The Nervous System

The human nervous system, by far the most complex system in the human body, is formed by a network of more than ***100 million*** nerve cells (**neurons**), assisted by many ***more*** **glial cells**. Each neuron has, on average, at least 1000 interconnections with other neurons, forming a very complex system for communication.

Neurons are grouped as **circuits.** Like electronic circuits, neural circuits are highly specific combinations of elements that make up systems of various sizes and complexities. Although a neural circuit may be single, in most cases it is a combination of two or more circuits that interacts to generate a function. A neural function is a set of coordinated processes intended to produce a definite result. A number of elementary circuits may be combined to form higher-order systems.

Nerve tissue is distributed throughout the body as an integrated communications network. Anatomically, the nervous system is divided into the **central nervous system,** consisting of the brain and the spinal cord, and the **peripheral nervous system,** composed of nerve fibers and small aggregates of nerve cells called **nerve ganglia** Structurally, nerve tissue consists of two cell types: **nerve cells,** or **neurons,** which usually show numerous long processes, and several types of **glial cells** (Gr. *glia*, glue), which have short processes, support and protect neurons, and participate in neural activity, neural nutrition, and the defense processes of the central nervous system.

Neurons

Nerve cells, or neurons, are responsible for the reception, transmission, and processing of stimuli; the triggering of certain cell activities; and the release of neurotransmitters and other informational molecules.

Most neurons consist of three parts: the **dendrites,** which are multiple elongated processes specialized in receiving stimuli from the environment, sensory epithelial cells, or other neurons; the **cell body,** or **perikaryon** (Gr. *peri*, around, + *karyon*, nucleus), which is the trophic center for the whole nerve cell and is also receptive to stimuli; and the **axon** (from Greek, meaning axis), which is a single process specialized in generating or conducting nerve impulses to other cells (nerve, muscle, and gland cells). Axons may also receive information from other neurons; this information mainly modifies the transmission of action potentials to other neurons. The distal portion of the axon is usually branched and constitutes the **terminal arborization.** Each branch of this arborization terminates on the next cell in dilatations called **end bulbs** (**boutons**), which interact with other neurons or nonnerve cells, forming structures called **synapses.** Synapses transmit information to the next cell in the circuit. Neurons and their processes are extremely variable in size and shape. Cell bodies can be spherical, ovoid, or angular; some are very large, measuring up to 150 µm in diameter—large enough to be visible to

the naked eye. Other nerve cells are among the smallest cells in the body; for example, the cell bodies of granule cells of the cerebellum are only 4–5 μm in diameter.

Based on the size and shape of their processes, most neurons can be placed in one of the following categories: **multipolar neurons,** which have more than two cell processes, one process being the axon and the others dendrites; **bipolar neurons,** with one dendrite and one axon; and **pseudounipolar neurons,** which have a single process that is close to the perikaryon and divides into two branches. The process then forms a **T shape**, with one branch extending to a peripheral ending and the other toward the central nervous system. In pseudounipolar neurons, stimuli that are picked up by the dendrites travel directly to the axon terminal without passing through the perikaryon.

During the maturation process of pseudounipolar neurons, the central (axon) and the peripheral (dendrite) fibers fuse, becoming one single fiber. In these neurons, the cell body does not seem to be involved in the conduction of impulses, although it does synthesize many molecules, including neurotransmitters that migrate to the peripheral fibers.

Most neurons of the body are multipolar. Bipolar neurons are found in the cochlear and vestibular ganglia as well as in the retina and the olfactory mucosa. Pseudounipolar neurons are found in the spinal ganglia (the sensory ganglia located in the dorsal roots of the spinal nerves). They are also found in most cranial ganglia.

Neurons can also be classified according to their functional roles. **Motor** (**efferent**) **neurons** control effector organs such as muscle fibers and exocrine and endocrine glands. **Sensory** (**afferent**) **neurons** are involved in the reception of sensory stimuli from the environment and from within the body. **Interneurons** establish relationships among other neurons, forming complex functional networks or circuits (as in the retina).

During mammalian evolution a great increase in the number and complexity of interneurons has occurred. Highly developed functions of the nervous system cannot be ascribed to simple neuron circuits; rather, they depend on complex interactions established by the integrated functions of many neurons.

