsynaptic structures, separated by a synaptic cleft. They rely on chemical messengers, released from the presynaptic neuron, that cross the synaptic cleft and then interact with receptors on the postsynaptic neuron.

Neurotransmitters are chemical messengers that control neural function; they selectively cause excitation or inhibition of action potentials. Three major types of neurotransmitters are known: amino acids such as glutamic acid and GABA, peptides such as the endorphins and enkephalins, and monoamines such as epinephrine and norepinephrine. Neurotransmitters interact with cell membrane receptors to produce either excitatory or inhibitory actions. Neuromodulators are chemical messengers that react with membrane receptors to produce slower and longer-acting changes in membrane permeability. Neurotrophic or growth factors, also released from presynaptic terminals, are required to maintain the long-term survival of postsynaptic neurons.

## DEVELOPMENT AND ORGANIZATION OF THE NERVOUS SYSTEM

The development of the nervous system can be traced far back into evolutionary history. During its development, newer functional features and greater complexity resulted from the modification and enlargement of more primitive structures. Survival of the species depended on the rapid reaction to environmental danger, to potential food sources, or to a sexual partner.

The front, or *rostral*, end of the CNS became specialized for sensing the external environment and controlling reactions to it. In time, the ancient organization, which is largely retained in the spinal cord segments, was expanded in the forward segments of the nervous system. Of these, the most forward segments have undergone the most radical modification and have developed into the forebrain: the diencephalon and the cerebral hemispheres. The dominance of the front end of the CNS is reflected in a hierarchy of control levels: brain stem over spinal cord, and forebrain over brain stem. Throughout evolution, newer functions were added to the surface of functionally more ancient systems. As newer functions became concentrated at the rostral end of the nervous system, they also became more vulnerable to injury.

### Embryonic Development

The nervous system appears very early in embryonic development (week 3). This early development is essential because it influences the development and organization of many other body systems, including the axial skeleton, skeletal muscles, and sensory organs such as the eyes and ears. During later fetal life and thereafter, the nervous system provides communication, signal processing, integrative, and memory functions. The early induction and later lifelong communication functions of the nervous system are at the center of the integrity, survival, and individuality of each person.

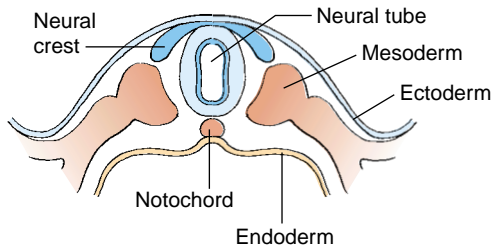
All body tissues and organs have developed from the three embryonic layers (*i.e.*, endoderm, ectoderm, and mesoderm) that were present during the third week of embryonic life (Fig. 36-8). The body is organized into the soma and viscera.

### KEY CONCEPTS

#### HIERARCHY OF NERVOUS SYSTEM CONTROL

- No part of the nervous system functions independently of other parts.
- Progressively greater complexity in the responses and greater precision in their control occur at each higher level of the nervous system.
- The more rostral, recently developed parts of the neural tube gain dominance or control over lower levels.
- As newer functions became concentrated at the rostral end of the nervous system, they also became more vulnerable to injury.





■ **FIGURE 36-8** ■ Transverse section of a 22–23-day-old embryo showing the ectoderm, mesoderm, endoderm, neural crest cells, notochord, and neural tube. During development, the neural tube develops into the CNS and the notochord becomes the foundation upon which the vertebral column develops. The neural crest cells become the progenitors of the neurons and supporting cells of the peripheral nervous system.

The *soma*, or body wall, includes all of the structures derived from the embryonic ectoderm, such as the epidermis of the skin and the CNS. The mesodermal connective tissues of the soma include the dermis of the skin, skeletal muscle, bone, and the outer lining of the body cavity (*i.e.*, parietal pleura and peritoneum). The nervous system innervates all somatic structures as well as the internal structures making up the viscera. The *viscera* includes the great vessels derived from the intermediate mesoderm, the urinary system, and the gonadal structures; it also includes the inner lining of the body cavities, such as the visceral pleura and peritoneum, and the mesodermal tissues that surround the endoderm-lined gut and its derivative organs (*e.g.*, lungs, liver, pancreas).

There are both somatic and visceral nerves. The somatic nerves innervate the skeletal muscles and the smooth muscle and glands of skin and body wall. The visceral nerves supply the visceral organs of the body, transmitting information through the autonomic nerves in the PNS to control the smooth muscle and cardiac muscle as well as the glands of the visceral organs.

## Segmental Organization

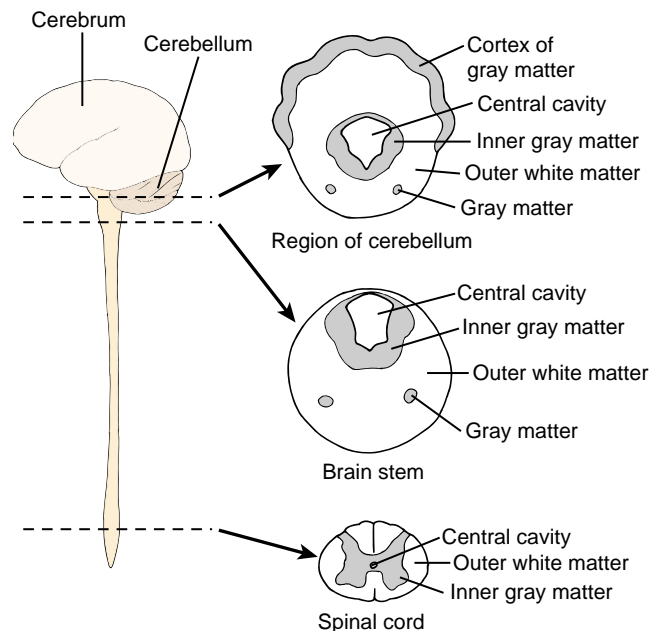
The early pattern of segmental development is presented as a framework for understanding the nervous system. Although the early muscular, skeletal, vascular, and excretory systems and the nerves that supply the somatic and visceral structures have the same segmental pattern, it is the nervous system that most clearly retains this organization in postnatal life. Developmentally, the basic organizational pattern of the body is that of a longitudinal series of segments, each repeating the same fundamental pattern. The CNS and its associated peripheral nerves consist of approximately 43 segments, 33 of which form the spinal cord and spinal nerves, and 10 of which form the brain and its cranial nerves.

The basic pattern of the CNS is that seen in the spinal cord—a central cavity surrounded by inner core of gray matter and a superficial layer of white matter (Fig. 36-9). The brain retains this organization, but it also contains additional regions of gray matter that are not evident in the spinal cord. The gray matter is functionally divided into longitudinal columns of nerve cell bodies called the *cell columns*. The superficial white matter region contains the longitudinal tract systems of the CNS. The dorsal half of the gray matter is called the *dorsal horn*.

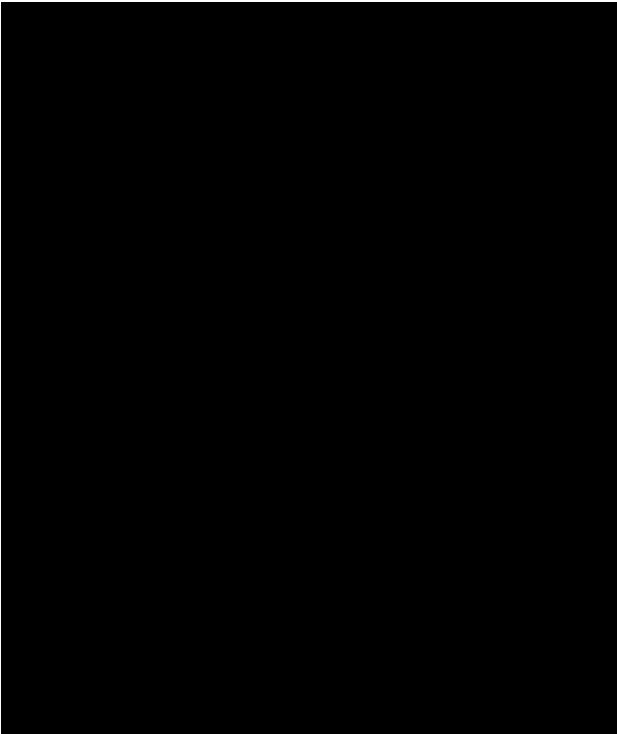
## KEY CONCEPTS

### THE DEVELOPMENTAL ORGANIZATION OF THE NERVOUS SYSTEM

- On cross section, the embryonic neural tube develops into a central canal surrounded by gray matter, or cellular portion (cell columns), and white matter, or tract system of the central nervous system (CNS).
- As the nervous system develops, it becomes segmented, with a repeating pattern of afferent neuron axons forming the dorsal roots of each succeeding segmental nerve and the exiting efferent neurons forming the ventral roots of each succeeding segmental nerve.
- The nerve cells in the gray matter are arranged longitudinally in cell columns, with afferent sensory neurons located in the dorsal columns and efferent motor neurons located in the ventral columns.
- The axons of the cell column neurons project out into the white matter of the CNS, forming the longitudinal tract systems.



■ **FIGURE 36-9** ■ Segmental organization of gray and white matter in the CNS (highly simplified). From top to bottom, the diagrams represent cross-sections at the levels of cerebellum, brain stem, and spinal cord. In each section, the dorsal aspect is on top. In general, white matter lies external to gray matter; however, collections of gray matter migrate externally into the white matter in the developing brain (*see arrows*). The cerebrum resembles the cerebellum in its external cortex of gray matter. (Marieb E.N. [1995]. *Human anatomy and physiology*. [3rd edition, p. 383]. Redwood City, CA. The Benjamin/Cummings Publishing Company)



The ventral portion, or *ventral horn*, contains efferent neurons that communicate by way of the ventral roots with effector cells of the body segment. Many CNS neurons develop axons that grow longitudinally as tract systems that communicate between neighboring and distal segments of the neural tube.

Each segment of the CNS is accompanied by bilateral pairs of bundled nerve fibers, or roots, a ventral pair and a dorsal pair (Fig. 36-10). The paired dorsal roots connect a pair of dorsal root ganglia and their corresponding CNS segment. The dorsal root ganglia contain many afferent nerve cell bodies, each hav-

ing two axon-like processes—one that ends in a peripheral receptor and the other that enters the central neural segment. The axon-like process that enters the central neural segment communicates with a neuron called an *input association (IA) neuron*. The paired ventral roots of each segment are bundles of axons that provide efferent output to effector sites such as the muscles and glandular cells of the body segment.

### Cell Columns

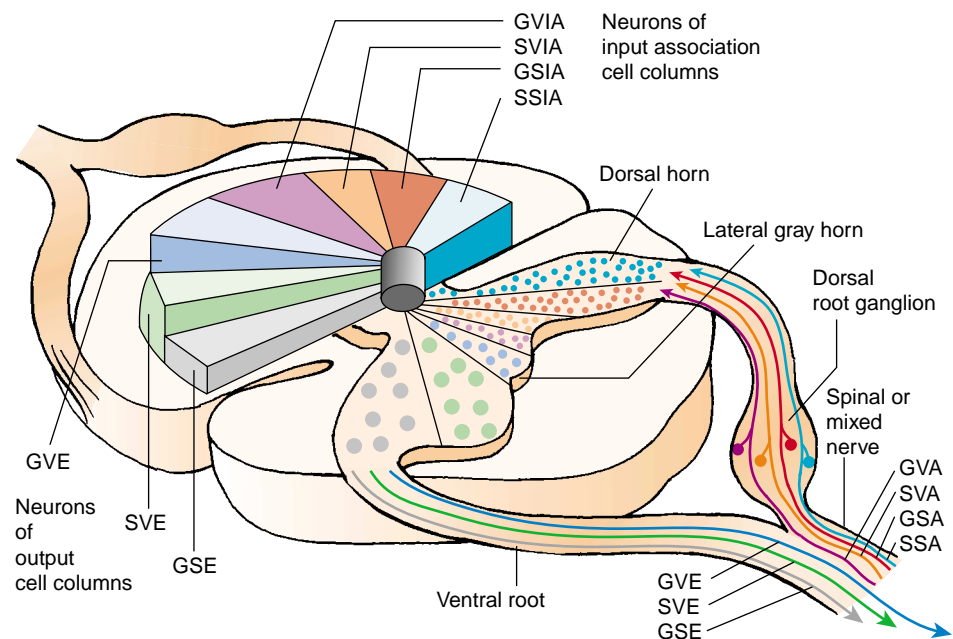
The organizational structure of the nervous system can be best explained and simplified as a pattern in which functionally specific PNS and CNS neurons are repeated as parallel cell columns running lengthwise along the nervous system. In this organizational pattern, afferent neurons, dorsal horn cells, and ventral horn cells are organized as a bilateral series of 11 cell columns.

The cell columns on each side can be further grouped according to their location in the PNS: four in the dorsal ganglia that contain sensory neurons; four in the dorsal horn containing sensory IA neurons; and three in the ventral horn that contain motoneurons (Fig. 36-11). Each column of dorsal root ganglia projects to its particular column of IA neurons in the dorsal horn. The IA neurons distribute afferent information to local reflex circuitry and to more rostral and elaborate segments of the CNS. The ventral horns contain output association (OA) neurons and lower motoneurons, which project to the effector muscles. The afferent and efferent cell columns of the PNS and CNS, their projections, and the type of information they transmit are summarized in Table 36-1.

Between the IA neurons and the OA neurons are networks of small internuncial neurons arranged in complex circuits. Internuncial neurons provide the discreteness, appropriateness, and intelligence of responses to stimuli. Most of the billions of CNS cells in the spinal cord and brain gray matter are internuncial neurons.

