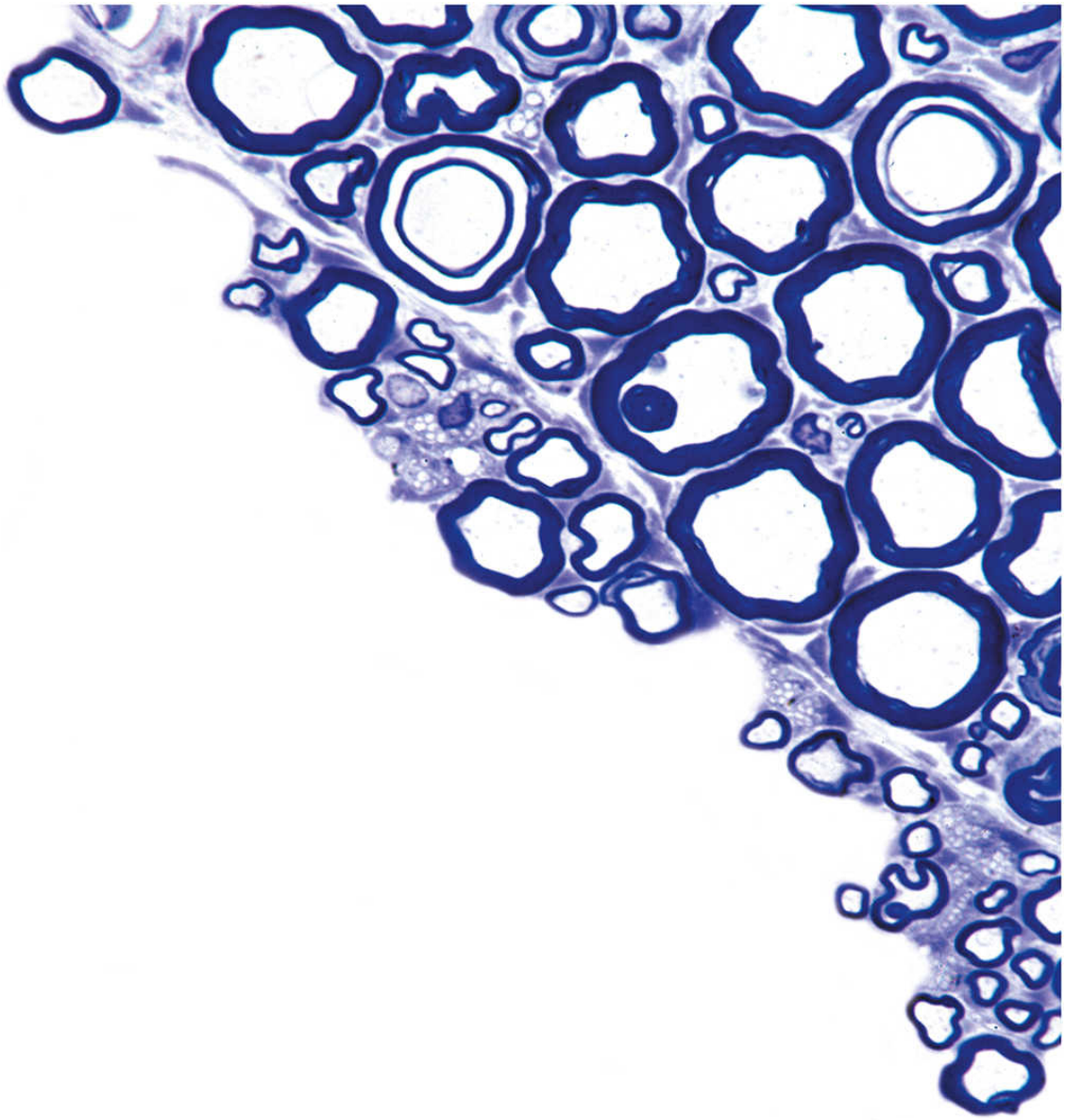


12 NERVE TISSUE

OVERVIEW OF THE NERVOUS SYSTEM
COMPOSITION OF NERVE TISSUE
THE NEURON

OVERVIEW OF THE NERVOUS SYSTEM

The **nervous system** enables the body to respond to continuous changes in its external and internal environment. It controls and integrates the functional activities of organs and organ systems. Anatomically, the nervous system is divided into the following:

- The **central nervous system (CNS)** consists of the brain and the spinal cord, which are located in the cranial cavity and spinal canal, respectively.
- The **peripheral nervous system (PNS)** consists of cranial, spinal, and peripheral **nerves** that conduct impulses from (efferent or motor nerves) and to (the afferent or sensory nerves of) the CNS; collections of nerve cell bodies outside the CNS called **ganglia**; and specialized nerve endings (both motor and sensory). Interactions between sensory (afferent) nerves that receive stimuli, the CNS that interprets them, and motor (efferent) nerves that initiate responses create **neural pathways**. These pathways mediate reflex actions called **reflex arcs**. In humans, most sensory neurons do not pass directly into the brain but instead communicate by specialized terminals (synapses) with motor neurons in the spinal cord.

Functionally, the nervous system is divided into the following:

- The **somatic nervous system (SNS)** consists of somatic *[Gr. soma, body]* parts of the CNS and PNS. The SNS controls functions that are under conscious voluntary control, with the exception of reflex arcs. It provides sensory and motor innervation to all parts of the body except viscera, smooth and cardiac muscle, and glands.
- The **autonomic nervous system (ANS)** consists of autonomic parts of the CNS and PNS. The ANS provides efferent involuntary motor innervation to smooth muscle, the conducting system of the heart, and glands. It also provides afferent sensory innervation from the viscera (pain and autonomic reflexes). The ANS is further subdivided into a **sympathetic division** and a **parasympathetic division**. A third division of ANS, the **enteric division**, serves the alimentary canal. It

communicates with the CNS through the parasympathetic and sympathetic nerve fibers; however, it can also function independently of the other two divisions of the ANS (see page 418).

COMPOSITION OF NERVE TISSUE

Nerve tissue consists of two principal types of cells: neurons and supporting cells.

The **neuron** or **nerve cell** is the functional unit of the nervous system. It consists of a cell body, containing the nucleus, and several processes of varying length. Nerve cells are specialized to receive stimuli from other cells and to conduct electrical impulses to other parts of the system via their processes. Several neurons are typically involved in sending impulses from one part of the system to another. These neurons are arranged in a chain-like manner as an integrated communications network. Specialized contacts between neurons that provide for transmission of information from one neuron to the next are called **synapses**.

Supporting cells are nonconducting cells that are located close to the neurons. They are referred to as **neuroglial cells** or simply **glia**. The CNS contains four types of glial cells: oligodendrocytes, astrocytes, microglia, and ependymal cells (see page 409). Collectively, these cells are called the **central neuroglia**. In the PNS, supporting cells are called **peripheral neuroglia** and include Schwann cells, satellite cells, and a variety of other cells associated with specific structures. Schwann cells surround the processes of nerve cells and isolate them from adjacent cells and extracellular matrix. Within the ganglia of the PNS, peripheral neuroglial cells are called **satellite cells**. They surround the nerve cell bodies, the part of the cell that contains the nucleus, and are analogous to nonmyelinating Remak Schwann cells. The supporting cells of the ganglia in the wall of the alimentary canal are called **enteric neuroglial cells**. They are morphologically and functionally similar to central neuroglia (see page 409).

Functions of the various neuroglial cell types include the following:

- Physical support (protection) for neurons
- Insulation for nerve cell bodies and processes, which facilitates rapid transmission of nerve impulses
- Repair of neuronal injury
- Regulation of the internal fluid environment of the CNS
- Clearance of neurotransmitters from synaptic clefts

- Metabolic exchange between the vascular system and the neurons of the nervous system

In addition to neurons and supporting cells, an extensive vasculature is present in both the CNS and the PNS. The **blood vessels** are separated from the nerve tissue by the basal laminae and variable amounts of connective tissue, depending on vessel size. The boundary between blood vessels and nerve tissue in the CNS excludes many substances that normally leave blood vessels to enter other tissues. This selective restriction of blood-borne substances in the CNS is called the **blood–brain barrier**, which is discussed on page 424.

The nervous system allows rapid response to external stimuli.

The nervous system evolved from the simple neuroeffector system of invertebrate animals. In primitive nervous systems, only simple receptor–effector reflex loops exist to respond to external stimuli. In higher level animals and humans, the SNS retains the ability to respond to stimuli from the external environment through the action of effector cells (such as skeletal muscle), but the neuronal responses are infinitely more varied. They range from simple reflexes that require only the spinal cord to complex operations of the brain, including memory and learning.

The autonomic part of the nervous system regulates the function of internal organs.

The specific effectors in the internal organs that respond to the information carried by autonomic neurons include the following:

- **Smooth muscle**. Contraction of smooth muscle modifies the diameter or shape of tubular or hollow viscera, such as the blood vessels, gut, gallbladder, and urinary bladder.
- **Cardiac-conducting cells (Purkinje fibers)**. These cells are located within the conductive system of the heart. The inherent frequency of Purkinje fiber depolarization regulates the rate of cardiac muscle contraction and can be modified by autonomic impulses.
- **Glandular epithelium**. The ANS regulates the synthesis, composition, and release of secretions.

The regulation of the function of internal organs involves close cooperation between the nervous system and the endocrine system. Neurons in several parts of the brain and other sites behave as secretory cells and are referred to as **neuroendocrine tissue**. The varied roles of neurosecretions

in regulating the functions of the endocrine, digestive, respiratory, urinary, and reproductive systems are described in subsequent chapters.

THE NEURON

The neuron is the structural and functional unit of the nervous system.

The human nervous system contains more than 10 billion neurons. Although neurons show the greatest variation in size and shape of any group of cells in the body, they can be grouped into three general categories.

- **Sensory neurons** convey impulses from receptors to the CNS. Processes of these neurons are included in somatic afferent and visceral afferent nerve fibers. **Somatic afferent fibers** convey sensations of pain, temperature, touch, and pressure from the body surface. In addition, these fibers convey pain and proprioception (nonconscious sensation) from organs within the body (e.g., muscles, tendons, and joints) to provide the brain with information related to the orientation of the body and limbs. **Visceral afferent fibers** transmit pain impulses and other sensations from internal organs, mucous membranes, glands, and blood vessels.
- **Motor neurons** convey impulses from the CNS or ganglia to effector cells. Processes of these neurons are included in somatic efferent and visceral efferent nerve fibers. **Somatic efferent neurons** send voluntary impulses to skeletal muscles. **Visceral efferent neurons** transmit involuntary impulses to smooth muscle, cardiac-conducting cells (Purkinje fibers), and glands (Fig. 12.1).

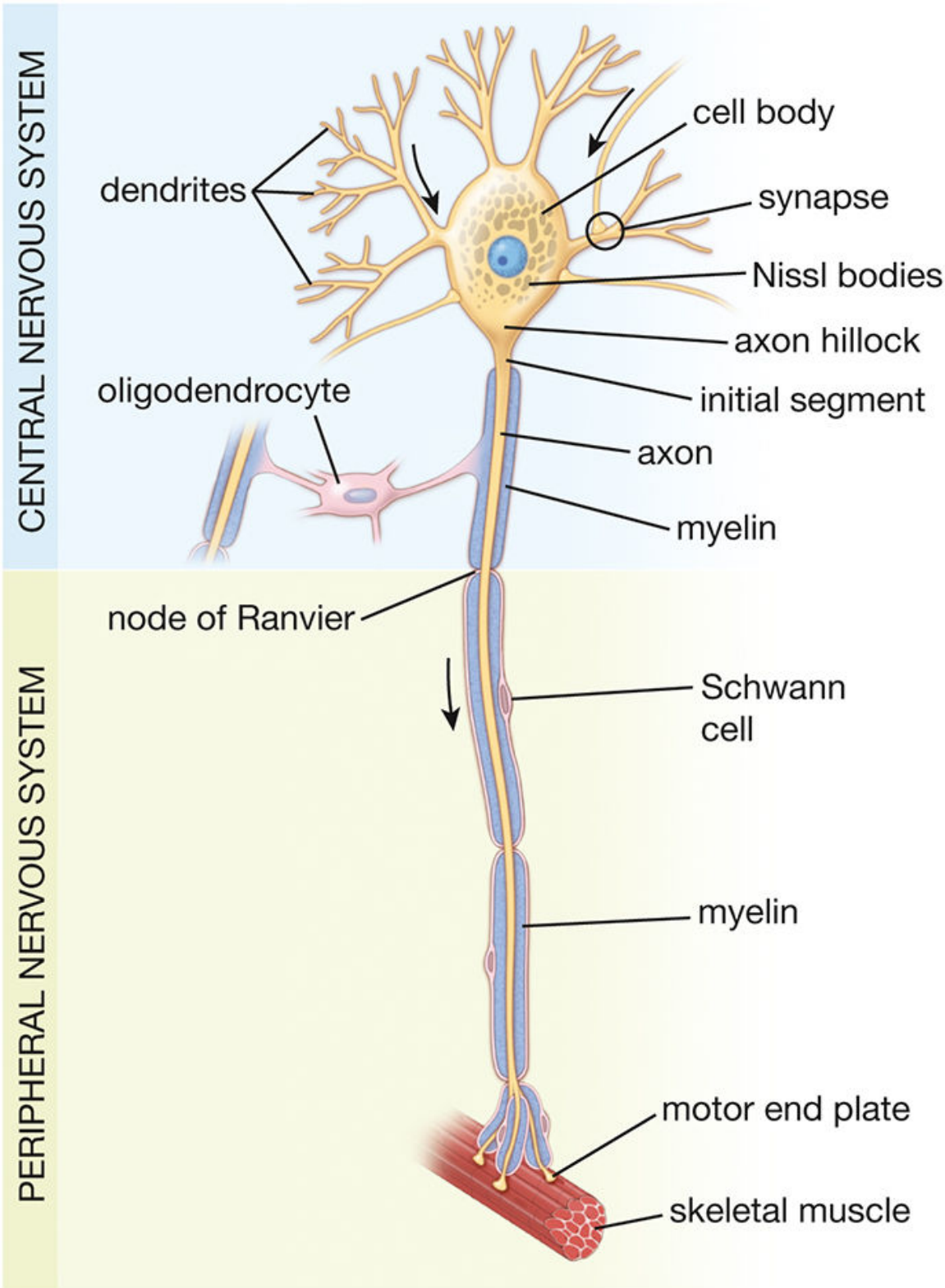


FIGURE 12.1. Diagram of a motor neuron. The nerve cell body, dendrites, and proximal part of the axon are within the central nervous system (CNS). The axon leaves the CNS and, while in the peripheral nervous system (PNS), is part of a nerve (not shown) as it courses to its effectors (striated muscle). In the CNS, the myelin for the axon is

produced by, and is part of, an oligodendrocyte; in the PNS, the myelin is produced by, and is part of, a Schwann cell.

- **Interneurons**, also called **intercalated neurons**, form a communicating and integrative network between the sensory and motor neurons. It is estimated that more than 99.9% of all neurons belong to this integrative network.

The functional components of a neuron include the cell body, axon, dendrites, and synaptic junctions.

The **cell body (perikaryon)** of a neuron contains the nucleus and the organelles that maintain the cell. The processes extending from the cell body constitute the single common structural characteristic of all neurons. Most neurons have only one **axon**, usually the longest process extending from the cell, which transmits impulses away from the cell body to a specialized terminal (synapse). The synapse makes contact with another neuron or an effector cell (e.g., a muscle cell or glandular epithelial cell). A neuron usually has many **dendrites**, shorter processes that transmit impulses from the periphery (i.e., other neurons) toward the cell body.

Neurons are classified on the basis of the number of processes extending from the cell body.

Most neurons can be anatomically characterized as the following:

- **Multipolar** neurons have one axon and two or more dendrites (Fig. 12.2). The direction of impulses is from dendrite to cell body to axon or from cell body to axon. Functionally, the dendrites and cell body of multipolar neurons are the receptor portions of the cell, and their plasma membrane is specialized for impulse generation. The axon is the conducting portion of the cell, and its plasma membrane is specialized for impulse conduction. The terminal portion of the axon, the synaptic ending, contains various neurotransmitters—that is, small molecules released at the synapse that affect other neurons as well as muscle cells and glandular epithelium. **Motor neurons** and **interneurons** constitute most of the multipolar neurons in the nervous system.

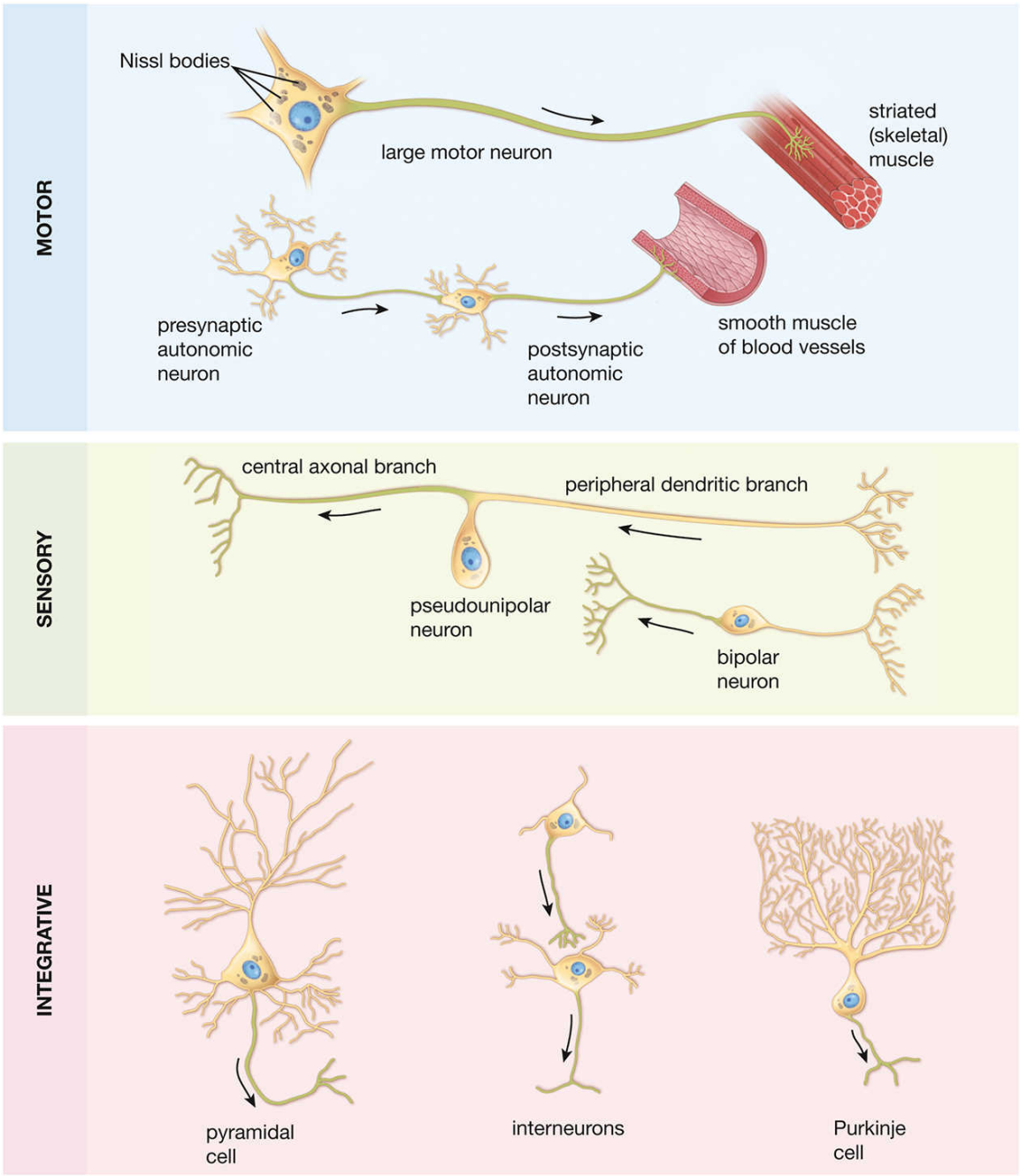


FIGURE 12.2. Diagram illustrating different types of neurons. The cell bodies of pseudounipolar (unipolar), bipolar, and postsynaptic autonomic neurons are located outside the central nervous system (CNS). Purkinje and pyramidal cells are restricted to the CNS; many of them have elaborate dendritic arborizations that facilitate their identification. The central axonal branch and all axons are indicated in *green*.

- **Bipolar** neurons have one axon and one dendrite (see Fig. 12.2). Bipolar neurons are rare. They are most often associated with the receptors for the **special senses** (taste, smell, hearing, sight, and equilibrium). They are generally found within the retina of the eye and the ganglia of the

vestibulocochlear nerve (cranial nerve VIII) of the ear. Some neurons in this group do not fit the abovementioned generalizations. For example, amacrine cells of the retina have no axons, and olfactory receptors resemble neurons of primitive neural systems in that they retain a surface location and regenerate at a much slower rate than other neurons.

- **Pseudounipolar** (unipolar) neurons have one process, the axon that divides close to the cell body into two long axonal branches. One branch extends to the periphery (**peripheral dendritic branch**), and the other extends to the CNS (**central axonal branch**; see Fig. 12.2). The two axonal branches are the conducting units. Impulses are generated in the peripheral arborizations (branches) of the neuron that are the receptor portions of the cell. Each pseudounipolar neuron develops from a bipolar neuron as its axon and dendrite migrate around the cell body and fuse into a single process. The majority of pseudounipolar neurons are **sensory neurons** located close to the CNS (Fig. 12.3). Cell bodies of sensory neurons are situated in the **dorsal root ganglia** and **cranial nerve ganglia**.

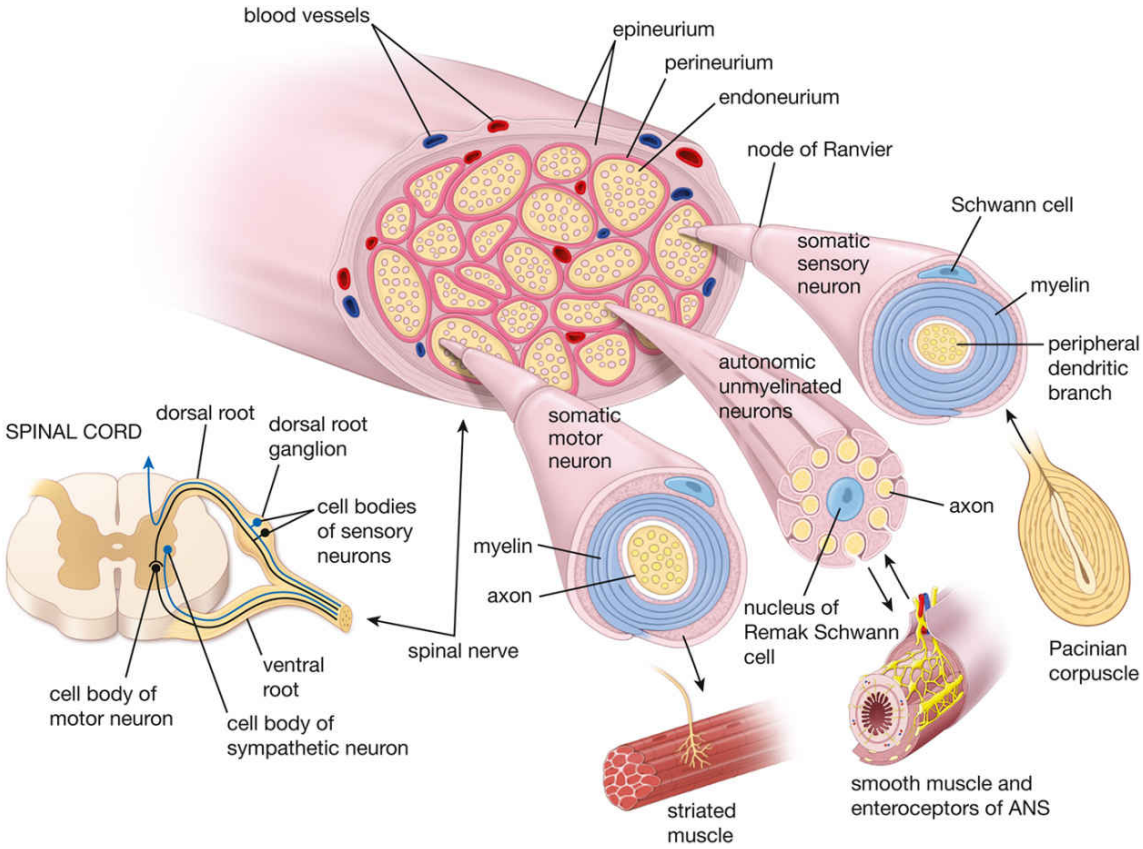


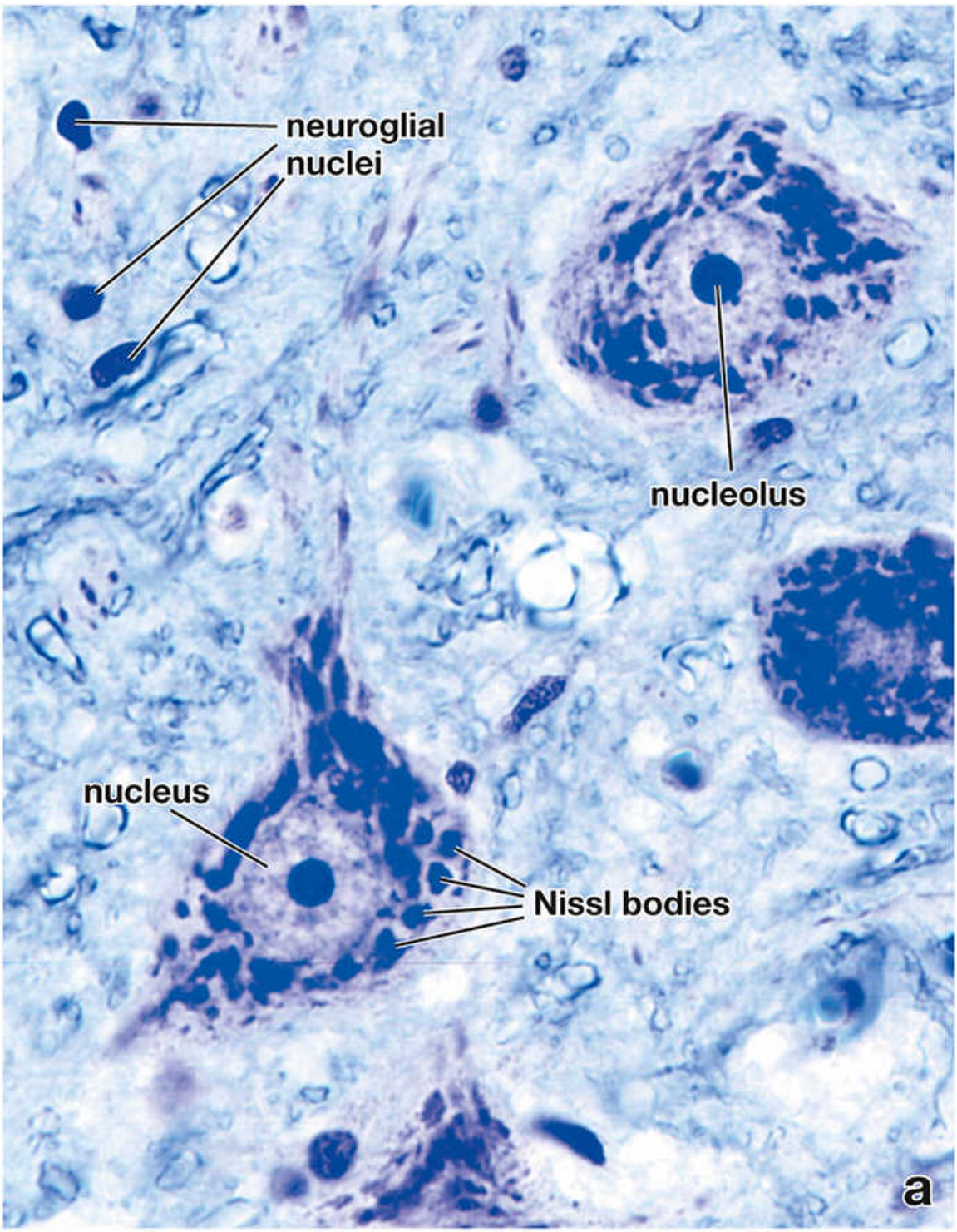
FIGURE 12.3. Schematic diagram showing arrangement of motor and sensory neurons. The cell body of a motor neuron is located in the ventral (anterior) horn of the gray matter of the spinal cord. Its axon, surrounded by myelin, leaves the spinal cord via a ventral (anterior) root

and becomes part of a spinal nerve that carries it to its destination on striated (skeletal) muscle fibers. The sensory neuron originates in the skin within a receptor (here, a Pacinian corpuscle) and continues as a component of a spinal nerve, entering the spinal cord via the dorsal (posterior) root. Note the location of its cell body in the dorsal root ganglion (sensory ganglion). A segment of the spinal nerve is enlarged to show the relationship of the nerve fibers to the surrounding connective tissue (endoneurium, perineurium, and epineurium). In addition, segments of the sensory, motor, and autonomic unmyelinated neurons have been enlarged to show the relationship of the axons to the Schwann cells. *ANS*, autonomic nervous system.

Cell Body

The cell body of a neuron has characteristics of a protein-producing cell.

The **cell body** is the dilated region of the neuron that contains a large, euchromatic **nucleus** with a prominent nucleolus and surrounding **perinuclear cytoplasm** (Fig.12.4a and Plate 12.1, page 432). The perinuclear cytoplasm reveals abundant rough-surfaced endoplasmic reticulum (rER) and free ribosomes when observed with the transmission electron microscope (TEM), a feature consistent with its protein synthetic activity. In the light microscope (LM), the ribosomal content appears as small bodies called **Nissl bodies** that stain intensely with basic dyes and metachromatically with thionine dyes (see Fig. 12.4a). Each Nissl body corresponds to a stack of rER.


neuroglial
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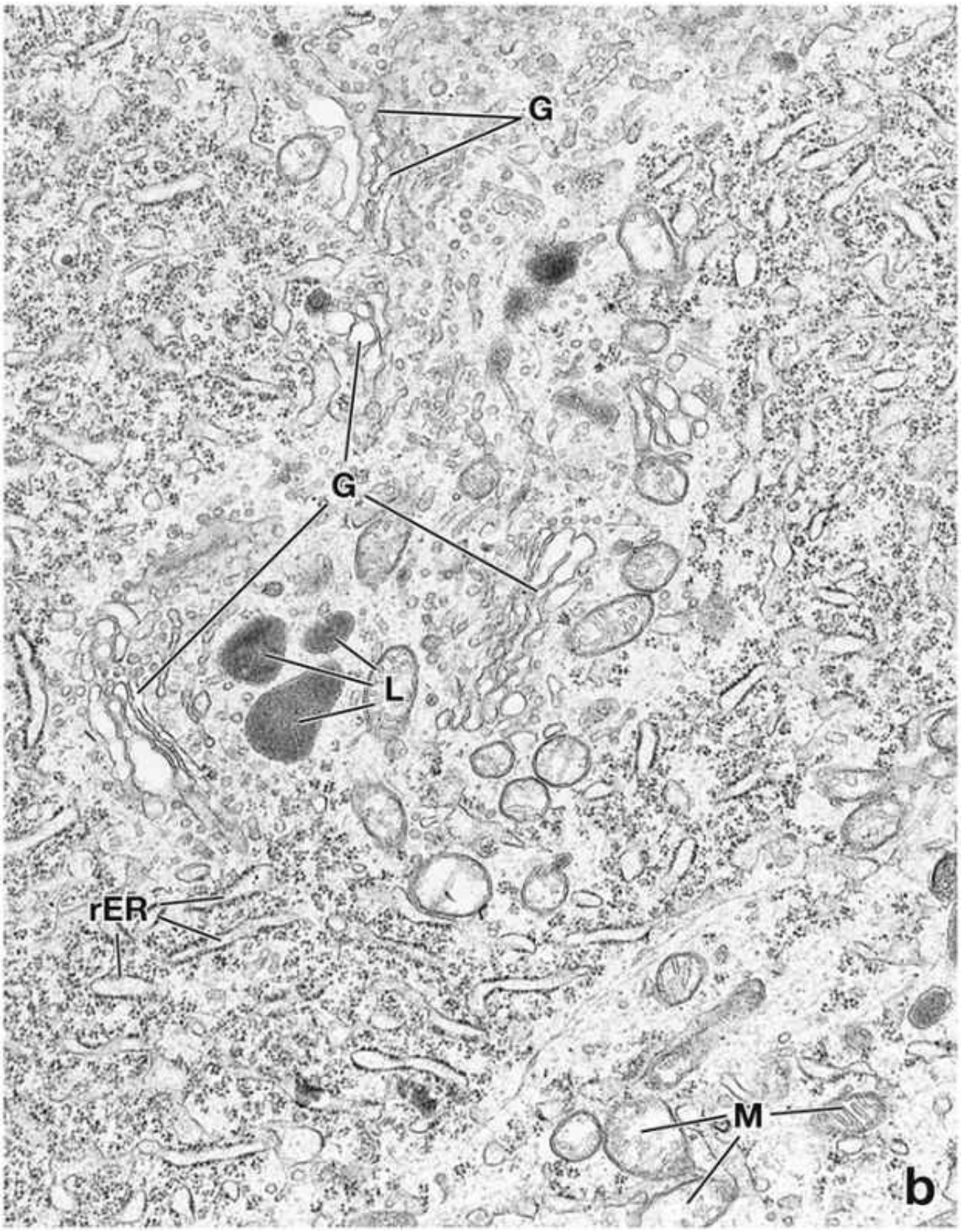


FIGURE 12.4. Nerve cell bodies. a. This photomicrograph shows a region of the ventral (anterior) horn of a human spinal cord stained with toluidine blue. Typical features of the nerve cell bodies visible in this image include large, spherical, pale-stained nuclei with a single prominent nucleolus and abundant Nissl bodies within the cytoplasm of the nerve cell body. Most of the small nuclei belong to neuroglial cells. The remainder of the field consists of nerve fibers and cytoplasm of central neuroglial cells. ×640. **b.** Electron micrograph of a nerve cell body. The cytoplasm is occupied by aggregates of

free ribosomes and profiles of rough-surfaced endoplasmic reticulum (*rER*) that constitute the Nissl bodies of light microscopy. The Golgi apparatus (*G*) appears as isolated areas containing profiles of flattened sacs and vesicles. Other characteristic organelles include mitochondria (*M*) and lysosomes (*L*). The neurofilaments and neurotubules are difficult to discern at this relatively low magnification. ×15,000.