In the central nervous system, nerve cell bodies are present only in the gray matter. White matter contains neuronal processes but no nerve cell bodies. In the peripheral nervous system, cell bodies are found in ganglia and in some sensory regions (eg, olfactory)

*Cell Body (***perikaryon***)*

The cell body, also called **perikaryon,** is the part of the neuron that contains the nucleus and surrounding cytoplasm, exclusive of the cell processes. It is primarily a trophic center, although it also has receptive capabilities. The perikaryon of most neurons

receives a great number of nerve endings that convey excitatory or inhibitory stimuli generated in other nerve cells.

Most nerve cells have a spherical, unusually large, euchromatic (pale-staining) nucleus with a prominent nucleolus. Binuclear nerve cells are seen in sympathetic and sensory ganglia. The chromatin is finely dispersed, reflecting the intense synthetic activity of these cells.

The cell body contains a highly developed rough endoplasmic reticulum organized into aggregates of parallel cisternae. In the cytoplasm between the cisternae are numerous polyribosomes, suggesting that these cells synthesize both structural proteins and proteins for transport. When appropriate stains are used, rough endoplasmic reticulum and free ribosomes appear under the light microscope as basophilic granular areas called **Nissl bodies**. The number of Nissl bodies varies according to neuronal type and functional state. They are particularly abundant in large nerve cells such as motor neurons. The **Golgi complex** is located only in the cell body and consists of multiple parallel arrays of smooth cisternae arranged around the periphery of the nucleus. Mitochondria are especially abundant in the axon terminals. They are scattered throughout the cytoplasm of the cell body.

Neurofilaments are abundant in perikaryons and cell processes. Neurofilaments bundle together as a result of the action of certain fixatives. When impregnated with silver, they form **neurofibrils** that are visible with the light microscope. The neurons also contain microtubules that are identical to those found in many other cells. Nerve cells occasionally contain inclusions of pigments, such as **lipofuscin,** which is a residue of undigested material by lysosomes.

Dendrites

Dendrites (Gr. *dendron,* tree) are usually short and divide like the branches of a tree. They receive many synapses and are the principal signal reception and processing sites on neurons. Most nerve cells have numerous dendrites, which considerably increase the receptive area of the cell. The arborization of dendrites allows one neuron to receive and integrate a great number of axon terminals from other nerve cells. It has been estimated that up to 200,000 axonal terminations establish functional contact with the dendrites of a Purkinje cell of the cerebellum. That number may be even higher in other nerve cells. Bipolar neurons, with only one dendrite, are uncommon and are found only in special sites. Unlike axons, which maintain a constant diameter from one end to the other, dendrites become thinner as they subdivide into branches. The cytoplasmic composition of the dendrite base, close to the neuron body, is similar to that of the perikaryon but is devoid of Golgi complexes. Most synapses impinging on neurons are located in **dendrite spines,** which are usually mushroom-shaped structures (an expanded head connected to the dendrite shaft by a narrower neck) measuring 1–3 μm long and less than 1 μm in diameter. These spines, which play relevant functions, occur in vast numbers, estimated

to be on the order of 10^{14} for the human cerebral cortex. Dendrite spines are the first processing locale for synaptic signals arriving on a neuron. The processing apparatus is contained in a complex of proteins attached to the cytosolic surface of the postsynaptic membrane, which is visible under the electron microscope and received the name postsynaptic membrane long before its function was disclosed. Dendritic spines participate in the plastic changes that underlie adaptation, learning, and memory. They are dynamic structures with a morphological plasticity based on the cytoskeletal protein actin, which is related to the development of the synapses and their functional adaptation in adults.

Axons

Most neurons have only one axon; a very few have no axon at all. An axon is a cylindrical process that varies in length and diameter according to the type of neuron. Although some neurons have short axons, axons are usually very long processes. For example, axons of the motor cells of the spinal cord that innervate the foot muscles may be up to 100 cm (about 40 inches) in length. All axons originate from a short pyramid-shaped region, the **axon hillock,** that usually arises from the perikaryon. The plasma membrane of the axon is called the **axolemma** (*axon* + Gr. *eilema,* sheath); its contents are known as **axoplasm**.