**Dorsal Horn Cell Columns.** Four columns of afferent (sensory) neurons in the dorsal root ganglia directly innervate four

■ **FIGURE 36-11** ■ Cell columns of the central nervous system. The cell columns in the dorsal horn contain input association (IA) neurons for the general visceral afferent (GVA), special visceral afferent (SVA), special sensory afferent (SSA), and general somatic afferent (GSA) neurons with cell bodies in the dorsal root ganglion. The cell columns in the ventral horn contain the general visceral efferent (GVE), pharyngeal efferent (PE), and general somite efferent (GSE) neurons and their output association (OA) neurons.



**TABLE 36-1** The Segmental Nerves and Their Components

Segment and Nerve	Component	Innervation	Function
<b>1. Forebrain</b>			
I. Olfactory	SVA	Receptors in olfactory mucosa	Reflexes, olfaction (smell)
<b>2. II. Optic nerve</b>			
		Optic nerve and retina (part of brain system, not a peripheral nerve)	
<b>3. Midbrain</b>			
V. Trigeminal (V <sub>1</sub> ) ophthalmic division	SSA GSA	Muscles: upper face: forehead, upper lid Skin, subcutaneous tissue; conjunctiva; frontal/ethmoid sinuses	Facial expression, proprioception Somesthesia Reflexes (blink)
III. Oculomotor	GVE	Iris sphincter	Pupillary constriction
	GSE	Ciliary muscle	Accommodation
		Extrinsic eye muscles	Eye movement, lid movement
<b>4. Pons</b>			
V. Trigeminal (V <sub>2</sub> ) maxillary division	SSA GSA	Muscles: facial expression Skin, oral mucosa, upper teeth, hard palate, maxillary sinus	Proprioception Reflexes (sneeze), somesthesia
V. Trigeminal (V <sub>3</sub> ) mandibular division	SSA GSA PE	Lower jaw, muscles: mastication Skin, mucosa, teeth, anterior 2/3 of tongue Muscles: mastication tensor tympani tensor veli palantini	Proprioception, jaw jerk Reflexes, somesthesia Mastication: speech Protects ear from loud sound Tenses soft palate
IV. Trochlear	GSE	Extrinsic eye muscle	Moves eye down and in
<b>5. Caudal Pons</b>			
VIII. Vestibular, cochlear (vestibulocochlear)	SSA	Vestibular end organs Organ of Corti	Reflexes, sense of head position Reflexes, hearing
VII. Facial nerve, intermedius portion	GSA GVA SVA GVE	External auditory meatus Nasopharynx Taste buds of anterior 2/3 of tongue Nasopharynx	Somesthesia Gag reflex: sensation Reflexes: gustation (taste) Mucous secretion, reflexes
Facial nerve	PE	Lacrimal, sublingual, submandibular glands Muscles: facial expression, stapedius	Lacrimation, salivation Facial expression Protects ear from loud sounds
VI. Abducens	GSE	Extrinsic eye muscle	Lateral eye deviation
<b>6. Middle Medulla</b>			
IX. Glossopharyngeal	SSA GSA SVA GVA GVE PE	Stylopharyngeus muscle Posterior external ear Taste buds of posterior 1/3 of tongue Oral pharynx Parotid gland; pharyngeal mucosa Stylopharyngeus muscle	Proprioception Somesthesia Gustation (taste) Gag reflex: sensation Salivary reflex: mucous secretion Assists swallowing
<b>7,8,9,10. Caudal Medulla</b>			
X. Vagus	SSA GSA SVA GVA	Muscles: pharynx, larynx Posterior external ear Taste buds, pharynx, larynx Visceral organs (esophagus to midtransverse colon, liver, pancreas, heart, lungs)	Proprioception Somesthesia Reflexes, gustation Reflexes, sensation
	GVE	Visceral organs as above	Parasympathetic efferent
	PE	Muscles: pharynx, larynx	Swallowing, phonation, emesis
XIII. Hypoglossal	GSE	Muscles of tongue	Tongue movement, reflexes
<b>Spinal Segments</b>			
<b>C1–C4 Upper Cervical</b>			
XI. Spinal accessory nerve	PE	Muscles: sternocleidomastoid, trapezius	Head, shoulder movement
Spinal nerves	SSA GSA GSE	Muscles of neck Neck, back of head Neck muscles	Proprioception, DTRs Somesthesia Head, shoulder movement

(continued)

**TABLE 36-1** The Segmental Nerves and Their Components (Continued)

Segment and Nerve	Component	Innervation	Function
<b>C5–C8 Lower Cervical</b>	SSA	Upper limb muscles	Proprioception, DTRs
	GSA	Upper limbs	Reflexes, somesthesia
	GSE	Upper limb muscles	Movement, posture
<b>T1–L2 Thoracic, Upper Lumbar</b>	SSA	Muscles: trunk, abdominal wall	Proprioception
	GSA	Trunk, abdominal wall	Reflexes, somesthesia
	GVA	All of viscera	Reflexes and sensation
	GVE	All of viscera	Sympathetic reflexes, vasomotor control, sweating, piloerection
	GSE	Muscles: trunk, abdominal wall, back	Movement, posture, respiration
<b>L2–S1 Lower Lumbar, Upper Sacral</b>	SSA	Lower limb muscles	Proprioception, DTRs
	GSA	Lower trunk, limbs, back	Reflexes, somesthesia
	GSE	Muscles: trunk, lower limbs, back	Movement, posture
<b>S2–S4 Lower Sacral</b>	SSA	Muscles: pelvis, perineum	Proprioception
	GSA	Pelvis, genitalia	Reflexes, somesthesia
	GVA	Hindgut, bladder, uterus	Reflexes, sensation
	GVE	Hindgut, visceral organs	Visceral reflexes, defecation, urination, erection
<b>S5–Co2 Lower Sacral, Coccygeal</b>	SSA	Perineal muscles	Proprioception
	GSA	Lower sacrum, anus	Reflexes, somesthesia
	GSE	Perineal muscles	Reflexes, posture

Afferent (sensory) components: SSA, special somatic afferent; GSA, general somatic afferent; SVA, special visceral afferent; GVA, general visceral afferent.

Efferent (motor) components: GVE, general visceral efferent (autonomic nervous system); PE, pharyngeal efferent; GSE, general somatic efferent; DTRs, deep tendon reflexes.

corresponding columns of SIA neurons in the dorsal horn. These columns are categorized as special and general afferents: special somatic afferent (SSA), general somatic afferent (GSA), special visceral afferent (SVA), and general visceral afferent (GVA).

The SSA fibers are concerned with internal sensory information such as joint and tendon sensation (*i.e.*, proprioception). Neurons in the special sensory IA cell columns relay their information to local reflexes concerned with posture and movement. These neurons also relay information to the cerebellum, contributing to coordination of movement, and to the forebrain, contributing to experience. Afferents innervating the vestibular system of the inner ear also belong to the special somatic afferent category.

The GSA neurons innervate the skin and other somatic structures, responding to stimuli such as those that produce pressure or pain. General sensory IA column neurons relay information to protective and other local reflex circuits and project the information to the forebrain, where it is perceived as painful, warm, cold, and the like.

The SVAs innervate specialized gut-related receptors, such as the taste buds and receptors of the olfactory mucosa. Their central processes communicate with special visceral IA column neurons that project to reflex circuits producing salivation, chewing, swallowing, and other responses. Forebrain projection fibers from these association cells provide sensations of taste (*i.e.*, gustation) and smell (*i.e.*, olfaction).

GVA neurons innervate visceral structures such as the gastrointestinal tract, urinary bladder, and heart and great vessels; they project to the general visceral IA column, which relays information to vital reflex circuits and sends information to the

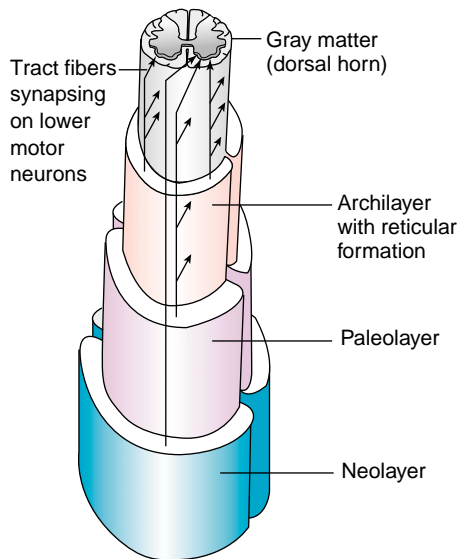
forebrain regarding visceral sensations such as stomach fullness and bladder pressure.

**Ventral Horn Cell Columns.** The ventral horn contains three longitudinal cell columns: general visceral efferent (GVE), pharyngeal efferent (PE), and general somatic efferent (GSE) (Fig. 36-11). The efferent neurons for the OA in the ventral horn originate in brain centers (motor cortex and autonomic nervous system centers) that control skeletal muscle and visceral function. Each of these cell columns contains OA and efferent neurons. The OA neurons coordinate and integrate the function of the efferent motoneurons of its column.

GVE neurons transmit the efferent output of the autonomic nervous system and are called *preganglionic neurons*. These neurons are structurally and functionally divided between either the sympathetic or the parasympathetic nervous systems (discussed later in this chapter). Their axons project through the segmental ventral roots to innervate smooth and cardiac muscle and glandular cells of the body, most of which are in the viscera. In the viscera, three additional cell columns are present on each side of the body. These become the postganglionic neurons of the autonomic nervous system. In the sympathetic nervous system, the columns are represented by the paravertebral or sympathetic chain ganglia and the prevertebral series of ganglia (*e.g.*, celiac ganglia) associated with the dorsal aorta. For the parasympathetic nervous system, these become the enteric plexus in the wall of the gut-derived organs and a series of ganglia in the head.

The PE neurons innervate the muscles of mastication, facial expression, and muscles of the pharynx and larynx. PE neurons also innervate the muscles responsible for moving the head.





■ **FIGURE 36-12** ■ The three concentric subdivisions of the tract systems of the white matter. Migration of neurons into the archilayer converts it into the reticular formation of the white matter.

The GSE neurons supply skeletal muscles of the body and head, including those of the body, limbs, tongue, and extrinsic eye muscles. These efferent neurons transmit the commands of the CNS to peripheral effectors, the skeletal muscles. They are the “final common pathway neurons” in the sequence leading to motor activity. They often are called *lower motoneurons (LMNs)* because they are under the control of higher levels of the CNS, including precise control by *upper motoneurons (UMNs)*.

### Longitudinal Tracts

The gray matter of the cell columns in the CNS is surrounded by bundles of myelinated axons (*i.e.*, white matter) and unmyelinated axons that travel longitudinally along the length of the neural axis. This white matter can be divided into three layers: an inner, a middle, and an outer layer (Fig. 36-12). The inner layer contains short fibers that project for a maximum of approximately five segments before re-entering the gray matter. The middle layer projects to six or more segments. The inner and middle layer fibers have many branches, or collaterals, that enter the gray matter of intervening segments. The outer layer contains large-diameter axons that can travel the entire length of the nervous system (Table 36-2). *Suprasegmental* is a term that refers to higher levels of the CNS, such

as the brain stem and cerebrum and structures above a given CNS segment. The middle and outer layer fibers have suprasegmental projections.

The longitudinal layers are arranged in bundles, or fiber tracts, that contain axons that have the same destination, origin, and function (Fig. 36-13). These longitudinal tracts are named systematically to reflect their origin and destination; the origin is named first, and the destination is named second. For example, the spinothalamic tract originates in the spinal cord and terminates in the thalamus. The corticospinal tract originates in the cerebral cortex and ends in the spinal cord.

**The Inner Layer.** The inner layer of white matter contains the axons of neurons that connect neighboring segments of the nervous system. Axons of this layer permit the pool of motoneurons of several segments to work together as a functional unit. They also allow the afferent neurons of one segment to trigger reflexes that activate motor units in neighboring and in the same segments. In terms of evolution, this is the oldest of the three layers, and it is sometimes called the archilayer. It is the first of the longitudinal layers to become functional, and its circuitry may be limited to reflex types of movements, including reflex movements of the fetus (*i.e.*, quickening) that begin during the fifth month of intrauterine life.

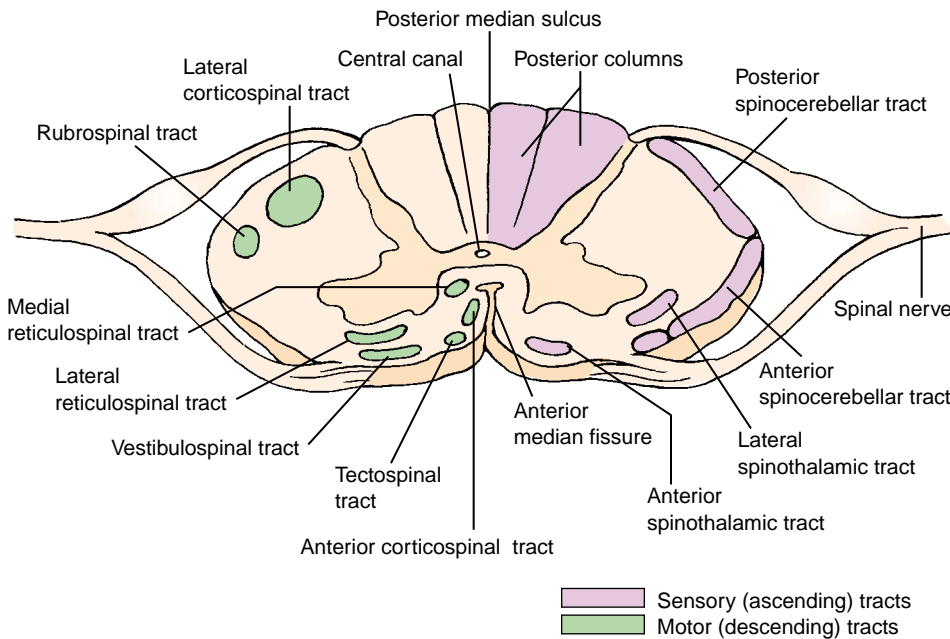
The archilayer of the white matter differs from the other two layers in one important aspect. Many neurons in the embryonic gray matter migrate out into this layer, resulting in a rich mixture of neurons and local fibers called the *reticular formation*. The circuitry of most reflexes is contained in the reticular formation. In the brain stem, the reticular formation becomes quite large and contains major portions of vital reflexes, such as those controlling respiration, cardiovascular function, swallowing, and vomiting. A functional system called the *reticular activating system* operates in the lateral portions of the reticular formation of the medulla, pons, and especially the midbrain. Information converging from all sensory modalities, including those of the somesthetic, auditory, visual, and visceral afferent nerves, bombards the neurons of this system.