The perinuclear cytoplasm also contains numerous mitochondria, a large perinuclear Golgi apparatus, lysosomes, microtubules, microtubule-organizing center (MTOC) (centrosome), neurofilaments (intermediate filaments), transport vesicles, and inclusions (Fig. 12.4b). Nissl bodies, free ribosomes, and, occasionally, the Golgi apparatus extend into the dendrites, but not into the axon. The euchromatic nucleus, large nucleolus, prominent Golgi apparatus, and Nissl bodies indicate the high level of anabolic activity needed to maintain these large cells.

Location of the MTOC in the perinuclear cytoplasm usually corresponds to the site of the axon origin. This area of the cell body, called the **axon hillock**, lacks large cytoplasmic organelles and serves as a landmark to distinguish between axons and dendrites in both LM and TEM preparations.

Neurons do not divide; however, in some areas of the brain, neural stem cells are present and are able to differentiate and replace damaged nerve cells.

Although neurons do not replicate, the subcellular components of the neurons are regularly renewed and have life spans measured in hours, days, and weeks. The constant need to replace enzymes, neurotransmitter substances, membrane components, and other complex molecules is consistent with the morphologic features characteristic of a high level of synthetic activity. Newly synthesized protein molecules are transported to distant locations within a neuron in a process referred to as **neuronal transport** (pages 396-397).

It is generally accepted that nerve cells do not divide. However, recently, it has been shown that the adult brain retains some cells that exhibit the potential to regenerate. In certain regions of the brain, such as the olfactory bulb and dentate gyrus of the hippocampus, these **neural stem cells** are able to divide and generate new neurons. They are characterized by continuous expression of a 240-kDa intermediate filament protein **nestin**, which is used to identify these cells by histochemical methods. **Neural stem cells** are also able to migrate to the sites of injury and differentiate into new nerve cells. Research studies on animal models demonstrate that newly generated cells mature into functional neurons in the adult mammalian brain. These findings may lead to

therapeutic strategies that use neural cells to replace nerve cells lost or damaged by neurodegenerative disorders, such as Alzheimer and Parkinson diseases.

Dendrites and Axons

As mentioned earlier, neurons extend two distinct types of nerve processes: dendrites and axons, which contain different types of proteins and organelles and thus differ in both structure and function.

Dendrites are receptor processes that receive stimuli from other neurons or the external environment.

The main function of **dendrites** is to receive information from other neurons or the external environment and carry that information to the cell body. Generally, dendrites are located in the vicinity of the cell body. They have a greater diameter than axons and are usually unmyelinated and tapered. Dendrites form extensive arborizations called **dendritic trees**. Dendritic trees significantly increase the receptor surface area of a neuron. Many neuron types are characterized by the extent and shape of their dendritic trees (see Fig. 12.2). In most of the excitatory neurons, they possess **dendritic spines**.

In general, the contents of the perinuclear cytoplasm of the cell body and cytoplasm of dendrites are quite similar. Other organelles characteristic of the cell body, including **ribosomes** and **rER**, are found in the dendrites, especially in the base of the dendrites. In addition, small **Golgi outposts**, which are discrete functional Golgi structures not connected with the Golgi apparatus in the cell body, are present in the cytoplasm of dendrites and may serve as nucleation centers for microtubules.

Dendrites are characterized by the presence of dendritic spines that are involved in synaptic plasticity, learning, and memory formation.

Many neurons in the CNS have dendrites that can be identified by the presence of **dendritic spines** (Fig. 12.5). They represent small protrusions of the dendritic plasma membrane containing actin filaments and postsynaptic density. Their shape varies considerably from short projections, resembling thin filopodia–like structures to mushroom-shaped structures. The mushroom-shaped spines are regarded as mature spines and account for the majority (~70%–80%) of spines found on dendrites.

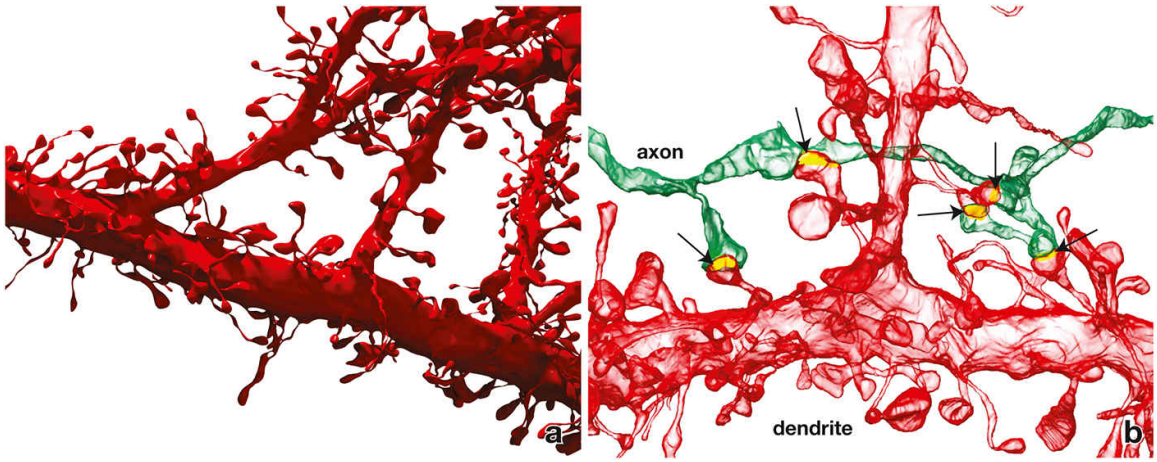


FIGURE 12.5. Three-dimensional (3D) computer reconstructions of nerve cell processes from the mouse somatosensory cerebral cortex. These images represent computer-generated 3D renderings of nerve cells and their processes extracted from a high-resolution stack of 1,850 scanning electron microscope (SEM) images of serially sectioned brain tissue. The automated tape-collecting ultramicrotome (ATUM) was used to cut 29-nm-thick sections that were stained with osmium and carbon coated for imaging with the SEM at sufficient resolution to detect individual synaptic vesicles. A multiscale digital volume image set was then processed for automated annotation and segmentation of nerve cell processes and organelles. Segmented structures were manually painted with a computer-assisted program and combined in a 3D data set. **a.** This image shows the 3D rendering of a single dendrite containing spines. Note the branching pattern of the dendrite. **b.** Semitransparent rendering of synaptic interactions between dendrite (*red*) and axon (*green*). In this image, dendritic spines form five synapses (arrows) with the same axon; the postsynaptic densities are indicated in *yellow*. ×13,000. (Courtesy of Drs. Daniel Berger and Jeff W. Lichtman, Harvard University, Cambridge, MA.)

Electron micrographs of mature dendritic spines reveal the presence of a **postsynaptic density** that contains clusters of neurotransmitter receptors as well as voltage-gated Na^+ and K^+ channels similar to those found in nerve synapses. The spines also appear to have a well-developed actin cytoskeleton associated with a variety of actin-binding proteins, occasional microtubules, and vesicles with elongated profiles of endoplasmic reticulum. The postsynaptic density is apposed by a plasma membrane of the neighboring axon containing an active zone with round synaptic vesicles (Fig. 12.6) that forms a fully functional synapse. Most of the synapses formed between dendritic spines and axons contain the neurotransmitter **glutamate (GLU)**, which mediates fast **excitatory synaptic transmission** in the CNS (see pages 401-403).

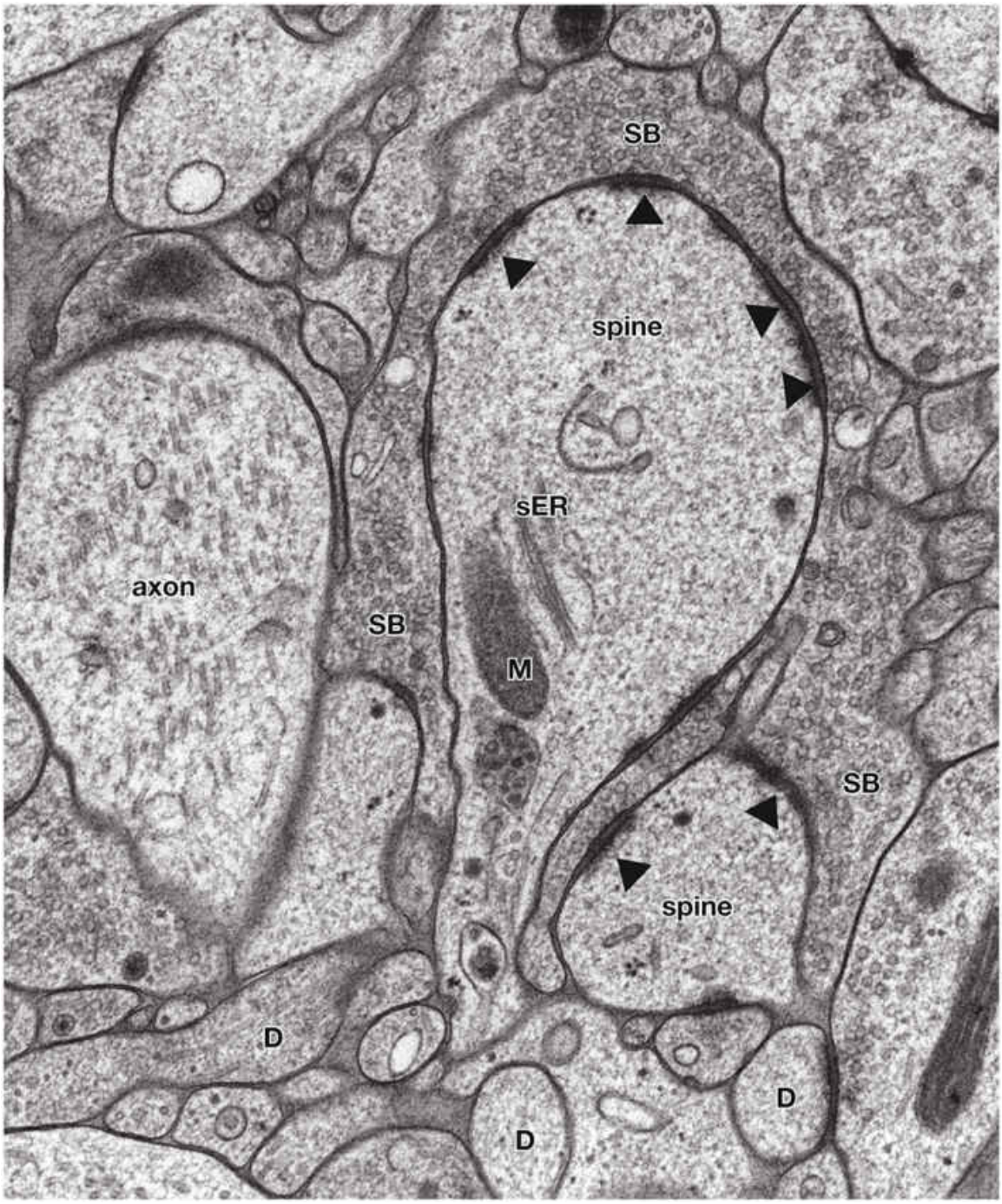


FIGURE 12.6. Electron micrograph of dendritic spines in proximal dendrites of pyramidal nerve cells in the mouse hippocampus. Thin slices (300 µm) of brain tissue were cultured for a period of 1–2 weeks, allowing for damaged tissue to recover and reorganize in vitro by removing cell debris from the tissue slices. After incubation, slices were prepared for electron microscopy (EM) using high-pressure freezing followed by cryosubstitution of tissue water with acetone, stained with osmium, and embedded in an EM-suitable medium. This preparation provides exceptional quality of EM images by avoiding that distortion of the tissue by protein denaturation that occurs in conventional fixation in aldehydes. Note that dendritic spines are surrounded by a large synaptic button (*SB*) containing

synaptic vesicles. *Arrowheads* indicate postsynaptic densities. In these areas, synaptic clefts are visible separating active zones of presynaptic elements from postsynaptic densities. Spine cytoplasm contains an actin cytoskeleton with occasional profiles of smooth-surfaced endoplasmic reticulum (*sER*) and transport vesicles visible in the narrow part of the spine. Note an electron-dense organelle, which most likely represents mitochondrion (*M*). Several profiles of dendrites (*D*) are also visible. The large profile on the *left* most likely represents an oblique section of the unmyelinated axon with visible profiles of microtubules. ×95,000. (Courtesy of Prof. Michael Frotscher, Institute for Structural Neurobiology, Center for Molecular Neurobiology Hamburg, Germany.)

Dendritic spines are dynamic and can quickly be formed and dismantled; however, some remain stable and persist for months and years. In experimental animal models, acquisition of new memories is associated with increased spine density in pyramidal cells in the CNS. The learning process induces the formation of stable spines that are able to persist for months after training. These experimental findings provide evidence that dendritic spines are involved in **synaptic plasticity and learning** and mediate the long-term encoding for **memory** in the brain cortex.

Axons are effector processes that transmit stimuli to other neurons or effector cells.

The main function of the **axon** is to convey information away from the cell body to another neuron or to an effector cell, such as a muscle cell. *Each neuron has only one axon*, and it may be extremely long. Axons that originate from neurons in the motor nuclei of the CNS **(Golgi type I neurons)** may travel more than a meter to reach their effector targets, skeletal muscle. In contrast, interneurons of the CNS **(Golgi type II neurons)** have very short axons. Although an axon may give rise to a recurrent branch near the cell body (i.e., one that turns back toward the cell body) and to other collateral branches, the branching of the axon is most extensive in the vicinity of its targets.

The axon originates from the **axon hillock**. The axon hillock usually lacks large cytoplasmic organelles, such as Nissl bodies and Golgi cisternae. Microtubules, neurofilaments, mitochondria, and vesicles, however, pass through the axon hillock into the axon (Fig. 12.7). The surface region of the axon between the apex of the axon hillock and the beginning of the myelin sheath (see later in this chapter) is called the **axon initial segment (AIS)**. The molecular composition of the plasma membrane of the AIS acts as a diffusion barrier or "picket fence" to exclude passage of proteins and lipids that do not belong to the axonal plasma membrane. The underlying actin

cytoskeleton also acts as a selective filter for organelles and transport vesicles that attempt to enter the axonal cytoplasm. This function can be likened to that of a border crossing checkpoint, where travelers are inspected for proper authorization required to enter the country.

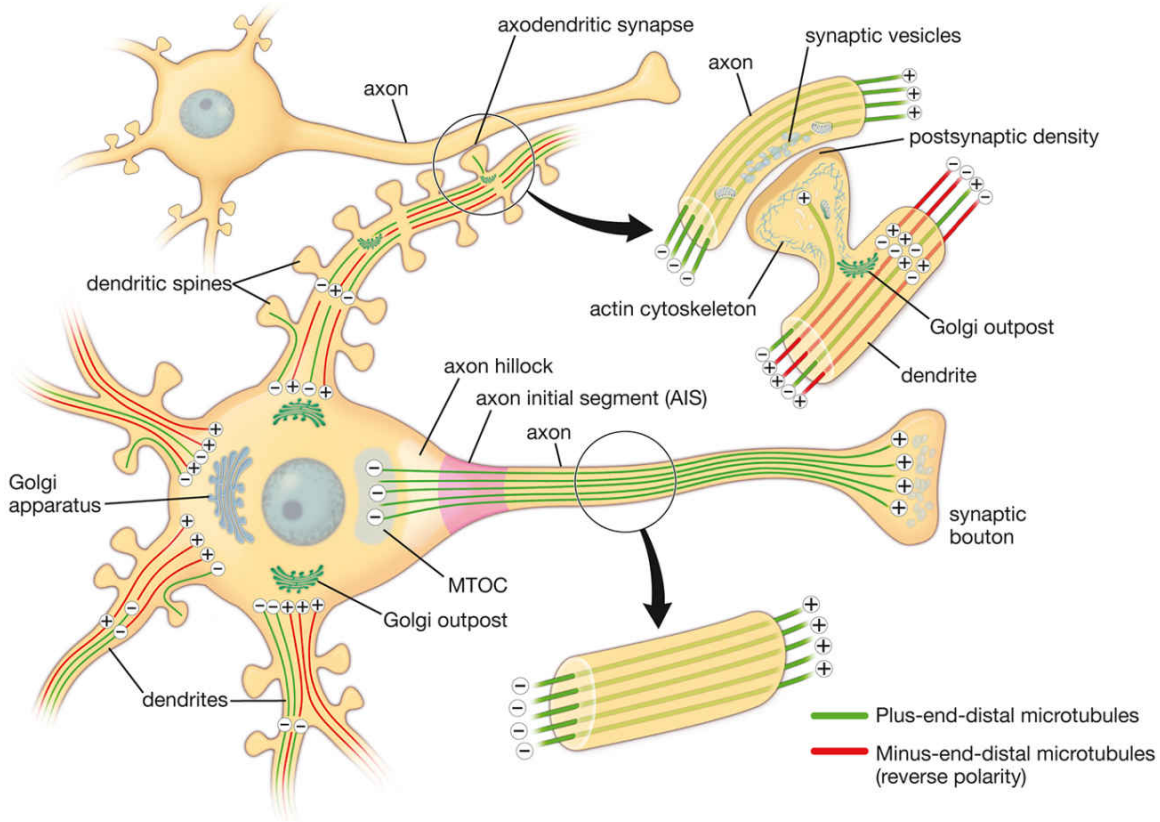


FIGURE 12.7. Organization of microtubules in axons and dendrites. Organization of the microtubule network in the neuron differs between dendrites and axons. All microtubules in axons originate from the microtubule-organizing center (*MTOC*), and they are uniformly oriented with their plus (+) ends directed distally. In contrast, microtubules in dendrites display a mixed polar orientation. The majority of microtubules in dendrites have reversed polarity with their minus (–) ends directed distally away from the cell body. Microtubules of normal polarity (with plus [+] ends directed distally) in dendrites are in the minority. In the central nervous system (CNS), some of them terminate in the cytoplasm of dendritic spines. Note the location of the axon hillock, an area where cargo materials destined for axonal transport are loaded on microtubule-associated motor proteins known as *kinesins*. Also, the axon initial segment (*AIS*) separates proteins and lipids of the axonal plasma membrane from the plasma membrane of the rest of the axon. Note also that dendritic spines form axodendritic synapses with neighboring presynaptic axons. A Golgi apparatus is positioned within the nerve cell body; however, a more characteristic feature of dendrites is the inclusion of small Golgi outposts. These are functional Golgi structures not connected with the main Golgi apparatus that can be found within dendrites

and at their junctions with the nerve cell body. Reversed polarity microtubules are not anchored in the *MTOC*, and the Golgi outpost may serve as their nucleation centers.

The AIS is the site at which an **action potential** is generated in the axon. The action potential (described in more detail later) is stimulated by impulses carried to the axon hillock on the membrane of the cell body after other impulses are received on the dendrites or the cell body itself.

Organization of microtubules and their arrangement in axons and dendrites are unique and critical to the functional polarity of neurons.

Microtubules are important regulators of cell polarity. As discussed in Chapter 2, Cell Cytoplasm (pages 65-69), microtubules are part of the cell's cytoskeleton. They are composed of tubulin heterodimers and consist of two distinct ends: a plus (+) end and a minus (–) end. At the plus (+) end, microtubules elongate via tubulin polymerization and extend into the cell's periphery. The minus ends are often anchored to an MTOC.

The microtubule network within neurons has certain unique characteristics. In general, microtubules are more stable in axons than in dendrites owing to post-translational modification of tubulin and the protective role of microtubule-associated proteins (MAPs). **Microtubules in axons** are uniformly **oriented with their plus (+) ends directed distally** (see Fig 12.7). These microtubules originate from the area of the MTOC located in the perinuclear cytoplasm. In contrast, **microtubules in dendrites** display a **mixed polar orientation**: Both plus (+) and minus (–) ends are directed distally away from the cell body, although microtubules with reverse polarity (those with their minus [–] ends directed distally) comprise most of the microtubules within dendrites (see Fig. 12.7). These microtubules are generally more stable and are comparable to the plus (+) end–oriented microtubules in axons. These findings suggest that microtubules of reverse polarity are not anchored in the MTOC and that their nucleation occurs independently from the MTOC in the cytoplasm of dendrites. This arrangement is a critical regulator of cell polarity and thus has implications for dendritic transport.

Some large axon terminals are capable of local protein synthesis, which may be involved in memory processes.

Almost all of the structural and functional protein molecules are synthesized in the nerve cell body. These molecules are distributed to the axons and dendrites via **neuronal transport systems** (described on pages 396-397). However, contrary to the common view that the nerve cell body is the only

site of protein synthesis, recent studies indicate that limited local synthesis of axonal proteins takes place in some large nerve terminals. Some vertebral axon terminals (i.e., from the retina) contain polyribosomes with complete translational machinery for protein synthesis. These discrete areas within the axon terminals, called **periaxoplasmic plaques**, possess biochemical and molecular characteristics of active protein synthesis. Protein synthesis within the periaxoplasmic plaques is modulated by neuronal activity. These proteins may be involved in the processes of **neuronal cell memory**.

Neuronal Transport Systems

Substances needed in the axons and dendrites are synthesized in the cell body and require transport to those sites.

Because the synthetic activity of the neuron is concentrated in the nerve cell body, microtubule-based **neuronal transport** is required to convey newly synthesized material to the correct neuronal compartment. Transport often takes place over long distances from the site of synthesis to its target destination in the axons or dendrites. Neuronal transport serves as a mode of intracellular communication, carrying molecules and information along the microtubules. Neuronal transport is bidirectional and occurs in both neurons and axons. Neurons are especially vulnerable to defects in neuronal transport because of the extreme length of the neuronal processes. Mutations in α-or β-tubulin and microtubule-based molecular motors have been directly linked to several neurologic disorders in both the CNS and the PNS. Disruption of neuronal transport is most likely responsible for abnormal accumulations of cytoskeletal proteins and organelles in axons in **Alzheimer disease**, **Parkinson disease**, **Huntington disease**, and **amyotrophic lateral sclerosis (ALS)**.

Kinesin and dynein motors drive axonal transport by directing the movement of cargo vesicles and organelles between the nerve cell body and the axon terminal.

Axonal transport is essential for supplying the distal part of the axon and its terminal with newly synthesized proteins, lipids, and neurotransmitters required to maintain synaptic transmission. In addition, aging proteins and organelles from the distal axon are transported for degradation and recycling to the nerve cell body. Molecular motors drive axonal transport along tracks formed by a uniform arrangement of microtubules with their plus (+) ends extending distally toward the axon terminal. Axonal transport is described as follows:

- **Anterograde transport** carries material from the nerve cell body to the axon periphery. Because all microtubules in axons are polarized in the same directions with their plus (+) ends directed toward the axon terminal, **kinesins**, microtubule-associated motor proteins, are involved in anterograde transport. Kinesins move the transport vesicles destined for axons along the microtubules toward their plus (+) ends. They utilize energy from adenosine triphosphate (ATP) hydrolysis to power their movement.
- **Retrograde transport** carries material from the axon terminal to the nerve cell body. This transport is mediated by the microtubule-associated motor proteins called **dyneins** that travel along the microtubules toward their minus (–) ends (see page 69).

The **motor properties** of both **kinesin** and **dynein** are regulated by external signals to allow transported cargo vesicles to slow down or speed up their movement. This is most likely achieved by alternate use of active and inactive conformations of these motor proteins that are attached to the same cargo vesicle. The presence of several motor proteins on the same cargo vesicle allows them to step around obstacles to resolve "road blocks" or "traffic jams" by switching to different microtubule tracks without exchanging the motors attached to the cargo vesicle.

Transport systems may also be distinguished by the rate at which substances are transported.

- A **slow anterograde transport system** conveys substances from the cell body to the axon terminal at the speed of 0.2–4 mm/d. Structural elements, such as tubulin molecules (microtubule precursors), actin molecules, and the proteins that form neurofilaments, are carried from the nerve cell body by this transport system. Cytoplasmic matrix proteins such as actin, calmodulin, and various metabolic enzymes are also transported this way.
- A **fast transport system** conveys substances in both directions at a rate of 20–400 mm/d. Thus, it is both an anterograde and a retrograde system. The **fast anterograde** transport system carries different membrane-limited organelles, such as smooth-surfaced endoplasmic reticulum (sER) components, synaptic vesicles, and mitochondria, and low-molecular-weight materials, such as sugars, amino acids, nucleotides, some neurotransmitters, and calcium to the axon terminal. The **fast retrograde** transport system carries many of the same materials as well as proteins and other molecules endocytosed at the axon terminal to the nerve cell body. Fast transport in either direction requires ATP, which is used by microtubule-associated motor proteins, and depends on the microtubule

arrangement that extends from the nerve cell body to the termination of the axon. Retrograde transport is the pathway followed by toxins and viruses that enter the CNS at nerve endings. Retrograde transport of exogenous enzymes, such as horseradish peroxidase, and radiolabeled or immunolabeled tracer materials is now used to trace neuronal pathways and to identify the nerve cell bodies related to specific nerve endings.

Dynein molecular motors are preferentially involved in dendritic transport, which is more complex than axonal transport owing to the antiparallel organization of microtubules.

Dendritic transport progresses along bundles of **mixed polarity microtubules**, which contain both "normal" microtubules' plus (+) ends and "reversed" microtubules' minus (–) ends oriented away from the nerve cell body. Therefore, a single unidirectional type of motor protein carrying transport vesicle could mediate bidirectional (anterograde and retrograde) transport by switching between normal and reverse polarity microtubule tracts. Recent studies indicate that **dyneins** play an important role in the initial sorting of vesicles that are destined for dendritic transport. Dyneins, which travel along the microtubules toward their minus (–) ends, are also **exclusively involved in anterograde transport** of cargo vesicles into dendrites utilizing microtubules with reversed polarity. Dyneins are also responsible for retrograde transport of vesicles from the dendritic processes into the body of the neuron. Kinesins play only a supporting role and providing assistance in dendritic transport once the transport vesicle is inside the dendrite.

Synapses

Neurons communicate with other neurons and effector cells by synapses.

Synapses are specialized junctions between neurons that facilitate the transmission of impulses from one (presynaptic) neuron to another (postsynaptic) neuron. Synapses also occur between axons and effector (target) cells, such as muscle and gland cells. Synapses between neurons may be classified morphologically as follows:

- **Axodendritic**. These synapses occur between axons and dendrites. In the CNS, some axodendritic synapses are found between axons and dendritic spines (Fig. 12.8).

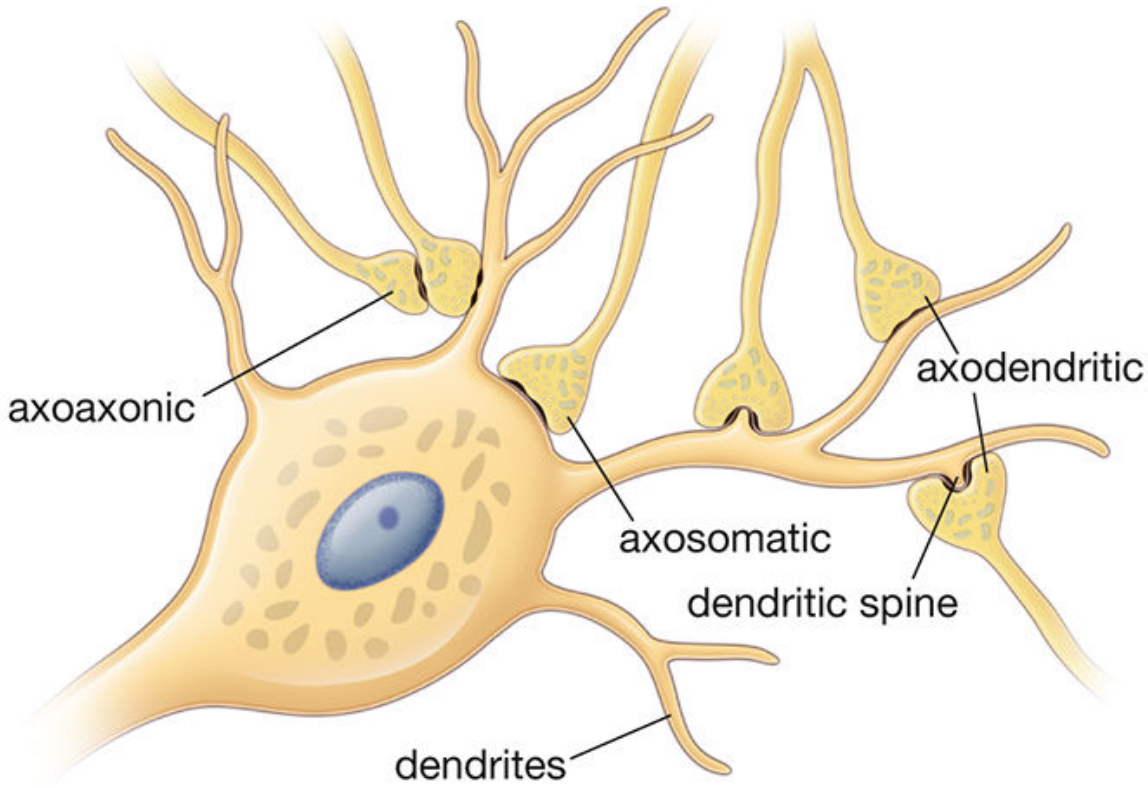


FIGURE 12.8. Schematic diagram of different types of synapses. Axodendritic synapses represent the most common type of connection between the presynaptic axon terminal and the dendrites of the postsynaptic neuron. Note that some axodendritic synapses possess dendritic spines, which are linked to learning and memory. Axosomatic synapses are formed between a presynaptic axon terminal and the postsynaptic nerve cell body; axoaxonic synapses are formed between the axon terminal of a presynaptic neuron and the axon of a postsynaptic neuron. The axoaxonic synapse may enhance or inhibit axodendritic (or axosomatic) synaptic transmission.

- **Axosomatic**. These synapses occur between axons and the cell body.
- **Axoaxonic**. These synapses occur between axons and axons (see Fig. 12.8).

Synapses are not resolvable in routine hematoxylin and eosin (H&E) preparations. However, silver precipitation staining methods (e.g., Golgi method) not only demonstrate the overall shape of some neurons but also show synapses as oval bodies on the surface of the receptor neuron. Typically, a presynaptic axon makes several of these button-like contacts with the receptor portion of the postsynaptic neuron. Often, the axon of the presynaptic neuron travels along the surface of the postsynaptic neuron, making several synaptic contacts along the way that are called **boutons en passant** *[Fr. buttons in passing]*. The axon then continues, ending finally as

a terminal branch with an enlarged tip, a **bouton terminal** *[Fr. terminal button]*, or end bulb. The number of synapses on a neuron or its processes vary from a few to tens of thousands per neuron (Fig. 12.9); this number appears to be directly related to the number of impulses that a neuron is receiving and processing.

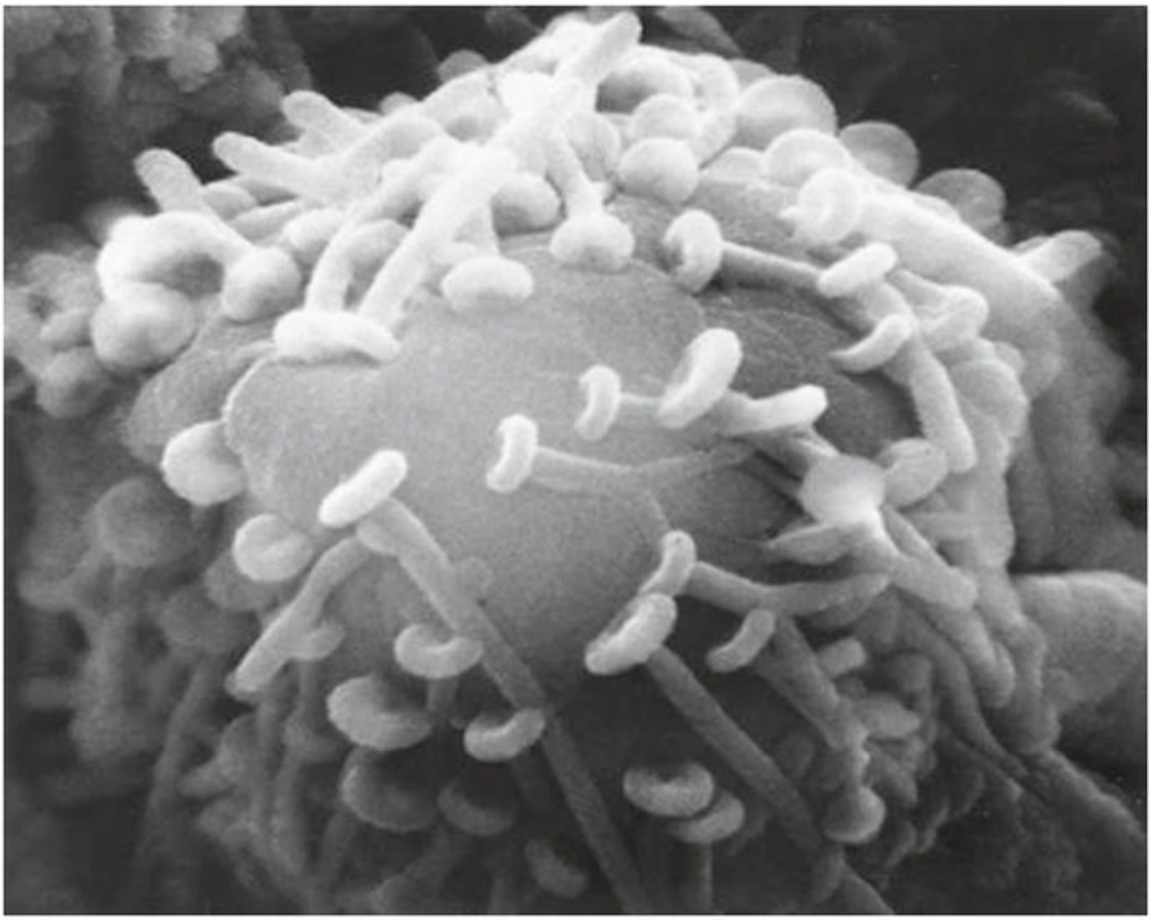


FIGURE 12.9. Scanning electron micrograph of the nerve cell body. This micrograph shows the cell body of a neuron. Axon endings forming axosomatic synapses are visible, as are numerous oval bodies with tail-like appendages. Each oval body represents a presynaptic axon terminal from different neurons making contact with the large postsynaptic nerve cell body. ×76,000. (Courtesy of Dr. George Johnson.)