In neurons that give rise to a myelinated axon, the portion of the axon between the axon hillock and the point at which myelination begins is called the **initial segment.** This is the site at which various excitatory and inhibitory stimuli impinging on the neuron are algebraically summed, resulting in the decision to propagate—or not to propagate—an action potential, or nerve impulse. It is known that several types of ion channels are localized in the initial segment and that these channels are important in generating the change in electrical potential that constitutes the action potential. In contrast to dendrites, axons have a constant diameter and do not branch profusely. Occasionally, the axon, shortly after its departure from the cell body, gives rise to a branch that returns to the area of the nerve cell body. All axon branches are known as **collateral branches**. Axonal cytoplasm (axoplasm) possesses mitochondria, microtubules, neurofilaments, and some cisternae of smooth endoplasmic reticulum. The absence of polyribosomes and rough endoplasmic reticulum emphasizes the dependence of the axon on the perikaryon for its maintenance. If an axon is severed, its peripheral parts degenerate and die.

There is a lively bidirectional transport of small and large molecules along the axon.

Macromolecules and organelles that are synthesized in the cell body are transported continuously by an **anterograde flow** along the axon to its terminals.

Anterograde flow occurs at three distinct speeds. A slow stream (a few millimeters per day) transports proteins and actin filaments. A flow of intermediate speed transports

mitochondria, and a fast stream (100 times more rapid) transports the substances contained in vesicles that are needed at the axon terminal during neurotransmission.

Simultaneously with anterograde flow, a **retrograde flow** in the opposite direction transports several molecules, including material taken up by endocytosis (including viruses and toxins), to the cell body. This process is used to study the pathways of neurons; peroxidase or another marker is injected in regions with axon terminals, and its distribution is followed after a certain period of time.

Motor proteins related to axon flow include **dynein,** a protein with ATPase activity present in microtubules (related to retrograde flow), and **kinesin,** a microtubule-activated ATPase that, when attached to vesicles, promotes anterograde flow in the axon.

Synaptic Communication

The synapse (Gr. *synapsis,* union) is responsible for the unidirectional transmission of nerve impulses. Synapses are sites of functional contact between neurons or between neurons and other effector cells (eg, muscle and gland cells). The function of the synapse is to convert an electrical signal (impulse) from the presynaptic cell into a chemical signal that acts on the **postsynaptic** cell. Most synapses transmit information by releasing **neurotransmitters** during the signaling process. Neurotransmitters are chemicals that, when combined with a receptor protein, either open or close ion channels or initiate second-messenger cascades. **Neuromodulators** are chemical messengers that do not act directly on synapses but modify neuron sensitivity to synaptic stimulation or inhibition. Some neuromodulators are neuropeptides or steroids produced in the nerve tissue; others are circulating steroids. The synapse itself is formed by an axon terminal (**presynaptic terminal**) that delivers the signal, a region on the surface of another cell at which a new signal is generated (**postsynaptic terminal**), and a thin intercellular space called the **synaptic cleft**. If an axon forms a synapse with a cell body, the synapse is called **axosomatic;** if it forms a synapse with a dendrite, it is called **axodendritic;** and if it forms a synapse with an axon, it is called **axoaxonic**.

Although most synapses are **chemical synapses** and use chemical messengers, a few synapses transmit ionic signals through gap junctions that cross the pre- and postsynaptic membranes, thereby conducting neuronal signals directly. These synapses are called **electrical synapses.**

The presynaptic terminal always contains **synaptic vesicles** with neurotransmitters and numerous **mitochondria**.

Neurotransmitters are generally synthesized in the cell body; they are then stored in vesicles in the presynaptic region of a synapse. During transmission of a nerve impulse, they are released into the synaptic cleft by **exocytosis.** The extra membrane that collects at the presynaptic region as a result of exocytosis of the synaptic vesicles is recycled by

endocytosis. Retrieved membrane fuses with the smooth endoplasmic reticulum of the presynaptic compartment to be reused in the formation of new synaptic vesicles. Some neurotransmitters are synthesized in the presynaptic compartment, using enzymes and precursors brought by axonal transport.

The first neurotransmitters to be described were acetylcholine and norepinephrine. Most neurotransmitters are amines, amino acids, or small peptides (neuropeptides). Inorganic substances such as nitric oxide have also been shown to act as neurotransmitters. Several peptides that act as neurotransmitters are used elsewhere in the body, eg, as hormones in the digestive tract. Neuropeptides are important in regulating feelings and drives, such as pain, pleasure, hunger, thirst, and sex.