The reticular activating system has descending and ascending portions. The descending portion communicates with all spinal segmental levels through middle layer reticulospinal tracts and serves to facilitate many cord-level reflexes. For example, it speeds reaction time and stabilizes postural reflexes. The ascending portion accelerates brain activity, particularly thalamic and cortical activity. This is reflected by the appearance of awake brain-wave patterns. Sudden stimuli result in protective and attentive postures and cause increased awareness.

**TABLE 36-2**

**Characteristics of the Concentric Subdivisions of the Longitudinal Tracts in the White Matter of the Central Nervous System**

Characteristics	Archilayer Tracts	Paleolayer Tracts	Neolayer Tracts
Segmental span	Intersegmental (<5 segments)	Suprasegmental (≥5 segments)	Suprasegmental
Number of synapses	Multisynaptic	Multisynaptic but fewer than archilayer tracts	Monosynaptic with target structures
Conduction velocity	Very slow	Fast	Fastest
Examples of functional systems	Flexor withdrawal reflex circuitry	Spinothalamic tracts	Corticospinal tracts



■ **FIGURE 36-13** ■ Transverse section of the spinal cord showing selected sensory and motor tracts. The tracts are bilateral but are only indicated on one half of the cord.

**The Middle Layer.** The middle layer of the white matter contains most of the major fiber tract systems required for sensation and movement. It contains the ascending spinothalamic and spinothalamic tracts. This layer consists of larger-diameter and longer suprasegmental fibers, which ascend to the brain stem and are largely functional at birth. In terms of evolutionary development, these tracts are quite old, and this layer is sometimes called the *paleolayer*. It facilitates many primitive functions, such as the auditory startle reflex, which occurs in response to loud noises. This reflex consists of turning the head and body toward the sound, dilating the pupils of the eyes, catching of the breath, and quickening of the pulse.

**The Outer Layer.** The outer layer of the tract systems is the newest of the three layers with respect to evolutionary development, and it is sometimes called the *neolayer*. It becomes functional approximately the second year of life, and it includes the pathways needed for bladder training. Myelination of these suprasegmental tracts, which include many pathways required for delicate and highly coordinated skills, is not complete until approximately the fifth year of life. This includes the development of tracts needed for fine manipulative skills, such as the finger-thumb coordination required for using tools and the toe movements needed for acrobatics. Neolayer tracts are the most recently evolved systems and, being more superficial on the brain and spinal cord, are the most vulnerable to injury.

**Collateral Communication Pathways.** Axons in the archilayer and paleolayer characteristically possess many collateral branches that move into the gray cell columns or synapse with fibers of the reticular formation as the axon passes each succeeding CNS segment. Should a major axon be destroyed at some point along its course, these collaterals provide multi-synaptic alternative pathways that bypass the local damage. Damage usually is followed by slow return of function, presumably through the collateral connections.

Neolayer tracts do not possess these collaterals but instead project mainly to the target neurons with which they communicate. When neolayer tracts are damaged, the paleolayer and archilayer tracts often remain functional, and rehabilitation methods can result in effective use of the older systems. Delicacy and refinement may be lost, but basic function remains. For example, when the corticospinal system, an important neolayer system that permits the fine manipulative control required for writing, is damaged, the remaining paleolayer systems, if intact, permit the grasping and holding of objects. The hand can still be used to perform its basic function, but the individual manipulation of the fingers is permanently lost.

**In summary,** the nervous system can be divided into two parts: the CNS, which consists of the brain and spinal cord, and the PNS, which contains the neurons and neuronal processes that leave the CNS and innervate skeletal muscles and visceral structures of the body. The brain stem and spinal cord are subdivided into the dorsal horn, which contains neurons that receive and process incoming or afferent information, and the ventral horn, which contains efferent motoneurons that handle the final stages of output processing.

Throughout life, the organization of the nervous system retains many patterns established during early embryonic life. Each of the 43 or more body segments is connected to corresponding CNS or neural tube segments by segmental afferent and efferent neurons. Afferent or sensory neuronal processes that carry afferent or sensory information enter the CNS through the dorsal root ganglia and the dorsal roots. Afferent neurons of the dorsal root ganglia are of four types: GSA, SSA, GVA, and SVA. Each of these afferent neurons synapses with its appropriate IA neurons in the cell columns of the dorsal horn. There are three cell columns in the ventral horn. The OA neurons in these columns synapse with ventral horn motoneurons that exit the CNS in the ventral roots. GSE

neurons are LMNs that innervate skeletal muscles; PE neurons innervate pharyngeal muscles; and GVE neurons innervate visceral structures. This pattern of afferent and efferent neurons, which in general is repeated in each segment of the body, forms parallel cell columns running lengthwise through the CNS and PNS.

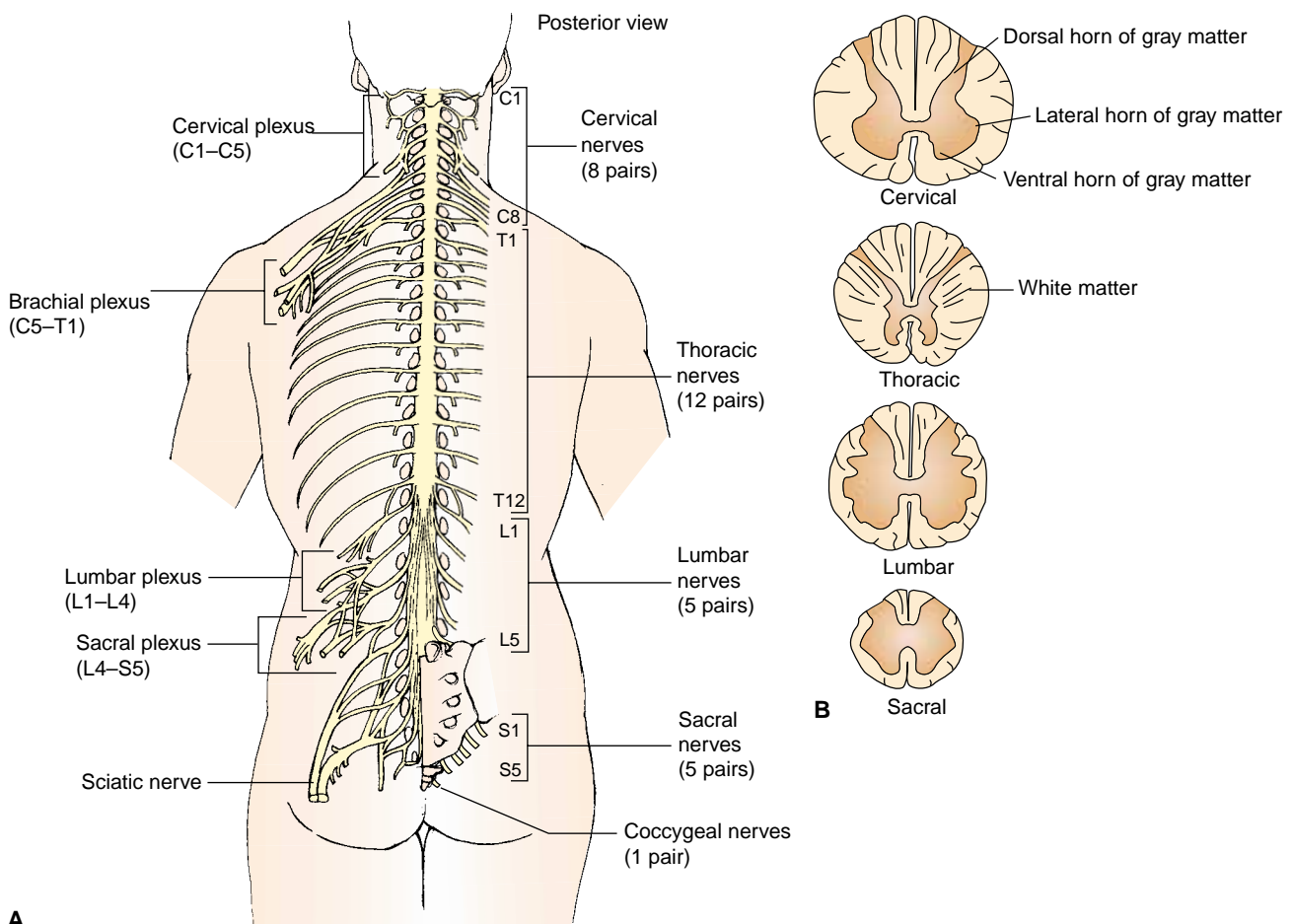
Longitudinal communication between CNS segments is provided by tracts that are arranged in three layers: an inner, middle, and outer layer. The inner layer of white matter contains the axons of neurons that connect neighboring segments of the nervous system. It contains a mix of nerve cells and axons called the reticular formation and is the site of many important spinal cord and brain stem reflex circuits. The middle layer tracts provide the longitudinal communication between more distant segments of the nervous system; it contains most of the major fiber tract systems required for sensation and movement. The recently evolved outer or neolayer systems, which become functional during infancy and childhood, provide the means for very delicate and discriminative function. The outer position of the neolayer tracts and their lack of collateral and redundant pathways make them the most vulnerable to injury.

## THE SPINAL CORD AND BRAIN

### The Spinal Cord

In the adult, the spinal cord is found in the upper two thirds of the spinal canal of the vertebral column (Fig. 36-14A). It extends from the foramen magnum at the base of the skull to a cone-shaped termination, the *conus medullaris*, usually at the level of the first or second lumbar vertebra (L1 or L2) in the adult. The dorsal and ventral roots of the more caudal portions of the cord elongate during development and angle downward from the cord, forming what is called the *cauda equina* (from the Latin for "horse's tail"). The filum terminale, which is composed of non-neural tissues and the pia mater, continues caudally and attaches to the second sacral vertebra (S2).

The spinal cord is somewhat oval on transverse section. Internally, the gray matter has the appearance of a butterfly or the letter "H" on cross section (Fig. 36-14B). The extensions of the gray matter that form the letter "H" are called the *horns*. Those that extend posteriorly are called the *dorsal horns*, and those that extend anteriorly are called the *ventral horns*. The central portion of the cord, which connects the dorsal and ventral horns, is called the *intermediate gray matter*. The inter-



**A**

■ **FIGURE 36-14** ■ (A) Dorsal view of the spinal cord including portions of the major spinal nerves and some of the components of the major nerve plexuses. (B) Cross-sectional views of the spinal cord, showing regional variations in gray matter and increasing white matter as the cord ascends.

mediate gray matter surrounds the central canal. In the thoracic area, the small, slender projections that emerge from the intermediate gray matter are called the *intermediolateral columns* of the horns. These columns contain the visceral OA neurons and the efferent neurons of the sympathetic nervous system.

The gray matter is proportional to the amount of tissue innervated by a given segment of the cord (Fig. 36-14B). Larger amounts of gray matter are present in the lower lumbar and upper sacral segments, which supply the lower extremities, and in the fifth cervical segment to the first thoracic segment, which supply the upper limbs. The white matter in the spinal cord also increases progressively toward the brain because ever more ascending fibers are added and the number of descending axons is greater.

The spinal cord and the dorsal and ventral roots are covered by a connective tissue sheath, the pia mater, which also contains the blood vessels that supply the white and gray matter of the cord (Fig. 36-15). On the lateral sides of the spinal cord, extensions of the pia mater, the denticulate ligaments, attach the sides of the spinal cord to the bony walls of the spinal canal. Thus, the cord is suspended by both the denticulate ligaments and the segmental nerves. A fat- and vessel-filled epidural space intervenes between the spinal dura mater and the inner wall of the spinal canal. Each vertebral body has two pedicles that extend posteriorly and support the laterally oriented transverse processes of the neural laminae, which arch medially and fuse to continue as the spinal processes.

The spaces between the vertebral bodies are filled with fibrocartilaginous discs and stabilized with tough ligaments. A gap, the intervertebral foramen, occurs between each two succeeding pedicles, allowing for the exit of the segmental nerves and passage of blood vessels. The spinal cord lives in the protective confines of this series of concentric flexible tissue and body sheaths. Supporting structures of the spinal cord are discussed further in Chapter 37.

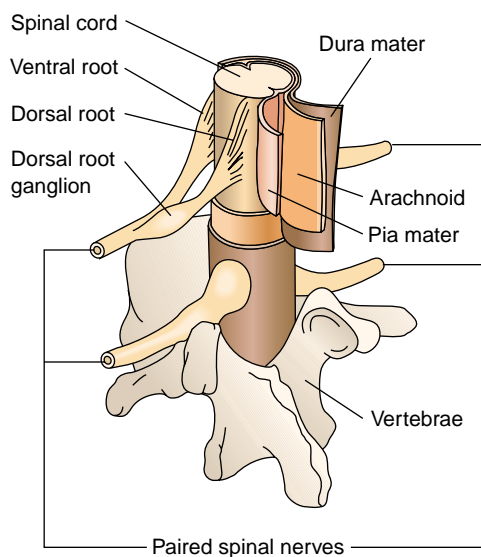
Early in fetal life, the spinal cord extends the entire length of the vertebral column and the spinal nerves exit through the intervertebral foramina (openings) near their level of origin. Because the vertebral column and spinal dura grow faster than

the spinal cord, a disparity develops between each succeeding cord segment and the exit of its dorsal and ventral nerve roots through the corresponding intervertebral foramina. In the newborn, the cord terminates at the level of L2 or L3. In the adult, the cord usually terminates in the inferior border of L1, and the arachnoid and its enclosed subarachnoid space, which is filled with CSF, do not close down on the filum terminale until they reach the level of S2 (Fig. 36-16). This results in the formation of a pocket of CSF, the *dural cisterna spinalis*, which extends from approximately L2 to S2. Because this area contains an abundant supply of CSF and the spinal cord does not extend this far, the area often is used for sampling the CSF. A procedure called a *spinal tap*, or puncture, can be done by inserting a special needle into the dural sac at L3 or L4. The spinal roots, which are covered with pia mater, are in little danger of trauma from the needle used for this purpose.