FOLDER 12.1

CLINICAL CORRELATION: PARKINSON DISEASE

Parkinson disease is a slowly progressive neurologic disorder caused by the loss of dopamine (DA)-secreting cells in the substantia nigra and basal ganglia of the brain. DA is a neurotransmitter responsible for synaptic transmission in the nerve pathways coordinating smooth and

focused activity of skeletal muscles. Loss of DA-secreting cells is associated with a classic pattern of symptoms, including the following:

- Resting tremor in the limb, especially of the hand when in a relaxed position; tremor usually increases during stress and is often more severe on one side of the body
- Rigidity or increased tone (stiffness) in all muscles
- Slowness of movement (bradykinesia) and inability to initiate movement (akinesia)
- Lack of spontaneous movements
- Loss of postural reflexes, which leads to poor balance and abnormal walking (festinating gait)
- Slurred speech, slowness of thought, and small, cramped handwriting

The cause of **idiopathic Parkinson disease**, in which DA-secreting neurons in the substantia nigra are damaged and lost by degeneration or apoptosis, is not known. However, some evidence suggests a hereditary predisposition; about 20% of Parkinson patients have a family member with similar symptoms.

Symptoms that resemble idiopathic Parkinson disease may also result from infections (e.g., encephalitis), toxins (e.g., MPTP), drugs used in the treatment of neurologic disorders (e.g., neuroleptics used to treat schizophrenia), and repetitive trauma. Symptoms with these causes are called **secondary parkinsonism**.

On the microscopic level, degeneration of neurons in the substantia nigra is very evident. This region loses its typical pigmentation, and an increase in the number of glial cells is noticeable (**gliosis**). In addition, nerve cells in this region display characteristic intracellular inclusions called **Lewy bodies**, which represent accumulation of intermediate neurofilaments in association with proteins α-synuclein and ubiquitin.

Treatment of Parkinson disease is primarily symptomatic and must strike a balance between relieving symptoms and minimizing psychotic side effects. L-Dopa is a precursor of DA that can cross the blood–brain barrier and is then converted to DA. It is often the primary agent used to treat Parkinson disease. Other drugs that are used include a group of cholinergic receptor blockers and amantadine, a drug that stimulates the release of DA from neurons.

Some patients may benefit from a therapeutic approach called *deep brain stimulation*. In this procedure, electrodes attached to a pulse-generating electrical stimulator are implanted into the subthalamic nucleus of the brain. The electrical pulses act on neurons to modulate nerve impulses. This therapy has been shown to reduce tremor, slowness of movement, and rigidity associated with Parkinson disease. It also reduces the need for L-Dopa to control signs and symptoms, which helps mitigate the debilitating side effects of this medication.

Synapses are classified as chemical or electrical.

Classification of synapses depends on the mechanism of conduction of the nerve impulses and the way the action potential is generated in the target cells. Thus, synapses may also be classified as follows:

- **Chemical synapses**. Conduction of impulses is achieved by the release of chemical substances (neurotransmitters) from the presynaptic neuron. Neurotransmitters then diffuse across the narrow intercellular space that separates the presynaptic neuron from the postsynaptic neuron or target cell. A specialized type of chemical synapse called a **ribbon synapse** is found in the receptor hair cells of the internal ear and photoreceptor cells of the retina (see Chapter 25, Ear, pages 1028-1029).
- **Electrical synapses**. Common in invertebrates, these synapses contain gap junctions that permit the movement of ions between cells and consequently permit the direct spread of electrical current from one cell to another. These synapses do not require neurotransmitters for their function. Mammalian equivalents of electrical synapses include **gap junctions** in smooth muscle and cardiac muscle cells.

A typical chemical synapse contains a presynaptic element, synaptic cleft, and postsynaptic membrane.

Components of a typical chemical synapse include the following:

- A **presynaptic element** (presynaptic knob, presynaptic component, or synaptic bouton) is the end of the neuronal process from which neurotransmitters are released. The presynaptic element is characterized by the presence of **synaptic vesicles**, membrane-bound structures that range from 30 to 100 nm in diameter and contain neurotransmitters (Fig. 12.10). The binding and fusion of synaptic vesicles to the presynaptic plasma membrane are mediated by a family of transmembrane proteins called **SNAREs** (which stands for "**S**oluble **N**SF **A**ttachment **RE**ceptors"; see pages 42-43). The specific SNARE proteins involved in this activity include **synaptobrevin**, a vesicle-bound v-SNARE, and **syntaxin** and **SNAP-25**, which are target membrane-bound t-SNARE proteins found in specialized areas of the presynaptic membrane. Another vesicle-bound protein called **synaptotagmin 1** then displaces the SNARE complex, which is subsequently dismantled and recycled by NSF/SNAP25 protein complexes. Dense accumulations of proteins are present on the cytoplasmic side of the presynaptic plasma membrane. These presynaptic densities represent specialized areas called **active zones** where synaptic vesicles are docked and where neurotransmitters are released. Active

zones are rich in **Rab-GTPase docking complexes** (see pages 42-43), **t-SNAREs**, and **synaptotagmin-binding proteins**. The vesicle membrane that is added to the presynaptic membrane is retrieved by endocytosis and reprocessed into synaptic vesicles by the sER located in the nerve ending. Numerous small mitochondria are also present in the presynaptic element.

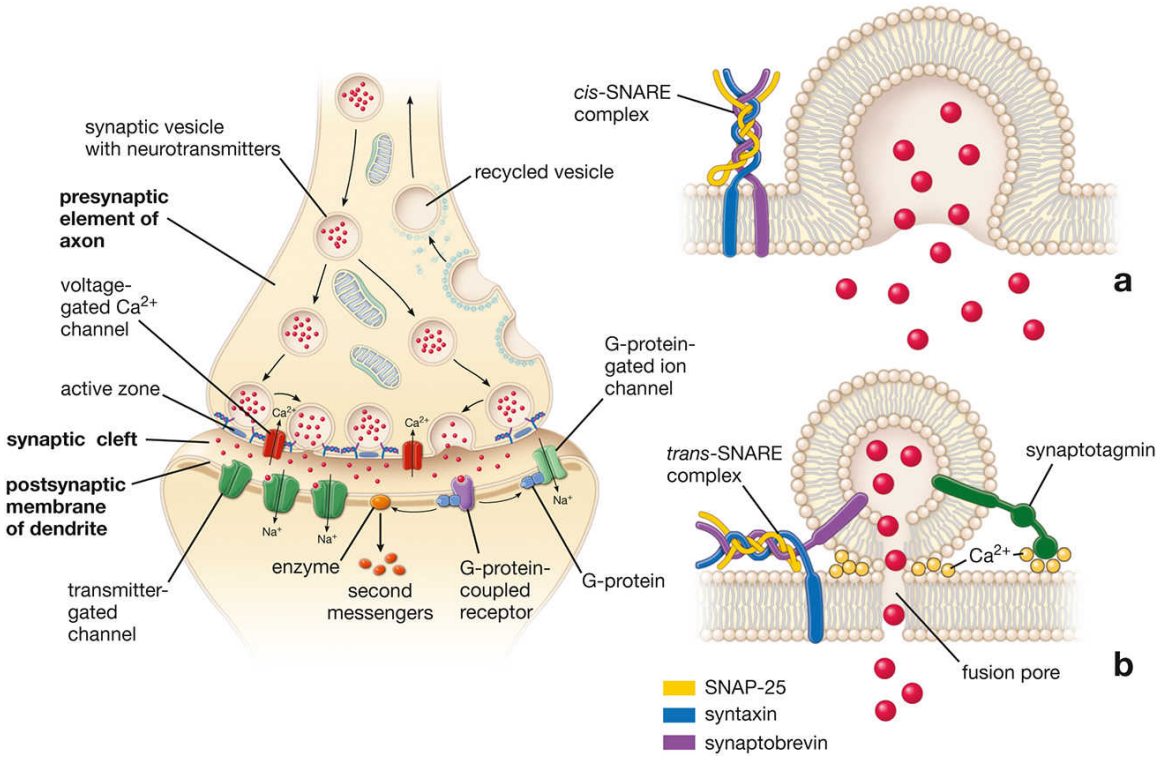


FIGURE 12.10. Diagram of a chemical axodendritic synapse. This diagram illustrates three components of a typical synapse. The presynaptic knob is located at the distal end of the axon from which neurotransmitters are released. The presynaptic element of the axon is characterized by the presence of numerous neurotransmitter-containing synaptic vesicles. The plasma membrane of the presynaptic knob is recycled by the formation of clathrin-coated endocytotic vesicles. The synaptic cleft separates the presynaptic knob of the axon from the postsynaptic membrane of the dendrite. The postsynaptic membrane of the dendrite is frequently characterized by a postsynaptic density and contains receptors with an affinity for the neurotransmitters. Note two types of receptors: *Green*-colored molecules represent transmitter-gated channels, and the *purple*-colored structure represents a G-protein–coupled receptor that, when bound to a neurotransmitter, may act on G-protein–gated ion channels or on enzymes producing a second messenger. **a.** Diagram showing neurotransmitter release from a presynaptic knob by fusion of the synaptic vesicles with the presynaptic membrane. The fusion mechanism that involves SNARE proteins is

described in Chapter 2, Cell Cytoplasm **(pages 42-44)**. Note the *cis*-SNARE complex, which is formed after the vesicle fuses to the presynaptic membrane. **b.** Diagram showing a proposed model of neurotransmitter release via porocytosis. In this model, the synaptic vesicle is anchored and juxtaposed to calcium-selective channels in the presynaptic membrane. In the presence of Ca^{2+}, the bilayers of the vesicle and presynaptic membranes are reorganized to create a 1-nm transient fusion pore connecting the lumen of the vesicle, with the synaptic cleft allowing the release of a neurotransmitter. Note the presence of the *trans*-SNARE complex and the synaptotagmin that anchor the vesicle to the active zones within the plasma membrane of the presynaptic element.

- The **synaptic cleft** is the 20-to 30-nm space that separates the presynaptic neuron from the postsynaptic neuron or target cell, which the neurotransmitter must cross.
- The **postsynaptic membrane** (postsynaptic component) contains receptor sites with which the neurotransmitter interacts. This component is formed from a portion of the plasma membrane of the postsynaptic neuron (Fig. 12.11) and is characterized by an underlying layer of dense material. This **postsynaptic density** represents an elaborate complex of interlinked proteins that serve numerous functions, such as translation of the neurotransmitter–receptor interaction into an intracellular signal, anchoring of and trafficking neurotransmitter receptors to the plasma membrane, and anchoring various proteins that modulate receptor activity.

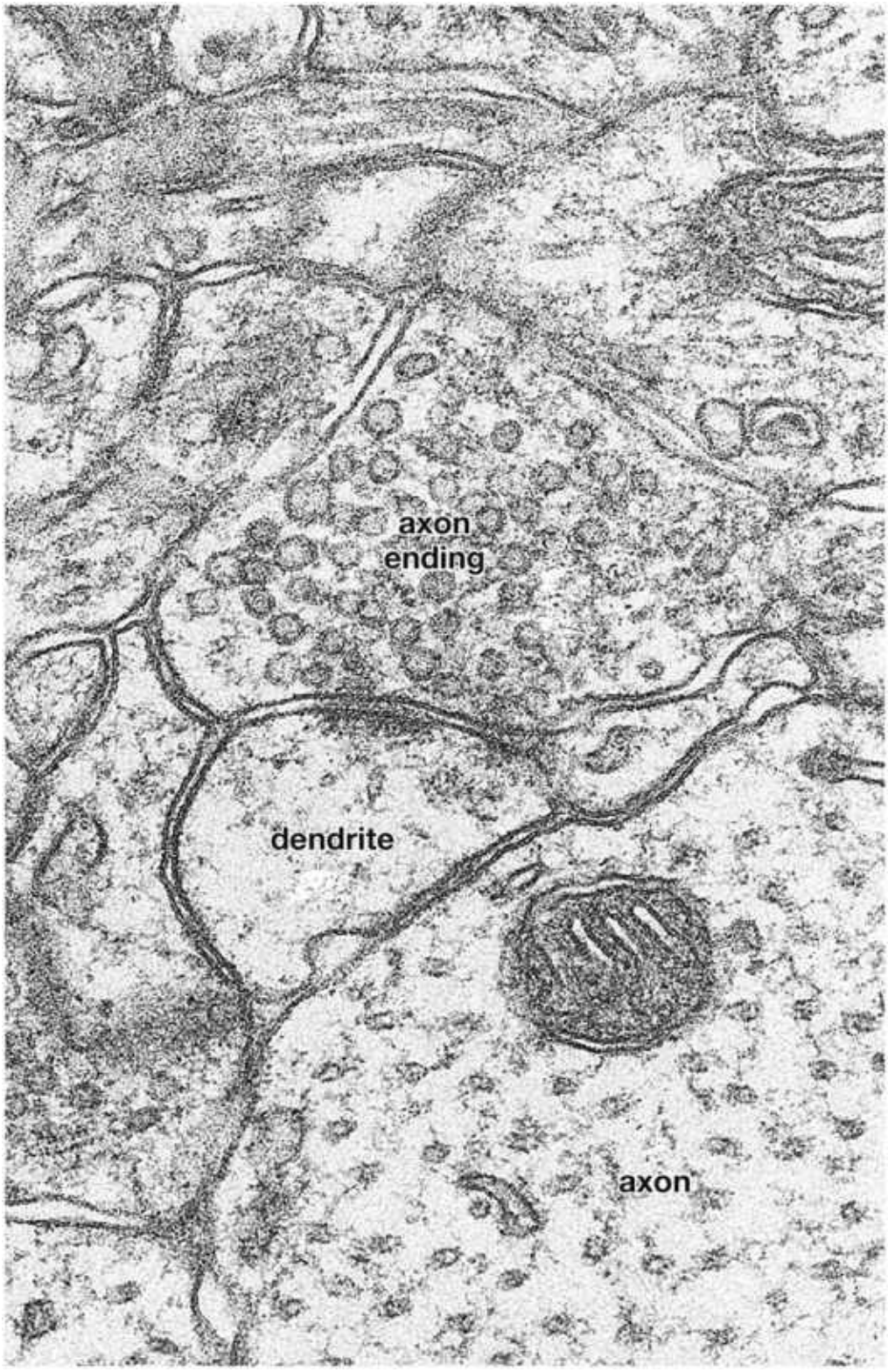


FIGURE 12.11. Electron micrograph of nerve processes in the cerebral cortex. A synapse can be seen in the *center* of the micrograph, where an axon ending is in apposition to a dendrite. The ending of the axon exhibits numerous neurotransmitter-containing synaptic vesicles that appear as circular profiles. The postsynaptic membrane of the dendrite shows a postsynaptic density. A substance of similar density is also

present in the synaptic cleft (intercellular space) at the synapse. ×76,000. (Courtesy of Drs. George D. Pappas and Virginia Kriho.)

Synaptic Transmission

Voltage-gated Ca^{2+} channels in the presynaptic membrane regulate transmitter release.

When a nerve impulse reaches the synaptic bouton, the voltage reversal across the membrane produced by the impulse (called **depolarization**) causes **voltage-gated Ca^{2+} channels** to open in the plasma membrane of the bouton. The influx of Ca^{2+} from the extracellular space causes the synaptic vesicles to migrate, anchor, and fuse with the presynaptic membrane, thereby releasing the neurotransmitter into the synaptic cleft by exocytosis. Vesicle docking and fusion are mainly driven by the actions of SNARE and synaptotagmin proteins. An alternative process that releases neurotransmitter following vesicle fusion is called **porocytosis**, in which vesicles anchored at the active zones release neurotransmitters through a transient fusion pore connecting the lumen of the vesicle with the synaptic cleft. At the same time, the presynaptic membrane of the synaptic bouton that released the neurotransmitter quickly forms endocytotic vesicles that return to the endosomal compartment of the bouton for recycling or reloading with neurotransmitter.

The neurotransmitter binds to either transmitter-gated channels or G-protein–coupled receptors on the postsynaptic membrane.

The released neurotransmitter molecules bind to the extracellular part of postsynaptic membrane receptors called **transmitter-gated channels**. Binding of neurotransmitter induces a conformational change in these channel proteins that causes their pores to open. The response that is ultimately generated depends on the identity of the ion that enters the cell. For instance, influx of Na^+ causes local depolarization in the postsynaptic membrane, which, under favorable conditions (sufficient amount and duration of neurotransmitter release), prompts the opening of **voltage-gated Na^+ channels**, thereby generating a nerve impulse.

Some amino acid and amine neurotransmitters may bind to **G-protein–coupled receptors** to produce longer lasting and more diverse postsynaptic responses. The neurotransmitter binds to a transmembrane receptor protein on the postsynaptic membrane. Receptor binding activates G-proteins, which move along the intracellular surface of the postsynaptic membrane and eventually activate effector proteins. These effector proteins may include transmembrane **G-protein–gated ion channels** or **enzymes**

that synthesize second messenger molecules (page 401). Several neurotransmitters (e.g., acetylcholine [ACh]) can generate different postsynaptic actions, depending on which receptor system they act (see later in this chapter).

Porocytosis describes the secretion of neurotransmitter that does not involve the fusion of synaptic vesicles with the presynaptic membrane.

Based on evaluation of physiologic data and the structural organization of nerve synapses, an alternate model of neurotransmitter secretion called **porocytosis** has recently been proposed to explain the regulated release of neurotransmitters. In this model, secretion from the vesicles occurs without the fusion of the vesicle membrane with the presynaptic membrane. Instead, the synaptic vesicle is anchored to the presynaptic membrane next to Ca^{2+}-selective channels by SNARE and synaptotagmin proteins. In the presence of Ca^{2+}, the vesicle and presynaptic membranes are reorganized to create a 1-nm transient **fusion pore** that connects the lumen of the vesicle with the synaptic cleft. Neurotransmitters can then be released in a controlled manner through these transient membrane pores (see Fig. 12.10).

The chemical nature of the neurotransmitter determines the type of response at that synapse in the generation of neuronal impulses.

The release of neurotransmitter by the presynaptic component can cause either **excitation** or **inhibition** at the postsynaptic membrane.

- In **excitatory synapses**, the release of neurotransmitters such as **acetylcholine**, **glutamine**, or **serotonin** opens **transmitter-gated Na^+ channels** (or other cation channels), prompting an influx of Na^+ that causes local reversal of voltage of the postsynaptic membrane to a threshold level (depolarization). This leads to initiation of an action potential and generation of a nerve impulse.
- In **inhibitory synapses**, the release of neurotransmitters such as **γ-aminobutyric acid (GABA)** or **glycine** opens **transmitter-gated Cl^- channels** (or other anion channels), causing Cl^- to enter the cell and hyperpolarize the postsynaptic membrane, making it even more negative. In these synapses, the generation of an action potential then becomes more difficult.

The ultimate generation of a nerve impulse in a postsynaptic neuron (firing) depends on the summation of excitatory and inhibitory impulses reaching that neuron. This allows precise regulation of the reaction of a postsynaptic neuron (or muscle fiber or gland cell). The function of synapses

is not simply to transmit impulses in an unchanged manner from one neuron to another. Rather, synapses allow for the processing of neuronal input. Typically, the impulse passing from the presynaptic to the postsynaptic neuron is modified at the synapse by other neurons that, although not in the direct pathway, nevertheless have access to the synapse (see Fig. 12.8). These other neurons may influence the membrane of the presynaptic neuron or the postsynaptic neuron and facilitate or inhibit the transmission of impulses. The firing of impulses in the postsynaptic neuron is caused by the summation of the actions of hundreds of synapses.

Neurotransmitters

Many molecules that serve as **neurotransmitters** have been identified in various parts of the nervous system. A neurotransmitter that is released from the presynaptic element diffuses through the synaptic cleft to the postsynaptic membrane, where it interacts with a specific receptor. Action of the neurotransmitter depends on its chemical nature and the characteristics of the receptor present on the postsynaptic plate of the effector cell.

Neurotransmitters act on either ionotropic receptors to open membrane ion channels or metabotropic receptors to activate G-protein signaling cascade.

Almost all known neurotransmitters act on multiple receptors, which are integral membrane proteins. These receptors can be divided into two major classes: ionotropic and metabotropic receptors. **Ionotropic receptors** contain integral transmembrane ion channels, also referred to as **transmitter-gated channels** or **ligand-gated channels**. Binding of neurotransmitter to ionotropic receptors triggers a conformational change of the receptor proteins that leads to the opening of the channel and subsequent movement of selective ions into or out of the cell. This generates an action potential in the effector cell. In general, signaling using ionotropic channels is very rapid and occurs in the major neuronal pathways of the brain and somatic motor pathways in the PNS. **Metabotropic channels** are responsible not only for binding a specific neurotransmitter but also for interacting with **G-protein** at their intracellular domain. G-protein is an important protein that is involved in intracellular signaling. It conveys signals from the outside to the inside of the cell by altering the activities of enzymes involved in the synthesis of a second messenger. Activation of metabotropic receptors is mostly involved in the modulation of neuronal activity.

The most common neurotransmitters are described as follows. A summary of selected neurotransmitters and their characteristics in both the PNS and the CNS is provided in Table 12.1.

TABLE 12.1 Characterizations of the Most Common Neurotransmitters

Class of Molecule	Neurotransmitter	Receptor Type and Action: Ionotropic	Receptor Type and Action: Metabotropic	Physiologic Role
Ester	ACh	Nicotinic ACh receptors (nAChR); activates Na^+ channels	Muscarinic ACh receptor (mAChR); acts via G-protein	Fast excitatory synaptic transmission at the neuromuscular junction (acting on nAChR); also present in PNS (e.g., sympathetic ganglia, adrenal medulla) and CNS; both excitatory and inhibitory action (acting on mAChR) (e.g., decreases heart rate, smooth muscle relaxation of gastrointestinal tract)
Monoamine	Epinephrine, norepinephrine	NA	α- and β-adrenergic receptors; acts via G-protein	Slow synaptic transmission in CNS and in smooth muscles
	Dopamine	NA	D_1 and D_2 dopamine receptors; acts via G-protein	Slow synaptic transmission in CNS
	Serotonin	5-HT_3 ligand–gated Na^+/K^+ channel; activates ion channels	5-$HT_{1,2,4–7}$ receptors	Fast excitatory synaptic transmission (acting on 5-HT_3); both excitatory and inhibitory depending on receptor; acts in CNS and PNS (enteric system)
Amino acids	Glutamate	NMDA, kainite, and AMPA; activates Na^+, K^+, and Ca^{2+} channels	mGluR receptor; acts via G-protein	Fast excitatory synaptic transmission in CNS
	GABA	$GABA_A$ receptor; activates Cl^- channels	$GABA_B$ receptor; acts via G-protein	Both fast and slow inhibitory synaptic transmission in CNS
	Glycine	Glycine receptor (GlyR); activates Cl^- channels	NA	Fast inhibitory synaptic transmission in CNS
Small peptides	Substance P	NA	Neurokinin-1 (NK1) receptor; acts via G-protein	Slow excitation of smooth muscles and sensory neurons in CNS, especially when conveying pain sensation
	Enkephalins	NA	δ (DOP) and μ (MOP) opioid receptors; acts via G-protein	Reduces synaptic excitability (slow synaptic signaling); relaxes smooth muscles in gastrointestinal tract; causes analgesia
	β-Endorphin	NA	κ Opioid (KOP) receptor; acts via G-protein	Slow synaptic signaling in brain and spinal cord; causes analgesia
Free radical	NO	NO does not act on receptors; it activates guanylyl cyclase and then via cGMP signaling increases G-protein synthesis in target cells		Influences neurotransmitter release in CNS and PNS; acts as potent vasodilator, relaxes smooth muscles in gastrointestinal tract

5-HT, 5-hydroxytryptamine; *ACh*, acetylcholine; *AMPA*, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; *cGMP*, cyclic guanosine monophosphate; *CNS*, central nervous system; *GABA*, γ-aminobutyric acid; *mGluR*, metabotropic glutamate receptor; *NA*, not applicable; *NMDA*, N-methyl D-aspartate receptor; *NO*, nitric oxide; *PNS*, peripheral nervous system.

- **Acetylcholine (ACh)**. ACh is the neurotransmitter between axons and striated muscle at the neuromuscular junction (see page 357) and serves as a neurotransmitter in the ANS. ACh is released by the presynaptic sympathetic and parasympathetic neurons and their effectors. ACh is also secreted by postsynaptic parasympathetic neurons as well as by a specific type of postsynaptic sympathetic neuron that innervates sweat glands. Neurons that use ACh as their neurotransmitter are called **cholinergic**

neurons. The receptors for ACh in the postsynaptic membrane are known as **cholinergic receptors** and are divided into two classes. Metabotropic receptors interact with muscarine, a substance isolated from poisonous mushrooms **(muscarinic ACh receptors)**, and ionotropic receptors interact with nicotine isolated from tobacco plants **(nicotinic ACh receptors)**. The muscarinic ACh receptor in the heart is an example of a G-protein–coupled receptor that is linked to K^+ channels. Parasympathetic stimulation of the heart releases ACh, which, in turn, opens K^+ channels, causing hyperpolarization of cardiac muscle fibers. This hyperpolarization slows rhythmic contraction of the heart. In contrast, the nicotinic ACh receptor in skeletal muscles is an ionotropic ligand–gated Na^+ channel. Opening of this channel causes rapid depolarization of skeletal muscle fibers and initiation of contraction. Various drugs affect the release of ACh into the synaptic cleft as well as its binding to its receptors. For instance, **curare**, the South American arrow-tip poison, binds to nicotinic ACh receptors, blocking their integral Na^+ channels and causing muscle paralysis. **Atropine**, an alkaloid extracted from the belladonna plant *(Atropa belladonna)*, blocks the action of muscarinic ACh receptors.

- **Catecholamines** such as **norepinephrine (NE)**, **epinephrine (EPI, adrenaline)**, and **dopamine (DA)**. These neurotransmitters are synthesized in a series of enzymatic reactions from the amino acid tyrosine. Neurons that use catecholamines as their neurotransmitter are called **catecholaminergic neurons**. Catecholamines are secreted by cells in the CNS that are involved in the regulation of movement, mood, and attention. Neurons that utilize EPI (adrenaline) as their neurotransmitter are called **adrenergic neurons**. They all contain an enzyme that converts NE to adrenaline (EPI), which serves as a transmitter between postsynaptic sympathetic axons and effectors in the ANS. EPI is also released into the bloodstream by the endocrine cells (chromaffin cells) of the adrenal medulla during the **fight-or-flight response**.
- **Serotonin** or **5-hydroxytryptamine (5-HT)**. Serotonin is formed by the hydroxylation and decarboxylation of tryptophan. It functions as a neurotransmitter in the neurons of the CNS and enteric nervous system. Neurons that use serotonin as their neurotransmitter are called **serotonergic**. After the release of serotonin, a portion is recycled by reuptake into presynaptic serotonergic neurons. Serotonin has been found to be an important molecule that helps establish **asymmetrical right–left development** in embryos.
- **Amino acids** such as GABA, GLU, aspartate (ASP), and glycine (GLY) act as neurotransmitters, mainly in the CNS.

- **Nitric oxide (NO)**, a simple gas with free radical properties, also has been identified as a neurotransmitter. At low concentrations, NO carries nerve impulses from one neuron to another. Unlike other neurotransmitters, which are synthesized in the nerve cell body and stored in synaptic vesicles, NO is synthesized within the synapse and used immediately. It is postulated that excitatory neurotransmitter GLU induces a chain reaction in which **NO synthase** is activated to produce NO, which, in turn, diffuses from the presynaptic knob via the synaptic cleft and postsynaptic membrane to the adjacent cell. Biological actions of NO are due to the activation of guanylyl cyclase, which then produces cyclic guanosine monophosphate (cGMP) in target cells. cGMP, in turn, acts on G-protein synthesis, ultimately resulting in generation/modulation of neuronal action potentials.
- **Small peptides** have been shown to act as synaptic transmitters. Among these are **substance P** (so named because it was originally found in a powder of acetone extracts of brain and intestinal tissue), **hypothalamic-releasing hormones**, **endogenous opioid peptides** (e.g., **β-endorphin**, **enkephalins**, **dynorphins**), **vasoactive intestinal peptide (VIP)**, **cholecystokinin (CCK)**, and **neurotensin**. Many of these same substances are synthesized and released by **enteroendocrine cells** of the intestinal tract. They may act immediately on neighboring cells (paracrine secretion) or be carried in the bloodstream as hormones to act on distant target cells (endocrine secretion). They are also synthesized and released by endocrine organs and the neurosecretory neurons of the hypothalamus.

Neurotransmitters released into the synaptic cleft may be degraded or recaptured.

The degradation or recapture of neurotransmitters is necessary to limit the duration of stimulation or inhibition of the postsynaptic membrane. The most common process of neurotransmitter removal after its release into the synaptic cleft is called **high-affinity reuptake**. About 80% of released neurotransmitters are removed by this mechanism, in which they are bound into **specific neurotransmitter transport proteins** located in the presynaptic membrane. Neurotransmitters that were transported into the cytoplasm of the presynaptic bouton are either enzymatically destroyed or reloaded into empty synaptic vesicles. For example, the action of **catecholamines** on postsynaptic receptors is terminated by the reuptake of neurotransmitters into the presynaptic bouton utilizing **Na^+-dependent transporters**. The efficiency of this uptake can be regulated by several pharmacologic agents such as amphetamine and cocaine,

which block catecholamine reuptake and prolong the actions of neurotransmitters on the postsynaptic neurons. Once inside the presynaptic bouton, catecholamines are reloaded into synaptic vesicles for future use. The excess of catecholamines is inactivated by the enzyme **catechol *O*-methyltransferase (COMT)** or is destroyed by another enzyme found on the outer mitochondrial membrane, **monoamine oxidase (MAO)**. Therapeutic substances that inhibit the action of MAO are frequently used in the treatment of **clinical depression**; selective COMT inhibitors have been also developed.

Enzymes associated with the postsynaptic membrane degrade the remaining 20% of neurotransmitters. For example, **acetylcholinesterase (AChE)**, which is secreted by the muscle cell into the synaptic cleft, rapidly degrades ACh into acetic acid and choline. Choline is then taken up by the cholinergic presynaptic bouton and reused for ACh synthesis. The **AChE action** at the **neuromuscular junction** can be inhibited by various pharmacologic compounds, nerve agents, and pesticides, resulting in prolonged muscle contraction. Clinically, **AChE inhibitors** have been used in the treatment of **myasthenia gravis** (see Folder 11.3 in Chapter 11, Muscle Tissue, page 358), an autoimmune neuromuscular disorder, and **glaucoma**. AChE inhibitors also improve many of the symptoms of **Alzheimer disease** and are considered the first-line therapeutic agents for these patients.

■ SUPPORTING CELLS OF THE NERVOUS SYSTEM: THE NEUROGLIA

In the PNS, supporting cells are called **peripheral neuroglia**; in the CNS, they are called **central neuroglia**.

Peripheral Neuroglia

Peripheral neuroglia include **Schwann cells**, **satellite cells**, and a variety of other cells associated with specific organs or tissues. Examples of the latter include **terminal neuroglia (terminal Schwann cells, teloglia)**, which are associated with the motor end plate; **enteric neuroglia** associated with the ganglia located in the wall of the alimentary canal; and **Müller cells** in the retina.

Schwann Cell Development and Synthesis of Myelin Sheath

In mature peripheral nerves, **Schwann cells** adopt one of the three distinct phenotypes: (1) a **myelinating phenotype** that is responsible for myelinating large-diameter axons in the PNS; (2) a **nonmyelinating phenotype** (also known as a **Remak Schwann cell)**, which is characterized by the enclosure of multiple small-diameter axons within grooves of the plasma membrane that invaginate deep into the cell cytoplasm; and (3) a **repair cell** phenotype that plays a major role during nerve injury, repair, and regeneration. Although Remak Schwann cells do not produce myelin, they are essential for the proper development and function of the peripheral nerves. During nerve injury, both myelinating Schwann cells and Remak Schwann cells undergo reprogramming and dedifferentiation into repair cells. For the purpose of this discussion, the term "Schwann cell" is used to describe myelin-producing cells, and "Remak Schwann cells" refers to the nonmyelin-producing cells that provide support for unmyelinated nerve fibers in the PNS.

- **Myelinating Schwann cells** are the major glial cell type in PNS. They produce the myelin that surrounds all large-diameter peripheral nerve processes and play essential roles in the development, maintenance, function, and regeneration of peripheral nerves. A detailed description of Schwann cell development, structure, and function is explained.

  Nonmyelinating Remak Schwann cells are the second major phenotype of Schwann cells. In the PNS, Remak Schwann cells do not produce myelin; instead, they envelope multiple small-diameter axons to form **unmyelinated fibers** called *Remak bundles*. Most unmyelinated fibers are composed of postsynaptic sympathetic and parasympathetic axons. Some nonmyelinating Schwann cells migrate toward the neuromuscular junction and cover the axon terminals, where they become **perisynaptic/terminal Schwann cells (teloglia)**. These cells are found at the distal ends of motor nerve terminals at neuromuscular junctions (see Fig. 11.14).
- **Repair Schwann cells** are the third phenotype of Schwan cells and are specialized to promote the repair of injured nerves in the PNS. Repair Schwann cells are derived from the conversion of myelinating Schwann cells and nonmyelinating Remak Schwann cells in response to nerve injury (Fig 12.12). This injury-induced conversion of Schwann and Remak Schwann cells is driven by the dedifferentiation of mature cells and cell reprogramming that involves the downregulation of myelin genes combined with activation of specific features used in nerve repair. These features include upregulation of trophic factors, increased synthesis of cytokines (i.e., for macrophage recruitment), activation of myelin autophagy (myelin clearance), and the formation of **regeneration tracks**

called **bands of Büngner** that direct growing axonal sprouts to their targets. A detailed description of nerve regeneration is found in the section on response of neurons to injury (see pages 426-429).