Glial Cells & Neuronal Activity

Glial cells are 10 times more abundant in the mammalian brain than neurons; they surround both cell bodies and their axonal and dendritic processes that occupy the interneuronal spaces.

Nerve tissue has only a very small amount of extracellular matrix, and glial cells furnish a microenvironment suitable for neuronal activity.

Origin and Principal Functions of Neuroglial Cells.

Glial Cell	**Origin**	**Location**	**Main Functions**
Oligodendroc	Neural tube	Central nervous system	Myelin production, electric insulation
Schwann cell	Neural tube	Peripheral nerves	Myelin production, electric insulation
Astrocyte	Neural tube	Central nervous system	Structural support, repair processes
			Blood–brain barrier, metabolic exchanges
Ependymal	Neural tube	Central nervous system	Lining cavities of central nervous system
Microglia	Bone marrow	Central nervous system	Macrophagic activity

Oligodendrocytes

Oligodendrocytes (Gr. *oligos,* small, + *dendron* + *kytos,* cell) produce the myelin sheath that provides the electrical insulation of neurons in the central nervous system. These cells have processes that wrap around axons.

Schwann Cells

Schwann cells have the same function as oligodendrocytes but are located around axons in the peripheral nervous system. One Schwann cell forms myelin around a segment of one axon, in contrast to the ability of oligodendrocytes to branch and serve more than one neuron and its processes.

Astrocytes

Astrocytes (Gr. *astron,* star, + *kytos*) are star-shaped cells with multiple radiating processes. These cells have bundles of intermediate filaments made of **glial fibrillary acid protein** that reinforce their structure. Astrocytes bind neurons to capillaries and to the pia mater (a thin connective tissue that covers the central nervous system). Astrocytes with few long processes are called **fibrous astrocytes** and are located in the white matter; **protoplasmic astrocytes,** with many short-branched processes, are found in the gray matter. Astrocytes are by far the most numerous glial cells and exhibit an exceptional morphological and functional diversity.

In addition to their supporting function, astrocytes participate in controlling the ionic and chemical environment of neurons. Some astrocytes develop processes with expanded **end feet** that are linked to endothelial cells. It is believed that through the end feet, astrocytes transfer molecules and ions from the blood to the neurons. Expanded processes are also present at the external surface of the central nervous system, where they make a continuous layer. Furthermore, when the central nervous system is damaged, astrocytes proliferate to form cellular scar tissue.

Astrocytes also play a role in regulating the numerous functions of the central nervous system.

Astrocytes can influence neuronal survival and activity through their ability to regulate constituents of the extracellular environment, absorb local excess of neurotransmitters, and release metabolic and neuroactive molecules. The latter molecules include peptides of the angiotensinogen family, vasoactive endothelins, opioid precursors called **enkephalins,** and the potentially neurotrophic somatostatin. On the other hand, there is some evidence that astrocytes transport energy-rich compounds from the blood to the neurons and also metabolize glucose to lactate, which is then supplied to the neurons.

Finally, astrocytes are in direct communication with one another via gap junctions, forming a network through which information can flow from one point to another, reaching distant sites. For example, by means of gap junctions and the release of various cytokines, astrocytes can interact with oligodendrocytes to influence myelin turnover in both normal and abnormal conditions.

Ependymal Cells

Ependymal cells are low columnar epithelial cells lining the ventricles of the brain and central canal of the spinal cord. In some locations, ependymal cells are ciliated, which facilitates the movement of cerebrospinal fluid.

Microglia

Microglia (Gr. *micros,* small, + *glia*) are small elongated cells with short irregular processes. They can be recognized in routine hematoxylin and eosin (H&E) preparations by their dense elongated nuclei, which contrast with the spherical nuclei of other glial cells. Microglia, phagocytic cells that represent the mononuclear phagocytic system in nerve tissue, are derived from precursor cells in the bone marrow. They are involved with inflammation and repair in the adult central nervous system, and they produce and release neutral proteases and oxidative radicals. When activated, microglia retract their processes and assume the morphological characteristics of macrophages, becoming phagocytic and acting as antigen-presenting cells. Microglia secrete a number of immunoregulatory cytokines and dispose of unwanted cellular debris caused by central nervous system lesions.