### Spinal Nerves

The peripheral nerves that carry information to and from the spinal cord are called *spinal nerves*. There are 32 or more pairs of spinal nerves (*i.e.*, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 2 or more coccygeal); each pair is named for the segment of the spinal cord from which it exits. Because the first cervical spinal nerve exits the spinal cord just above the first cervical vertebra (C1), the nerve is given the number of the bony vertebra just below it. However, the numbering is changed for all lower levels. An extra cervical nerve, the C8 nerve, exits above the T1 vertebra, and each subsequent nerve is numbered for the vertebra just above its point of exit (Fig. 36-17).

Each spinal cord segment communicates with its corresponding body segment through the paired segmental spinal nerves. Each spinal nerve, accompanied by the blood vessels supplying the spinal cord, enters the spinal canal through an intervertebral foramen, where it divides into two branches, or



■ **FIGURE 36-15** ■ Spinal cord and meninges.



After emerging from the vertebral column, the spinal nerve divides into two branches or *rami* (singular, *ramus*): a small dorsal primary ramus and a larger ventral primary ramus (Fig. 36-18). The thoracic and upper lumbar spinal nerves also lead to a third branch, the *ramus communicans*, which contains sympathetic axons supplying the blood vessels, the genitourinary system, and the gastrointestinal system. The dorsal ramus contains sensory fibers from the skin and motor fibers to muscles of the back. The anterior primary ramus contains motor fibers that innervate the skeletal muscles of the anterior body wall and the legs and arms.

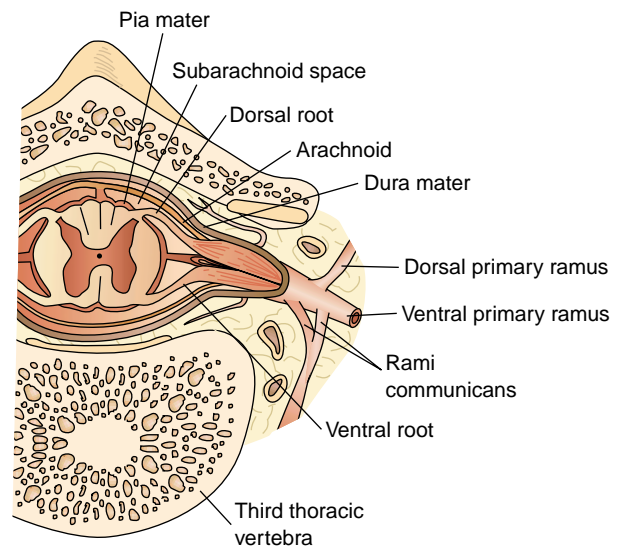
Spinal nerves do not go directly to skin and muscle fibers; instead, they form complicated nerve networks called *plexuses* (Fig. 36-14A). A plexus is a site of intermixing nerve branches. Many spinal nerves enter a plexus and connect with other spinal nerves before exiting from the plexus. Nerves emerging from a plexus form progressively smaller branches that supply the skin and muscles of the various parts of the body. The PNS contains four major plexuses: the cervical plexus, the brachial plexus, the lumbar plexus, and the sacral plexus.

## The Brain

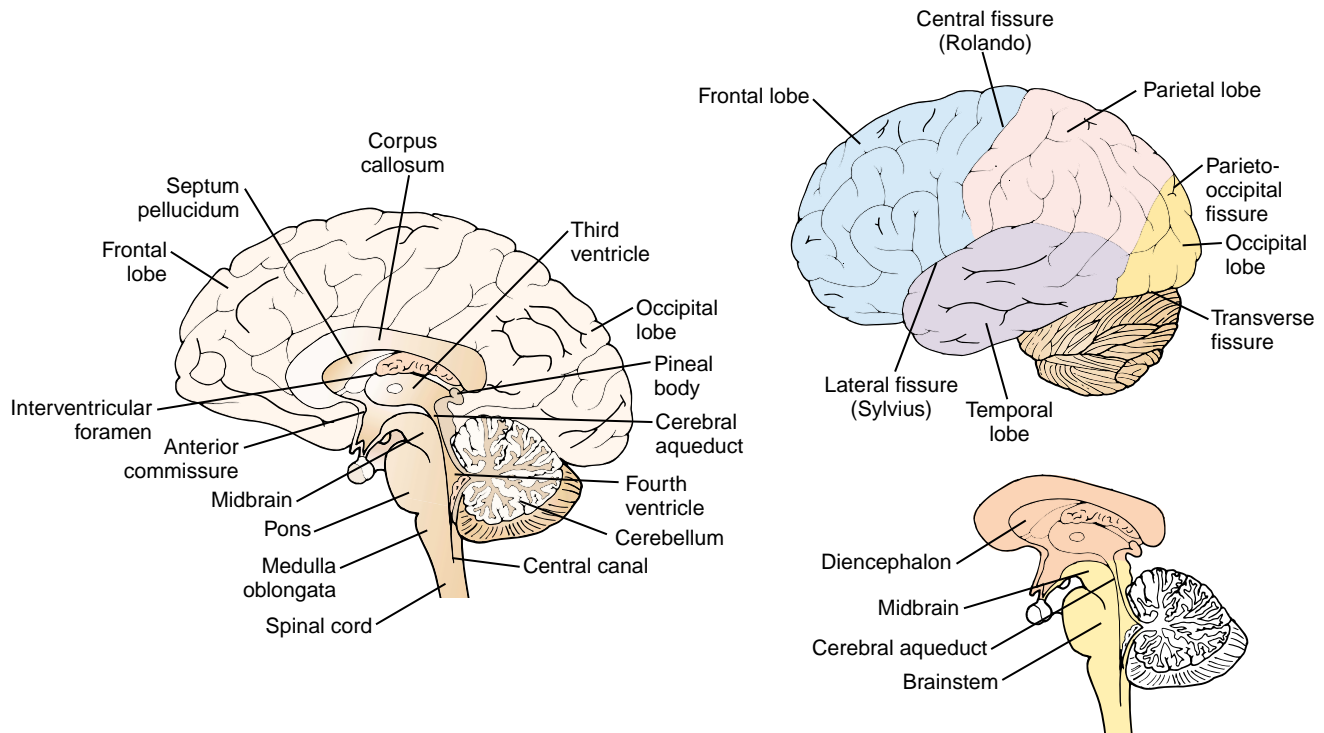
The brain is divided into three regions, the hindbrain, the midbrain, and the forebrain (Fig. 36-19A). The hindbrain includes the medulla oblongata, the pons, and its dorsal outgrowth, the cerebellum (see Chapter 38). Midbrain structures include two pairs of dorsal enlargements: the superior and inferior colliculi. The forebrain, which consists of two hemispheres and is covered by the cerebral cortex, contains central masses of gray matter, the basal ganglia (discussed in Chapter 38), and the rostral end of the neural tube, the diencephalon with its adult derivatives—the thalamus and hypothalamus.

An important concept is that the more rostral, recently developed parts of neural tube gain dominance or control over regions and functions at lower levels. They do not replace the more ancient circuitry but merely dominate it. After damage to

roots. One branch enters the dorsolateral surface of the cord (*i.e.*, dorsal root), carrying the axons of afferent neurons into the CNS. The other branch leaves the ventrolateral surface of the cord (*i.e.*, ventral root), carrying the axons of efferent neurons into the periphery. These two branches or roots fuse at the intervertebral foramen, forming the mixed spinal nerve—"mixed" because it has both afferent and efferent axons.



■ **FIGURE 36-18** ■ Cross-section of vertebral column at the level of the third thoracic vertebra, showing the meninges, the spinal cord, and the origin of a spinal nerve and its branches or rami.



■ **FIGURE 36-19** ■ (A) Midsagittal section of the brain showing the structures of the forebrain, midbrain, and hindbrain. (B) Lateral view of the cerebral hemispheres. (C) Diencephalon, brain stem, and the cerebral aqueduct connecting the 3rd and 4th ventricles.

the more vulnerable parts of the forebrain, as occurs with brain death, a brain stem-controlled organism remains that is capable of breathing and may survive if the environmental temperature is regulated and nutrition and other aspects of care are provided. However, all aspects of intellectual function, experience, perception, and memory usually are permanently lost. The organization of content in this section moves from the more ancient circuitry of the hindbrain to the more dominant and recently developed structures of the forebrain.

### Hindbrain

The term *brain stem* often is used to include the hindbrain, pons, and the midbrain. These regions of the neural tube have the organization of spinal cord segments, except that more of the longitudinal cell columns are present, reflecting the increased complexity of the cranial segmental nerves. In the brain stem, the structure and function of the reticular formation have been greatly expanded. In the pons and medulla, the reticular formation contains networks controlling basic breathing, eating, and locomotion functions. Higher-level integration of these functions occurs in the midbrain. The reticular formation is surrounded on the outside by the long tract systems that connect the forebrain with lower parts of the CNS.

**Medulla.** The *medulla oblongata* represents the caudal five segments of the brain part of the neural tube; the cranial nerve branches entering and leaving it have functions similar to the spinal segmental nerves. Although the ventral horn areas in the medulla are quite small, the dorsal horn areas are enlarged,

processing a large amount of the information pouring through the cranial nerves. Cranial nerves XII (hypoglossal), X (vagus), and (IX) glossopharyngeal have their origin in the medulla (see Table 36-1).

**Pons.** The pons, which develops from the fifth neural tube segment, is located between the medulla oblongata and the midbrain. Dorsally, it forms part of the anterior wall of the fourth ventricle (Fig. 36-19B).

As the name implies (pons = bridge), the pons is composed chiefly of conduction fibers. The enlarged area on the ventral surface of the pons contains the pontine nuclei, which receive information from all parts of the cerebral cortex. The axons of these neurons form a massive bundle that swings around the lateral side of the fourth ventricle to enter the cerebellum. In the pons, the reticular formation is large and contains the circuitry for masticating food and manipulating the jaws during speech. Cranial nerves VIII, VII, and VI have their origin in the pons (see Table 36-1).

### Midbrain

The midbrain develops from the fourth segment of the neural tube, and its organization is similar to that of a spinal segment. The central canal is re-established as the cerebral aqueduct, connecting the fourth ventricle with the third ventricle (see Fig. 36-19B).

Two prominent bundles of nerve fibers, the *cerebral peduncles*, pass along the ventral surface of the midbrain. These fibers include the corticospinal tracts and are the main motor pathways between the forebrain and the pons. On the dorsal

surface, four “little hills,” the *superior* and *inferior colliculi*, are areas of cortical formation. The inferior colliculus is involved in directional turning and, to some extent, in experiencing the direction of sound sources. The superior colliculi are essential to the reflex mechanisms that control conjugate eye movements when the visual environment is surveyed. Two general somatic efferent cranial nerves, the oculomotor nerve, or cranial nerve III, and the trochlear nerve, or cranial nerve IV, exit the midbrain (see Table 36-1).

### Forebrain

The most rostral part of the brain, the forebrain consists of the telencephalon, or “end brain,” and the diencephalon, or “between brain.” The diencephalon forms the core of the forebrain, and the telencephalon forms the cerebral hemispheres.

**Diencephalon.** Three of the most forward brain segments form an enlarged dorsal horn and ventral horn with a narrow, deep, enlarged central canal—the third ventricle—separating the two sides. This region is called the *diencephalon*. The dorsal horn part of the diencephalon is the thalamus and subthalamus, and the ventral horn part is the hypothalamus (Fig. 36-20). The optic nerve, or cranial nerve II, and retina are outgrowths of the diencephalon.

The thalamus consists of two large, egg-shaped masses, one on either side of the third ventricle. The thalamus is divided into several major parts, and each part is divided into distinct nuclei, which are the major relay stations for information going to and from the cerebral cortex. All sensory pathways have direct projections to thalamic nuclei, which convey the information to restricted areas of the sensory cortex. Coordination and integration of peripheral sensory stimuli occur in the thalamus, along with some crude interpretation of highly emotion-laden auditory experiences that not only occur but can be remembered. For example, a person can recover from a deep coma in which cerebral cortex activity is minimal and remember some of what was said at the bedside.