Schwann cell precursors originate from neural crest cells and further differentiate into myelinating Schwann cells or nonmyelinating Remak Schwan cells according to axon-derived signals.

During nerve development in the PNS, some **neural crest cells** give rise to **Schwann cell precursors** under the influence of transcription factor SOX10 (see Fig 12.12). Schwann cell precursors migrate along developing axons to their final destination. Once this migration is complete, the Schwann cell precursors transition into **immature Schwann cells** and perform **radial sorting**, which sorts the axons based on their diameter. This process determines the final phenotype of the Schwann cell and the designation of the nerve fiber as myelinated or unmyelinated.

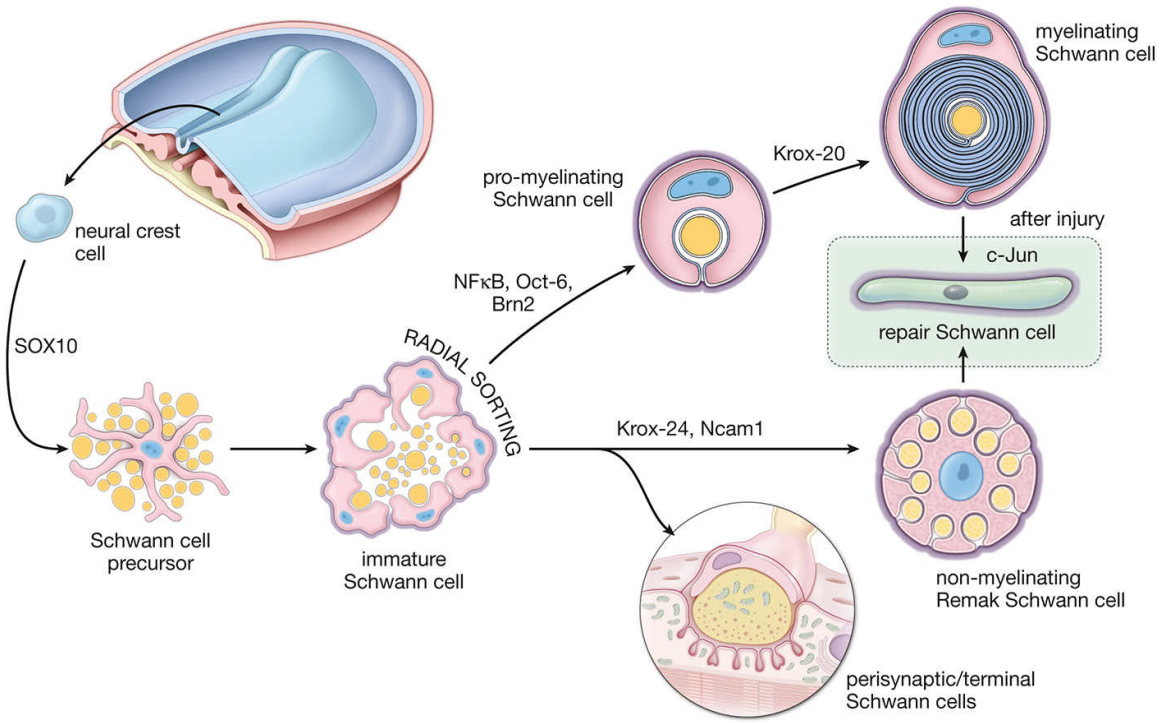


FIGURE 12.12. Schwann cell development and transformation after peripheral nerve injury. Schwann cell precursors originate from neural crest cells under the influence of transcription factor Sox-10. They further transition into immature Schwann cells and perform radial sorting of the axons based on their diameter. Immature Schwann cells, which have a one-to-one relationship with large-diameter axons, under influence of NF-κB, Oct-6, and Brn2 transcription factors, become promyelinating Schwan cells. Under further influence of Krox-20 transcription factor, these cells develop into

myelinating Schwann cells. The remaining small-diameter fibers are engulfed in the cytoplasm of the remaining immature Schwan cells and eventually, under the influence of Krox-24 and Ncam1, differentiate into nonmyelinated Remak Schwann cells. Some immature Schwann cells near the neuromuscular junctions develop into perisynaptic/terminal Schwann cells, which also do not produce myelin. Radial sorting determines the final phenotype of the Schwann cell and the designation of the nerve fiber as myelinated or unmyelinated. Following peripheral nerve injury, c-Jun transcription factor is rapidly upregulated, downregulating the expression of Krox-20 and causing dedifferentiation of Schwann cells into repair Schwann cells. Similar processes occur in the Remak Schwan cells, leading to their differentiation during nerve injury.

Radial sorting begins by secluding a cohort of axons of mixed diameters into small bundles. These bundles are surrounded by three to eight immature Schwann cells that organize a common external lamina around them. Next, the immature Schwan cells extend their cytoplasmic processes between axons to progressively choose, segregate, and reposition larger axons (>6–7 μm in diameter) toward their own cell body at the periphery of the bundle. As immature Schwann cells continue to proliferate, large-diameter axons are sorted into a one-to-one relationship with immature Schwann cells. This close interaction with a single large axon allows immature Schwann cells to receive axonal signals from a transmembrane protein expressed on the axolemma of the axon called **neuregulin-1 (Nrg1)**. The Nrg1 signal upregulates the expression of **promyelinating transcription factors**, including nuclear factor κB (NF-κB), octamer-binding transcription factor 6 (Oct-6), and brain 2 class III POU-domain protein (Brn2) (see Fig 12.12). These transcription factors promote promyelination, in which **promyelinating Schwann cells** express early myelin markers. Further upregulation of KROX20 is required for maturation to **myelinated Schwann cells**, which express myelin-specific proteins and produce myelin sheaths.

As myelinating Schwann cell development progresses, large axons are pooled out from the initial axonal bundles. The bundles become smaller and smaller until they contain only the remaining small-diameter axons (<1 μm in diameter). They are subsequently engulfed by the cytoplasm of the remaining immature Schwan cells and eventually differentiate into **nonmyelinated Remak Schwann cells** (see Fig 12.12).

In the PNS, myelinating Schwann cells produce the myelin sheath.

The main function of Schwann cells is to support myelinated and unmyelinated nerve cell fibers. In the PNS, **Schwann cells** produce a lipid-

rich layer called the **myelin sheath** that surrounds the axons (Fig. 12.13). The myelin sheath isolates the axon from the surrounding extracellular compartment of endoneurium. Its presence ensures the rapid conduction of nerve impulses. The axon hillock and the terminal arborizations where the axon synapses with its target cells are not covered by myelin. Unmyelinated fibers are also enveloped and nurtured by Remak Schwann cell's cytoplasm. In addition, Schwann cells aid in removing PNS debris and guide the regrowth of PNS axons (see pages 426-429).

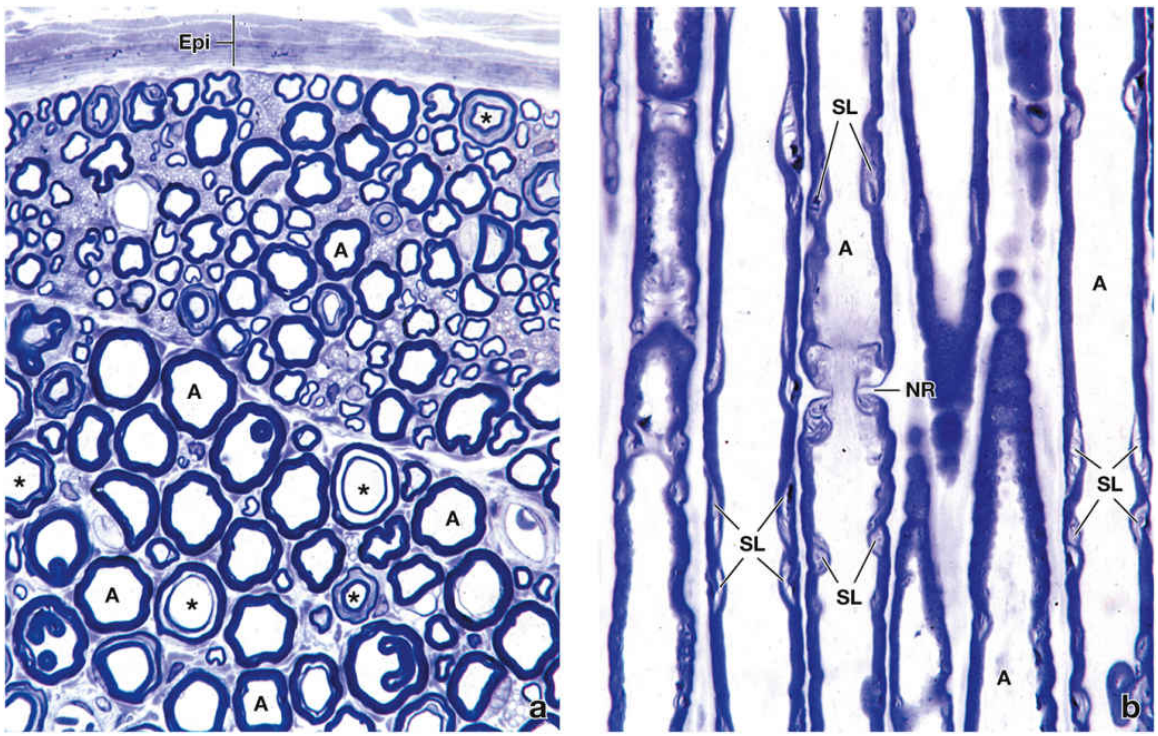


FIGURE 12.13. Photomicrographs of a peripheral nerve in cross and longitudinal sections. a. Photomicrograph of an osmium-fixed, toluidine blue–stained peripheral nerve cut in cross section. The axons (*A*) appear clear. The myelin is represented by the *dark ring* surrounding the *A*. Note the variation in diameter of the individual *A*. In some of the nerves, the myelin appears to consist of two separate rings (*asterisks*). This is caused by the section passing through a Schmidt–Lanterman cleft. *Epi*, epineurium. ×640. **b.** Photomicrograph showing longitudinally sectioned myelinated nerve *A* in the same preparation as earlier. A node of Ranvier (*NR*) is seen *near the center* of the micrograph. In the same *A*, a Schmidt–Lanterman cleft (*SL*) is seen on each side of the node. In addition, a number of *SL* clefts can be seen in the adjacent *A*. The perinodal cytoplasm of the Schwann cell at the *NR* and the Schwann cell cytoplasm at the *SL* cleft appear virtually unstained. ×640.

Myelination begins when a Schwann cell surrounds the axon and its cell membrane becomes polarized.

During formation of the myelin sheath (also called **myelination**), the axon initially lies in a groove on the surface of the Schwann cell (Fig. 12.14a). A 0.08-to 0.1-mm segment of the axon then becomes enclosed within each Schwann cell that lies along the axon. The Schwann cell surface becomes polarized into two functionally distinct membrane domains. The part of the Schwann cell membrane that is exposed to the external environment or endoneurium, the **abaxonal plasma membrane**, represents one domain. The other domain is represented by the **adaxonal** or **periaxonal plasma membrane**, which is in direct contact with the axon. When the axon is completely enclosed by the Schwann cell membrane, a third domain, the **mesaxon**, is created (Fig. 12.14b). This third domain is a double membrane that connects the abaxonal and adaxonal membranes and encloses the narrow extracellular space.

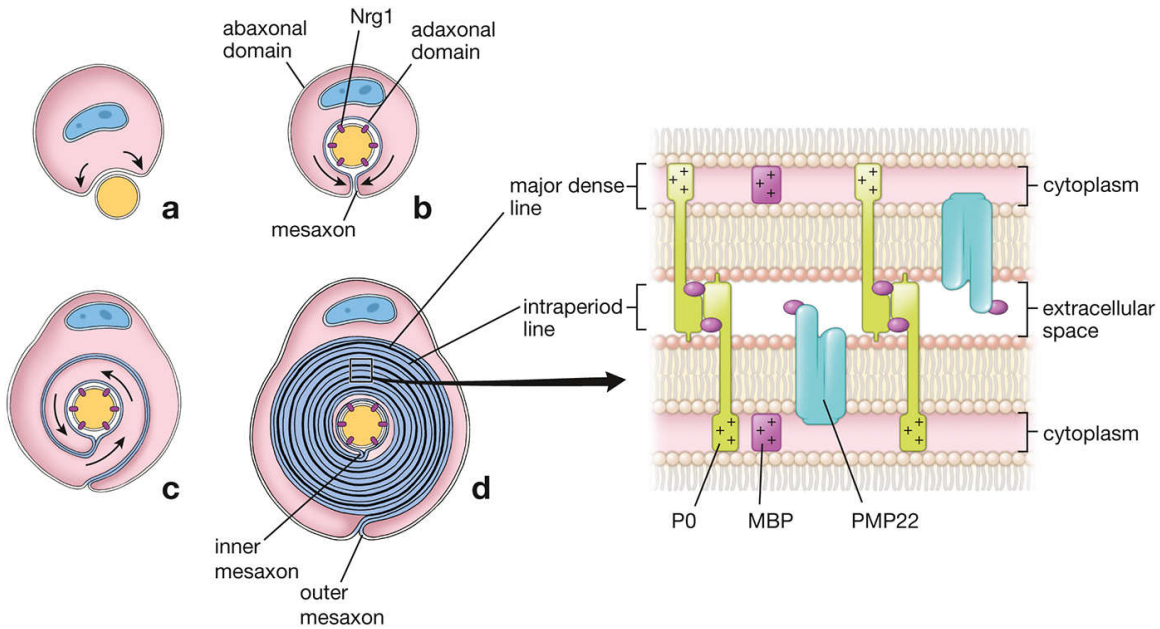


FIGURE 12.14. Diagram showing successive stages in the formation of myelin sheath by a Schwann cell. a. The axon initially lies in a groove on the surface of the immature Schwann cell. **b.** The axon is surrounded by a promyelinating Schwann cell. Note the two domains of the Schwann cell, the adaxonal plasma membrane domain and abaxonal plasma membrane domain. The mesaxon plasma membrane links these domains. The mesaxon membrane initiates myelination by surrounding the embedded axon. **c.** A sheet-like extension of the mesaxon membrane then wraps around the axon, forming multiple membrane layers. **d.** During the wrapping process, the cytoplasm is extruded from between the two apposing plasma membranes of the Schwann cell, which then become compacted to form myelin. The outer mesaxon represents the invaginated plasma membrane extending from the abaxonal surface of the Schwann cell to the myelin sheath. The inner mesaxon extends from the adaxonal surface of the Schwann cell (the part

facing the axon) to the innermost layer of the myelin sheath. The *inset* shows the major proteins responsible for compaction of the myelin sheath. *MBP*, myelin basic protein; *Nrg1*, neuregulin; *P0*, protein 0; *PMP22*, peripheral myelin protein of 22 kDa.

The myelin sheath develops from compacted layers of Schwann cell mesaxon wrapped concentrically around the axon.

Myelin sheath formation is initiated when the Schwann cell mesaxon surrounds the axon. A sheet-like extension of the mesaxon then wraps around the axon in a spiraling motion. The first few layers or **lamellae** of the spiral are not compactly arranged—that is, some cytoplasm is left in the first few concentric layers (Fig. 12.14c). The TEM reveals the presence of a 12-to 14-nm gap between the outer (extracellular) leaflets and the Schwann cell's cytoplasm that separates the inner (cytoplasmic) leaflets. As the wrapping progresses, cytoplasm is squeezed out from between the membrane of the concentric layers of the Schwann cell.

External to, and contiguous with, the developing myelin sheath is a thin **outer collar of perinuclear cytoplasm** called the **sheath of Schwann**. This part of the cell is enclosed by an abaxonal plasma membrane and contains the nucleus and most of the organelles of the Schwann cell. Surrounding the Schwann cell is a basal or external lamina. The apposition of the mesaxon of the last layer to itself as it closes the ring of the spiral produces the **outer mesaxon**, the narrow intercellular space adjacent to the external lamina. Internal to the concentric layers of the developing myelin sheath is a narrow **inner collar of Schwann cell cytoplasm** surrounded by the adaxonal plasma membrane. The narrow intercellular space between mesaxon membranes communicates with the adaxonal plasma membrane to produce the **inner mesaxon** (Fig. 12.14d).

Once the mesaxon spirals on itself, the 12-to 14-nm gaps disappear and the membranes form the compact **myelin sheath**. Compaction of the sheath corresponds with the expression of transmembrane **myelin-specific proteins**, such as **protein 0 (P0)**, a **peripheral myelin protein of 22 kDa (PMP22)**, and **myelin basic protein (MBP)**. The inner (cytoplasmic) leaflets of the plasma membrane come close together as a result of the positively charged cytoplasmic domains of P0 and MBP. With the TEM, these closely aligned inner leaflets are electron opaque, appearing as the **major dense lines** in the TEM image of myelin (see Fig. 12.14d). The concentric dense lamellae alternate with the slightly less dense **intraperiod lines** that are formed by closely apposed, but not fused, outer (extracellular) membrane leaflets. The narrow 2.5-nm gap corresponds to the remaining extracellular space containing the extracellular domains of P0 protein (see

Fig. 12.14d). P0 is a 30-kDa cell adhesion molecule expressed within the mesoaxial plasma membrane during myelination. This transmembrane glycoprotein mediates strong adhesions between the two opposite membrane layers and represents a key structural component of peripheral nerve myelin. Structural and genetic studies indicate that mutations in human genes encoding P0 produce unstable myelin and may contribute to the development of **demyelinating diseases** (see Folder 12.2).

FOLDER 12.2

CLINICAL CORRELATION: DEMYELINATING DISEASES

In general, **demyelinating diseases** are characterized by preferential damage to the myelin sheath. Clinical symptoms of these diseases are related to decreased or lost ability to transmit electrical impulses along nerve fibers. Several immune-mediated diseases affect the myelin sheath.

Guillain–Barré syndrome, also known as **acute inflammatory demyelinating polyradiculoneuropathy**, is one of the most common life-threatening diseases of the peripheral nervous system (PNS). Microscopic examination of nerve fibers obtained from patients affected by this disease shows a large accumulation of lymphocytes, macrophages, and plasma cells around nerve fibers within nerve fascicles. Large segments of the myelin sheath are damaged, leaving the axons exposed to the extracellular matrix. These findings are consistent with a T-cell–mediated immune response directed against myelin, which causes its destruction and slows or blocks nerve conduction. Patients exhibit symptoms of ascending muscle paralysis, loss of muscle coordination, and loss of cutaneous sensation.

Multiple sclerosis (MS) is a disease that attacks myelin in the central nervous system (CNS). MS is also characterized by immune-mediated damage to myelin, which becomes detached from the axon and is eventually destroyed. In addition, destruction of oligodendroglia, the cells responsible for the synthesis and maintenance of myelin, occurs. Myelin basic protein appears to be the major autoimmune target in this disease. Chemical changes in the lipid and protein constituents of myelin produce irregular, multiple **plaques** throughout the white matter of the brain. Symptoms of MS depend on the area in the CNS in which myelin is damaged. MS is usually characterized by distinct episodes of neurologic deficits, such as unilateral vision impairment, loss of cutaneous sensation, lack of muscle coordination and movement, and loss of bladder and bowel control.

Treatment of both diseases is related to diminishing the causative immune response by immunomodulatory therapy with interferon and monoclonal antibodies directed against specific molecular targets on

immune cells. For more severe, progressive forms, immunosuppressive drugs may be used.

The thickness of the myelin sheath at myelination is determined by axon diameter and not by the Schwann cell.

Myelination is an example of cell-to-cell communication in which the axon interacts with the Schwann cell. Experimental studies show that the number of layers of myelin is determined by the axon and not by the Schwann cell. Myelin sheath thickness is regulated by a glial growth factor (GGF) called **neuregulin (Ngr1)** that induces growth, differentiation, and migration of Schwann cells throughout their development. Ngr1 is a transmembrane protein expressed on the axolemma (cell membrane) of the axon.

The node of Ranvier represents the junction between two adjacent Schwann cells.

The myelin sheath is segmented because it is formed by numerous Schwann cells arrayed sequentially along the axon. The junction where two adjacent Schwann cells meet is devoid of myelin. This site is called the **node of Ranvier**. Therefore, the myelin between two sequential nodes of Ranvier is called an **internodal segment** (Plate 12.2, page 434). The node of Ranvier constitutes a region where the electrical impulse is regenerated for high-speed propagation down the axon. The highest density of voltage-gated Na^+ channels in the nervous system occurs at the node of Ranvier; their expression is regulated by interactions with the perinodal cytoplasm of Schwann cells.

Myelin is composed of about 80% lipids because, as the Schwann cell membrane winds around the axon, the cytoplasm of the Schwann cell, as noted, is extruded from between the opposing layers of the plasma membranes. Electron micrographs, however, typically show small amounts of cytoplasm in several locations (Figs. 12.15 and 12.16): the inner collar of Schwann cell cytoplasm, between the axon and the myelin; the **Schmidt–Lanterman clefts**, small islands within successive lamellae of the myelin; **perinodal cytoplasm**, at the node of Ranvier; and the outer collar of perinuclear cytoplasm, around the myelin (Fig. 12.17). These areas of cytoplasm are what light microscopists identified as the Schwann sheath.

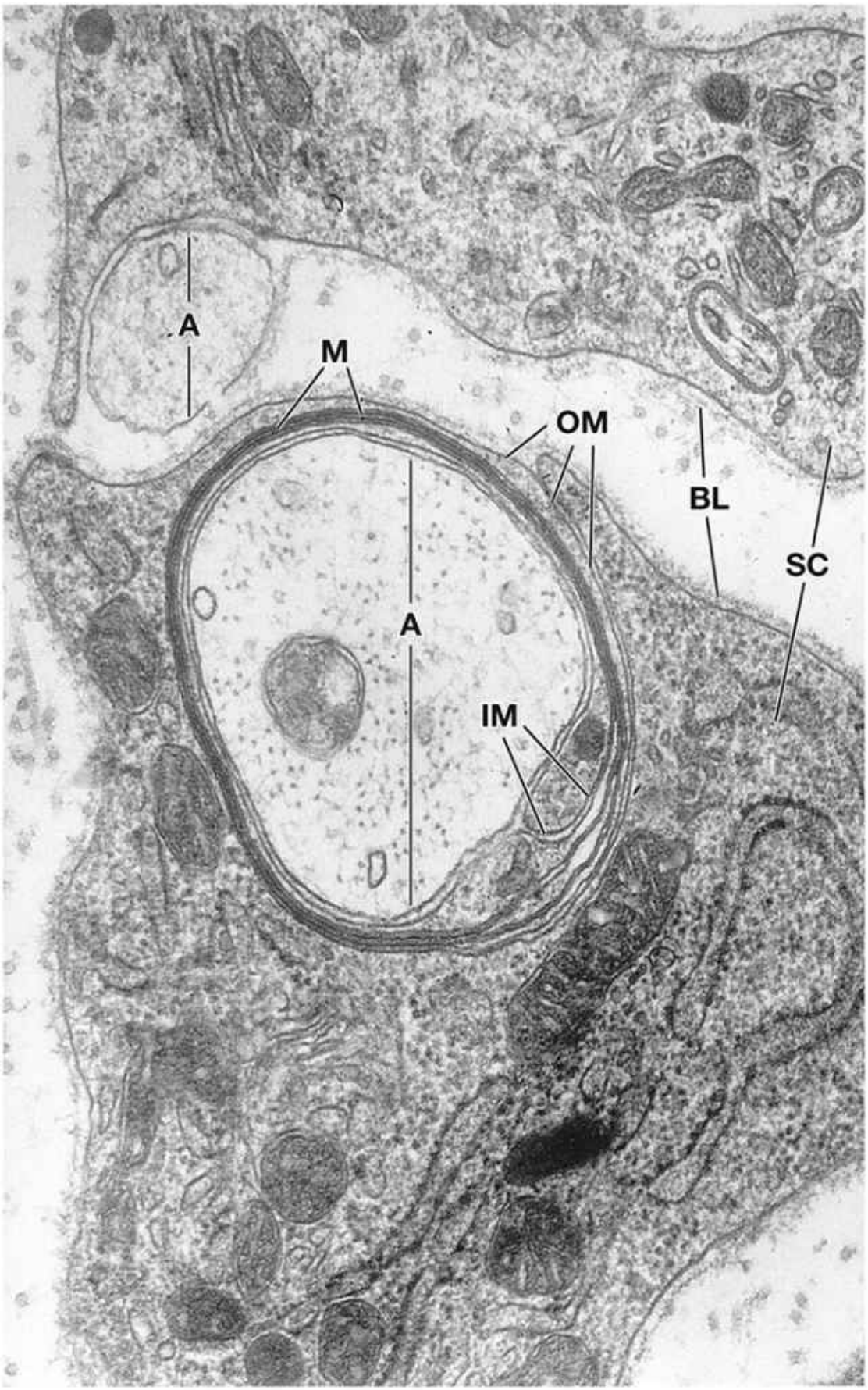

A
M
OM
BL
SC
A
IM

FIGURE 12.15. Electron micrograph of an axon in the process of myelination. At this stage of development, the myelin (*M*) sheath consists of about six membrane layers. The inner mesaxon (*IM*) and outer mesaxon (*OM*) of the Schwann cell (*SC*) represent parts of the mesaxon membrane. Another axon (see *upper left A*) is present that has not yet been embedded within an *SC* mesaxon. Other notable features include the *SC* basal (external) lamina (*BL*) and the considerable amount of Schwann cell cytoplasm associated with the myelination process. ×50,000. (Courtesy of Dr. Stephen G. Waxman.)

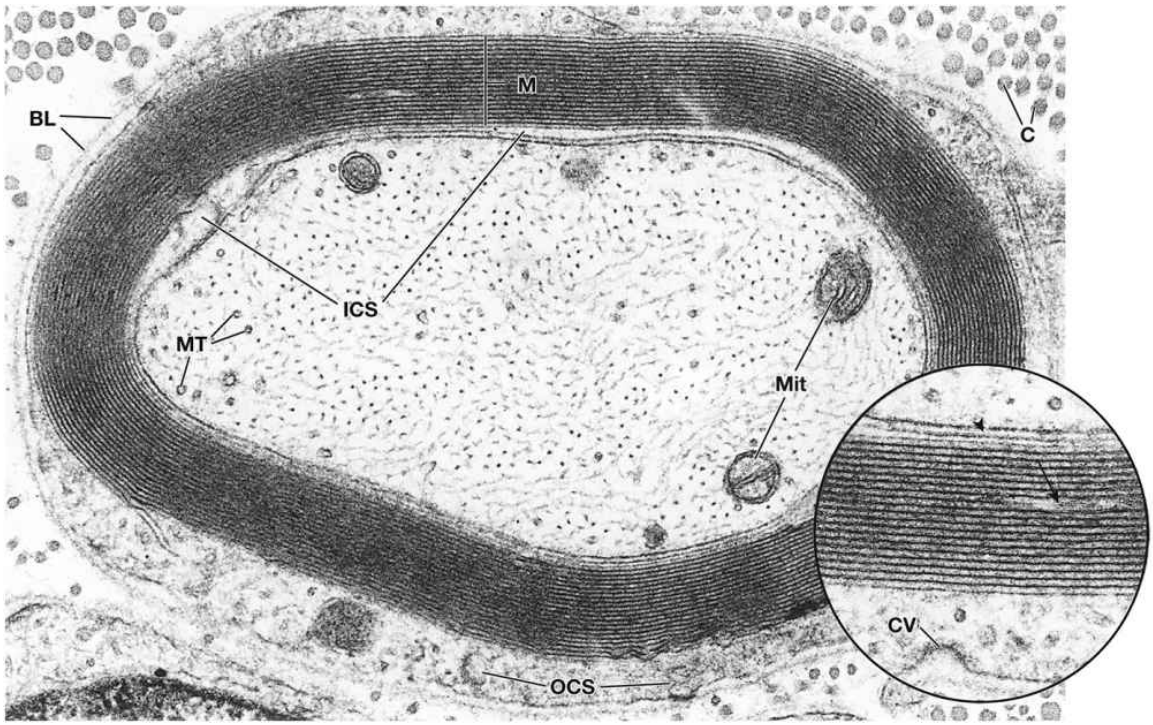


FIGURE 12.16. Electron micrograph of a mature myelinated axon. The myelin sheath (*M*) shown here consists of 19 paired layers of Schwann cell membrane. The pairing of membranes in each layer is caused by the extrusion of the Schwann cell's cytoplasm. The axon displays an abundance of neurofilaments, most of which have been cross-sectioned, giving the axon a stippled appearance. Also evident in the axon are microtubules (*MT*) and several mitochondria (*Mit*). The outer collar of Schwann cell's cytoplasm (*OCS*) is relatively abundant compared with the inner collar of Schwann cell's cytoplasm (*ICS*). The collagen fibrils (*C*) constitute the fibrillar component of the endoneurium. *BL*, basal (external) lamina. ×70,000. **Inset.** Higher magnification of the myelin. The *arrow* points to cytoplasm within the myelin that would contribute to the appearance of the Schmidt–Lanterman cleft as seen in the light microscope. It appears as an isolated region here because of the thinness of the section. The intercellular space between the axon and Schwann cell is indicated by the *arrowhead*. A coated vesicle (*CV*) in an early stage of formation appears in the outer collar of the Schwann cell cytoplasm. ×130,000. (Courtesy of Dr. George D. Pappas.)

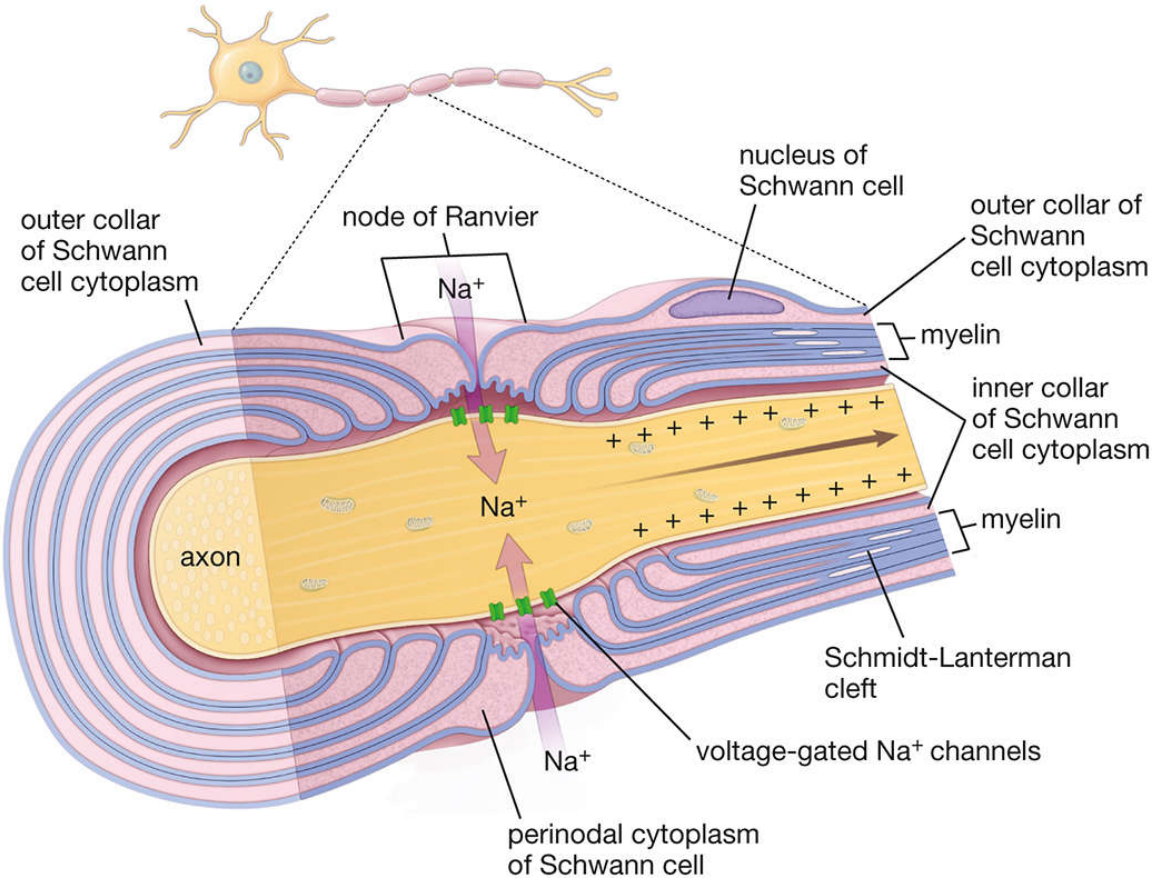


FIGURE 12.17. Diagram of the node of Ranvier and associated Schwann cells. This diagram shows a longitudinal section of the axon and its relationships to the myelin, cytoplasm of the Schwann cell, and node of Ranvier. Schwann cell's cytoplasm is present at four locations: the inner and the outer cytoplasmic collar of the Schwann cell, the nodes of Ranvier, and the Schmidt–Lanterman clefts. Note that the cytoplasm throughout the Schwann cell is continuous (see Fig. 12.18); it is not a series of cytoplasmic islands as it appears on the longitudinal section of the myelin sheath. The node of Ranvier is the site at which successive Schwann cells meet. The adjacent plasma membranes of the Schwann cells are not tightly apposed at the node, and extracellular fluid has free access to the neuronal plasma membrane. The node of Ranvier is also the site of depolarization of the neuronal plasma membrane during nerve impulse transmission and contains clusters of high-density, voltage-gated Na^+ channels.

However, if one conceptually unrolls the Schwann cell process, as shown in Fig. 12.18, its full extent can be appreciated, and the inner collar of Schwann cell cytoplasm can be seen to be continuous with the body of the Schwann cell through the Schmidt–Lanterman clefts and the perinodal cytoplasm. Cytoplasm of the clefts contains lysosomes and occasional mitochondria and microtubules, as well as cytoplasmic inclusions, or dense

bodies. The number of Schmidt–Lanterman clefts correlates with the diameter of the axon; larger axons have more clefts.