The Central Nervous System

The central nervous system consists of the **cerebrum, cerebellum,** and **spinal cord.** It has almost no connective tissue and is therefore a relatively soft, gel-like organ.

When sectioned, the cerebrum, cerebellum, and spinal cord show regions that are white (**white matter**) and that are gray (**gray matter**). The differential distribution of myelin in the central nervous system is responsible for these differences: The main component of white matter is myelinated axons and the myelin-producing oligodendrocytes. White matter does not contain neuronal cell bodies.

Gray matter contains neuronal cell bodies, dendrites, and the initial unmyelinated portions of axons and glial cells. This is the region at which synapses occur. Gray matter is prevalent at the surface of the cerebrum and cerebellum, forming the **cerebral and cerebellar cortex**, whereas white matter is present in more central regions. Aggregates of neuronal cell bodies forming islands of gray matter embedded in the white matter are called **nuclei.** In the **cerebral cortex,** the gray matter has six layers of cells with different forms and sizes. Neurons of some regions of the cerebral cortex register **afferent** (**sensory**) impulses; in other regions, **efferent** (**motor**) neurons generate motor impulses that control voluntary movements. Cells of the cerebral cortex are related to the integration of sensory information and the initiation of voluntary motor responses.

The **cerebellar cortex** has three layers: an outer molecular layer, a central layer of large Purkinje cells, and an inner granule layer. The Purkinje cells have a conspicuous cell body and their dendrites are highly developed, assuming the aspect of a fan. These dendrites occupy most of the molecular layer and are the reason for the sparseness of nuclei. The granule layer is formed by very small neurons (the smallest in the body), which are compactly disposed, in contrast to the less cell-dense molecular layer.

In cross sections of the **spinal cord,** white matter is peripheral and gray matter is central, assuming the shape of an **H**. In the horizontal bar of this **H** is an opening, the **central canal,** which is a remnant of the lumen of the embryonic neural tube. It is lined with ependymal cells. The gray matter of the legs of the **H** forms the **anterior horns.** These contain motor neurons whose axons make up the ventral roots of the spinal nerves. Gray matter also forms the posterior horns (the arms of the **H**), which receive sensory fibers from neurons in the spinal ganglia (dorsal roots).

Meninges

The skull and the vertebral column protect the central nervous system. It is also encased in membranes of connective tissue called the **meninges**. Starting with the outermost layer, the meninges are the **dura mater, arachnoid,** and **pia mater.** The arachnoid and the pia mater are linked together and are often considered a single membrane called the **pia-arachnoid.**

The dura mater is always separated from the arachnoid by the thin subdural space. The internal surface of all dura mater, as well as its external surface in the spinal cord, is covered by simple squamous epithelium of mesenchymal in origin.

1- Dura Mater

The dura mater is the external layer and is composed of dense connective tissue continuous with the periosteum of the skull. The dura mater that envelops the spinal cord is separated from the periosteum of the vertebrae by the epidural space, which contains thin-walled veins, loose connective tissue, and adipose tissue.

2- Arachnoid

The arachnoid (Gr. *arachnoeides*, cobweblike) has two components: a layer in contact with the dura mater and a system of trabeculae connecting the layer with the pia mater. The cavities between the trabeculae form the **subarachnoid space,** which is filled with cerebrospinal fluid and is completely separated from the **subdural space.** This space forms a hydraulic cushion that protects the central nervous system from trauma. The subarachnoid space communicates with the ventricles of the brain. The arachnoid is composed of connective tissue devoid of blood vessels. The same type of simple squamous epithelium that covers the dura mater covers its surfaces. Because the

arachnoid has fewer trabeculae in the spinal cord, it can be more clearly distinguished from the pia mater in that area. In some areas, the arachnoid perforates the dura mater, forming protrusions that terminate in venous sinuses in the dura mater. These protrusions, which are covered by endothelial cells of the veins, are called **arachnoid villi.** Their function is to reabsorb cerebrospinal fluid into the blood of the venous sinuses.

3- Pia Mater

The pia mater is a loose connective tissue containing many blood vessels. Although it is located quite close to the nerve tissue, it is not in contact with nerve cells or fibers. Between the pia mater and the neural elements is a thin layer of neuroglial processes, adhering firmly to the pia mater and forming a physical barrier at the periphery of the central nervous system. This barrier separates the central nervous system from the cerebrospinal fluid.