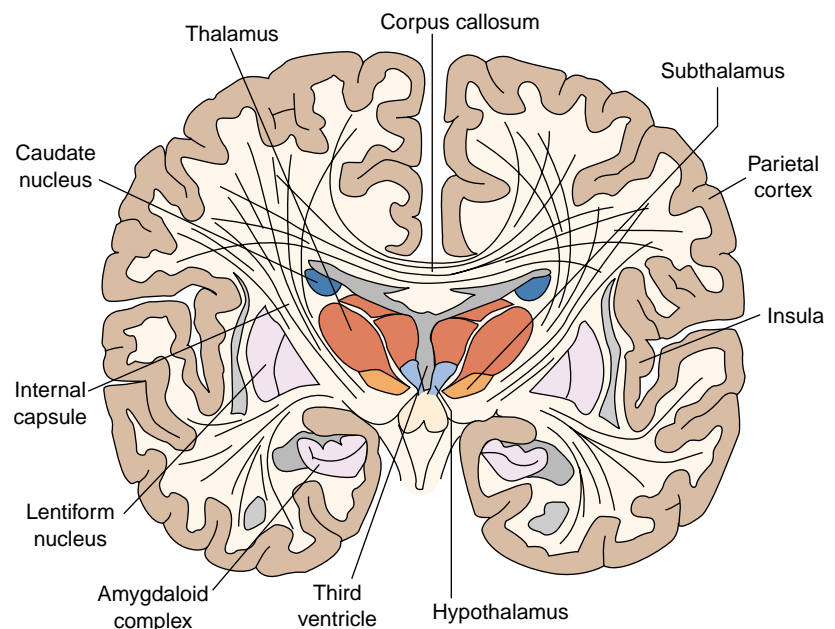
The thalamus also plays a role in relaying critical information regarding motor activities to and from selected areas of the motor cortex. Two neuronal circuits are significant in this regard. One is the pathway from the cerebral cortex to the pons and cerebellum and then, by way of the thalamus, back to the motor cortex. The second is the feedback circuit that travels from the cortex to the basal ganglia, then to the thalamus, and from the thalamus back to the cortex. The subthalamus also contains movement control systems related to the basal ganglia.

Through its connections with the ascending reticular activating system, the thalamus processes neural influences that are basic to cortical excitatory rhythms (*i.e.*, those recorded on the electroencephalogram), to essential sleep-wakefulness cycles, and to the process of attending to stimuli. Besides their cortical connections, the thalamic nuclei have connections with each other and with neighboring nonthalamic brain structures such as the limbic system. Through their connections with the limbic system, some thalamic nuclei are involved in the relation between stimuli and the emotional responses they evoke.

The ventral horn portion of the diencephalon is the hypothalamus, which borders the third ventricle and includes a ventral extension, the neurohypophysis (*i.e.*, posterior pituitary). The hypothalamus is the area of master-level integration of homeostatic control of the body's internal environment. Maintenance of blood gas concentration, water balance, food consumption, and major aspects of endocrine and autonomic nervous system control require hypothalamic function.

The internal capsule is a broad band of projection fibers that lies between the thalamus medially and the basal ganglia laterally (see Fig. 36-20). It contains all of the fibers that connect the cerebral cortex with deeper structures, including the basal ganglia, thalamus, midbrain, pons, medulla, and spinal cord.

**Cerebral Hemispheres.** The two cerebral hemispheres are lateral outgrowths of the diencephalon. The cerebral hemispheres contain the lateral ventricles (*i.e.*, ventricles I and II), which are



■ **FIGURE 36-20** ■ Frontal section of the brain passing through the third ventricle, showing the thalamus, subthalamus, hypothalamus, internal capsule, corpus callosum, basal ganglia (caudate nucleus, lenticular nucleus), amygdaloid complex, insula, and parietal cortex.

connected with the third ventricle of the diencephalon by a small opening called the *interventricular foramen* (*i.e.*, foramen of Monro). Axons of the olfactory nerve, or cranial nerve I, terminate in the most ancient portion of the cerebrum—the olfactory bulb, where initial processing of olfactory information occurs. Projection axons from the olfactory bulb relay information through the olfactory tracts to the thalamus and to other parts of the cerebral cortex (*i.e.*, orbital cortex), where olfactory-related reflexes and olfactory experience occur.

The *corpus callosum* is a massive commissure, or bridge, of myelinated axons that connects the cerebral cortex of the two sides of the brain. Two smaller commissures, the anterior and posterior commissures, connect the two sides of the more specialized regions of the cerebrum and diencephalon.

The surfaces of the hemispheres are lateral (side), medial (area between the two sides of the brain), and basal (ventral). The cerebral cortex observed laterally is the recently evolved six-layered neocortex. The surface of the hemispheres contains many ridges and grooves. A *gyrus* is the ridge between two grooves, and the groove is called a *sulcus* or *fissure*. The cerebral cortex is arbitrarily divided into lobes named after the bones that cover them: the frontal, parietal, temporal, and occipital lobes (Fig. 36-19C).

**Frontal Lobe.** The frontal lobe extends from the frontal pole to the central sulcus (*i.e.*, fissure) and is separated from the temporal lobe by the lateral sulcus. The frontal lobe can be subdivided rostrally into the frontal pole and laterally into the superior, middle, and inferior gyri, which continue on the undersurface over the eyes as the orbital cortex. These areas are associated with the medial thalamic nuclei, which also are related to the limbic system. In terms of function, the prefrontal cortex is thought to be involved in anticipation and prediction of consequences of behavior.

The precentral gyrus (area 4), next to the central sulcus, is the *primary motor cortex* (Fig. 36-21). This area of the cortex provides precise movement control for distal flexor muscles of the hands and feet and of the phonation apparatus required for speech. Just rostral to the precentral gyrus is a region of the frontal cortex called the *premotor* or *motor association cortex*. This

region (area 8 and rostral area 6) is involved in the planning of complex learned movement patterns. The primary motor cortex and the association motor cortex are connected with lateral thalamic nuclei, through which they receive feedback information from the basal ganglia and cerebellum. On the medial surface of the hemisphere, the premotor area includes a *supplementary motor cortex* involved in the control of bilateral movement patterns requiring great dexterity.

**Parietal Lobe.** The parietal lobe of the cerebrum lies behind the central sulcus (*i.e.*, postcentral gyrus) and above the lateral sulcus. The strip of cortex bordering the central sulcus is called the *primary somatosensory cortex* (areas 3, 1, and 2) because it receives very discrete sensory information from the lateral nuclei of the thalamus. Just behind the primary sensory cortex is the *somatosensory association cortex* (areas 5 and 7), which is connected with the thalamic nuclei and with the primary sensory cortex. This region is necessary for perceiving the meaningfulness of integrated sensory information from various sensory systems, especially the perception of “where” the stimulus is in space and in relation to body parts. Localized lesions of this region can result in the inability to recognize the meaningfulness of an object (*i.e.*, agnosia). With the person’s eyes closed, a screwdriver can be felt and described as to shape and texture. Nevertheless, the person cannot integrate the sensory information required to identify it as a screwdriver (discussed further in Chapter 39).

**Temporal Lobe.** The temporal lobe lies below the lateral sulcus and merges with the parietal and occipital lobes. It includes the temporal pole and three primary gyri: the superior, middle, and inferior gyri. The primary auditory cortex (area 41) involves the part of the superior temporal gyrus that extends into the lateral sulcus (see Fig. 36-21). This area is particularly important in discrimination of sounds entering opposite ears. It receives auditory input projections by way of the inferior colliculus of the midbrain and a ventrolateral thalamic nucleus. The more exposed part of the superior temporal gyrus involves the auditory association area (area 22). The recognition of certain sound patterns and their meaning requires the function



of this area. The remaining portion of the temporal cortex is less defined functionally but apparently is important in long-term memory recall. This is particularly true with respect to perception and memory of complex sensory patterns, such as geometric figures and faces (*i.e.*, recognition of “what” or “who” the stimulus is). Irritation or stimulation can result in vivid hallucinations of long-past events.

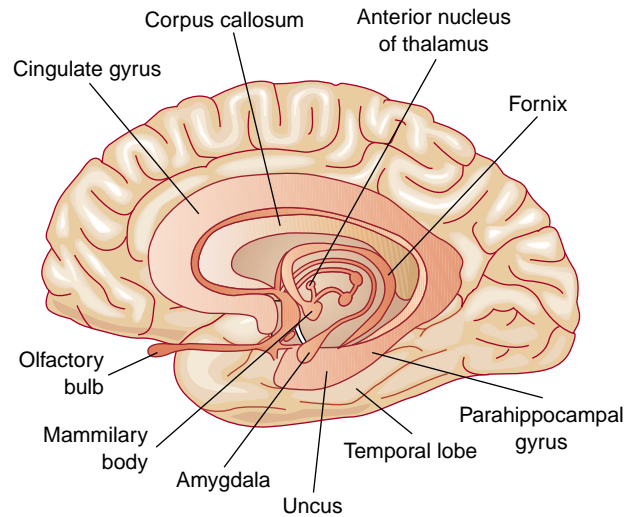
**Occipital Lobe.** The occipital lobe lies posterior to the temporal and parietal lobes and is only arbitrarily separated from them. The medial surface of the occipital lobe contains a deep sulcus extending from the limbic lobe to the occipital pole, the *calcarine sulcus*, which is surrounded by the primary visual cortex (area 17). Stimulation of this cortex causes the experience of bright lights (phosphenes) in the visual field. Just superior and inferior and extending onto the lateral side of the occipital pole is the *visual association cortex* (areas 18 and 19). This area is closely connected with the primary visual cortex and with complex nuclei of the thalamus. Integrity of the association cortex is required for gnostic visual function, by which the meaningfulness of visual experience, including experiences of color, motion, depth perception, pattern, form, and location in space, occurs.

The neocortical areas of the parietal lobe, between the somatosensory and the visual cortices, have a function in relating the texture, or “feel,” and location of an object with its visual image. Between the auditory and visual association areas, the *parieto-occipital region* is necessary for relating the meaningfulness of a sound and image to an object or person.

**Limbic System.** The medial aspect of the cerebrum is organized into concentric bands of cortex, the *limbic system* (*limbic* = borders), which surrounds the connection between the lateral and third ventricles. The innermost band just above and below the cut surface of the corpus callosum is folded out of sight but is an ancient, three-layered cortex ending as the hippocampus in the temporal lobe. Just outside the folded area is a band of transitional cortex, which includes the cingulate and the parahippocampal gyri (Fig. 36-22). This limbic lobe has reciprocal connections with the medial and the intralaminar nuclei of the thalamus, with the deep nuclei of the cerebrum (*e.g.*, amygdaloid nuclei, septal nuclei), and with the hypothalamus. Overall, this region of the brain is involved in emotional experience and in the control of emotion-related behavior. Stimulation of specific areas in this system can lead to feelings of dread, high anxiety, or exquisite pleasure. It also can result in violent behaviors, including attack, defense, or explosive and emotional speech.

### Meninges

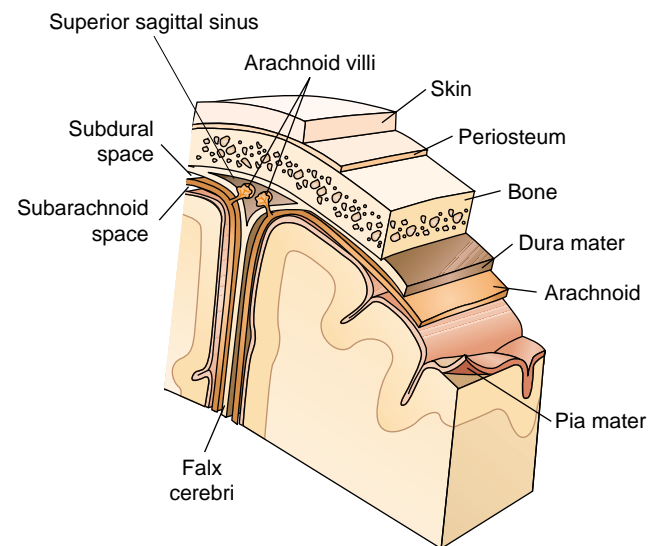
Inside the skull and vertebral column, the brain and spinal cord are loosely suspended and protected by several connective tissue sheaths called the *meninges* (Fig. 36-23). The surfaces of the spinal cord, brain, and segmental nerves are covered with a delicate connective tissue layer called the *pia mater* (Latin for “delicate mother”). The surface blood vessels and those that penetrate the brain and spinal cord are encased in this protective tissue layer. A second, very delicate, nonvascular, and waterproof layer, called the *arachnoid*, encloses the entire CNS. The arachnoid layer is named for its spider web appearance. The CSF is contained in the subarachnoid space. Immediately



■ **FIGURE 36-22** ■ The limbic system includes the limbic cortex (cingulate gyrus, parahippocampal gyrus, uncus) and associated subcortical structures (thalamus, hypothalamus, amygdala).

outside the arachnoid is a continuous sheath of strong connective tissue, the *dura mater* (*i.e.*, “tough mother”), which provides the major protection for the brain and spinal cord. The cranial dura often splits into two layers, with the outer layer serving as the periosteum of the inner surface of the skull.

The inner layer of the dura forms two major folds. The first, a longitudinal fold called the *falx cerebri*, separates the cerebral hemispheres and fuses with a second transverse fold, called the *tentorium cerebelli* (Fig. 36-24). The tentorium cerebelli separates the anterior and middle depression in the skull (cranial fossae), which contains the cerebral hemispheres, from the posterior fossa, found inferiorly and containing the brain stem and cerebellum. A semicircular gap, or incisura, is formed at the midline to permit the midbrain to pass forward from the posterior fossa.



■ **FIGURE 36-23** ■ The cranial meninges. Arachnoid villi, shown within the superior sagittal sinus, are one site of cerebrospinal fluid absorption into the blood.

■ **FIGURE 36-24** ■ Cranial dura mater. The skull is open to show the falx cerebri and the tentorium cerebelli, as well as some of the cranial venous sinuses.

### Ventricular System and Cerebrospinal Fluid

The ventricular system is a series of CSF-filled cavities in the brain (Fig. 36-25). The CSF provides a supporting and protective fluid in which the brain and spinal cord float. CSF helps maintain a constant ionic environment that serves as a medium for diffusion of nutrients, electrolytes, and metabolic end-products into the extracellular fluid surrounding CNS neurons and glia. Filling the ventricles, the CSF supports the mass of the brain. Because it fills the subarachnoid space surrounding the CNS, a physical force delivered to either the skull or spine is to some extent diffused and cushioned.