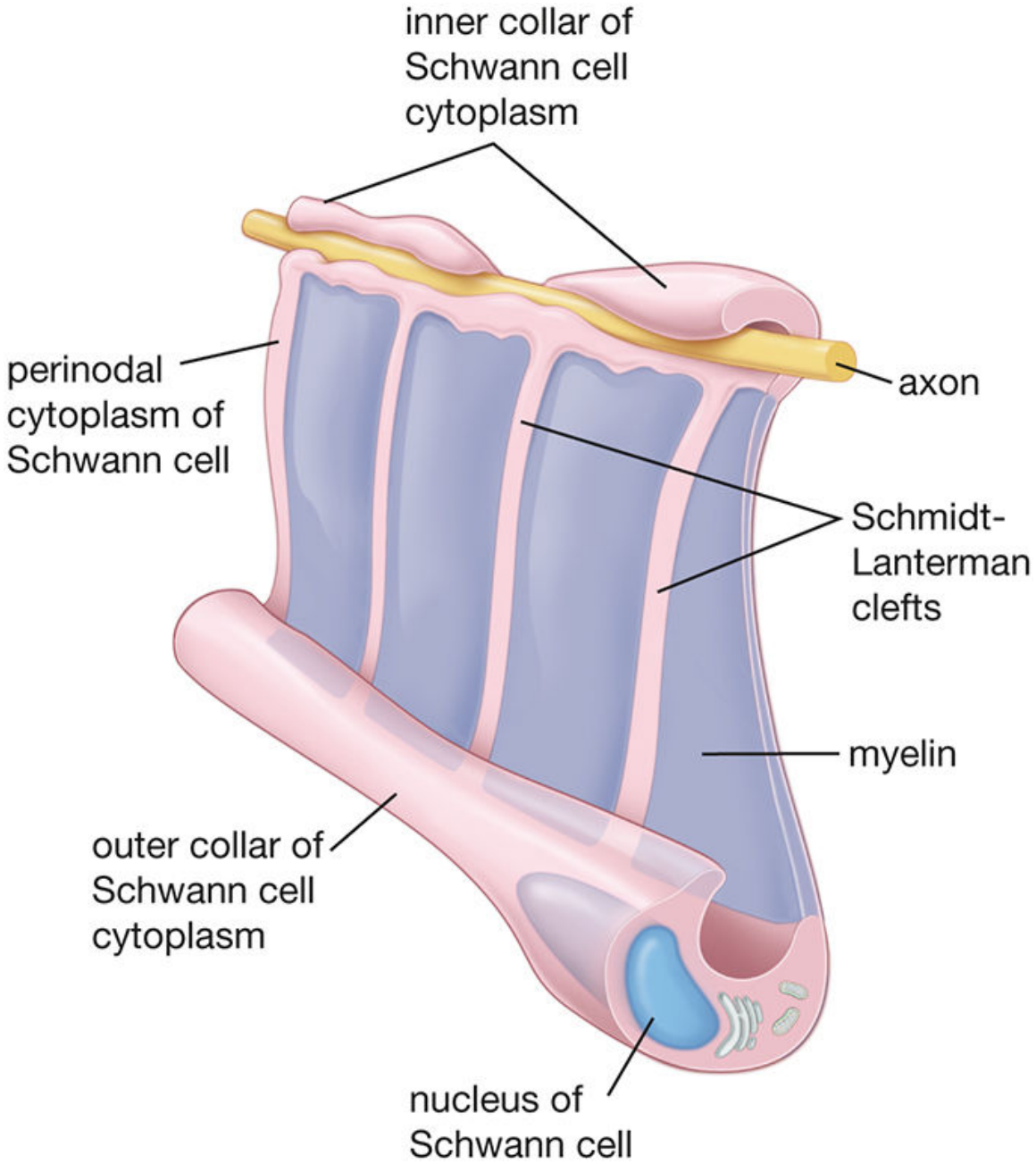


FIGURE 12.18. Three-dimensional diagram conceptualizing the relationship of myelin and cytoplasm of a Schwann cell. This diagram shows a hypothetically uncoiled Schwann cell. Note how the inner collar of the Schwann cell's cytoplasm is continuous with the outer collar of Schwann cell's cytoplasm via Schmidt–Lanterman clefts.

Unmyelinated axons in the peripheral nervous system are enveloped by nonmyelinating Remak Schwan cells and their external lamina.

The nerves in the PNS described as **unmyelinated** are nevertheless enveloped by **nonmyelinating Remak Schwann cell's** cytoplasm, as shown in Fig. 12.19, and can accommodate multiple small-diameter axons. The Remak Schwann cells are elongated in parallel to the long axis of the axons, and the axons fit into grooves on the cell surface. The lips of the groove may be open, exposing a portion of the axolemma of the axon to the adjacent external lamina of the Remak Schwann cell, or the lips may be closed, forming a mesaxon.

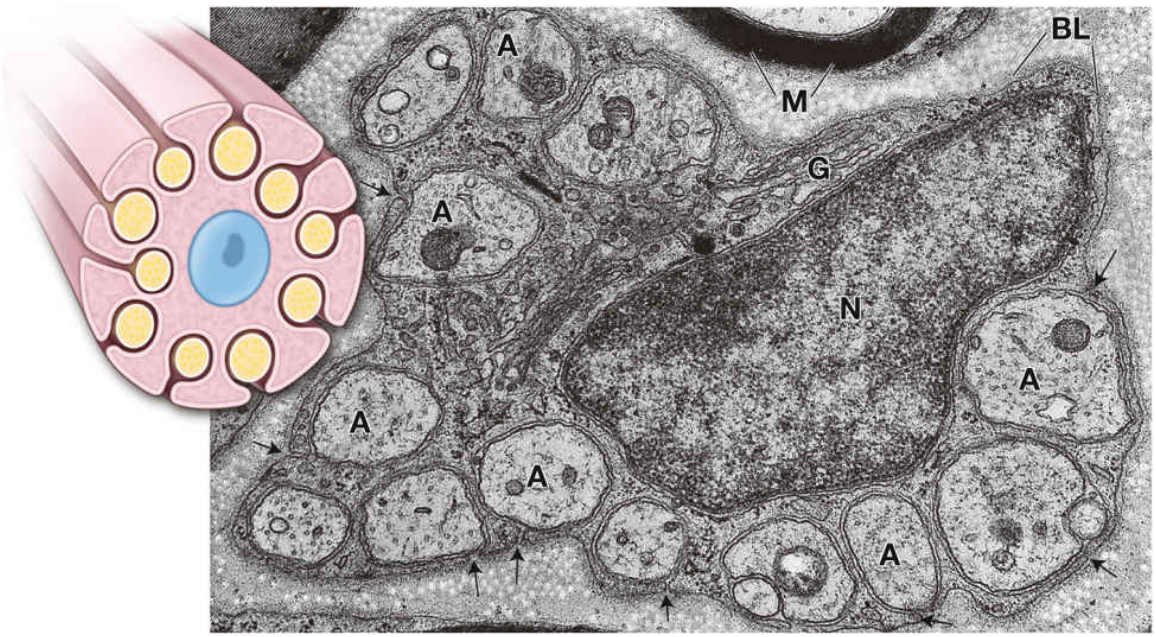


FIGURE 12.19. Electron micrograph of unmyelinated nerve fibers. The individual fibers or axons (*A*) are engulfed by the cytoplasm of a nonmyelinating Remak Schwann cell. The *arrows* indicate the site of mesaxons. In effect, each *A* is enclosed by the Remak Schwann cell's cytoplasm, except for the intercellular space of the mesaxon. Other features evident in the Remak Schwann cell are its nucleus (*N*), the Golgi apparatus (*G*), and the surrounding basal (external) lamina (*BL*). In the *upper part* of the micrograph, myelin (*M*) of two myelinated nerves is also evident. ×27,000. **Inset.** Schematic diagram showing the relationship of *A* engulfed by the Remak Schwann cell.

A single axon or a group of axons may be enclosed in a single invagination of the Remak Schwann cell surface. Large Remak Schwann cells in the PNS may have 20 or more grooves, each containing either one completely isolated axon (in the distal part of the nerve) or multiple axons (in the proximal part of the nerve close to ganglia). In the ANS, it is common for bundles of unmyelinated axons to occupy a single groove. Because they form bundles within the Remak Schwann cell's cytoplasm,

unmyelinated nerves are often called **Remak bundles**. An interesting feature of unmyelinated nerve fibers has been observed in which axons may switch their position between neighboring Remak bundles along the nerve.

Satellite Cells

The neuronal cell bodies of ganglia are surrounded by a layer of small cuboidal cells called **satellite cells**. Although they form a complete layer around the cell body, only their nuclei are typically visible in routine H&E preparations (Fig. 12.20a and b). In paravertebral and peripheral ganglia, neural cell processes must penetrate between the satellite cells to establish a synapse (there are no synapses in sensory ganglia). They help to establish and maintain a controlled microenvironment around the neuronal body in the ganglion, providing electrical insulation as well as a pathway for metabolic exchanges. Thus, the functional role of the satellite cell is analogous to that of the Schwann cell, except that it does not make myelin.

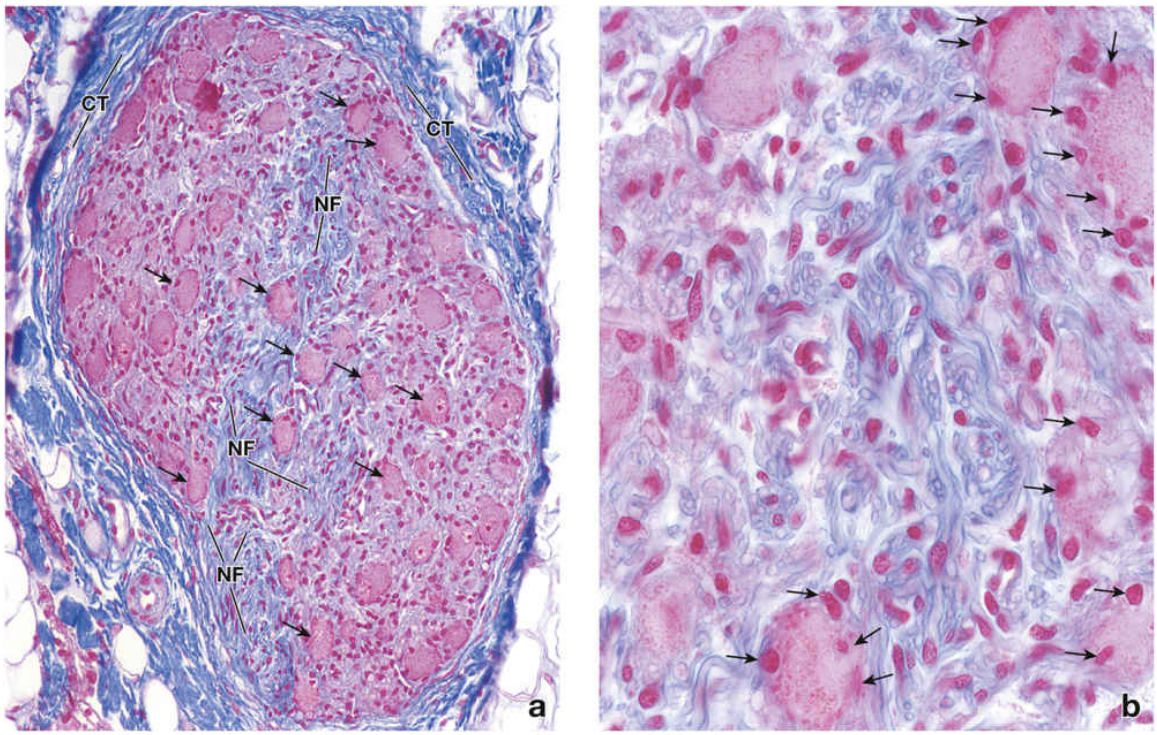


FIGURE 12.20. Photomicrograph of a nerve ganglion. a. Photomicrograph showing a ganglion stained by the Mallory–Azan method. Note the large nerve cell bodies (*arrows*) and nerve fibers (*NF*) in the ganglion. Satellite cells are represented by the very small nuclei at the periphery of the neuronal cell bodies. The ganglion is surrounded by a dense irregular connective tissue capsule (*CT*) that is comparable to, and continuous with, the epineurium of the nerve. ×200. **b.** Higher magnification of the ganglion showing individual axons and a few neuronal cell bodies with

their satellite cells (*arrows*). The nuclei in the region of the axons are mostly Schwann cell's nuclei. ×640.

Enteric Neuroglial Cells

Neurons and their processes located within ganglia of the enteric division of the ANS are associated with **enteric neuroglial cells**. These cells are morphologically and functionally similar to **astrocytes** in the CNS (see later). Enteric neuroglial cells share common functions with astrocytes, such as structural, metabolic, and protective support of neurons. However, recent studies indicate that enteric glial cells may also participate in enteric neurotransmission and help coordinate activities of the nervous and immune systems of the gut.

Central Neuroglia

There are four types of central neuroglia:

- **Astrocytes** are morphologically heterogeneous cells that provide physical and metabolic support for neurons of the CNS.
- **Oligodendrocytes** are small cells that are active in the formation and maintenance of myelin in the CNS.
- **Microglia** are inconspicuous cells with small, dark, elongated nuclei that possess phagocytotic properties.
- **Ependymal cells** are columnar cells that line the ventricles of the brain and the central canal of the spinal cord.

Only the nuclei of glial cells are seen in routine histologic preparations of the CNS. Heavy metal staining or immunocytochemical methods are necessary to demonstrate the shape of the entire glial cell.

Although **glial cells** have long been described as supporting cells of nerve tissue in the purely physical sense, current concepts emphasize the **functional interdependence** of neuroglial cells and **neurons**. The most obvious example of physical support occurs during development. The brain and spinal cord develop from the **embryonic neural tube**. In the head region, the neural tube undergoes remarkable thickening and folding, leading ultimately to the final structure, the brain. During the early stages of the process, embryonic glial cells extend through the entire thickness of the neural tube in a radial manner. These **radial glial** cells serve as the physical scaffolding that directs the migration of neurons to their appropriate position in the brain.

Astrocytes are closely associated with neurons to support and modulate their activities.

Astrocytes are the largest of the neuroglial cells. They form a network of cells within the CNS and communicate with neurons to support and modulate many of their activities. Some astrocytes span the entire thickness of the brain, providing a scaffold for migrating neurons during brain development. Other astrocytes stretch their processes from blood vessels to neurons. The ends of the processes expand, forming end-feet that cover large areas of the outer surface of the vessel or axolemma. Recently, it has been shown that **reactive astrocytes** possess **phagocytic ability** and are involved in eliminating parts of live neurons such as synapses, nerve cell processes, as well as neuronal debris in the developing and injured brain. During brain development, neurons generate excess synapses. Astrocytic phagocytosis selectively eliminates these unnecessary synapses to achieve precise neural connectivity. Although astrocytes do not form myelin, they provide a compensatory mechanism to clear myelin debris after nerve cell injury if microglia (the primary phagocytic cells in the brain) are unable to execute phagocytosis (see page 413).

Two kinds of astrocytes are identified:

- **Protoplasmic astrocytes** are more prevalent in the outermost covering of the brain called *gray matter*. These astrocytes have numerous short, branching cytoplasmic processes (Fig. 12.21). Fine processes of a single protoplasmic astrocyte form an extensive network interacting with up to two million synapses in humans, allowing the gray matter to relay information at neuronal synapses. They also contribute to neurotransmitter, ion, and energy homeostasis.

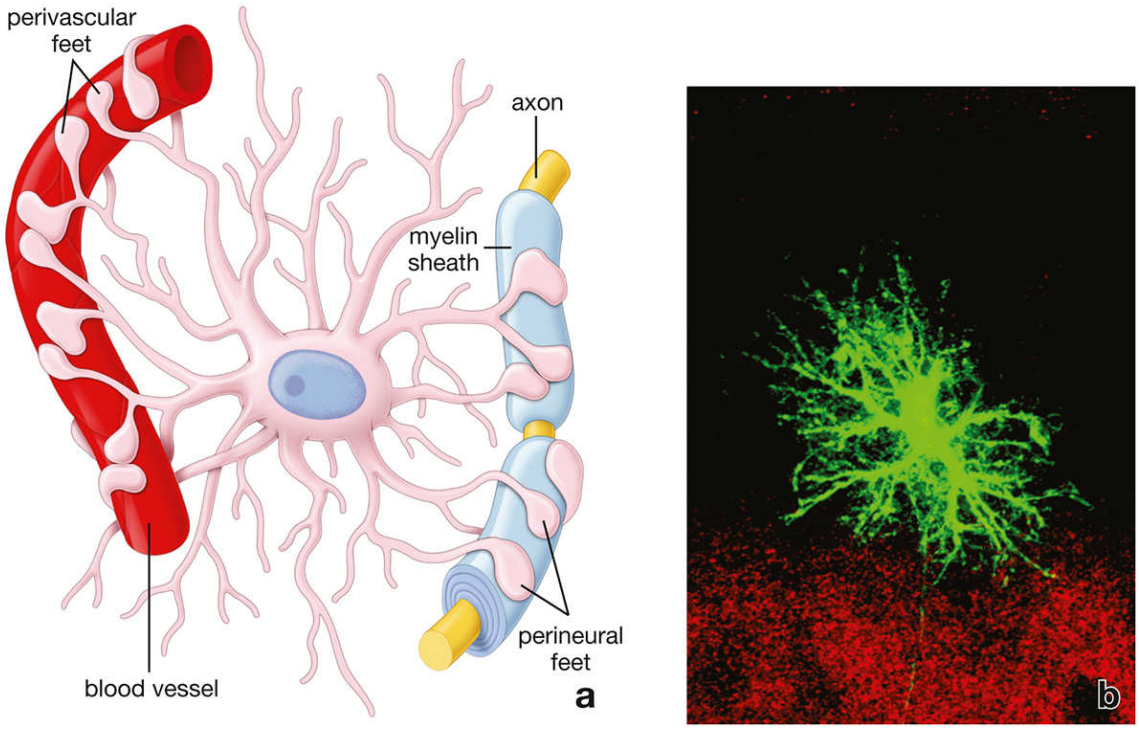


FIGURE 12.21. Protoplasmic astrocyte in the gray matter of the brain. **a.** This schematic drawing shows the foot processes of a protoplasmic astrocyte terminating on a blood vessel and the axonal process of a nerve cell. The foot processes terminating on the blood vessel contribute to the blood–brain barrier. The bare regions of the vessel as shown in the drawing would be covered by processes of neighboring astrocytes, thus forming the overall barrier. **b.** This laser scanning confocal image of a protoplasmic astrocyte in the gray matter of the dentate gyrus was visualized by intracellular labeling method. In lightly fixed tissue slices, selected astrocytes were impaled and iontophoretically injected with fluorescent dye (Alexa Fluor 568) using pulses of negative current. Note the density and spatial distribution of cell processes. ×480. (Reprinted with permission from Bushong EA, Martone ME, Ellisman MH. Examination of the relationship between astrocyte morphology and laminar boundaries in the molecular layer of adult dentate gyrus. *J Comp Neurol*. 2003;462:241–251.)

- **Fibrous astrocytes** are more common in the inner core of the brain called *white matter*. These astrocytes have fewer, longer, relatively straight, and less branched processes (Fig. 12.22). In the white matter, electrical impulses are mainly propagated along the axons (most often myelinated), with little information processing. The processes of fibrous astrocytes run along axons throughout the white matter and make contact with axons only at the node of Ranvier.

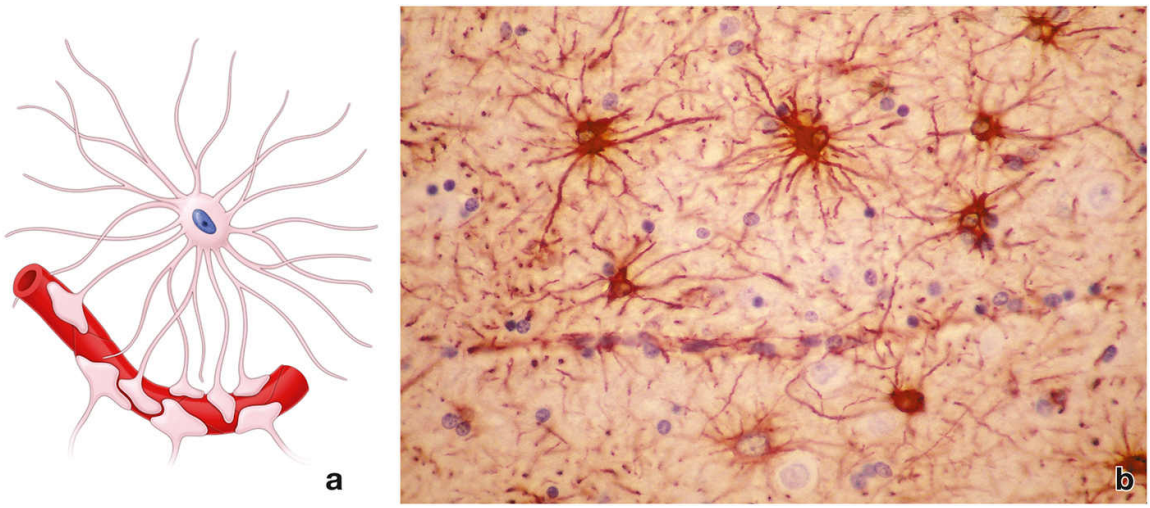


FIGURE 12.22. Fibrous astrocytes in the white matter of the brain. a. Schematic drawing of a fibrous astrocyte in the white mater of the brain. **b.** Photomicrograph of the white matter of the brain showing the extensive radiating cytoplasmic processes for which astrocytes are named. They are best visualized, as shown here, with immunostaining methods that use antibodies against glial fibrillary acidic protein (GFAP). ×220. (Reprinted with permission from Fuller GN, Burger PC. Central nervous system. In: Sternberg SS, ed. *Histology for Pathologists*. Lippincott-Raven; 1997.)

Both types of astrocytes contain prominent bundles of intermediate filaments composed of **glial fibrillary acidic protein (GFAP)**. The filaments are much more numerous in the fibrous astrocytes, however, hence the name. Antibodies to GFAP are used as specific stains to identify astrocytes in sections and tissue cultures (see Fig. 12.22b). Tumors arising from fibrous astrocytes, **fibrous astrocytomas**, account for about 80% of adult primary brain tumors. They can be identified microscopically and by their **GFAP specificity**.

Astrocytes play important roles in the movement of metabolites and wastes to and from neurons. They help maintain the tight junctions of the capillaries that form the **blood–brain barrier** (see pages 424-425). In addition, astrocytes provide a covering for the "bare areas" of myelinated axons—for example, at the nodes of Ranvier and synapses. They may confine neurotransmitters to the synaptic cleft and remove excess neurotransmitters by pinocytosis. **Protoplasmic astrocytes** on the brain and spinal cord surfaces extend their processes (subpial feet) to the basal lamina of the pia mater to form the **glia limitans**, a relatively impermeable barrier surrounding the CNS (Fig. 12.23).

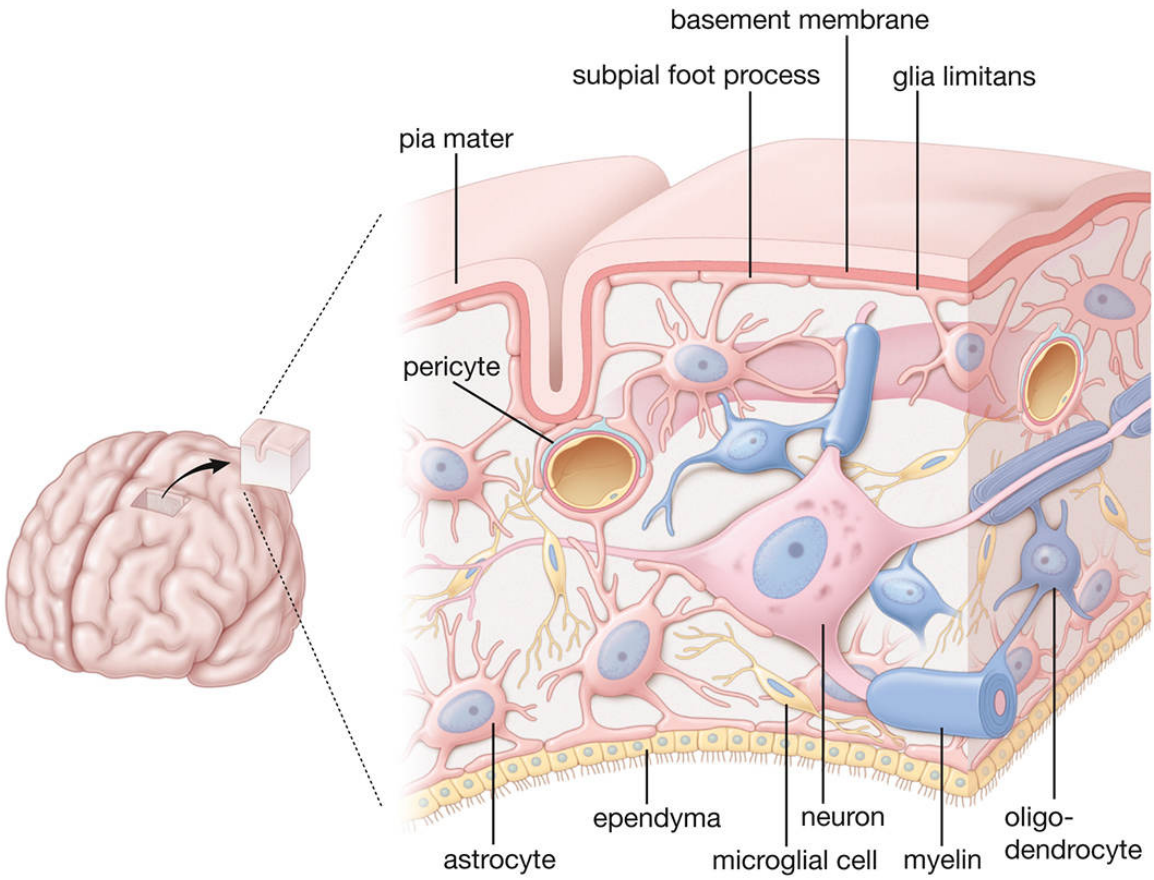


FIGURE 12.23. Distribution of glial cells in the brain. This diagram shows the four types of glial cells—astrocytes, oligodendrocytes, microglial cells, and ependymal cells—interacting with several structures and cells found in the brain tissue. Note that the astrocytes and their processes interact with the blood vessels as well as with axons and dendrites. Astrocytes also send their processes toward the brain surface, where they contact the basement membrane of the pia mater, forming the glia limitans. In addition, processes of astrocytes extend toward the fluid-filled spaces in the central nervous system (CNS), where they contact the ependymal lining cells. Oligodendrocytes are involved in myelination of the nerve fibers in the CNS. Microglia exhibit phagocytotic functions.

Astrocytes modulate neuronal activities by buffering the K^+ concentration in the extracellular space of the brain.

It is now generally accepted that astrocytes **regulate K^+ concentrations** in the brain's extracellular compartment, thus maintaining the microenvironment and modulating the activities of the neurons. The astrocyte plasma membrane contains an abundance of K^+ pumps and K^+ channels that mediate the transfer of K^+ ions from areas of high to low concentration. Accumulation of large amounts of intracellular K^+ in astrocytes decreases local extracellular K^+ gradients. The astrocyte membrane becomes depolarized, and the charge is dissipated over a large

area by the extensive network of astrocyte processes. The maintenance of the K^+ concentration in the brain's extracellular space by astrocytes is called **potassium spatial buffering**.

Oligodendrocytes produce and maintain the myelin sheath in the CNS.

The **oligodendrocyte** is the cell responsible for producing CNS myelin. The myelin sheath in the CNS is formed by concentric layers of oligodendrocyte plasma membrane. The formation of the sheath in the CNS is more complex, however, than the simple wrapping of Schwann cell's mesaxon membranes that occurs in the PNS (pages 405-407).

Oligodendrocytes appear in specially stained LM preparations as small cells with relatively few processes compared with astrocytes. They are often aligned in rows between the axons. Each oligodendrocyte gives off several tongue-like processes that make contact with nearby axons. Each process wraps itself around a portion of an axon, forming an **internodal segment of myelin**. The multiple processes of a single oligodendrocyte may myelinate one axon or several nearby axons (Fig. 12.24). The nucleus-containing region of the oligodendrocyte may be at some distance from the axons it myelinates.

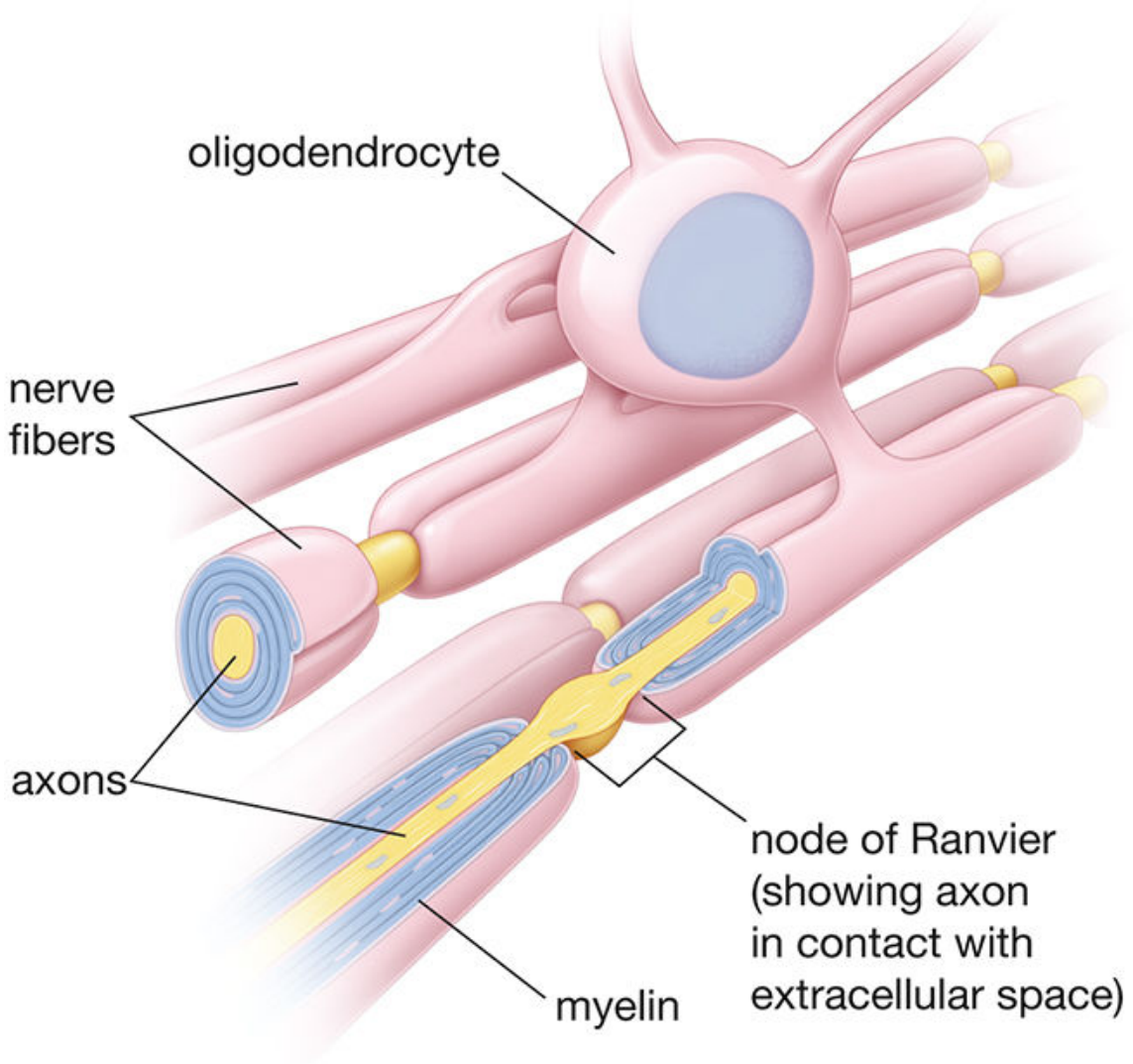


FIGURE 12.24. Three-dimensional view of an oligodendrocyte as it relates to several axons. Cytoplasmic processes from the oligodendrocyte cell body form flattened cytoplasmic sheaths that wrap around each of the axons. The relationship of cytoplasm and myelin is essentially the same as that of Schwann cells.

Because a single oligodendrocyte may myelinate several nearby axons simultaneously, the cell cannot embed multiple axons in its cytoplasm and allow the mesaxon membrane to spiral around each axon. Instead, each tongue-like process appears to spiral around the axon, always staying in proximity to it, until the myelin sheath is formed.

The myelin sheath in the CNS differs from that in the PNS.

There are several other important differences between the myelin sheaths in the CNS and those in the PNS. Oligodendrocytes in the CNS express different myelin-specific proteins during myelination than those expressed by Schwann cells in the PNS. Instead of P0 and PMP22, which are

expressed only in myelin of the PNS, other proteins, including **proteolipid protein (PLP)**, **myelin oligodendrocyte glycoprotein (MOG)**, and **oligodendrocyte myelin glycoprotein (OMgp)**, perform similar functions in CNS myelin. Deficiencies in the expression of these proteins appear to be important in the pathogenesis of several autoimmune **demyelinating diseases** of the CNS.

On the microscopic level, myelin in the CNS exhibits fewer Schmidt–Lanterman clefts because the astrocytes provide metabolic support for CNS neurons. Unlike Schwann cells of the PNS, oligodendrocytes do not have an external lamina. Furthermore, because of the manner in which oligodendrocytes form CNS myelin, little or no cytoplasm may be present in the outermost layer of the myelin sheath, and with the absence of external lamina, the myelin of adjacent axons may come into contact. Thus, where myelin sheaths of adjacent axons touch, they may share an intraperiod line. Finally, the nodes of Ranvier in the CNS are larger than those in the PNS. The larger areas of exposed axolemma thus make **saltatory conduction** (see later) even more efficient in the CNS.