The pia mater follows all the irregularities of the surface of the central nervous system and penetrates it to some extent along with the blood vessels. Squamous cells of mesenchymal origin cover pia mater.

Blood vessels penetrate the central nervous system through tunnels covered by pia mater—the **perivascular spaces.** The pia mater disappears before the blood vessels are transformed into capillaries. In the central nervous system, the blood capillaries are completely covered by expansions of the neuroglial cell processes.

Blood–brain Barrier

The blood–brain barrier results from the reduced permeability that is characteristic of blood capillaries of nerve tissue. Occluding junctions, which provide continuity between the endothelial cells of these capillaries, represent the main structural component of the barrier. The cytoplasm of these endothelial cells does not have the fenestrations found in many other locations, and very few pinocytotic vesicles are observed. The expansions of neuroglial cell processes that envelop the capillaries are partly responsible for their low permeability. The blood–brain barrier is a functional barrier that prevents the passage of some substances, such as antibiotics and chemical and bacterial toxic matter, from the blood to nerve tissue.

Choroid Plexus & Cerebrospinal Fluid

The choroid plexus consists of invaginated folds of pia mater, rich in dilated fenestrated capillaries, that penetrate the interior of the brain ventricles. It is found in the roofs of the third and fourth ventricles and in part in the walls of the lateral ventricles. The choroid plexus is composed of loose connective tissue of the pia mater, covered by a simple cuboidal or low columnar epithelium made of ion-transporting cells.

Peripheral Nervous System

The main components of the peripheral nervous system are the **nerves, ganglia,** and **nerve endings.** Nerves are bundles of nerve fibers surrounded by connective tissue sheaths.

Nerve Fibers

Nerve fibers consist of axons enveloped by a special sheath derived from cells of ectodermal origin. Groups of nerve fibers constitute the tracts of the brain, spinal cord, and peripheral nerves. Nerve fibers exhibit differences in their enveloping sheaths, related to whether the fibers are part of the central or the peripheral nervous system.

Single or multiple folds of a sheath cell cover most axons in adult nerve tissue. In peripheral nerve fibers, the sheath cell is the **Schwann cell,** and in central nerve fibers it is the **oligodendrocyte.** Axons of small diameter are usually **unmyelinated nerve fibers**. Progressively thicker axons are generally sheathed by increasingly numerous concentric wrappings of the enveloping cell, forming the **myelin sheaths.** These fibers are known as **myelinated nerve fibers**.

Myelinated Fibers

In myelinated fibers of the peripheral nervous system, the plasmalemma of the covering Schwann cell winds and wraps around the axon. The layers of membranes of the sheath cell unite and form **myelin,** a whitish lipoprotein complex whose lipid component can be partly removed by standard histological procedures.

Myelin consists of many layers of modified cell membranes. These membranes have a higher proportion of lipids than do other cell membranes. The myelin sheath shows gaps along its path called the **nodes of Ranvier**; these represent the spaces between adjacent Schwann cells along the length of the axon. Interdigitating processes of Schwann cells partially cover the node. The distance between two nodes is called an **internode** and consists of one Schwann cell. The length of the internode varies between 1 and 2 mm. There are no Schwann cells in the central nervous system; there, the processes of the oligodendrocytes form the myelin sheath. Oligodendrocytes differ from Schwann cells in that different branches of one cell can envelop segments of several axons.

Unmyelinated Fibers

In both the central and peripheral nervous systems, not all axons are sheathed in myelin. In the peripheral system, all unmyelinated axons are enveloped within simple clefts of the Schwann cells (Figure 9–26). Unlike their association with individual myelinated axons, each Schwann cell can sheathe many unmyelinated axons.

Unmyelinated nerve fibers do not have nodes of Ranvier, because abutting Schwann cells are united to form a continuous sheath. The central nervous system is rich in unmyelinated axons; unlike those in the peripheral system, these axons are not sheathed. In the brain and spinal cord, unmyelinated axonal processes run free among the other neuronal and glial processes.