The lining of the ventricles and central canal of the spinal cord is called the *ependyma*. There is a tremendous expansion of the ependyma in the roof of the lateral, third and fourth ventricles. The CSF is produced by tiny reddish masses of specialized capillaries from the pia mater, called the *choroid plexus*, that project into the ventricles. CSF is an ultrafiltrate of blood plasma, composed of 99% water with other constituents, mak-

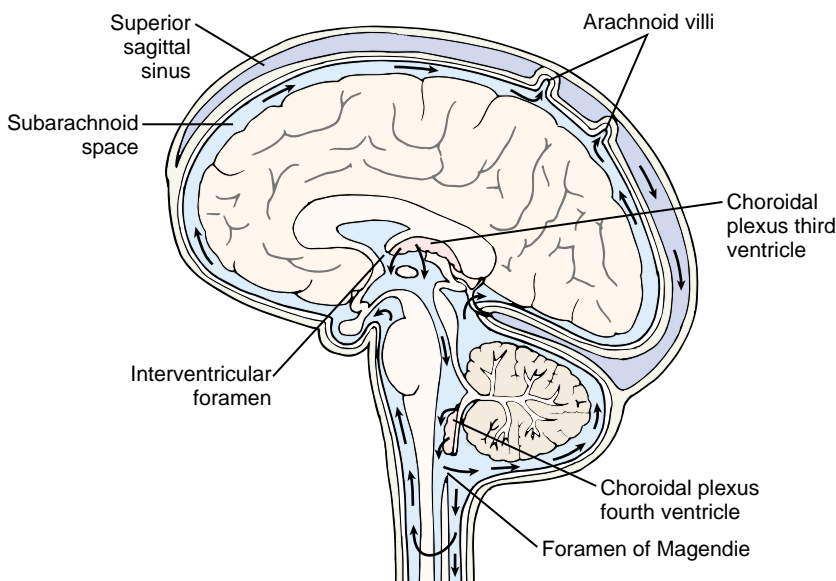
ing it close to the composition of the brain extracellular fluid. Humans secrete approximately 500 mL of CSF each day. However, only approximately 150 mL is in the ventricular system at any one time, meaning that the CSF is continuously being absorbed.

Once produced, the CSF flows freely through the ventricles. Three openings, or foramina, allow the CSF to pass into the subarachnoid space. Two of these, the foramina of Luschka, are located at the lateral corners of the fourth ventricle. The third, the medial foramen of Magendie, is in the midline at the caudal end of the fourth ventricle (see Fig. 36-25). Approximately 30% of the CSF passes down into the subarachnoid space that surrounds the spinal cord, mainly on its dorsal surface, and moves back up to the cranial cavity along its ventral surface.

Reabsorption of CSF into the vascular system occurs along the sides of the superior sagittal sinus in the anterior and middle fossa. Here, the waterproof arachnoid has protuberances, the *arachnoid villi*, that penetrate the inner dura and venous walls of the superior sagittal sinus. The arachnoid villi function as one-way valves, permitting CSF outflow into the blood but not allowing blood to pass into the arachnoid spaces.

### Blood-Brain and Cerebrospinal Fluid–Brain Barriers

Maintenance of a chemically stable environment is essential to the function of the brain. In most regions of the body, extracellular fluid undergoes small fluctuations in pH and concentrations of hormones, amino acids, and potassium ions during routine daily activities such as eating and exercising. If the brain were to undergo such fluctuations, the result would be uncontrolled neural activity because some substances such as amino acids act as neurotransmitters, and ions such as potassium influence the threshold for neural firing. Two barriers, the blood-brain barrier and the CSF-brain barrier, provide the means for maintaining the stable chemical environment of the brain. Only water, carbon dioxide, and oxygen enter the brain with relative ease; the transport of other substances between the brain and the blood is slow.

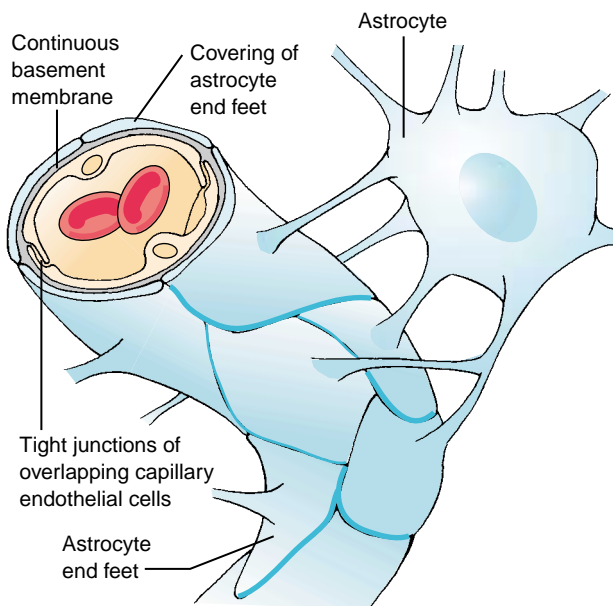


■ **FIGURE 36-25** ■ The flow of cerebrospinal fluid from the time of its formation from blood in the choroid plexuses until its return to the blood in the superior sagittal sinus. Plexuses in the lateral ventricles are not illustrated.

**Blood-Brain Barrier.** The blood-brain barrier depends on the unique characteristics of the brain capillaries. The endothelial cells of brain capillaries are joined by continuous tight junctions. In addition, most brain capillaries are completely surrounded by a basement membrane and by the processes of supporting cells of the brain, called *astrocytes* (Fig. 36-26). The blood-brain barrier permits passage of essential substances while excluding unwanted materials. Reverse transport systems remove materials from the brain. Large molecules such as proteins and peptides are largely excluded from crossing the blood-brain barrier. Acute cerebral lesions, such as trauma and infection, increase the permeability of the blood-brain barrier and alter brain concentrations of proteins, water, and electrolytes.

The blood-brain barrier prevents many drugs from entering the brain. Most highly water-soluble compounds are excluded from the brain, especially molecules with high ionic charge, such as many of the catecholamines. In contrast, many lipid-soluble molecules cross the lipid layers of the blood-brain barrier with ease. Some drugs, such as the antibiotic chloramphenicol, are highly lipid soluble and therefore enter the brain readily. Other medications have a low solubility in lipids and enter the brain slowly or not at all. Alcohol, nicotine, and heroin are very lipid soluble and rapidly enter the brain. Some substances that enter the capillary endothelium are converted by metabolic processes to a chemical form incapable of moving into the brain.

The cerebral capillaries are much more permeable at birth than in adulthood, and the blood-brain barrier develops during the early years of life. In severely jaundiced infants, bilirubin can cross the immature blood-brain barrier, producing kernicterus and brain damage (see Chapter 15). In adults, the mature blood-brain barrier prevents bilirubin from entering the brain, and the nervous system is not affected.



■ **FIGURE 36-26** ■ The three components of the blood-brain barrier: the astrocyte and astrocytic feet that encircle the capillary, the capillary basement membrane, and the tight junctions that join the overlapping capillary endothelial cells.

**Cerebrospinal Fluid–Brain Barrier.** The ependymal cells covering the choroid plexus are linked together by tight junctions, forming a blood-CSF barrier to diffusion of many molecules from the blood plasma of choroid plexus capillaries to the CSF. Water is transported through the choroid epithelial cells by osmosis. Oxygen and carbon dioxide move into the CSF by diffusion, resulting in partial pressures roughly equal to those of plasma. The high sodium and low potassium contents of the CSF are actively regulated and kept relatively constant. Lipids and nonpeptide hormones diffuse through the barrier rather easily, but most large molecules, such as proteins, peptides, many antibiotics, and other medications, do not normally get through. Many substances such as proteins; sodium ions; a number of micronutrients such as vitamins C, B<sub>6</sub> (pyridoxine), and folate are actively secreted into the CSF by the choroid epithelium. Because the resultant CSF has a relatively high sodium content, the negatively charged chloride and bicarbonate diffuse into the CSF along an ionic gradient. The choroid cells also generate bicarbonate from carbon dioxide in the blood. The generation of bicarbonate is important to the regulation of the pH of the CSF.

Mechanisms exist that facilitate the transport of other molecules such as glucose without energy expenditure. Ammonia, a toxic metabolite of neuronal activity, is converted to glutamine by astrocytes. Glutamine moves by facilitated diffusion through the choroid epithelium into the plasma. This exemplifies a major function of the CSF, that of providing a means of removal of toxic waste products from the CNS. Because the brain and spinal cord have no lymphatic channels, the CSF serves this function.

There are several specific areas of the brain where the blood-CSF barrier does not exist. One area is at the caudal end of the fourth ventricle, where specialized receptors for the carbon dioxide level of the CSF influence respiratory function. Another area consists of the walls of the third ventricle, which permit hypothalamic neurons to monitor blood glucose levels. This mechanism permits hypothalamic centers to respond to these blood glucose levels, contributing to hunger and eating behaviors.

**In summary,** in the adult, the spinal cord is in the upper two thirds of the spinal canal of the vertebral column. On transverse section, the spinal cord has an oval shape, and the internal gray matter has the appearance of a butterfly or letter “H.” The dorsal horns contain the IA neurons and receive afferent information from dorsal root and other connecting neurons. The ventral horns contain the OA neurons and efferent LMNs that leave the cord by the ventral roots. Thirty-two pairs of spinal nerves (*i.e.*, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 2 or more coccygeal) are present. Each pair communicates with its corresponding body segments. The spinal nerves and the blood vessels that supply the spinal cord enter the spinal canal through an intervertebral foramen. After entering the foramen, they divide into two branches, or roots, one of which enters the dorsolateral surface of the cord (*i.e.*, dorsal root), carrying the axons of afferent neurons into the CNS. The other root leaves the ventrolateral surface of the cord (*i.e.*, ventral root), carrying the axons of efferent neurons into the periphery. These two roots fuse at the intervertebral foramen, forming the mixed spinal nerve.

The brain can be divided into three regions: the hindbrain, the midbrain, and the forebrain. The hindbrain, consisting of the medulla oblongata, pons, and cerebellum, contains the neuronal circuits for the eating, breathing, and locomotive functions required for survival. Cranial nerves XII, XI, X, IX, VIII, VII, VI, and V are located in the hindbrain. The midbrain contains cranial nerves III and IV.

The forebrain is the most rostral part of the brain; it consists of the diencephalon and the telencephalon. The diencephalon forms the core of the forebrain, and telencephalon forms the cerebral hemispheres. The dorsal horn part of the diencephalon contains the thalamus and subthalamus, and the ventral horn contains the hypothalamus. All sensory pathways have direct projections to the thalamic nuclei, which convey the information to restricted parts of the sensory cortex. The hypothalamus functions in the homeostatic control of the internal environment. The cerebral hemispheres are the lateral outgrowths of the diencephalon and are arbitrarily divided into lobes—the frontal, parietal, temporal, and occipital lobes. The prefrontal premotor area and primary motor cortex are located in the frontal lobe; the primary sensory cortex and somatosensory association area are in the parietal cortex; the primary auditory cortex and the auditory association area are in the temporal lobe; and the primary visual cortex and association visual cortex are in the occipital lobe. The limbic system, which is involved in emotional experience and release of emotional behaviors, is located in the medial aspect of the cerebrum.

The brain is enclosed and protected by the pia mater, arachnoid, and dura mater. The protective CSF in which the brain and spinal cord float isolates them from minor and moderate trauma. The CSF is secreted into the ventricles, circulates through the ventricular system, passes outside to surround the brain, and is reabsorbed into the venous system through the arachnoid villi. The CSF-brain barrier and the blood-brain barrier protect the brain from substances in the blood that would disrupt brain function.

## THE AUTONOMIC NERVOUS SYSTEM

The ability to maintain homeostasis and perform the activities of daily living in an ever-changing physical environment is largely vested in the autonomic nervous system (ANS). The ANS functions at the subconscious level and is involved in regulating, adjusting, and coordinating vital visceral functions such as blood pressure and blood flow, body temperature, respiration, digestion, metabolism, and elimination. The ANS is strongly affected by emotional influences and is involved in many of the expressive aspects of behavior. Blushing, palpitations of the heart, clammy hands, and dry mouth are several emotional expressions that are mediated through the ANS.

As with the somatic nervous system, the ANS is represented in both the CNS and the PNS. Traditionally, the ANS has been defined as a general efferent system innervating visceral organs. The efferent outflow from the ANS has two divisions: the sympathetic nervous system and the parasympathetic nervous system. The afferent input to the ANS is pro-

## KEY CONCEPTS

### THE AUTONOMIC NERVOUS SYSTEM (ANS)

- The ANS functions at the subconscious level and is responsible for maintaining homeostatic functions of the body.
- The ANS has two divisions: the sympathetic and parasympathetic systems. Although the two divisions function in concert, they are generally viewed as having opposite and antagonistic actions.
- The sympathetic nervous system functions in maintaining vital functions and responding when there is a critical threat to the integrity of the individual—the “fight-or-flight” response.
- The parasympathetic nervous system functions in conserving energy, resource replenishment, and maintenance of organ function during periods of minimal activity.

vided by visceral afferent neurons, usually not considered to be part of the ANS.

The functions of the sympathetic nervous system include maintaining body temperature and adjusting blood flow and blood pressure to meet the changing needs of the body that occur with activities of daily living, such as moving from the supine to the standing position. The sympathoadrenal system also can discharge as a unit when there is a critical threat to the integrity of the individual—the so-called fight-or-flight response. During a stress situation, the heart rate accelerates; the blood pressure rises; blood flow shifts from the skin and gastrointestinal tract to the skeletal muscles and brain; blood sugar increases; the bronchioles and pupils dilate; the sphincters of the stomach and intestine and the internal sphincter of the urethra constrict; and the rate of secretion of exocrine glands that are involved in digestion diminishes. Emergency situations often require vasoconstriction and shunting of blood away from the skin and into the muscles and brain, a mechanism that, should a wound occur, provides for a reduction in blood flow and preservation of vital functions needed for survival. Sympathetic function often is summarized as catabolic in that its actions predominate during periods of pronounced energy expenditure, such as when survival is threatened.