Another difference between the CNS and the PNS in regard to the relationships between supporting cells and neurons is that unmyelinated neurons in the CNS are often found to be bare—that is, they are not embedded in glial cell processes. The lack of supporting cells around unmyelinated axons as well as the absence of basal lamina material and connective tissue within the substance of the CNS helps to distinguish the CNS from the PNS in histologic sections and TEM specimens.

Microglia possess phagocytotic properties.

Microglia are phagocytotic cells. They normally account for about 5% of all glial cells in the adult CNS but proliferate and become actively phagocytotic (**reactive microglial cells**) in regions of injury and disease. Microglial cells are considered part of the mononuclear phagocyte system (see Folder 6.4, page 203) and originate from erythro-myeloid progenitor cells in the yolk sac. Microglia precursor cells migrate to developing CNS during the embryonic and perinatal stages of development (see page 415). In the past, microglia have been regarded as the primary phagocytic cells in the brain. However, recent evidence shows that astrocytic phagocytosis provides a compensatory mechanism for microglial dysfunction. Similar to astrocytes, microglial cells are involved in synaptic pruning, a process that forms the cellular basis for learning and memory, especially during brain development and brain injury (see page 410). Recent evidence suggests that microglia play a critical role in **defense against invading microorganisms** and neoplastic cells. They remove bacteria, injured cells, and the debris of cells that undergo apoptosis. They also

mediate neuroimmune reactions, such as those occurring in chronic pain conditions.

Microglia are the smallest of the neuroglial cells and have relatively small, elongated nuclei (Fig. 12.25). When stained with heavy metals, microglia exhibit short, twisted processes. Both the processes and the cell body are covered with numerous spikes. The spikes may be the equivalent of the ruffled border seen on other phagocytotic cells. The TEM reveals numerous lysosomes, inclusions, and vesicles. However, microglia contain little rER and few microtubules or actin filaments.

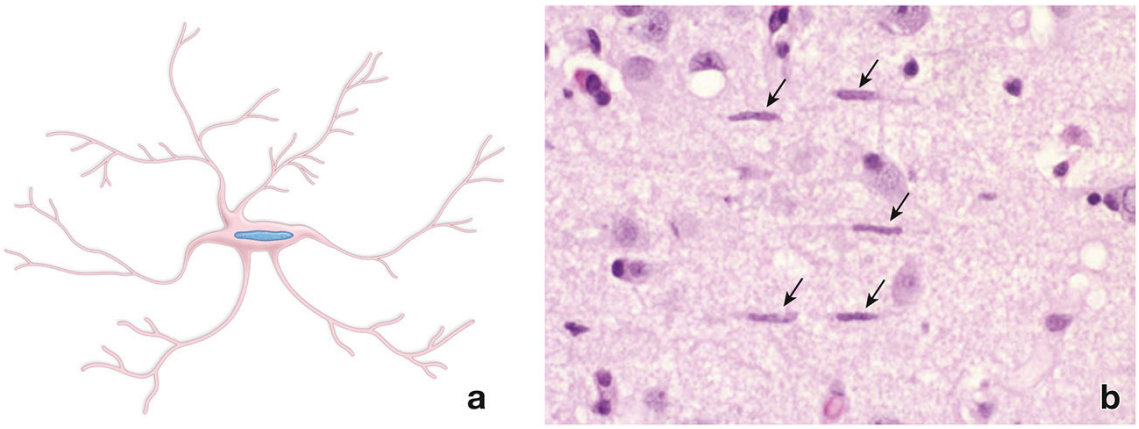


FIGURE 12.25. Microglial cell in the gray matter of the brain. a. This diagram shows the shape and characteristics of a microglial cell. Note the elongated nucleus and relatively few processes emanating from the body. **b.** Photomicrograph of microglial cells (*arrows*) showing their characteristic elongated nuclei. The specimen was obtained from an individual with diffuse microgliosis. In this condition, the microglial cells are present in large numbers and are readily visible in a routine hematoxylin and eosin (H&E) preparation. ×420. (Reprinted with permission from Fuller GN, Burger PC. Central nervous system. In: Sternberg SS, ed. *Histology for Pathologists*. Lippincott-Raven; 1997.)

Ependymal cells form the epithelial-like lining of the ventricles of the brain and spinal canal.

Ependymal cells form the epithelium-like lining of the fluid-filled cavities of the CNS. They form a single layer of cuboidal-to-columnar cells that have the morphologic and physiologic characteristics of fluid-transporting cells (Fig. 12.26). They are tightly bound by junctional complexes located at the apical surfaces. Unlike a typical epithelium, ependymal cells lack an external lamina. At the TEM level, the basal cell surface exhibits numerous infoldings that interdigitate with adjacent astrocyte processes. The apical

surface of the cell possesses cilia and microvilli. The latter are involved in absorbing cerebrospinal fluid (CSF).

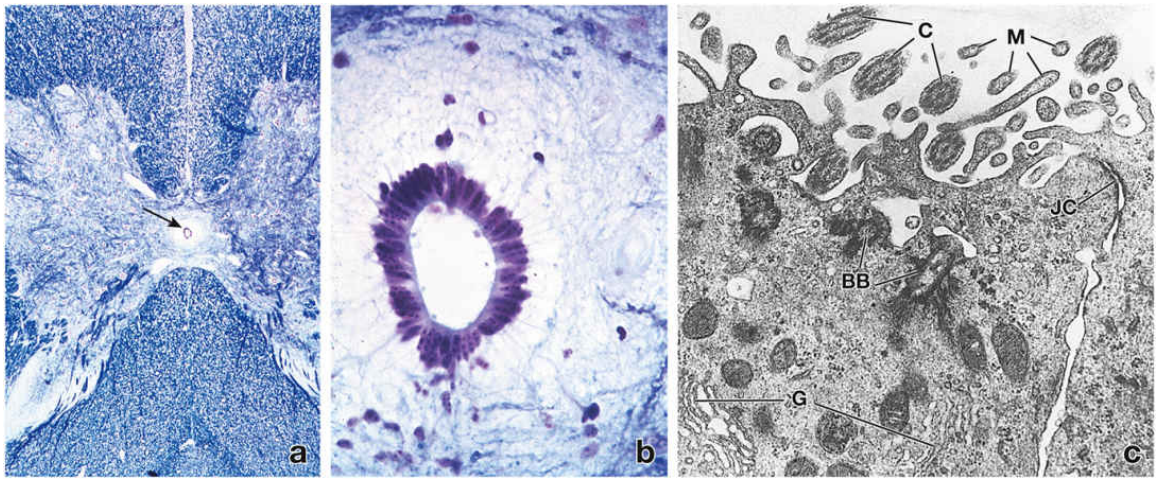


FIGURE 12.26. Ependymal lining of the spinal canal. a. Photomicrograph of the central region of the spinal cord stained with toluidine blue. The *arrow* points to the central canal. ×20. **b.** At higher magnification, ependymal cells, which line the central canal, can be seen to consist of a single layer of columnar cells. ×340. (Courtesy of Dr. George D. Pappas.) **c.** Transmission electron micrograph showing a portion of the apical region of two columnar ependymal cells. They are joined by a junctional complex (*JC*) that separates the lumen of the canal from the lateral intercellular space. The apical surface of the ependymal cells has both cilia (*C*) and microvilli (*M*). Basal bodies (*BB*) and a Golgi apparatus (*G*) within the apical cytoplasm are also visible. ×20,000. (Courtesy of Dr. Paul Reier.)

Tanycytes are specialized types of ependymal cells. They are most numerous in the floor of the third ventricle. The free surface of tanycytes is in direct contact with CSF, but in contrast to the ependymal cells, they do not possess cilia. The cell body of tanycytes gives rise to a long process that projects into the brain parenchyma. Their role remains unclear; however, they are involved in the transport of substances from the CSF to the blood within the portal circulation of the hypothalamus. Tanycytes are sensitive to glucose concentration; therefore, they may be involved in detecting and responding to changes in energy balance as well as in monitoring other circulating metabolites in the CSF.

Within the **system of brain ventricles**, the epithelium-like lining is further modified to produce the CSF by transport and secretion of materials derived from adjacent capillary loops. The modified ependymal cells and associated capillaries are called the **choroid plexus**.

Impulse Conduction

An action potential is an electrochemical process triggered by impulses carried to the axon hillock after other impulses are received on the dendrites or the cell body itself.

A **nerve impulse** is conducted along an axon much as a flame travels along the fuse of a firecracker. This electrochemical process involves the generation of an **action potential**, a wave of membrane depolarization that is initiated at the initial segment of the axon hillock. Its membrane contains a large number of **voltage-gated Na^+ and K^+ channels**. In response to a stimulus, voltage-gated Na^+ channels in the initial segment of the axon membrane open, causing an influx of Na^+ into the axoplasm. This influx of Na^+ briefly reverses (depolarizes) the negative membrane potential of the resting membrane (–70 mV) to positive (+30 mV). After depolarization, the voltage-gated Na^+ channels close and voltage-gated K^+ channels open. K^+ rapidly exits the axon, returning the membrane to its resting potential. Depolarization of one part of the membrane sends electrical current to neighboring portions of unstimulated membrane, which is still positively charged. This local current stimulates adjacent portions of the axon's membrane and repeats depolarization along the membrane. The entire process takes less than 1,000th of a second. After a very brief (refractory) period, the neuron can repeat the process of generating an action potential once again.

Rapid conduction of the action potential is attributable to the nodes of Ranvier.

Myelinated axons conduct impulses more rapidly than unmyelinated axons. Physiologists describe the nerve impulse as "jumping" from node to node along the myelinated axon. This process is called **saltatory** *[L. saltus, to jump]* or **discontinuous conduction**. In myelinated nerves, the myelin sheath around the nerve does not conduct an electric current and forms an insulating layer around the axon. However, the voltage reversal can *only* occur at the nodes of Ranvier, where the axolemma lacks a myelin sheath. Here, the axolemma is exposed to extracellular fluids and possesses a high concentration of voltage-gated Na^+ and K^+ channels (see Figs. 12.17 and 12.24). Thus, the voltage reversal (and thus the impulse) jumps as current flows from one node of Ranvier to the next. The speed of saltatory conduction is related not only to the thickness of the myelin but also to the diameter of the axon. Conduction is more rapid along axons of greater diameter.

In **unmyelinated axons**, Na^+ and K^+ channels are distributed uniformly along the length of the fiber. The nerve impulse is conducted more slowly and moves as a continuous wave of voltage reversal along the axon.

■ ORIGIN OF NERVE TISSUE CELLS

CNS neurons and central glia, except microglial cells, are derived from neuroectodermal cells of the neural tube.

Neurons, oligodendrocytes, astrocytes, and ependymal cells are derived from cells of the **neural tube**. After developing neurons have migrated to their predestined locations in the neural tube and have differentiated into mature neurons, they no longer divide. However, in the adult mammalian brain, a very small number of **neural stem cells** retain the ability to divide. These cells migrate into the sites of injury and differentiate into fully functional nerve cells.

Oligodendrocyte precursors are highly migratory cells. They appear to share a developmental lineage with motor neurons migrating from their site of origin to developing axonal projections (tracts) in the white matter of the brain or spinal cord. The precursors then proliferate in response to the local expression of mitogenic signals. The matching of oligodendrocytes to axons is accomplished through a combination of local regulation of cell proliferation, differentiation, and apoptosis.

Astrocytes are also derived from cells of the neural tube. During the embryonic and early postnatal stages, immature astrocytes migrate into the cortex, where they differentiate and become mature astrocytes. **Ependymal cells** are derived from the proliferation of neuroepithelial cells that immediately surround the canal of the developing neural tube.

In contrast to other central neuroglia, **microglia cells** are derived from mesodermal macrophage precursors, specifically from **erythro-myeloid progenitor cells** in the yolk sac. They infiltrate the neural tube in the early stages of its development and under the influence of growth factors such as colony-stimulating factor 1 (CSF-1) produced by developing neural cells as they undergo proliferation and differentiation into motile amoeboid cells. These motile cells are commonly observed in the developing brain. As the only glial cells of mesenchymal origin, microglia possess the **vimentin class of intermediate filaments**, which can be useful in identifying these cells with immunocytochemical methods.

PNS ganglion cells and peripheral glia are derived from the neural crest.

The development of the **ganglion cells** of the PNS involves the proliferation and migration of ganglion precursor cells from the **neural crest** to their future ganglionic sites, where they undergo further proliferation. Here, the cells develop processes that reach the cells' target tissues (e.g., glandular tissue or smooth muscle cells) and sensory territories. Initially, more cells are produced than are needed. Those that do not make functional contact with a target tissue undergo apoptosis.

Schwann cells also arise from migrating neural crest cells that become associated with the axons of early embryonic nerves. Several genes have been implicated in Schwann cell development. Sex-determining region Y (SRY) box 10 (*Sox10*) is required for the generation of all peripheral glia from neural crest cells. Axon-derived neuregulin-1 (*Nrg-1*) sustains the **Schwann cell precursors** that undergo differentiation and divide along the growing nerve processes. The fate of all immature Schwann cells is determined by the nerve processes with which they have immediate contact. Immature Schwann cells that associate with large-diameter axons mature into myelinating Schwann cells, whereas those that associate with small-diameter axons mature into nonmyelinating cells.

■ ORGANIZATION OF THE PERIPHERAL NERVOUS SYSTEM

The **peripheral nervous system (PNS)** consists of peripheral nerves with specialized nerve endings and ganglia-containing nerve cell bodies that reside outside the CNS.

Peripheral Nerves

A peripheral nerve is a bundle of nerve fibers held together by connective tissue.

The nerves of the PNS are made up of many nerve fibers that carry sensory and motor (effector) information between the organs and tissues of the body and between the brain and spinal cord. The term **nerve fiber** is used in different ways that can be confusing. It can connote the axon with all of its coverings (myelin and Schwann cell), as used earlier, or it can connote the axon alone. It is also used to refer to any process of a nerve cell, either dendrite or axon, especially if insufficient information is available to identify the process as either an axon or a dendrite.

The cell bodies of peripheral nerves may be located either within the CNS or outside the CNS in **peripheral ganglia**. Ganglia contain clusters of

neuronal cell bodies and the nerve fibers leading to and from them (see Fig. 12.20). The cell bodies in the dorsal root ganglia as well as ganglia of cranial nerves belong to sensory neurons (**somatic afferents** and **visceral afferents** that belong to the ANS discussed earlier), whose distribution is restricted to specific locations (Table 12.2 and Fig. 12.3). The cell bodies in the paravertebral, prevertebral, and terminal ganglia belong to postsynaptic "motor" neurons (**visceral efferents**) of the ANS (see Table 12.1 and Fig. 12.20).

TABLE 12.2 **Peripheral Ganglia**[a]

Ganglia that contain cell bodies of sensory neurons; these are not synaptic stations

- **Dorsal root ganglia of all spinal nerves**
- **Sensory ganglia of cranial nerves**
  - Trigeminal (semilunar, Gasserian) ganglion of the trigeminal (V) nerve
  - Geniculate ganglion of the facial (VII) nerve
  - Spiral ganglion (contains bipolar neurons) of the cochlear division of the vestibulocochlear (VIII) nerve
  - Vestibular ganglion (contains bipolar neurons) of the vestibular division of the vestibulocochlear (VIII) nerve
  - Superior and inferior ganglia of the glossopharyngeal (IX) nerve
  - Superior and inferior ganglia of the vagus (X) nerve

Ganglia that contain cell bodies of autonomic (postsynaptic) neurons; these are synaptic stations

- **Sympathetic ganglia**
  - Sympathetic trunk (paravertebral) ganglia (the highest of these is the superior cervical ganglion)
  - Prevertebral ganglia (adjacent to origins of large unpaired branches of abdominal aorta), including celiac, superior mesenteric, inferior mesenteric, and aorticorenal ganglia
  - Adrenal medulla, which may be considered a modified sympathetic ganglion (each of the secretory cells of the medulla, as well as the recognizable ganglion cells, is innervated by cholinergic presynaptic sympathetic nerve fibers)
- **Parasympathetic ganglia**
  - Head ganglia
    - Ciliary ganglion associated with the oculomotor (III) nerve
    - Submandibular ganglion associated with the facial (VII) nerve
    - Pterygopalatine (sphenopalatine) ganglion of the facial (VII) nerve
    - Otic ganglion associated with the glossopharyngeal (IX) nerve

- Terminal ganglia (near or in wall of organs), including ganglia of the submucosal (Meissner) and myenteric (Auerbach) plexuses of the gastrointestinal tract (these are also ganglia of the enteric division of the ANS) and isolated ganglion cells in a variety of organs

[a]Practical note: Neuron cell bodies seen in tissue sections such as tongue, pancreas, urinary bladder, and heart are invariably terminal ganglia or "ganglion cells" of the parasympathetic nervous system.

To understand the PNS, it is also necessary to describe some parts of the CNS.

Motor neuron cell bodies of the PNS lie in the CNS.

The cell bodies of motor neurons that innervate skeletal muscle (**somatic efferents**) are located in the brain, brainstem, and spinal cord. The axons leave the CNS and travel in peripheral nerves to the skeletal muscles that they innervate. A single neuron conveys impulses from the CNS to the effector organ.

Sensory neuron cell bodies are located in ganglia outside, but close to, the CNS.

In the sensory system (both the **somatic afferent** and the **visceral afferent** components), a single neuron connects the receptor, through a sensory ganglion, to the spinal cord or brainstem. **Sensory ganglia** are located in the dorsal roots of the spinal nerves and in association with sensory components of cranial nerves V, VII, VIII, IX, and X (see Table 12.2).

Connective Tissue Components of a Peripheral Nerve

The bulk of a **peripheral nerve** consists of nerve fibers and their supporting Schwann cells. The individual nerve fibers and their associated Schwann cells are held together by connective tissue organized into three distinctive components, each with specific morphologic and functional characteristics (Fig. 12.27; see also Fig. 12.3).

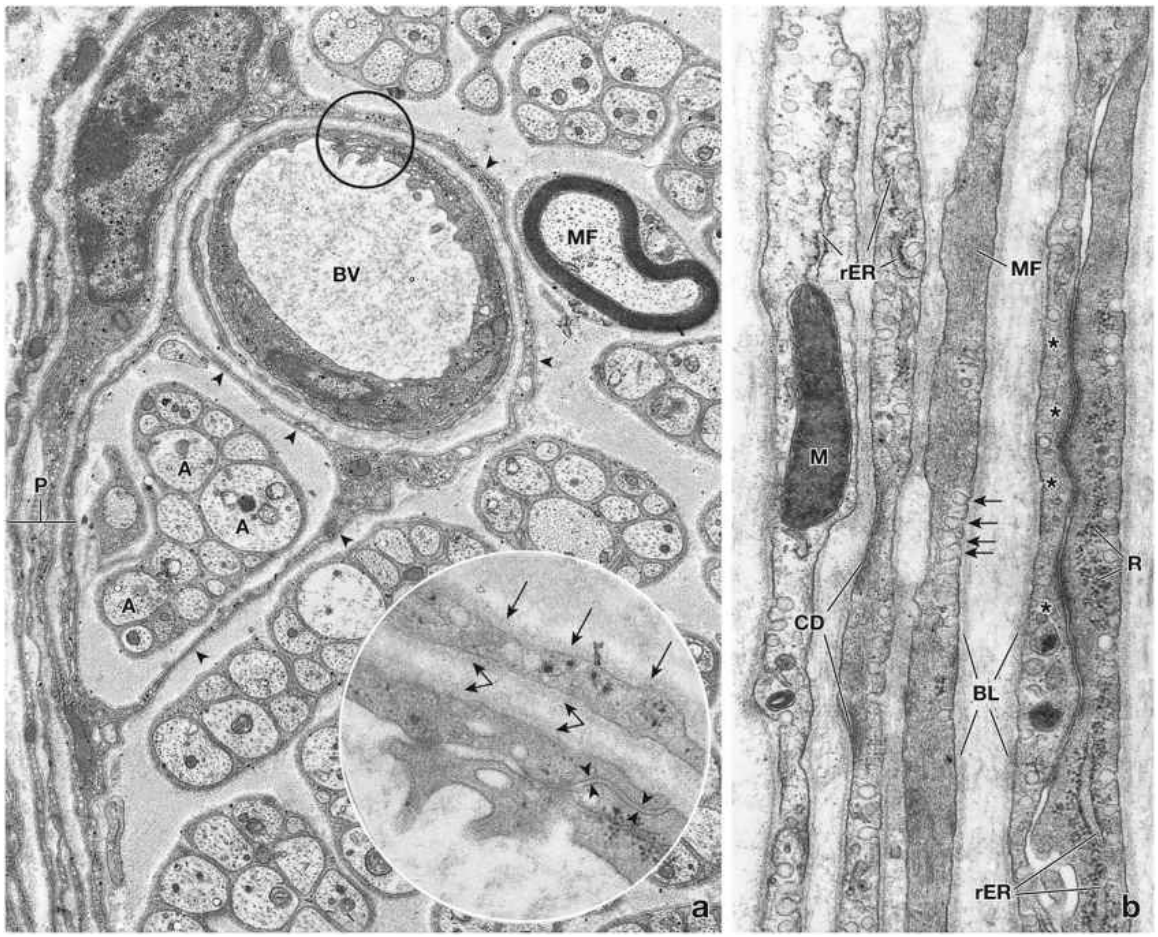


FIGURE 12.27. Electron micrograph of a peripheral nerve and its surrounding perineurium. a. Electron micrograph of unmyelinated nerve fibers and a single myelinated fiber (*MF*). The perineurium (*P*), consisting of several cell layers, is seen on the *left* of the micrograph. Perineurial cell processes (*arrowheads*) have also extended into the nerve to surround a group of axons (*A*) and their Remak Schwann cell as well as a small blood vessel (*BV*). The enclosure of this group of *A* represents the root of a small nerve branch that is joining or leaving the larger fascicle. ×10,000. The area within the *circle* encompassing the endothelium of the vessel and the adjacent perineurial cytoplasm is shown in the *inset* at higher magnification. Note the basal (external) laminae of the vessel and the perineurial cell (*arrows*). The junction between endothelial cells of the blood vessel is also apparent (*arrowheads*). ×46,000. **b.** Electron micrograph showing the perineurium of a nerve. Four cellular layers of the perineurium are present. Each layer has a basal (external) lamina (*BL*) associated with it on both surfaces. Other features of the perineurial cell include an extensive population of actin microfilaments (*MF*), pinocytotic vesicles (*arrows*), and cytoplasmic densities (*CD*). These features are characteristic of smooth muscle cells. The innermost perineurial cell layer (*right*) exhibits tight junctions (*asterisks*) where one cell is overlapping a second cell in forming the sheath. Other features seen in the cytoplasm are mitochondria (*M*),

rough-surfaced endoplasmic reticulum (*rER*), and free ribosomes (*R*). ×27,000.

- The **endoneurium** includes loose connective tissue surrounding each individual nerve fiber.
- The **perineurium** includes specialized connective tissue surrounding each nerve fascicle.
- The **epineurium** includes dense irregular connective tissue that surrounds a peripheral nerve and fills the spaces between nerve fascicles.

Endoneurium constitutes the loose connective tissue associated with individual nerve fibers.

The **endoneurium** is not conspicuous in routine LM preparations, but special connective tissue stains permit its demonstration. At the electron microscope level, collagen fibrils that constitute the endoneurium are readily apparent (see Figs. 12.15 and 12.16). The fibrils run both parallel to and around the nerve fibers, binding them together into a fascicle or bundle. Because **fibroblasts** are relatively sparse in the interstices of the nerve fibers, it is likely that most of the collagen fibrils are secreted by the Schwann cells. This conclusion is supported by tissue culture studies in which collagen fibrils are formed in pure cultures of Schwann cells and dorsal root neurons.

Other than occasional fibroblasts, the only other connective tissue cells normally found within the endoneurium are **mast cells** and **macrophages**. Macrophages mediate immunologic surveillance and also participate in nerve tissue repair. Following nerve injury, they proliferate and actively phagocytose myelin debris. In general, most of the nuclei (90%) found in cross sections of peripheral nerves belong to Schwann cells; the remaining 10% is equally distributed between the occasional fibroblasts and other cells, such as **endothelial cells** of capillaries, macrophages, and mast cells.

Perineurium is the specialized connective tissue surrounding a nerve fascicle that contributes to the formation of the blood–nerve barrier.

Surrounding the nerve bundle is a sheath of unique connective tissue cells that constitutes the **perineurium**. The perineurium serves as a metabolically active diffusion barrier that contributes to the formation of a **blood–nerve barrier**. This barrier maintains the ionic milieu of the ensheathed nerve fibers. In a manner similar to the properties exhibited by the endothelial cells of brain capillaries forming the blood–brain barrier (see pages 424-

425), **perineurial cells** possess receptors, transporters, and enzymes that provide for the active transport of substances.

The perineurium may be one or more cell layers thick, depending on the nerve diameter. The cells that compose this layer are squamous; each layer exhibits an external (basal) lamina on both surfaces (Fig. 12.27b and Plate 12.1, page 432). The cells are contractile and contain an appreciable number of actin filaments, a characteristic of smooth muscle cells and other contractile cells. Moreover, when there are two or more perineurial cell layers (as many as five or six layers may be present in larger nerves), collagen fibrils are present between the perineurial cell layers, but fibroblasts are absent. **Tight junctions** provide the basis for the **blood–nerve barrier** and are present between the cells located within the same layer of the perineurium. In effect, the arrangement of these cells as a barrier —the presence of tight junctions and external (basal) lamina material— likens them to an epithelioid tissue. On the other hand, their contractile nature and their apparent ability to produce collagen fibrils also liken them to smooth muscle cells and fibroblasts.

The limited number of connective tissue cell types within the endoneurium (page 416) undoubtedly reflects the protective role that the perineurium plays. Typical immune system cells (i.e., lymphocytes, plasma cells) are not found within the endoneurial and perineurial compartments. This absence of immune cells (other than the mast cells and macrophages) is accounted for by the protective barrier created by the perineurial cells. Typically, only fibroblasts, a small number of resident macrophages, and occasional mast cells are present within the nerve compartment.

Epineurium consists of dense irregular connective tissue that surrounds and binds nerve fascicles into a common bundle.

The **epineurium** forms the outermost tissue of the peripheral nerve. It is a typical **dense irregular connective tissue** that surrounds the fascicles formed by the perineurium (Plate 12.2, page 434). Adipose tissue is often associated with the epineurium in larger nerves.

The blood vessels that supply the nerves travel in the epineurium, and their branches penetrate into the nerve and travel within the perineurium. Tissue at the level of the endoneurium is poorly vascularized; metabolic exchange of substrates and wastes in this tissue depends on diffusion from and to the blood vessels through the perineurial sheath (see Fig. 12.27).

Afferent (Sensory) Receptors

Afferent receptors are specialized structures located at the distal tips of the peripheral processes of sensory neurons.

Although **receptors** may have many different structures, they have one basic characteristic in common: They can initiate a nerve impulse in response to a stimulus. Receptors may be classified as follows:

- **Exteroceptors** react to stimuli from the external environment—for example, temperature, touch, smell, sound, and vision.
- **Enteroceptors** react to stimuli from within the body—for example, the degree of filling or stretch of the alimentary canal, bladder, and blood vessels.
- **Proprioceptors**, which also react to stimuli from within the body, provide sensation of body position and muscle tone and movement.

The simplest receptor is a bare axon called a **nonencapsulated (free) nerve ending**. This ending is found in epithelia, connective tissue, and in close association with hair follicles.

Most sensory nerve endings acquire connective tissue capsules or sheaths of varying complexity.

Sensory nerve endings with connective tissue sheaths are called **encapsulated endings**. Many encapsulated endings are mechanoreceptors located in the skin and joint capsules (Krause end bulb, Ruffini corpuscles, Meissner corpuscles, and Pacinian corpuscles) and are described in Chapter 15, Integumentary System (pages 555-559). **Muscle spindles** are encapsulated sensory endings located in skeletal muscle; they are described in Chapter 11, Muscle Tissue (pages 359-360). Functionally, related Golgi tendon organs are encapsulated tension receptors found at musculotendinous junctions.

■ ORGANIZATION OF THE AUTONOMIC NERVOUS SYSTEM

Although the ANS was introduced early in this chapter (see page 389), it is useful here to describe some of the salient features of its organization and distribution. The ANS is classified into three divisions:

- **Sympathetic division**
- **Parasympathetic division**
- **Enteric division**

The ANS controls and regulates the body's internal environment.

The **ANS** is the portion of the PNS that conducts involuntary impulses to smooth muscle, cardiac muscle, and glandular epithelium. These effectors are the functional units in the organs that respond to regulation by nerve tissue. The term *visceral* is sometimes used to characterize the ANS and its neurons, which are referred to as **visceral motor (efferent) neurons**. However, visceral motor neurons are frequently accompanied by **visceral sensory (afferent) neurons** that transmit pain and reflexes from visceral effectors (i.e., blood vessels, mucous membrane, and glands) to the CNS. These pseudounipolar neurons have the same arrangement as other sensory neurons—that is, their cell bodies are located in sensory ganglia, and they possess long peripheral and central axons, as described earlier.

The main organizational difference between the efferent flow of impulses to skeletal muscle (somatic effectors) and the efferent flow to smooth muscle, cardiac muscle, and glandular epithelium (visceral effectors) is that one neuron conveys the impulses from the CNS to the somatic effector, whereas a chain of two neurons conveys the impulses from the CNS to the visceral effectors (Fig. 12.28). Thus, there is a synaptic station in an autonomic ganglion outside the CNS where a presynaptic neuron makes contact with postsynaptic neurons. Each presynaptic neuron synapses with several postsynaptic neurons.

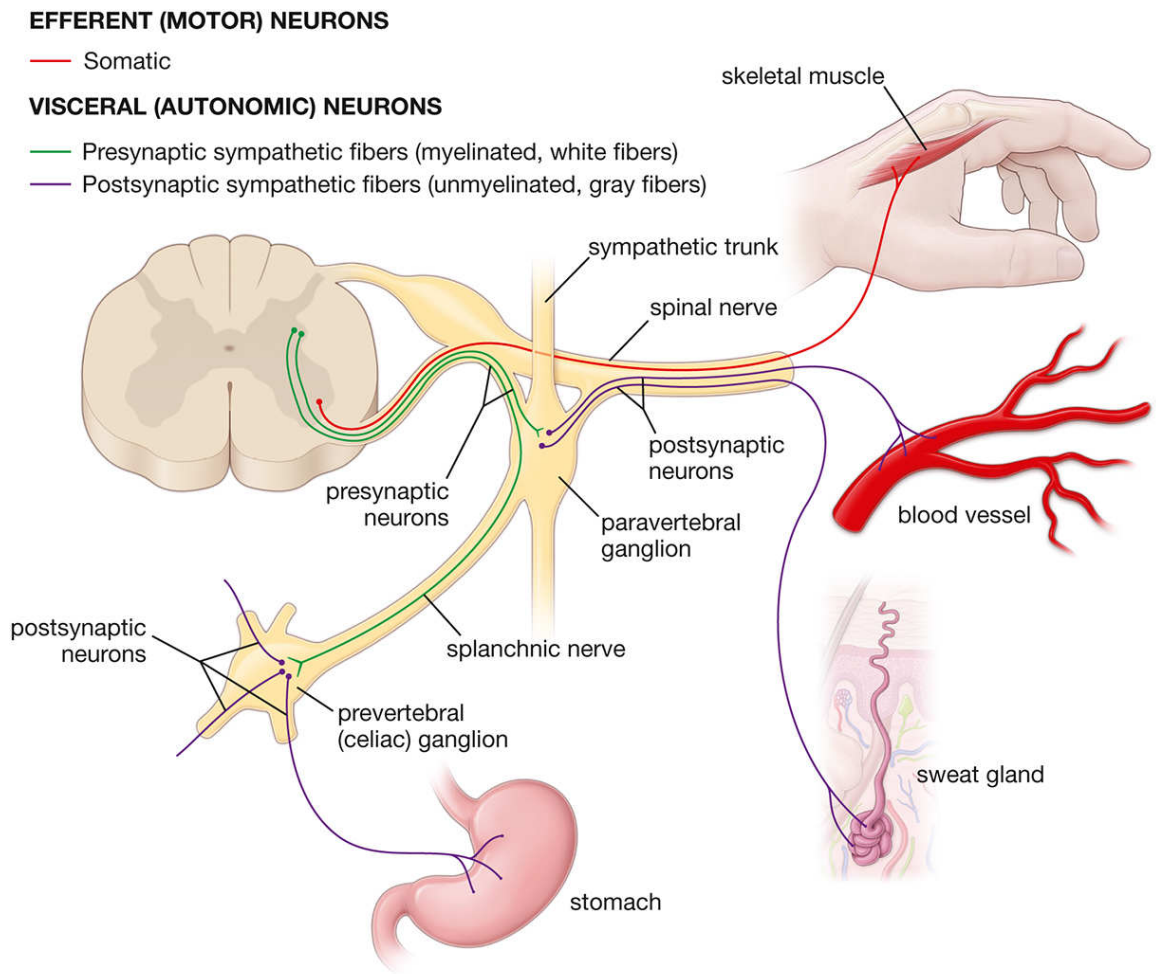


FIGURE 12.28. Schematic diagram of somatic efferent and visceral efferent neurons. In the somatic efferent (motor) system, one neuron conducts the impulses from the central nervous system (CNS) to the effector (skeletal muscle). In the visceral (autonomic) efferent system (represented in this drawing by the sympathetic division of the autonomic nervous system [ANS]), a chain of two neurons conducts the impulses: a presynaptic neuron located within the CNS and a postsynaptic neuron located in the paravertebral or prevertebral ganglia. Moreover, each presynaptic neuron makes synaptic contact with more than one postsynaptic neuron. Postsynaptic sympathetic fibers supply smooth muscles (as in blood vessels) or glandular epithelium (as in sweat glands). Neurons of the ANS that supply organs of the abdomen reach these organs by way of the splanchnic nerves. In this example, the splanchnic nerve joins with the celiac ganglion, where most of the synapses of the two-neuron chain occur.

Sympathetic and Parasympathetic Divisions of the Autonomic Nervous System

The presynaptic neurons of the sympathetic division are located in the thoracic and upper lumbar portions of the spinal cord.

The **presynaptic neurons** send axons from the thoracic and upper lumbar spinal cord to the vertebral and paravertebral ganglia. The **paravertebral ganglia** in the **sympathetic trunk** contain the cell bodies of the postsynaptic effector neurons of the **sympathetic division** (see Figs. 12.28 and 12.29).