Nerves

In the peripheral nervous system, the nerve fibers are grouped in bundles to form the nerves. Except for a few very thin nerves made up of unmyelinated fibers, nerves have a whitish, homogeneous, glistening appearance because of their myelin and collagen content. Nerves have an external fibrous coat of dense connective tissue called **epineurium,** which also fills the space between the bundles of nerve fibers. Each bundle is surrounded by the **perineurium,** a sleeve formed by layers of flattened epitheliumlike cells. The cells of each layer of the perineurial sleeve are joined at their edges by tight junctions, an arrangement that makes the perineurium a barrier to the passage of most macromolecules and has the important function of protecting the nerve fibers from aggression. Within the perineurial sheath run the Schwann cell-sheathed axons and their enveloping connective tissue, the **endoneurium**. The endoneurium consists of a thin layer of reticular fibers, produced by Schwann cells. The nerves establish communication between brain and spinal cord centers and the sense organs and effectors (muscles, glands, etc). They possess afferent and efferent fibers to and from the central nervous system. **Afferent** fibers carry the information obtained from the interior of the body and the environment to the central nervous system. **Efferent** fibers carry impulses from the central nervous system to the effector organs commanded by these centers. Nerves possessing only sensory fibers are called **sensory nerves;** those composed only of fibers carrying impulses to the effectors are called **motor nerves.** Most nerves have both sensory and motor fibers and are called **mixed nerves;** these nerves have both myelinated and unmyelinated axons.

Ganglia

Ganglia are ovoid structures containing neuronal cell bodies and glial cells supported by connective tissue. Because they serve as relay stations to transmit nerve impulses, one nerve enters and another exits from each ganglion. The direction of the nerve impulse determines whether the ganglion will be a **sensory** or an **autonomic** ganglion.

Sensory Ganglia

Sensory ganglia receive afferent impulses that go to the central nervous system. Two types of sensory ganglia exist. Some are associated with cranial nerves (**cranial ganglia**); others are associated with the dorsal root of the spinal nerves and are called

spinal ganglia. The latter comprise large neuronal cell bodies with prominent fine Nissl bodies surrounded by abundant small glial cells called **satellite cells.**

A connective tissue framework and capsule support the ganglion cells. The neurons of these ganglia are pseudounipolar and relay information from the ganglion's nerve endings to the gray matter of the spinal cord via synapses with local neurons.

Autonomic Ganglia

Autonomic ganglia appear as bulbous dilatations in autonomic nerves. Some are located within certain organs, especially in the walls of the digestive tract, where they constitute the **intramural ganglia.** These ganglia are devoid of connective tissue capsules, and their cells are supported by the stroma of the organ in which they are found.

Autonomic ganglia usually have multipolar neurons. As with craniospinal ganglia, autonomic ganglia have neuronal perikaryons with fine Nissl bodies.

A layer of satellite cells frequently envelops the neurons of autonomic ganglia. In intramural ganglia, only a few satellite cells are seen around each neuron.

Autonomic Nervous System

The autonomic (Gr. *autos,* self, + *nomos,* law) nervous system is related to the control of smooth muscle, the secretion of some glands, and the modulation of cardiac rhythm. Its function is to make adjustments in certain activities of the body to maintain a constant internal environment (**homeostasis**). Although the autonomic nervous system is by definition a motor system, fibers that receive sensation originating in the interior of the organism accompany the motor fibers of the autonomic system. The term "autonomic" is not correct—although it is widely used—inasmuch as most of the functions of the autonomic nervous system are not autonomous; they are organized and regulated in the central nervous system. The concept of the autonomic nervous system is mainly functional. Anatomically, it is composed of collections of nerve cells located in the central nervous system, fibers that leave the central nervous system through cranial or spinal nerves, and nerve ganglia situated in the paths of these fibers. The term "autonomic" covers all the neural elements concerned with visceral function. In fact, the so-called autonomic functions are as dependent on the central nervous system as are the motor neurons that trigger muscle contractions.

The autonomic nervous system is a two-neuron network. The first neuron of the autonomic chain is located in the central nervous system. Its axon forms a synapse with the second multipolar neuron in the chain, located in a ganglion of the peripheral nervous system. The nerve fibers (axons) of the first neuron are called **preganglionic fibers;** the

axons of the second neuron to the effectors—muscle or gland—are called **postganglionic fibers.** The chemical mediator present in the synaptic vesicles of all preganglionic endings and at anatomically parasympathetic postganglionic endings is **acetylcholine,** which is released from the terminals by nerve impulses.