In contrast to the sympathetic nervous system, the functions of the parasympathetic nervous system are concerned with conservation of energy, resource replenishment and storage (*i.e.*, anabolism), and maintenance of organ function during periods of minimal activity. The parasympathetic nervous system slows heart rate, stimulates gastrointestinal function and related glandular secretion, promotes bowel and bladder elimination, and contracts the pupil, protecting the retina from excessive light during periods when visual function is not vital to survival. The two divisions of the ANS usually are viewed as having opposite and antagonistic actions (*i.e.*, if one activates, the other inhibits a function). Exceptions are functions, such as sweating and regulation of arteriolar blood vessel diameter,



that are controlled by a single division of the ANS, in this case the sympathetic nervous system.

The sympathetic and parasympathetic nervous systems are continually active. The effect of this continual or basal (baseline) activity is referred to as *tone*. The tone of an effector organ or system can be increased or decreased and usually is regulated by a single division of the ANS. For example, vascular smooth muscle tone is controlled by the sympathetic nervous system. Increased sympathetic activity produces local vasoconstriction from increased vascular smooth muscle tone, and decreased activity results in vasodilatation caused by decreased tone. In structures such as the sinoatrial node and atrioventricular node of the heart, which are innervated by both divisions of the ANS, one division predominates in controlling tone. In this case, the tonically active parasympathetic nervous system exerts a constraining or braking effect on heart rate, and when parasympathetic outflow is withdrawn, similar to releasing a brake, the heart rate increases. The increase in heart rate that occurs with vagal withdrawal can be further augmented by sympathetic stimulation.

### Autonomic Efferent Pathways

The outflow of both divisions of the ANS follows a two-neuron pathway. The first motoneuron, called the *preganglionic neuron*, lies in the intermediolateral cell column in the ventral horn of the spinal cord or its equivalent location in the brain stem. The second motoneuron, called the *postganglionic neuron*, synapses with a preganglionic neuron in an autonomic ganglion located in the PNS. The two divisions of the ANS differ in terms of location of preganglionic cell bodies, relative length of preganglionic fibers, general function, nature of peripheral responses, and preganglionic and postganglionic neuromediators (Table 36-3). This two-neuron outflow pathway and the interneurons in the autonomic ganglia that add further modulation to ANS function are features distinctly different from the arrangement in somatic motor innervation.

Most visceral organs are innervated by both sympathetic and parasympathetic fibers. Exceptions include structures such

as blood vessels and sweat glands that have input from only one division of the ANS. The fibers of the sympathetic nervous system are distributed to effectors throughout the body, and as a result, sympathetic actions tend to be more diffuse than those of the parasympathetic nervous system, in which there is a more localized distribution of fibers. The preganglionic fibers of the sympathetic nervous system may traverse a considerable distance and pass through several ganglia before synapsing with postganglionic neurons, and their terminals make contact with a large number of postganglionic fibers. In some ganglia, the ratio of preganglionic to postganglionic cells may be 1:20; because of this, the effects of sympathetic stimulation are diffuse. There is considerable overlap, and one ganglion cell may be supplied by several preganglionic fibers. In contrast to the sympathetic nervous system, the parasympathetic nervous system has its postganglionic neurons located very near or in the organ of innervation. Because the ratio of preganglionic to postganglionic communication often is 1:1, the effects of the parasympathetic nervous system are much more circumscribed.

### Sympathetic Nervous System

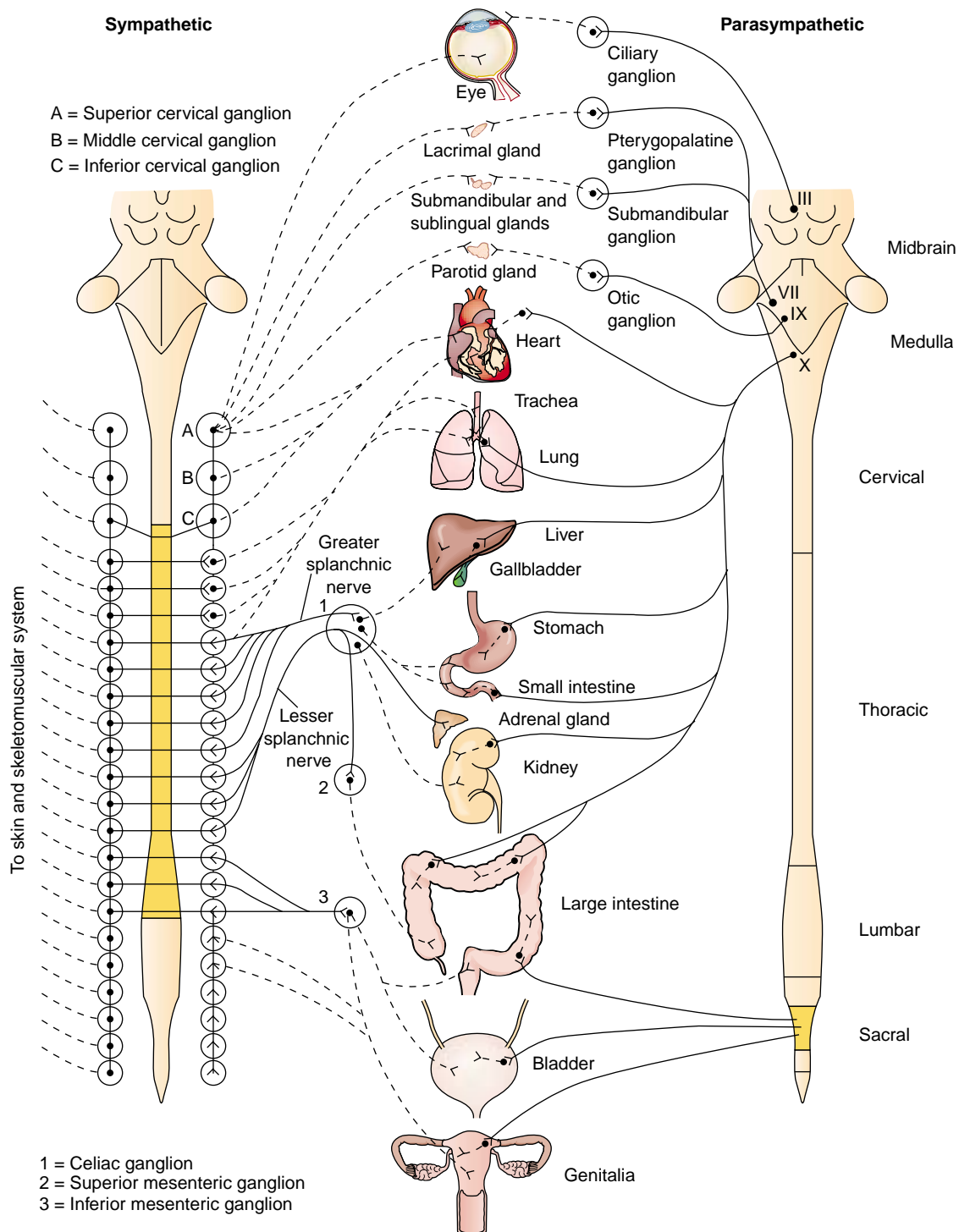
The preganglionic neurons of the sympathetic nervous system are located primarily in the thoracic and upper lumbar segments (T1 to L2) of the spinal cord; thus, the sympathetic nervous system often is referred to as the *thoracolumbar division* of the ANS. These preganglionic neurons, which are located primarily in the ventral horn intermediolateral cell column, have axons that are largely myelinated and relatively short. The postganglionic neurons of the sympathetic nervous system are located in the paravertebral ganglia of the sympathetic chain that lie on either side of the vertebral column, or in prevertebral sympathetic ganglia such as the celiac ganglia (Fig. 36-27). In addition to postganglionic efferent neurons, the sympathetic ganglia contain neurons of the internuncial, short-axon type, similar to those associated with complex circuitry in the brain and spinal cord. Many of these inhibit and others modulate preganglionic-to-postganglionic transmission.

The axons of the preganglionic neurons leave the spinal cord through the ventral root of the spinal nerves (T1 to L2),

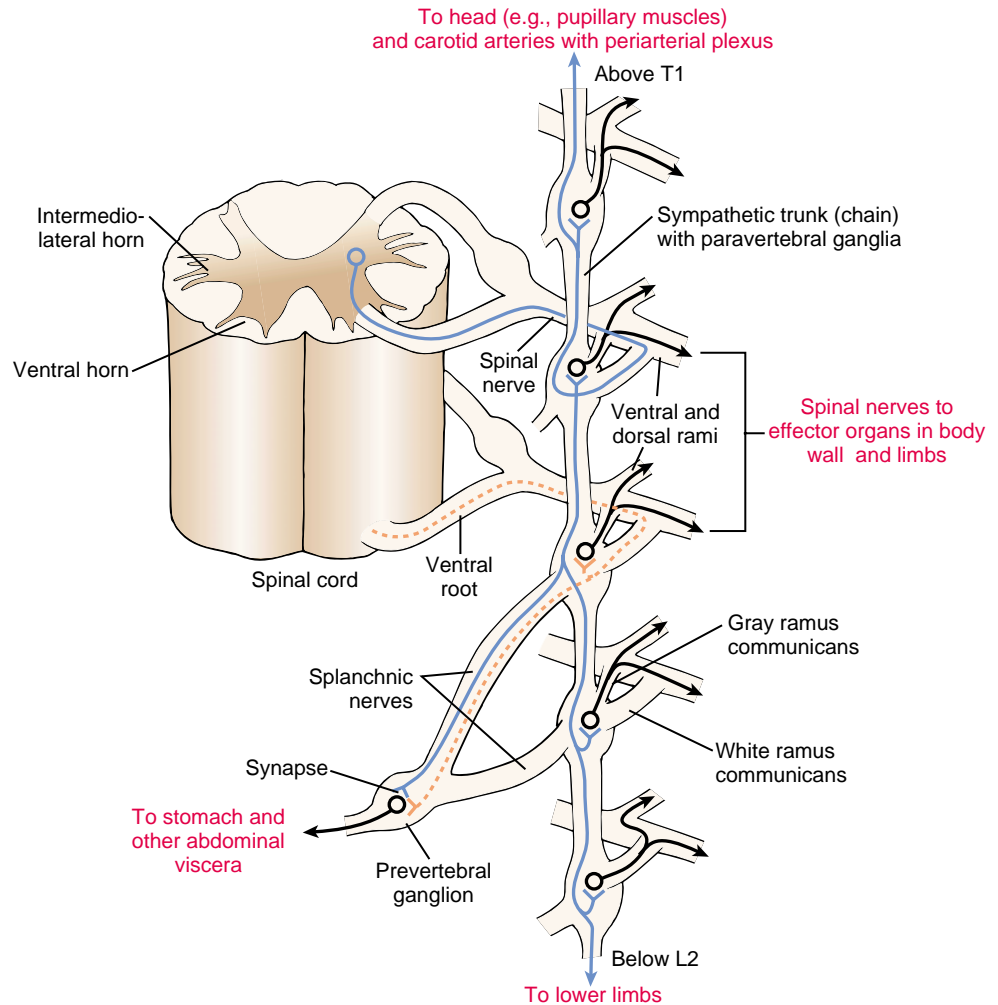
**TABLE 36-3** Characteristics of the Sympathetic and Parasympathetic Nervous Systems

Characteristic	Sympathetic Outflow	Parasympathetic Outflow
Location of preganglionic cell bodies	T1–T12, L1 and L2	Cranial nerves: III, VII (intermedius), IX, X; sacral segments 2, 3, and 4
Relative length of preganglionic fibers	Short—to paravertebral chain of ganglia or to aortic prevertebral of ganglia	Long—to ganglion cells near or in the innervated organ
General function	Catabolic—mobilizes resources in anticipation of challenge for survival (preparation for “fight-or-flight” response)	Anabolic—concerned with conservation, renewal, and storage of resources
Nature of peripheral response	Generalized	Localized
Transmitter between preganglionic terminals and postganglionic neurons	ACh	ACh
Transmitter of postganglionic neuron	ACh (sweat glands and skeletal muscle vasodilator fibers); norepinephrine (most synapses); norepinephrine and epinephrine (secreted by adrenal gland)	ACh

ACh, acetylcholine.



■ **FIGURE 36-27** ■ The autonomic nervous system. The involuntary organs are depicted with their parasympathetic innervation (craniosacral) indicated on the right and sympathetic innervation (thoracolumbar) on the left. Preganglionic fibers are *solid lines*; postganglionic fibers are *dashed lines*. For purposes of illustration, the sympathetic outflow to the skin and skeletomuscular system is shown separately (to the far left); effectors include sweat glands, pilomotor muscles and blood vessels of the skin, and blood vessels of the skeletal muscles and bones. (Modified from Hemer L. [1983]. *The human brain and spinal cord: Functional neuroanatomy and dissection guide*. New York: Springer-Verlag)



**FIGURE 36-28** Sympathetic pathways. Sympathetic fibers leave the spinal cord by way of the ventral root of the spinal nerves, enter the ventral primary rami, and pass through the white rami to the prevertebral or paravertebral ganglia of the sympathetic chain, where they synapse with postganglionic neurons. Some postganglionic fibers from the paravertebral ganglia reenter the segmental nerves through the gray rami and are then distributed in the spinal nerve branches that innervate the effector organs (eg., sweat glands and arrector pili muscles of skin and vascular smooth muscle of blood vessels). Other postganglionic neurons (dotted lines) travel directly to their destination in the various effector organs.

enter the ventral primary rami, and leave the spinal nerve through white rami of the rami communicantes to reach the paravertebral ganglionic chain (Fig. 36-28). In the sympathetic chain of ganglia, preganglionic fibers may synapse with neurons of the ganglion it enters, pass up or down the chain and synapse with one or more ganglia, or pass through the chain and move outward through a splanchnic nerve to terminate in one of the prevertebral ganglia (*i.e.*, celiac, superior mesenteric, or inferior mesenteric) that are scattered along the dorsal aorta and its branches. The adrenal medulla, which is part of the sympathetic nervous system, contains postganglionic sympathetic neurons that secrete sympathetic neurotransmitters directly into the bloodstream.