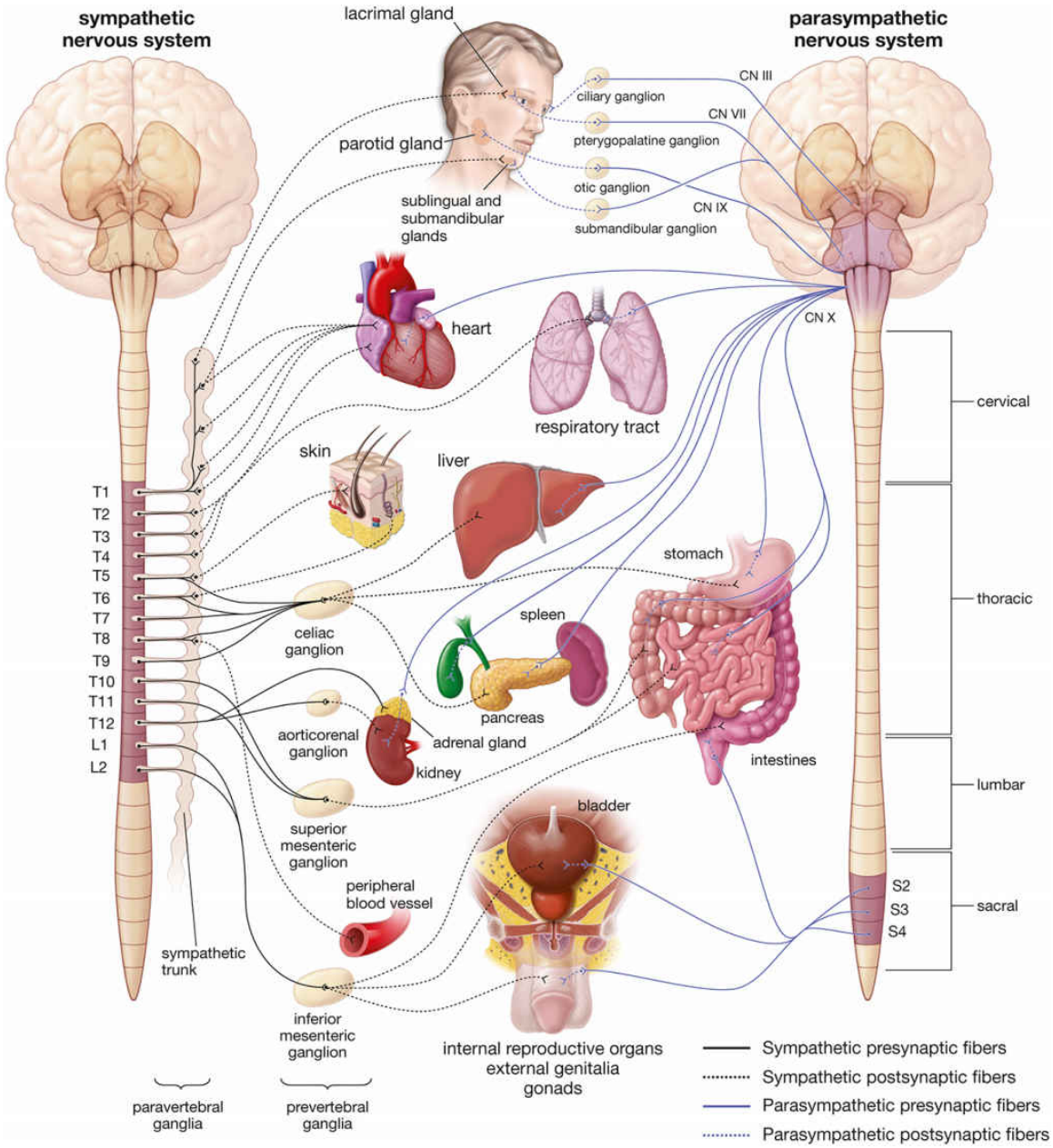


FIGURE 12.29. Schematic diagram showing the general arrangement of sympathetic and parasympathetic neurons of the autonomic nervous system (ANS). The sympathetic outflow is shown on the *left*, the parasympathetic on the *right*. The sympathetic (thoracolumbar) outflow leaves the central nervous system (CNS) from the thoracic and upper lumbar segments (T1–L2) of the spinal cord. These presynaptic fibers communicate with postsynaptic neurons in two locations: the paravertebral and

prevertebral ganglia. Paravertebral ganglia are linked together and form two sympathetic trunks on each side of the vertebral column (*drawn as a single column on the side of the spinal cord*). Prevertebral ganglia are associated with the main branches of the abdominal aorta (*yellow ovals*). Note the distribution of postsynaptic sympathetic nerve fibers to the viscera. The parasympathetic (craniosacral) outflow leaves the CNS from the gray matter of the brainstem within cranial nerve (CN) III, CN VII, CN IX, and CN X and the gray matter of sacral segments (S2–S4) of the spinal cord and is distributed to the viscera. The presynaptic fibers traveling with CN III, CN VII, and CN IX communicate with postsynaptic neurons in various ganglia located in the head and neck region (*yellow ovals in front of the head*). The presynaptic fibers traveling with CN X and those from sacral segments (S2–S4) have their synapses with postsynaptic neurons in the wall of visceral organs (terminal ganglia). The viscera thus contains both sympathetic and parasympathetic innervation. Note that a two-neuron chain carries impulses to all viscera, except the adrenal medulla.

The presynaptic neurons of the parasympathetic division are located in the brainstem and sacral spinal cord.

The **presynaptic parasympathetic neurons** send axons from the brainstem—that is, the midbrain, pons, medulla, and the sacral segments of the spinal cord (S2–S4)—to **visceral ganglia**. The ganglia in or near the wall of abdominal and pelvic organs and the visceral motor ganglia of cranial nerves III, VII, IX, and X contain cell bodies of the postsynaptic effector neurons of the **parasympathetic division** (see Figs. 12.28 and 12.29).

The sympathetic and parasympathetic divisions of the ANS often supply the same organs. In these cases, the actions of the two are usually antagonistic. For example, sympathetic stimulation increases the rate of cardiac muscle contractions, whereas parasympathetic stimulation reduces the rate.

Many functions of the SNS are similar to those of the adrenal medulla, an endocrine gland. This functional similarity is partly explained by the developmental relationships between the cells of the adrenal medulla and the postsynaptic sympathetic neurons. Both are derived from the neural crest, are innervated by presynaptic sympathetic neurons, and produce closely related physiologically active agents, EPI and NE. A major difference is that the sympathetic neurons deliver the agent directly to the effector, whereas the cells of the adrenal medulla deliver the agent indirectly through the bloodstream. The innervation of the adrenal medulla may constitute an exception to the rule that autonomic innervation consists of a two-neuron chain from the CNS to an effector unless the adrenal medullary

cell is considered the functional equivalent of the second neuron (in effect, a neurosecretory neuron).

Enteric Division of the Autonomic Nervous System

The enteric division of the ANS consists of the ganglia and their processes that innervate the alimentary canal.

The **enteric division of the ANS** represents a collection of neurons and their processes within the walls of the alimentary canal. It controls motility (contractions of the gut wall), exocrine and endocrine secretions, and blood flow through the gastrointestinal tract; it also regulates immunologic and inflammatory processes.

The enteric nervous system can function independently from the CNS and is regarded as the "**brain of the gut**." However, digestion requires communication between enteric neurons and the CNS, which is provided by parasympathetic and sympathetic nerve fibers. Enteroceptors located in the alimentary tract provide sensory information to the CNS regarding the state of digestive functions. The CNS then coordinates sympathetic stimulation, which inhibits gastrointestinal secretion, motor activity, and contraction of gastrointestinal sphincters and blood vessels as well as parasympathetic stimuli that produce opposite actions. **Interneurons** integrate information from sensory neurons and relay this information to enteric motor neurons in the form of reflexes. For instance, the gastrocolic reflex is elicited when distention of the stomach stimulates contraction of musculature of the colon, triggering defecation.

Ganglia and postsynaptic neurons of the enteric division are located in the lamina propria, muscularis mucosae, submucosa, muscularis externa, and subserosa of the alimentary canal from the esophagus to the anus (Fig. 12.30). Because the enteric division does not require presynaptic input from the vagus nerve and sacral outflow, the intestine will continue peristaltic movements, even after the vagus nerve or pelvic splanchnic nerves are severed.

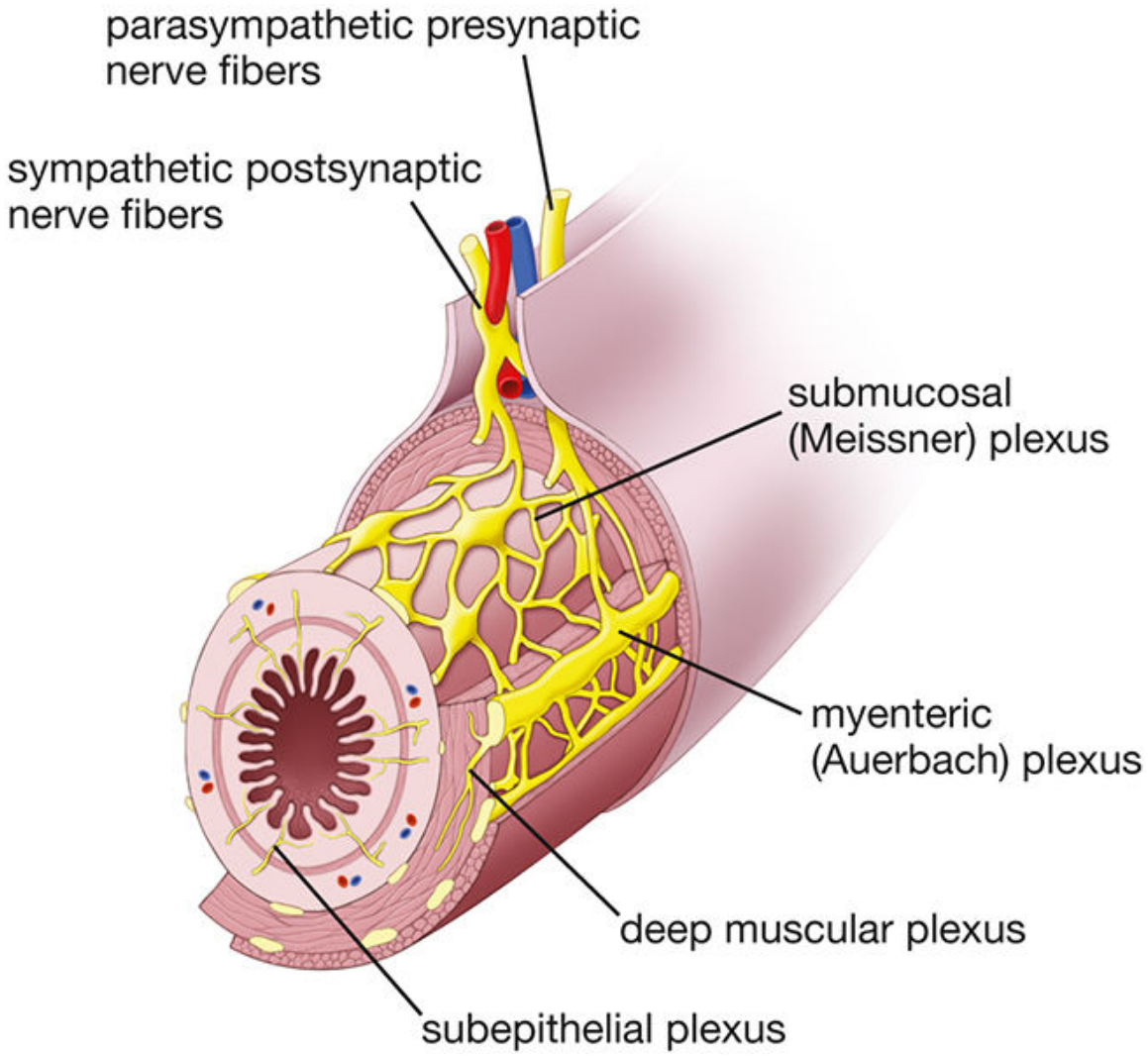


FIGURE 12.30. Enteric nervous system. This diagram shows the organization of the enteric system in the wall of the small intestine. Note the location of two nerve plexuses containing ganglion cells. The more superficial plexus, the myenteric plexus (Auerbach plexus), lies between two muscle layers. Deeper in the region of the submucosa is a network of unmyelinated nerve fibers and ganglion cells, forming the submucosal plexus (Meissner plexus). Parasympathetic fibers originating from the vagus nerve enter the mesentery of the small intestine and synapse with the ganglion cells of both plexuses. Postsynaptic sympathetic nerve fibers also contribute to the enteric nervous system.

Neurons of the enteric division are not supported by Schwann or satellite cells; instead, they are supported by **enteric neuroglial cells** that resemble astrocytes (see pages 410-411). Cells of the **enteric division** are also affected by the same pathologic changes that can occur in neurons of the brain. Lewy bodies associated with **Parkinson disease** (see Folder 12.1) as well as amyloid plaques and neurofibrillary tangles associated with **Alzheimer disease** have been found in the walls of

the large intestine. This finding may lead to the development of routine gastrointestinal biopsies for early diagnosis of these conditions rather than the more complex and risk-associated biopsy of the brain for Alzheimer disease and postmortem identification of Parkinson disease.

A Summarized View of Autonomic Distribution

Figures 12.28 and 12.29 summarize the origins and distribution of the ANS. Refer to these figures as you read the descriptive sections. Note that the diagrams indicate both the paired innervation (parasympathetic and sympathetic) common to the ANS and the important exceptions to this general characteristic.

Head

- **Parasympathetic presynaptic outflow** to the head leaves the brain with the cranial nerves, as indicated in Figure 12.29, but the routes are quite complex. Cell bodies may also be found in structures other than head ganglia listed in Table 12.1 and Figure 12.28 (e.g., in the tongue). These are "terminal ganglia" that contain nerve cell bodies of the parasympathetic system.
- **Sympathetic presynaptic outflow** to the head comes from the thoracic region of the spinal cord. The *postsynaptic neurons* have their cell bodies in the superior cervical ganglion; the axons leave the ganglion in a nerve network that hugs the wall of the internal and external carotid arteries to form the periarterial plexus of nerves. The internal carotid plexus and external carotid plexus follow the branches of the carotid arteries to reach their destination.

Thorax

- **Parasympathetic presynaptic outflow** to the thoracic viscera is via the vagus nerve (X). The *postsynaptic neurons* have their cell bodies in the walls or in the parenchyma of the organs of the thorax.
- **Sympathetic presynaptic outflow** to the thoracic organs is from the upper thoracic segments of the spinal cord. *Sympathetic postsynaptic neurons* for the heart are mostly in the cervical ganglia; their axons make up the cardiac nerves. *Postsynaptic neurons* for the other thoracic viscera are in ganglia of the thoracic part of the sympathetic trunk. The axons travel via small splanchnic nerves from the sympathetic trunk to organs within the thorax and form the pulmonary and esophageal plexuses.

Abdomen and pelvis

- **Parasympathetic presynaptic outflow** to the abdominal viscera is via the vagus (X) and pelvic splanchnic nerves. *Postsynaptic neurons* of the parasympathetic system to abdominopelvic organs are in terminal ganglia that generally are in the walls of the organs, such as the ganglia of the submucosal (Meissner) plexus and the myenteric (Auerbach) plexus in the alimentary canal. These ganglia are part of the enteric division of the ANS.
- **Sympathetic presynaptic outflow** to the abdominopelvic organs is from the lower thoracic and upper lumbar segments of the spinal cord. These fibers travel to the prevertebral ganglia through abdominopelvic splanchnic nerves consisting of the greater, lesser, and least thoracic splanchnic and lumbar splanchnic nerves. *Postsynaptic neurons* have their cell bodies mostly in the prevertebral ganglia (see Fig. 12.28). Only presynaptic fibers terminating on cells in the medulla of the suprarenal (adrenal) gland originate from paravertebral ganglia of the sympathetic trunk. The adrenal medullary cells function as a special type of postsynaptic neuron that releases neurotransmitter directly into the bloodstream instead of into the synaptic cleft.

Extremities and body wall

There is no parasympathetic outflow to the body wall and extremities. Anatomically, the autonomic innervation in the body wall is only sympathetic (see Fig. 12.28). Each spinal nerve contains postsynaptic sympathetic fibers—that is, unmyelinated visceral efferents of neurons whose cell bodies are in paravertebral ganglia of the sympathetic trunk. For sweat glands, the neurotransmitter released by the "sympathetic" neurons is ACh instead of NE.

■ ORGANIZATION OF THE CENTRAL NERVOUS SYSTEM

The **central nervous system** consists of the **brain** located in the cranial cavity and the **spinal cord** located in the vertebral canal. The CNS is protected by the skull and vertebrae and is surrounded by three connective tissue membranes called **meninges**. The brain and spinal cord essentially float in the CSF that occupies the space between the two inner meningeal layers. The brain is further subdivided into the **cerebrum**, **cerebellum**, and **brainstem**, which connects with the spinal cord.

In the brain, the gray matter forms an outer covering or cortex; the white matter forms an inner core or medulla.

The **cerebral cortex** that forms the outermost layer of the brain contains nerve cell bodies, axons, dendrites, and central glial cells, and it is the site of synapses. In a freshly dissected brain, the cerebral cortex has a gray color, hence the name **gray matter**. In addition to the cortex, islands of gray matter called **nuclei** are found in the deep portions of the cerebrum and cerebellum.

The **white matter** contains only axons of nerve cells plus the associated glial cells and blood vessels (axons in fresh preparations appear white). These axons travel from one part of the nervous system to another. Whereas many of the axons going to, or coming from, a specific location are grouped into functionally related bundles called **tracts**, the tracts themselves do not stand out as delineated bundles. The demonstration of a tract in the white matter of the CNS requires a special procedure, such as the destruction of cell bodies that contribute fibers to the tract. The damaged fibers can be displayed by the use of appropriate staining or labeling methods and then traced. Even in the spinal cord, where the grouping of tracts is most pronounced, there are no sharp boundaries between adjacent tracts.

Cells of the Gray Matter

The types of cell bodies found in the gray matter vary according to which part of the brain or spinal cord is being examined.

Each functional region of the gray matter has a characteristic variety of cell bodies associated with a meshwork of axonal, dendritic, and glial processes.

The meshwork of axonal, dendritic, and glial processes associated with the gray matter is called the **neuropil**. The organization of the neuropil is not demonstrable in H&E-stained sections. It is necessary to use methods other than H&E histology to decipher the cytoarchitecture of the gray matter (Plate 12.3, page 436).

Although general histology programs usually do not deal with the actual arrangements of the neurons in the CNS, the presentation of two examples will add to the appreciation of H&E sections that students usually examine. These examples present a region of the cerebral cortex (Fig. 12.31 and Plate 12.3, page 436) and the cerebellar cortex (Fig. 12.32 and Plate 12.4, page 438).

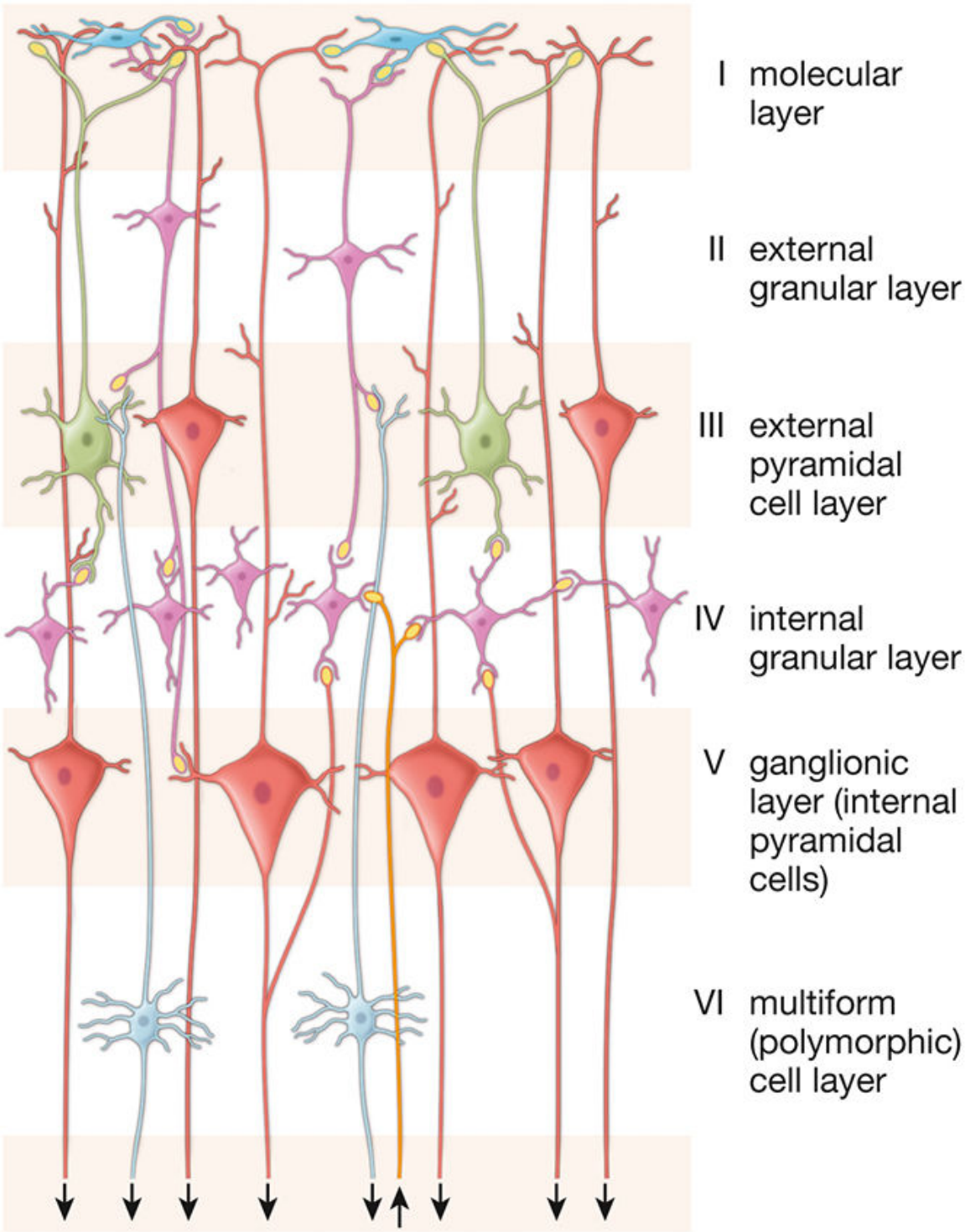


FIGURE 12.31. Nerve cells in intracortical cerebral circuits. This simplified diagram shows the organization and connections between cells in different layers of the cortex contributing to cortical afferent fibers (*arrows pointing up*) and cortical efferent fibers (*arrows pointing down*). The small interneurons are indicated in *yellow*.

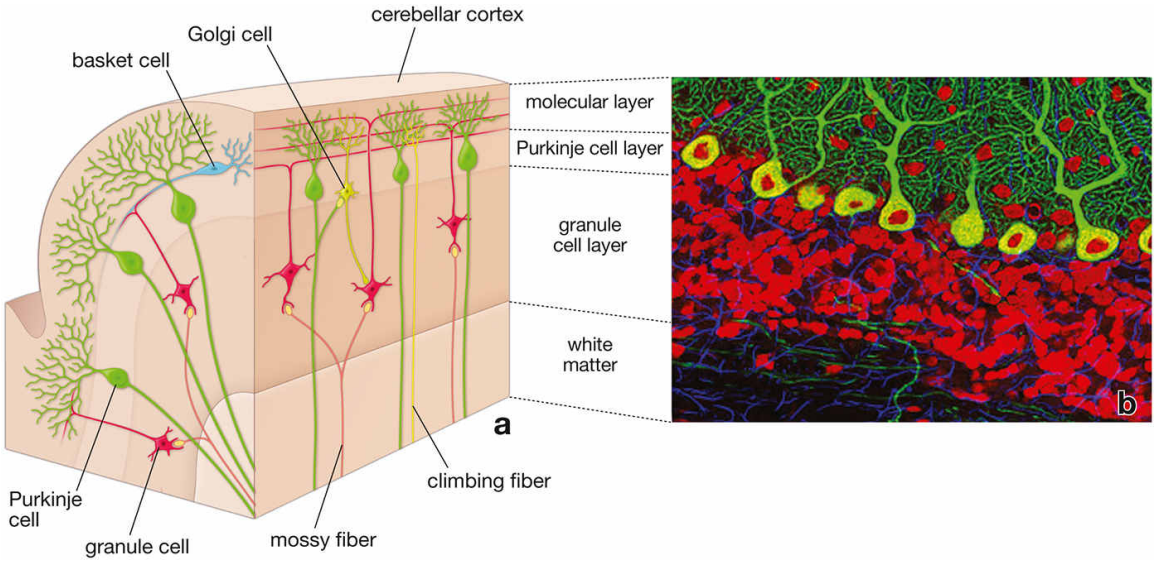


FIGURE 12.32. Cytoarchitecture of the cerebellar cortex. a. This diagram shows a section of the folium, a narrow, leaf-like gyrus of the cerebellar cortex. The longer cut edge is parallel to the folium. Note that the cerebellar cortex contains white matter and gray matter. Three distinct layers of gray matter are identified on this diagram: the superficially located molecular layer, the middle Purkinje cell layer, and the granule cell layer adjacent to the white matter. Mossy fibers and ascending fibers are major afferent fibers of the cerebellum. **b.** Purkinje cell layer from rat cerebellum visualized using double-fluorescent–labeling methods. Red DNA staining indicates the nuclei of cells in molecular and granule cell layer thin section. Note that each Purkinje cell exhibits an abundance of dendrites. ×380. (Courtesy of Thomas J. Deerinck.)

Notable in the cerebellar cortex (see Fig. 12.32) is the Purkinje cell layer. Individuals infected by **rabies virus (RABV)** have characteristic inclusions in the cytoplasm of affected neurons called **Negri bodies**. These eosinophilic, sharply outlined, 2–10 µm in diameter inclusions visible in LM represent intracellular **viral replication compartments** formed during viral infection. They are easily observed in the cytoplasm of the Purkinje cells and pyramidal cells of the hippocampus. Negri bodies have been used for decades as primary histologic proof of RABV infection. The current approach for postmortem diagnosis of human and animal rabies is based on the direct fluorescent antibody (DFA) test. Recently, an LN34 pan-lyssavirus real-time reverse transcription-polymerase chain reaction (RT-PCR) assay has been introduced and has improved rabies diagnostics and surveillance.

The **brainstem** is not clearly separated into regions of gray matter and white matter. The nuclei of the cranial nerves located in the brainstem,

however, appear as islands surrounded by more or less distinct tracts of white matter. The nuclei contain the cell bodies of the motor neurons of the cranial nerves and are both the morphologic and functional counterparts of the anterior horns of the spinal cord. In other sites in the brainstem, as in the **reticular formation**, the distinction between white matter and gray matter is even less evident.

Organization of the Spinal Cord

The **spinal cord** is a flattened cylindrical structure that is directly continuous with the brainstem. It is divided into 31 segments (8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal), and each segment is connected to a pair of **spinal nerves**. Each spinal nerve is joined to its segment of the cord by a number of rootlets grouped as dorsal (posterior) or ventral (anterior) roots (Fig. 12.33; see also Fig. 12.3).

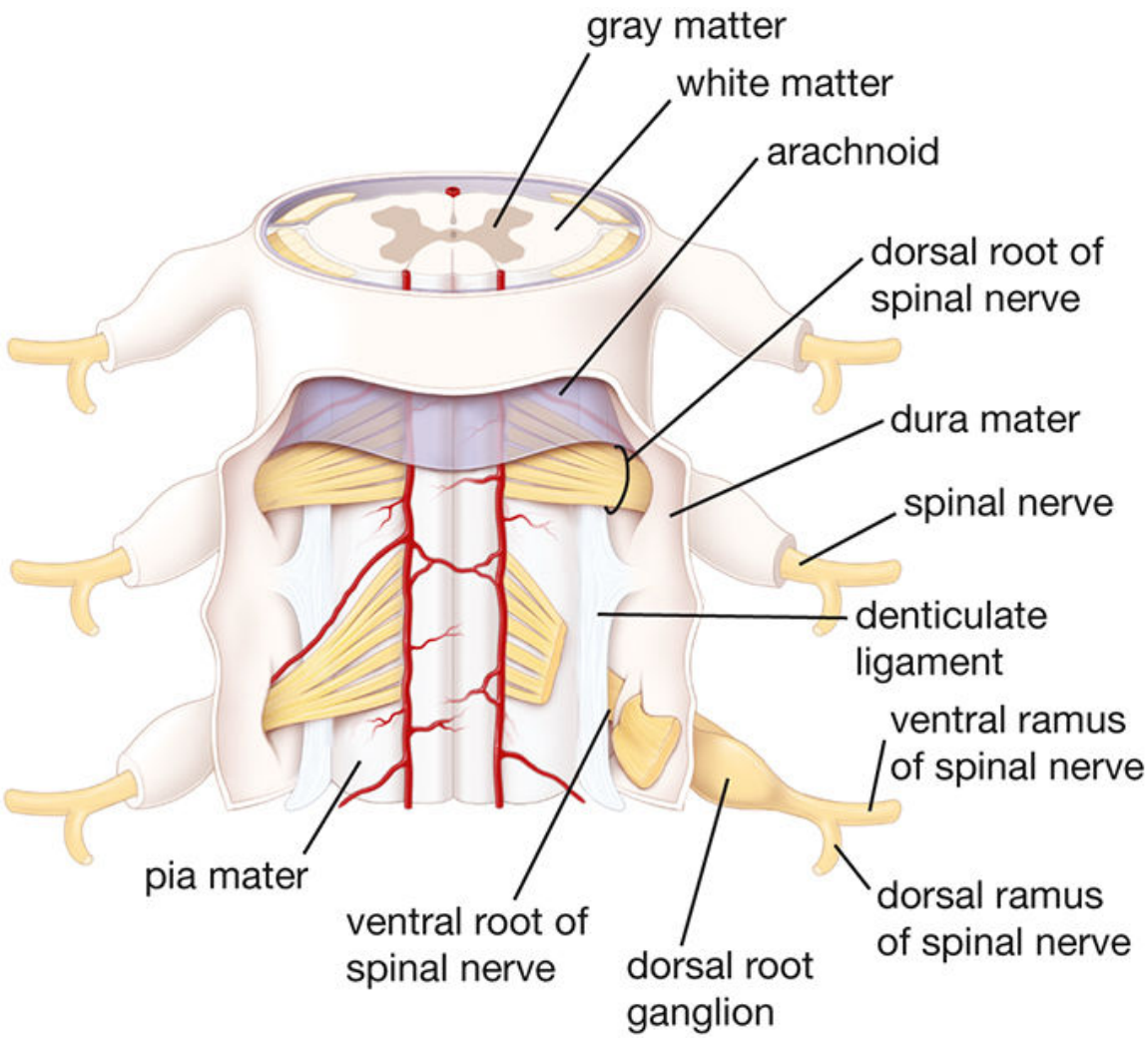


FIGURE 12.33. Posterior view of the spinal cord with surrounding meninges. Each spinal nerve arises from the spinal cord by rootlets, which

merge to form dorsal (posterior) and ventral (anterior) nerve roots. These roots unite to form a spinal nerve that, after a short course, divides into larger ventral (anterior) and smaller dorsal (posterior) primary rami. Note the dura mater (the outer layer of the meninges) that surrounds the spinal cord and emerging spinal nerves. The denticulate ligament of the pia mater that anchors the spinal cord to the wall of the spinal canal is also visible.

In cross section, the spinal cord exhibits a butterfly-shaped grayish-tan inner substance surrounding the **central canal**, the **gray matter**, and a whitish peripheral substance, the **white matter** (Fig. 12.34). White matter (see Fig. 12.3) contains only tracks of myelinated and unmyelinated axons traveling to and from other parts of the spinal cord and to and from the brain.