The adrenal medulla is the only organ that receives preganglionic fibers, because the majority of the cells, after migration into the gland, differentiate into secretory cells rather than ganglion cells. The autonomic nervous system is composed of two parts that differ both anatomically and functionally: the sympathetic system and the parasympathetic system. Nerve fibers that release acetylcholine are called **cholinergic.** Cholinergic fibers include all the preganglionic autonomic fibers (sympathetic as well as parasympathetic) and postganglionic parasympathetic fibers to smooth muscles, heart, and exocrine glands.

Sympathetic System

The nuclei (formed by a collection of nerve cell bodies) of the sympathetic system are located in the thoracic and lumbar segments of the spinal cord. Therefore, the sympathetic system is also called the **thoracolumbar division** of the autonomic nervous system. The axons of these neurons—preganglionic fibers—leave the central nervous system by way of the ventral roots and white communicating rami of the thoracic and lumbar nerves. The chemical mediator of the postganglionic fibers of the sympathetic system is **norepinephrine,** which is also produced by the adrenal medulla. Nerve fibers that release norepinephrine are called **adrenergic** (a word derived from noradrenalin, another term for norepinephrine). Adrenergic fibers innervate sweat glands and blood vessels of skeletal muscle. Cells of the adrenal medulla release epinephrine and norepinephrine in response to preganglionic sympathetic stimulation.

Parasympathetic System

The parasympathetic system has its nuclei in the medulla and midbrain and in the sacral portion of the spinal cord. The preganglionic fibers of these neurons leave through four of the cranial nerves (III, VII, IX, and X) and also through the second, third, and fourth sacral spinal nerves. The parasympathetic system is therefore also called the craniosacral division of the autonomic system. The second neuron of the parasympathetic series is found in ganglia smaller than those of the sympathetic system; it is always located near or within the effector organs. These neurons are usually located in the walls of organs (eg, stomach, intestines), in which case the preganglionic fibers enter the organs and form a synapse there with the second neuron in the chain.

The chemical mediator released by the pre- and postganglionic nerve endings of the parasympathetic system, **acetylcholine,** is readily inactivated by acetylcholinesterase—one of the reasons parasympathetic stimulation has both a more discrete and a more localized action than does sympathetic stimulation.

Degeneration & Regeneration of Nerve Tissue

Although it has been shown that neurons can divide in the brain of adult birds, mammalian neurons usually do not divide, and their degeneration represents a permanent loss. Neuronal processes in the central nervous system are, within very narrow limits, replaceable by growth through the synthetic activity of their perikaryons. Peripheral nerve fibers can also regenerate if their perikaryons are not destroyed.

Death of a nerve cell is limited to its perikaryon and processes. The neurons functionally connected to the dead neuron do not die, except for those with only one link. In this latter instance, the isolated neuron undergoes **transneuronal degeneration.** In contrast to nerve cells, neuroglia of the central nervous system—and Schwann cells and ganglionic satellite cells of the peripheral nervous system—are able to divide by mitosis. Spaces in the central nervous system left by nerve cells lost by disease or injury are invaded by neuroglia.

Skin Sensorial Receptors

One of the most important functions of the skin, with its great extension and abundant sensory innervation, is to receive stimuli from the environment. The skin is the most extensive sensory receptor. In addition to numerous free nerve endings in the epidermis, hair follicles, and cutaneous glands, encapsulated and expanded receptors are present in the dermis and subcutaneous tissue; they are more frequently found in the dermal papillae. Free nerve endings are sensitive to touch-pressure (pressure is sustained touch), tactile reception, high and low temperatures, pain, itching, and other sensations. The expanded ending includes the Ruffini endings, and the encapsulated ending includes the Pacini, Meissner, and Krause corpuscles. There is evidence that the expanded and encapsulated corpuscles are not necessary for cutaneous sensation. Their distribution is irregular, with many areas of skin containing only free nerve endings. However, when present, the expanded and encapsulated receptors respond to tactile stimuli, functioning as mechanoreceptors. Pacini corpuscles and Ruffini endings are also found in the connective tissue of organs located deep in the body, where they probably are sensitive to movements of internal organs and to pressure of one organ over another.