### Parasympathetic Nervous System

The preganglionic fibers of the parasympathetic nervous system, also referred to as the *craniosacral division* of the ANS, originate in some segments of the brain stem and sacral segments of the spinal cord (see Fig. 36-27). The central regions of origin are the midbrain, pons, medulla oblongata, and the sacral part of the spinal cord. Outflow from the midbrain passes through the oculomotor nerve (cranial nerve III) to supply the pupillary sphincter muscle of each eye and the ciliary muscles that control lens thickness for accommodation. Caudal pontine out-

flow comes from branches of the facial nerve (cranial nerve VII) that supply the lacrimal and nasal glands. The medullary outflow develops from cranial nerves VII, IX, and X. Fibers in the glossopharyngeal nerve (cranial nerve IX) supply the parotid salivary glands. Approximately 75% of parasympathetic efferent fibers are carried in the vagus nerve (cranial nerve X). The vagus nerve provides parasympathetic innervation for the heart, trachea, lungs, esophagus, stomach, small intestine, proximal half of the colon, liver, gallbladder, pancreas, kidneys, and upper portions of the ureters.

Sacral preganglionic axons leave the S2 to S4 segmental nerves by gathering into the pelvic nerves. The pelvic nerves leave the sacral plexus on each side of the cord and distribute their peripheral fibers to the bladder, uterus, urethra, prostate, distal portion of the transverse colon, descending colon, and rectum. The sacral parasympathetic fibers also supply the venous outflow from the external genitalia to facilitate erectile function.

With the exception of cranial nerves III, VII, and IX, which synapse in discrete ganglia, the long parasympathetic preganglionic fibers pass uninterrupted to short postganglionic fibers located in the organ wall. In the walls of these organs, postganglionic neurons send axons to smooth muscle and glandular cells that modulate their functions.

The gastrointestinal tract has its own intrinsic network of ganglionic cells located between the smooth muscle layers, called the *enteric* (or *intramural*) *plexus*, which controls local peristaltic movements and secretory functions. This network of parasympathetic postganglionic neurons and interneurons runs from the upper portion of the esophagus to the internal anal sphincter. Local afferent sensory neurons respond to mechanical and chemical stimuli and communicate these influences to motor fibers in the enteric plexus. The number of neurons in the enteric neural network ( $10^8$ ) is so large that it approximates that of the spinal cord. It is thought that this enteric nervous system is capable of independent function without control from CNS fibers. The CNS has a modulating role, by way of preganglionic innervation of the plexus, converting local peristalsis to longer-distance movements, thereby speeding the transit of intestinal contents.

### Central Integrative Pathways

General visceral afferent fibers accompany the sympathetic and parasympathetic outflow into the spinal and cranial nerves, bringing chemoreceptor, pressure, and nociceptive information from organs of the viscera to the brain stem, thoracolumbar cord, and sacral cord. Local reflex circuits relating visceral afferent and autonomic efferent activity are integrated into a hierarchic control system in the spinal cord and brain stem. Progressively greater complexity in the responses and greater precision in their control occur at each higher level of the nervous system. Most visceral reflexes contain contributions from the LMNs that innervate skeletal muscles as part of their response patterns.

For most autonomic-mediated functions, the hypothalamus serves as the major control center. The hypothalamus, which has connections with the cerebral cortex, the limbic system, and the pituitary gland, is in a prime position to receive, integrate, and transmit information to other areas of the nervous system. The neurons concerned with thermoregulation, thirst, and feeding behaviors are found in the hypothalamus. The hypothalamus also is the site for integrating neuroendocrine function. Hypothalamic releasing and inhibiting hormones control the secretion of anterior pituitary hormones (see Chapter 30).

The organization of many life-support reflexes occurs in the reticular formation of the medulla and pons. These areas of reflex circuitry, often called *centers*, produce complex combinations of autonomic and somatic efferent functions required for the cough, sneeze, swallow, and vomit reflexes, as well as for the more purely autonomic control of the cardiovascular system. At the hypothalamic level, these reflexes are integrated into more general response patterns, such as rage, defensive behavior, eating, drinking, voiding, and sexual function. Forebrain and especially limbic system control of these behaviors involves inhibiting or facilitating release of the response patterns according to social pressures during learned emotion-provoking situations.

Reflex adjustments of cardiovascular and respiratory function occur at the level of the brain stem. A prominent example is the carotid sinus baroreflex (see Chapter 14). One of the striking features of ANS function is the rapidity and intensity with which it can change visceral function. Within 3 to 5 seconds, it can increase heart rate to approximately twice its resting level.

Bronchial smooth muscle tone is largely controlled by parasympathetic fibers carried in the vagus nerve. These nerves produce mild to moderate constriction of the bronchioles.

Other important ANS reflexes are located at the level of the spinal cord. As with other spinal reflexes, these reflexes are modulated by input from higher centers. When there is loss of communication between the higher centers and the spinal reflexes, as occurs in spinal cord injury, these reflexes function in an unregulated manner (see Chapter 38).

### Autonomic Neurotransmission

The generation and transmission of impulses in the ANS occur in the same manner as in the CNS. There are self-propagating action potentials with transmission of impulses across synapses and other tissue junctions by way of neurohumoral transmitters. The postganglionic fibers of the ANS form a diffuse neural plexus at the site of innervation. The membranes of the cells of many smooth muscle fibers are connected by conductive protoplasmic bridges, called *gap junctions*, that permit rapid conduction of impulses through whole sheets of smooth muscle, often in repeating waves of contraction. Autonomic neurotransmitters released near a limited portion of these fibers provide a modulating function extending to a large number of effector cells. The muscle layers of the gut and of the bladder wall are examples.

The main neurotransmitters of the autonomic nervous system are acetylcholine and the catecholamines, epinephrine and norepinephrine. Acetylcholine is released at all of the sites of preganglionic transmission in the autonomic ganglia of sympathetic and parasympathetic nerve fibers and at the sites of postganglionic transmission in parasympathetic nerve endings. It also is released at sympathetic nerve endings that innervate the sweat glands and cholinergic vasodilator fibers found in skeletal muscle. Norepinephrine is released at most sympathetic nerve endings. The adrenal medulla, which is a modified prevertebral sympathetic ganglion, produces epinephrine along with small amounts of norepinephrine. Dopamine, which is an intermediate compound in the synthesis of norepinephrine, also acts as a neurotransmitter. It is the principal inhibitory transmitter of internuncial neurons in the sympathetic ganglia. It also has vasodilator effects on renal, splanchnic, and coronary blood vessels when given intravenously and is sometimes used in the treatment of shock (see Chapter 18).

### Acetylcholine and Cholinergic Receptors

Acetylcholine is synthesized in the cholinergic neurons from choline and acetyl coenzyme A (acetyl CoA). After acetylcholine is secreted by the cholinergic nerve endings, it is rapidly broken down by the enzyme acetylcholinesterase. The choline molecule is transported back into the nerve ending, where it is used again in the synthesis of acetylcholine.

Receptors that respond to acetylcholine are called *cholinergic receptors*. There are two types of cholinergic receptors: muscarinic and nicotinic. Muscarinic receptors are present on the innervational targets of postganglionic fibers of the parasympathetic nervous system and the sweat glands, which are innervated by the sympathetic nervous system. Nicotinic receptors are found in autonomic ganglia and the end plates of skeletal muscle. Acetylcholine has an excitatory effect on muscarinic and nicotinic receptors, except for those in the heart and



lower esophagus, where it has an inhibitory effect. The drug atropine is an antimuscarinic or muscarinic cholinergic-blocking drug that prevents the action of acetylcholine at excitatory and inhibitory muscarinic receptor sites. Because it is a muscarinic-blocking drug, it exerts little effect at nicotinic receptor sites.

### Catecholamines and Adrenergic Receptors

The catecholamines, which include norepinephrine, epinephrine, and dopamine, are synthesized in the sympathetic nervous system. Synthesis of dopamine and norepinephrine begins in the axoplasm of sympathetic nerve terminals with the conversion of the amino acid tyrosine to dopa; dopa to dopamine; and dopamine to norepinephrine. In the adrenal gland an additional step takes place during which approximately 80% the norepinephrine is transformed into epinephrine.

Each of the steps in sympathetic neurotransmitter synthesis requires a different enzyme, and the type of neurotransmitter that is produced depends on the types of enzymes that are available in a nerve terminal. For example, the postganglionic sympathetic neurons that supply blood vessels have the needed enzymes for the synthesis of norepinephrine, whereas those in the adrenal medulla have the enzymes needed to convert norepinephrine into epinephrine. As the catecholamines are synthesized, they are stored in vesicles. The final step of norepinephrine synthesis occurs in these vesicles. When an action potential reaches an axon terminal, the neurotransmitter molecules are released from the storage vesicles. The storage vesicles provide a means for concentrated storage of the catecholamines and protect them from the cytoplasmic enzymes that degrade the neurotransmitters.

In addition to neuronal synthesis, there is a second major mechanism for replenishment of norepinephrine in sympathetic nerve terminals. This mechanism consists of the active reuptake of the released neurotransmitter into the nerve terminal. Between 50% and 80% of the norepinephrine that is released during an action potential is removed from the synaptic area by an active reuptake process. This process terminates the action of the neurotransmitter and allows it to be reused by the neuron. The remainder of the released catecholamines diffuses into the surrounding tissue fluids or is degraded by two special enzymes: catechol-O-methyltransferase, which is diffusely present in all tissues, and monoamine oxidase (MAO), which is found in the nerve endings themselves.

Catecholamines can cause excitation or inhibition of smooth muscle contraction, depending on the site, dose, and type of receptor present. The excitatory or inhibitory responses of organs to sympathetic neurotransmitters are mediated by interaction with special structures in the cell membrane called *receptors*. There are two types of sympathetic receptors:  $\alpha$  and  $\beta$  receptors. In vascular smooth muscle, excitation of  $\alpha$  receptors causes vasoconstriction, and excitation of  $\beta$ -adrenergic receptors causes vasodilatation. Constriction of blood vessels in the skin, kidneys, and splanchnic circulation is mediated by  $\alpha$ -adrenergic receptors. The  $\beta$ -adrenergic receptors are most prevalent in the heart, the blood vessels of skeletal muscle, and the bronchioles.

$\alpha$ -Adrenergic receptors have been further subdivided into  $\alpha_1$  and  $\alpha_2$  receptors, and  $\beta$ -adrenergic receptors into  $\beta_1$  and  $\beta_2$  receptors.  $\beta_1$ -Adrenergic receptors are found primarily in the heart and can be selectively blocked by  $\beta_1$ -receptor-blocking drugs.  $\beta_2$ -Adrenergic receptors are found in the bronchioles and

in other sites that have  $\beta$ -mediated functions. The  $\alpha_1$  receptors are found primarily in postsynaptic effector sites; they mediate responses in vascular smooth muscle. The  $\alpha_2$  receptors are mainly located presynaptically and can inhibit the release of norepinephrine from sympathetic nerve terminals. The  $\alpha_2$  receptors are abundant in the CNS and are thought to influence the central control of blood pressure.

**In summary,** the ANS regulates, adjusts, and coordinates the visceral functions of the body. The ANS, which is divided into the sympathetic and parasympathetic systems, is an efferent system. It receives its afferent input from visceral afferent neurons. The ANS has CNS and PNS components. The outflow of the sympathetic and parasympathetic nervous system follows a two-neuron pathway, which consists of a preganglionic neuron located in the CNS and a postganglionic neuron located outside the CNS. Sympathetic fibers leave the CNS at the thoracolumbar level, and the parasympathetic fibers leave at the craniosacral level.

In general, the sympathetic and parasympathetic nervous systems have opposing effects on visceral function—if one excites, the other inhibits. The hypothalamus serves as the major control center for most ANS functions; local reflex circuits relating visceral afferent and autonomic efferent activity are integrated in a hierarchic control system in the spinal cord and brain stem.

The main neurotransmitters for the ANS are acetylcholine, the catecholamines, epinephrine, and norepinephrine. Acetylcholine is the transmitter for all preganglionic neurons, for postganglionic parasympathetic neurons, and for selected postganglionic sympathetic neurons. The catecholamines are the neurotransmitters for most postganglionic sympathetic neurons. The ANS neurotransmitters exert their action through specialized cell surface receptors—cholinergic receptors that bind acetylcholine and adrenergic receptors that bind the catecholamines. The cholinergic receptors are divided into nicotinic and muscarinic receptors, and adrenergic receptors are divided into  $\alpha$  and  $\beta$  receptors.

### REVIEW QUESTIONS

- The nervous system functions in much the same way as a computer system. Using this analogy, describe the relationship between the PNS and CNS in terms of input, output, and computational functions.
- The transmission of impulses in the nervous system occurs by way of chemical or electrical synapses. Compare the two types of synapses in terms of mechanism of impulse generation, speed of conduction, one-way conduction, and in the case of chemical synapses, the mechanism whereby the neurotransmitters are synthesized, stored, released, and inactivated.
- The poliovirus produces paralysis of skeletal muscles but does not affect somatosensory or visceral function. Based on your knowledge of cell columns, what neurons are susceptible to attack by the virus.
- The inner tract layer of the nervous system contains many of the neuronal processes for reflexes such as those involved in

swallowing and vomiting. Explain the advantages of this arrangement.

- State the structures innervated by general somatic afferent, special visceral afferent, general visceral afferent, special somatic afferent, general visceral efferent, pharyngeal efferent, and general somatic efferent neurons.
- List the structures of the hindbrain, midbrain, and forebrain and describe their functions.
- Name the cranial nerves and cite their location and function.
- Describe the characteristics of the CSF and trace its passage through the ventricular system.
- State the function of the autonomic nervous system.
- Compare the anatomic location and functions of the sympathetic and parasympathetic nervous systems.



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