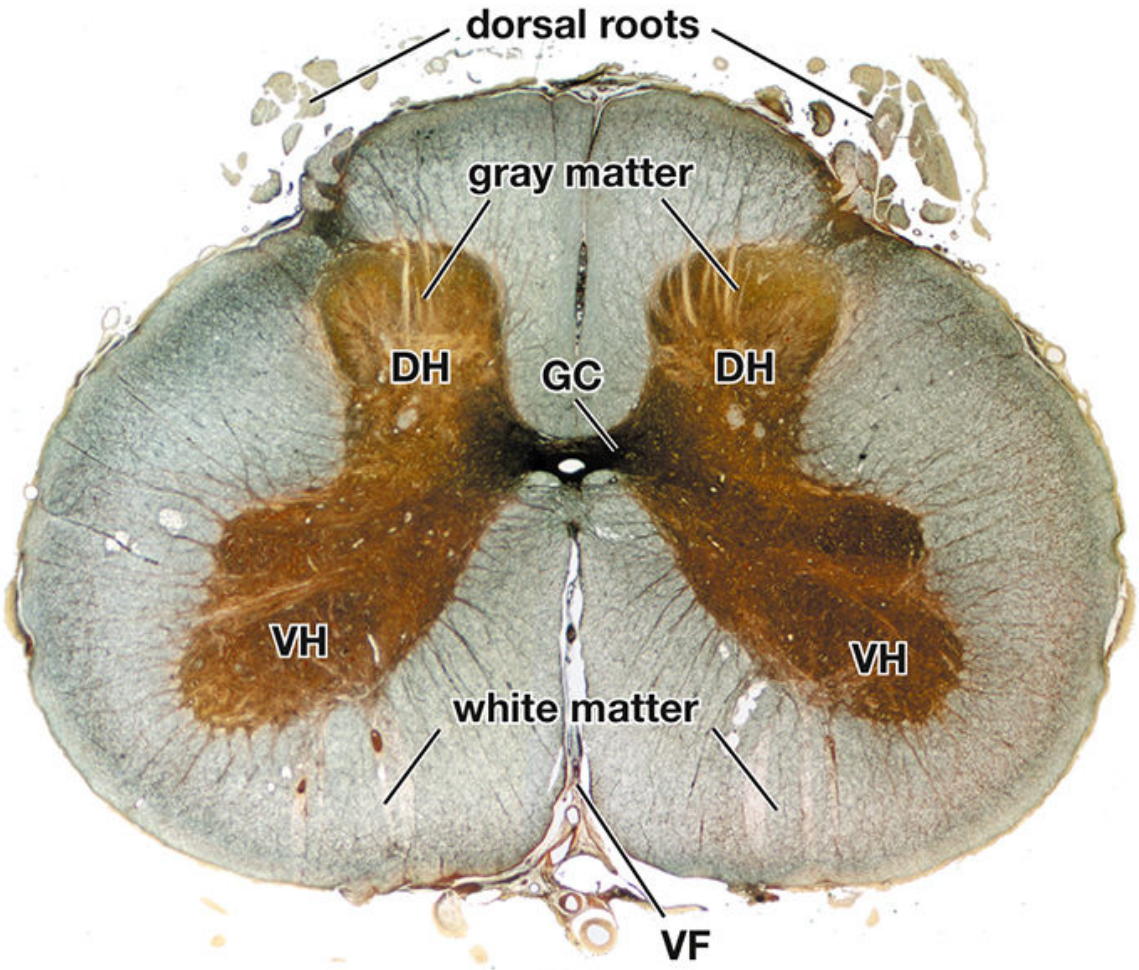


FIGURE 12.34. Cross section of the human spinal cord. This photomicrograph shows a cross section through the lower lumbar (most likely L4–L5) level of the spinal cord stained by the Bielschowsky silver method. The spinal cord is organized into an outer part, the white matter, and an inner part, the gray matter, which contains nerve cell bodies and

associated nerve fibers. The gray matter of the spinal cord appears roughly in the form of a butterfly. The anterior and posterior prongs are referred to as *ventral horns* (*VH*) and *dorsal horns* (*DH*), respectively. They are connected by the gray commissure (*GC*). The white matter contains nerve fibers that form ascending and descending tracts. The outer surface of the spinal cord is surrounded by the pia mater. Blood vessels of the pia mater, the ventral fissure (*VF*), and some dorsal roots of the spinal nerves are visible in the section. ×5.

Gray matter contains neuronal cell bodies and their dendrites, along with axons and central neuroglia (Plate 12.5, page 440). Functionally related groups of nerve cell bodies in the gray matter are called **nuclei**. In this context, the term *nucleus* means a cluster or group of neuronal cell bodies plus fibers and neuroglia. Nuclei of the CNS are the morphologic and functional equivalents of the ganglia of the PNS. Synapses occur only in the gray matter.

The cell bodies of motor neurons that innervate striated muscle are located in the ventral (anterior) horn of the gray matter.

Ventral motor neurons, also called **anterior horn cells**, are large basophilic cells easily recognized in routine histologic preparations (see Fig. 12.34 and Plate 12.5, page 440). Because the motor neuron conducts impulses away from the CNS, it is an efferent neuron.

The axon of a motor neuron leaves the spinal cord, passes through the ventral (anterior) root, becomes a component of the spinal nerve of that segment, and, as such, is conveyed to the muscle. The axon is myelinated, except at its origin and termination. Near the muscle cell, the axon divides into numerous terminal branches that form neuromuscular junctions with the muscle cell (see page 357).

The cell bodies of sensory neurons are located in ganglia that lie on the dorsal root of the spinal nerve.

Sensory neurons in the dorsal root ganglia are pseudounipolar (Plate 12.1, page 432). They have a single process that divides into a peripheral segment that brings information from the periphery to the cell body and a central segment that carries information from the cell body into the gray matter of the spinal cord. Because the sensory neuron conducts impulses to the CNS, it is an *afferent neuron*. Impulses are generated in the terminal receptor arborization of the peripheral segment.

Connective Tissue of the Central Nervous System

Three sequential connective tissue membranes, the **meninges**, cover the brain and spinal cord.

- The **dura mater** is the outermost layer.
- The **arachnoid** layer lies beneath the dura.
- The **pia mater** is a delicate layer resting directly on the surface of the brain and spinal cord.

Meninges develop from a single layer of mesenchyme surrounding the developing brain. This layer, called the **primary meninx**, is the primordium for the developing meninges, bones of the skull, and dermal layer of the skin. The primary meninx further differentiates into an outer dense layer (that gives rise to the dermal layer of the skin and bones of the skull) and an inner reticular layer, which is considered the **meningeal mesenchyme**. This layer is separated into the **pachymeninx** (which develops into the dura mater) and **leptomeninx** (which develops into the arachnoid and pia mater). The pachymeninx contains longitudinally arranged fibroblasts that produce collagen fibers, whereas the leptomeninx represents a meshwork of loosely organized leptomeningeal cells. The cavitation of the leptomeninx generates arachnoid trabeculae and the subarachnoid space. In adults, the pia mater represents the visceral portion, and the arachnoid represents the parietal portion of the leptomeninx. The common origin of both meninges is evident in adults in which numerous delicate arachnoid trabeculae composed of leptomeningeal cells and fine collagen bundles pass between the pia mater and the arachnoid.

The dura mater is a relatively thick sheet of dense irregular connective tissue.

In the cranial cavity, the thick layer of connective tissue that attaches to the inner surface of the skull forms the **dura mater** *[L. tough mother]*. It consists of two layers:

- The **periosteal (outer) layer** that serves as the periosteum of the internal surface of the skull bones
- The **meningeal (inner) layer** that is fused to the periosteal layer in most regions

These two layers are separated only at the sites of **venous (dural) sinuses**, which are lined by endothelium. Venous (dural) sinuses serve as the principal channels for blood returning from the brain; they receive blood from the cerebral veins and carry it to the internal jugular veins.

Sheet-like extensions of the inner (meningeal) layer of the dura mater are called **dural reflections**. They form partitions between parts of the brain, supporting those parts within the cranial cavity and carrying the arachnoid to deeper parts of the brain. For example, the **falx cerebri** separates the two cerebral hemispheres along the midline, and the **tentorium cerebelli** separates the cerebral hemispheres posteriorly from the cerebellum.

In the spinal canal, the periosteal layer becomes the periosteum of the vertebrae and is separated from the inner meningeal layer by the epidural space, which contains adipose tissue and venous plexuses. The meningeal layer of the dura mater forms a separate tube surrounding the spinal cord (see Fig. 12.33).

The arachnoid is a delicate sheet of connective tissue adjacent to the inner surface of the dura.

The **arachnoid** forms a water-proof layer that abuts the inner surface of the dura and extends delicate **arachnoid trabeculae** to the pia mater on the surface of the brain and spinal cord. The web-like trabeculae of the arachnoid give this tissue its name *[Gr. arachne—resembling a spider's web]*. Trabeculae are composed of loose connective tissue fibers containing elongated fibroblasts. The space bridged by these trabeculae is the **subarachnoid space**; it contains the **cerebrospinal fluid** (Fig. 12.35). In some areas, the arachnoid mater protrudes through the meningeal layer of the dura mater into the dural venous sinuses. These areas, called **arachnoid granulations**, are involved in the transport of CSF from the subarachnoid space into the venous sinuses (see Fig. 12.35).

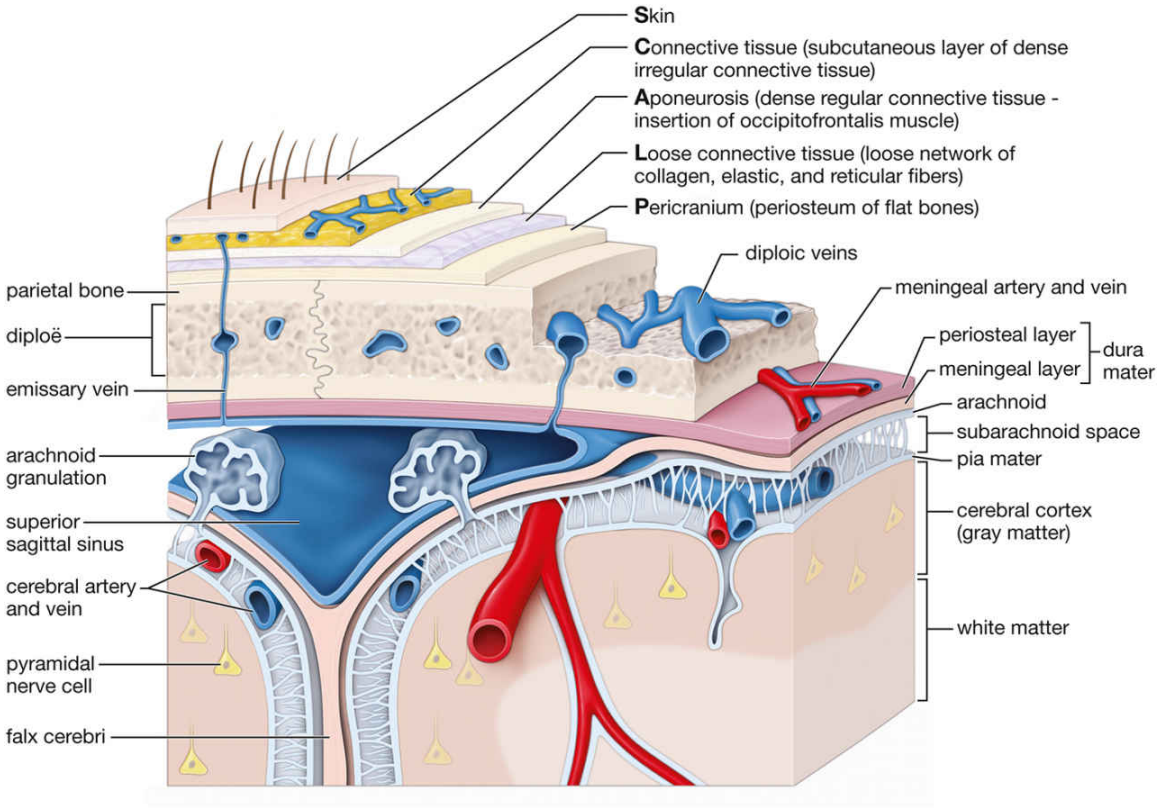


FIGURE 12.35. Schematic diagram of the layers of the scalp and cerebral meninges. This diagram of the frontal section of the top of the head shows the layers of the scalp, organization of the parietal bones of the skull, and arrangement of meninges and blood vessels within the cranial cavity. The five layers of the scalp can be remembered with the mnemonic SCALP: (1) Skin; (2) Connective tissue (dense irregular) located below the skin with an embedded subcutaneous layer of the vascular network; (3) Aponeurosis, which represents a flat tendon (dense regular connective tissue) for the attachment of occipital and frontalis muscles; (4) Loose connective tissue network of collagen, elastic, and reticular fibers; and (5) Pericranium, which represents the periosteum on the outer surface of the bone. Below the scalp, the section through the parietal bone reveals a middle spongy bone layer called *diploë* located between the inner and outer plates of compact bone. Diploic veins in the diploë connect dural sinuses with the extracranial venous systems through emissary veins. Within the cranial cavity, the superficial, outer layer of the dura mater, called the *periosteal layer*, is firmly attached to bone and serves as a periosteum (darker color). Note the branches of meningeal arteries with accompanying veins located between the periosteal layer of the dura mater and bone. The deeper, inner layer of the dura mater is called the *meningeal layer* (*lighter color*). In most regions of the cranial cavity, both layers of dura mater are fused, except at the sites of venous (dural) sinuses; here, the layers are separated from each other by a vascular space lined by endothelium. In a few regions of the cranial cavity, fused meningeal layers of the dura mater project away from the bone to form dural infoldings (reflections) that separate the different

regions of the brain. Note the falx cerebri, the largest dural infolding that separates the right and left cerebral hemispheres. Deep to the dura mater is the arachnoid. It is adjacent, but not attached, to the dura mater. The arachnoid sends numerous web-like arachnoid trabeculae to the pia mater that adheres to the brain surface and follows all its contours. The subarachnoid space is located between the arachnoid and the pia mater; it contains cerebrospinal fluid. The space also contains the larger blood vessels (cerebral arteries and veins) that send branches into and receive tributaries from the brain. Note that in some areas called *arachnoid granulations*, the arachnoid mater protrudes through the meningeal layer of the dura mater into the dural venous sinuses. Arachnoid granulations are involved in the transport of cerebrospinal fluid from the subarachnoid space into venous sinuses.

The pia mater lies directly on the surface of the brain and spinal cord.

The **pia mater** *[L. tender mother]* is also a delicate connective tissue layer. It lies directly on the surface of the brain and spinal cord and is continuous with the perivascular connective tissue sheath of the blood vessels of the brain and spinal cord. Both surfaces of the arachnoid, the inner surface of the pia mater, and the trabeculae are covered with a thin squamous epithelial layer. Both the arachnoid and the pia mater fuse around the opening for the cranial and spinal nerves as they exit the dura mater.

Blood–Brain Barrier

The blood–brain barrier protects the CNS from fluctuating levels of electrolytes, hormones, and tissue metabolites circulating in the blood vessels.

The observation more than 100 years ago that vital dyes injected into the bloodstream can penetrate and stain nearly all organs, except the brain, provided the first description of the **blood–brain barrier**. More recently, advances in microscopy and molecular biology techniques have revealed the precise location of this unique barrier and the role of brain endothelial cells in transporting essential substances to the brain tissue.

The blood–brain barrier maintains the optimal microenvironment in the CNS for proper brain function. In essence, it separates the brain tissue from circulating blood. The major functions of the blood–brain barrier are to:

- protect the brain from potential blood-borne toxins,
- meet the metabolic demands of the brain tissue, and
- regulate the homeostatic microenvironment in the CNS.

The blood–brain barrier resides in the single layer of uninterrupted vascular endothelial cells lining continuous capillaries in the CNS.

The blood–brain barrier develops early in the embryo through an interaction between glial astrocytes and capillary endothelial cells. The barrier is created largely by the elaborate **tight junctions** between the **endothelial cells**, which form continuous-type capillaries. Studies with the TEM using electron-opaque tracers show complex tight junctions between the endothelial cells. Morphologically, these junctions more closely resemble epithelial tight junctions than tight junctions present between other endothelial cells. In addition, TEM studies reveal a close association of astrocytes and their end-foot processes with the **endothelial basal lamina** (Fig. 12.36). The tight junctions eliminate gaps between endothelial cells and prevent simple diffusion of solutes and fluid into the neural tissue. Evidence suggests that the integrity of blood–brain barrier tight junctions depends on the normal functioning of the associated **astrocytes;** however, the astrocytes themselves and their end-foot processes do not significantly contribute to the physical barrier. Several brain diseases are characterized by a breakdown in the **blood–brain barrier**. Examination of brain tissue in these conditions with the TEM reveals loss of tight junctions as well as alterations in the morphology of astrocytes. Other experimental evidence has revealed that astrocytes release soluble factors that increase barrier properties and tight junction protein content.

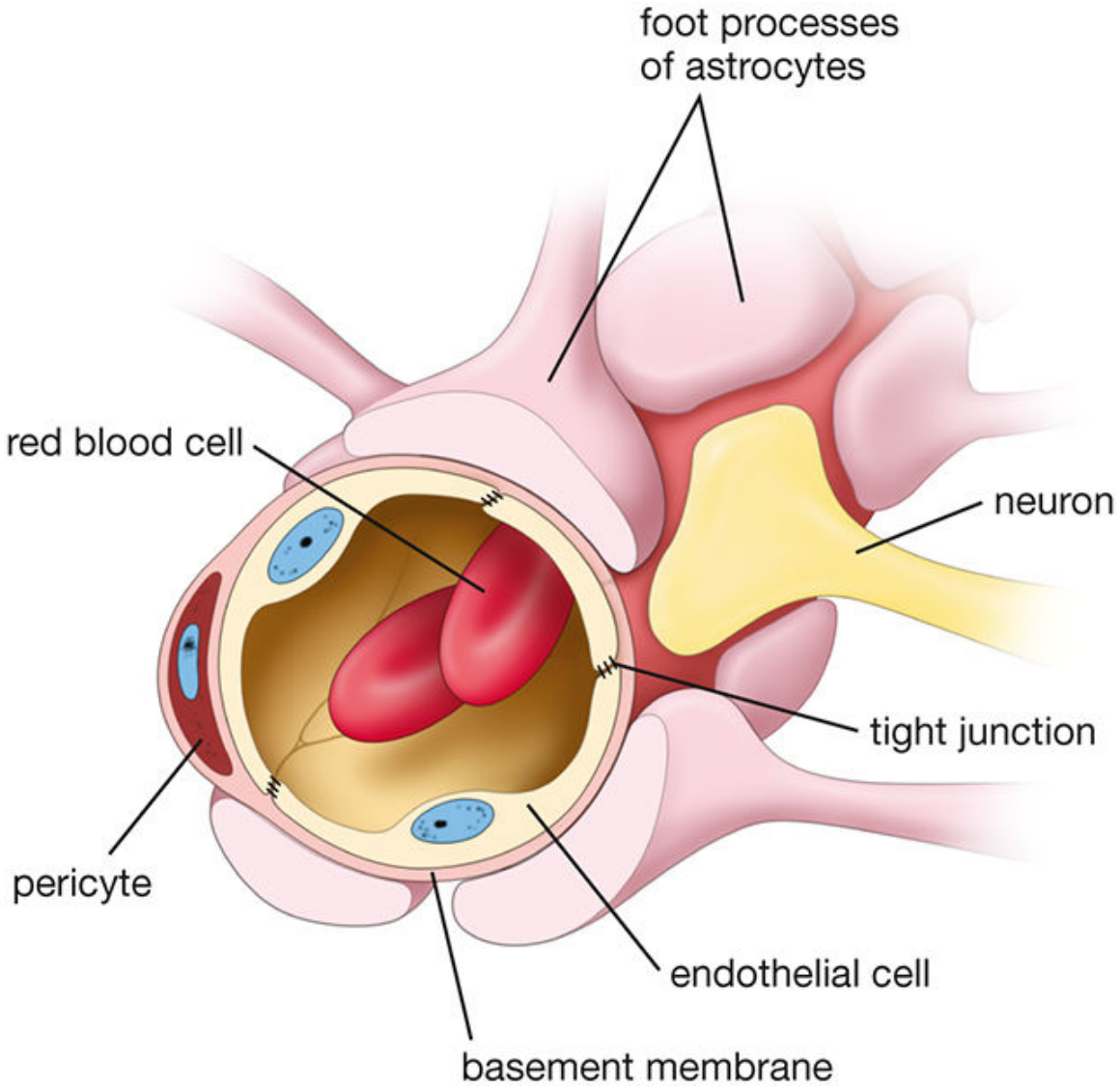


FIGURE 12.36. Schematic drawing of the blood–brain barrier. This drawing shows the blood–brain barrier, which consists of endothelial cells joined together by elaborate, complex tight junctions, endothelial basal lamina, and the end-foot processes of astrocytes.

The blood–brain barrier restricts passage of certain ions and substances from the bloodstream to tissues of the CNS.

The presence of only a few small vesicles indicates that pinocytosis across the brain endothelial cells is severely restricted. Substances with a molecular weight **greater than 500 Da** generally cannot cross the blood–brain barrier. However, some molecules leave and enter the blood capillaries through endothelial cells. For instance, O_2, CO_2, and certain lipid-soluble molecules (e.g., ethanol and steroid hormones) easily penetrate the endothelial cells and pass freely between the blood and extracellular fluid of the CNS. Owing to the high K^+ permeability of the neuronal membrane, neurons are

particularly sensitive to changes in the concentration of extracellular K^+. As previously discussed, astrocytes are responsible for buffering the concentration of K^+ in the brain extracellular fluid (see pages 411-412). They are assisted by endothelial cells of the blood–brain barrier that effectively limit the movement of K^+ into the extracellular fluid of the CNS.

Substances that do cross the brain capillary wall are actively transported by influx and efflux transporters.

Many molecules that are required for neuronal integrity leave and enter the blood capillaries through endothelial cells. Brain endothelial cells use highly polarized transmembrane transporters to regulate the influx of nutrients and efflux of metabolic waste and toxins between the blood and the extracellular fluid of the CNS. The major class of known **efflux transporters** is the **ATP-binding cassette (ABC)** transporters. These efflux transporters utilize ATP to transport molecules into the blood against their concentration gradients. Brain endothelial cells also express specialized **influx transporters** that facilitate the transport of nutrients such as glucose (which neurons depend on almost exclusively for energy), ions, amino acids, nucleotides, vitamins, and proteins from the blood to the extracellular fluid of the CNS. Many of these transporters belong to the superfamily **solute carrier proteins (SLCs)**, which include glucose transporters (GLUT1) and cationic amino acid transporters (SLC7A1). The permeability of the blood–brain barrier to these macromolecules is attributable to the level of expression of specific transporters on the brain endothelial cell surface.

Several other proteins that reside within the plasma membrane of endothelial cells protect the brain by metabolizing certain molecules, such as drugs and foreign proteins, thus preventing them from crossing the barrier. The restrictive nature of the blood–brain barrier hinders the delivery of therapeutics for many neurologic disorders. For example, **L-dopa (levodopa)**, the precursor of the neuromediators dopamine and noradrenaline, easily crosses the blood–brain barrier. However, the **dopamine** formed from the decarboxylation of L-dopa in endothelial cells cannot cross the barrier and is restricted from the CNS. In this case, the blood–brain barrier regulates the concentration of L-dopa in the brain. Clinically, this restriction explains why L-dopa is administered for the treatment of **dopamine deficiency** (e.g., Parkinson disease) rather than dopamine.

Recent studies indicate that the end-feet of astrocytes also play an important role in maintaining **water homeostasis** in brain tissue. **Water channels** (aquaporin AQP4) are found in end-foot processes in which water crosses the blood–brain barrier. In pathologic conditions, such as brain

edema, these channels play a key role in reestablishing osmotic equilibrium in the brain.

The midline structures bordering the third and fourth ventricles are unique areas of the brain that are outside the blood–brain barrier.

Some parts of the CNS, however, are not isolated from substances carried in the bloodstream. The barrier is ineffective or absent in the sites located along the third and fourth ventricles of the brain, which are collectively called **circumventricular organs**. Circumventricular organs include the pineal gland, median eminence, subfornical organ, area postrema, subcommissural organ, organum vasculosum of the lamina terminalis, and posterior lobe of the pituitary gland. These barrier-deficient areas are most likely involved in the sampling of materials circulating in the blood that are normally excluded by the blood–brain barrier and then conveying information about these substances to the CNS. Circumventricular organs are important in regulating body fluid homeostasis and controlling neurosecretory activity of the nervous system. Some researchers describe them as "windows of the brain" within the central neurohumoral system.

RESPONSE OF NEURONS TO INJURY

Neuronal injury induces a complex sequence of events termed **axonal degeneration** and **neural regeneration**. Neurons, Schwann cells, oligodendrocytes, macrophages, and microglia are involved in these responses. In contrast to the PNS, in which injured axons rapidly regenerate, axons severed in the CNS usually cannot regenerate. This striking difference is most likely related to the inability of oligodendrocytes and microglia cells to phagocytose myelin debris quickly and the restriction of large numbers of migrating macrophages by the blood–brain barrier. Because myelin debris contains several inhibitors of axon regeneration, its removal is essential to the regeneration progress.

Degeneration

The portion of a nerve fiber distal to a site of injury degenerates because of interrupted axonal transport.

Degeneration of an axon distal to a site of injury is called **anterograde (Wallerian) degeneration** (Fig. 12.37a and b). The first sign of injury, which occurs 8–24 hours after the axon is damaged, is axonal swelling. The axon then disintegrates, and the components of the cytoskeleton, including microtubules and neurofilaments, are disassembled, resulting in

fragmentation of the axon. Myelin is also destroyed. This process is known as **granular disintegration of the axonal cytoskeleton**. In the PNS, loss of axon contact induces several changes in myelinating Schwann cells. After injury, Schwann cells lose their characteristic gene expression pattern and undergo dedifferentiation and reprogramming into **repair Schwann cells**. This reprogramming involves the activation of a set of repair-related transcription factors and reexpression of molecules characteristic of immature Schwann cells during their early stages of development. Schwann cells undergoing reprogramming downregulate promyelin transcription factors and expression of myelin-specific proteins (see pages 405-407). Genes associated with epithelial-to-mesenchymal transition (EMT) are upregulated, triggering myelin autophagy that breaks down the myelin sheath enclosing the axon. At the same time, transformed repair Schwann cells upregulate and secrete several **glial growth factors (GGFs)**, members of a family of axon-associated neuregulins and potent stimulators of axonal proliferation. Increased secretion of cytokines allows repair Schwann cells to interact with immune cells and recruit **macrophages** to the site of nerve injury. Under the influence of GGFs, repair Schwann cells divide and arrange themselves in a line along their external laminae. Because axonal processes distal to the site of injury have been removed by phagocytosis, the linear arrangement of the repair Schwann cells' external laminae resembles a long tube with an empty lumen (Fig. 12.37b). In the CNS, oligodendrocyte survival is dependent on signals from axons. In contrast to Schwann cells, if oligodendrocytes lose contact with axons, they respond by initiating apoptotic programmed cell death.

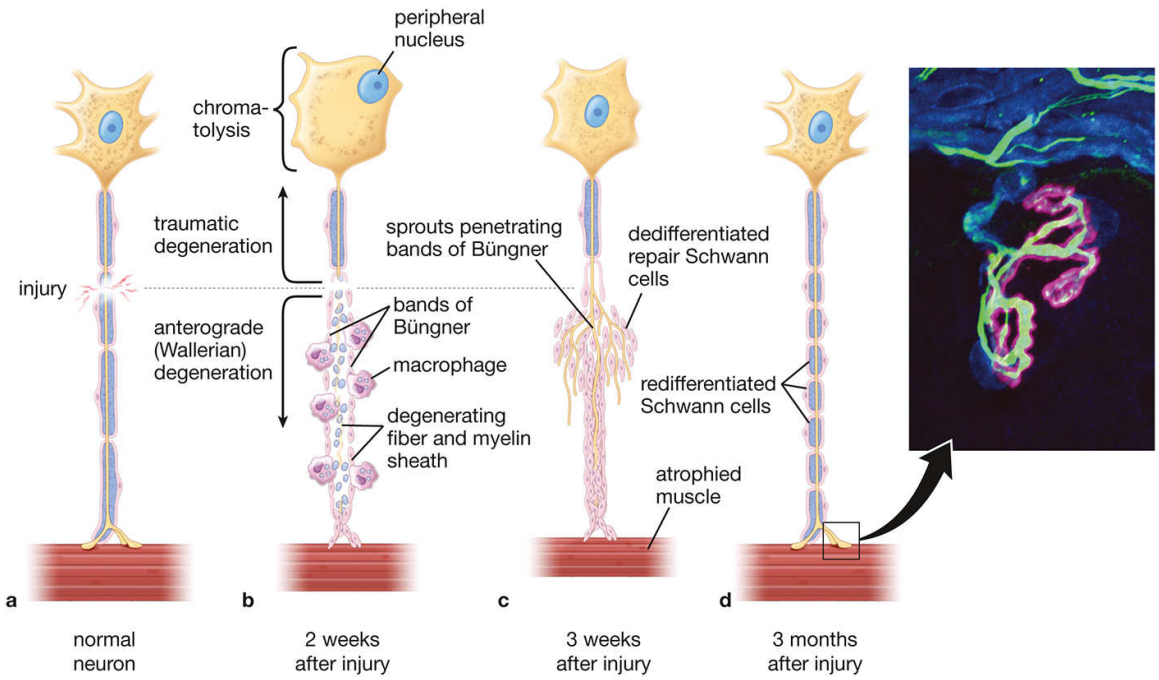


FIGURE 12.37. Response of a nerve fiber to injury. a. A normal nerve fiber at the time of injury, with its nerve cell body and the effector cell (striated skeletal muscle). Note the position of the neuron nucleus and the number and distribution of Nissl bodies. **b.** When the fiber is injured, the neuronal nucleus moves to the cell periphery, and the number of Nissl bodies is greatly reduced. The nerve fiber distal to the injury degenerates along with its myelin sheath. Schwann cells dedifferentiate into repair Schwann cell; myelin debris is phagocytosed by macrophages. **c.** Proliferating repair Schwann cells form cellular bands (of Büngner) that are penetrated by the growing axonal sprout. The axon grows at a rate of 0.5–3 mm/d. Note that the muscle fibers show a pronounced atrophy. **d.** If the growing axonal sprout reaches the muscle fiber, the regeneration is successful and new neuromuscular junctions are developed; thus, the function of skeletal muscle is restored. **Inset.** A confocal immunofluorescent image showing reinnervated skeletal muscle of the mouse. Regenerating motor axons are stained *green* for neurofilaments; reestablished connections with two neuromuscular junctions are visualized in *pink*, which reflects specific staining for postsynaptic acetylcholine receptors; repair Schwann cells are stained *blue* for S100, which represents a Schwann cell–specific calcium-binding protein. Regenerating axons have extended along repair Schwann cells, which has led them to the original synaptic sites of the muscle fibers. ×640. (Courtesy of Dr. Young-Jin Son.)

The most important cells in clearing myelin debris from the site of nerve injury are monocyte-derived macrophages.

In the PNS, even before the arrival of phagocytotic cells at the site of nerve injury, **repair Schwann cells** initiate the removal of myelin debris. It is estimated that during the first 5–7 days after nerve injury, about 50% of the myelin is degraded by repair Schwann cells. The rest of myelin clearance is performed by macrophages, which migrate to the site of injury and phagocytose myelin debris. Several cytokines, such as interleukin-6 (IL-6), leukemia inhibitory factor (LIF), and monocyte chemotactic protein 1 (MCP-1), are secreted by repair Schwann cells. These cytokines activate **resident macrophages** (normally present in small numbers in the peripheral nerves) to migrate to the site of nerve injury, proliferate, and then phagocytize remaining myelin debris.

The efficient clearance of myelin debris in the PNS is attributed to the massive recruitment of **monocyte-derived macrophages** that migrate from blood vessels and infiltrate the vicinity of the nerve injury (Fig. 12.38). When an axon is injured, the blood–nerve barrier (see pages 424-425) is disrupted along the entire length of the injured axon, which allows for the influx of these cells into the site of injury. The presence of large numbers of

monocyte-derived macrophages speeds up the process of myelin removal, which, in peripheral nerves, is usually completed within 2 weeks.

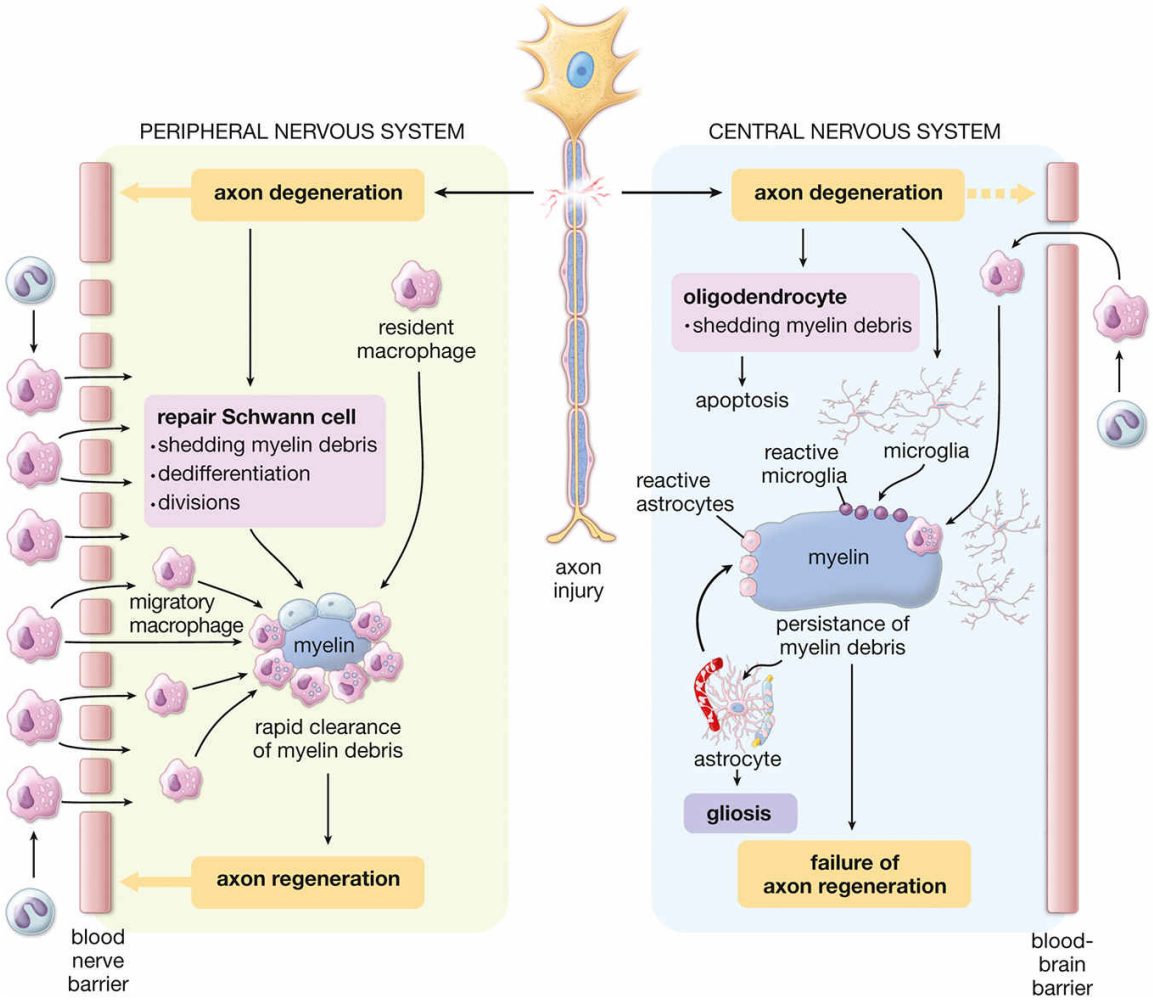


FIGURE 12.38. Schematic diagram of response to neuronal injury within peripheral and central nervous systems. Injuries of nerve processes (axons and dendrites) in both the peripheral nervous system (PNS) and the central nervous system (CNS) induce axonal degeneration and neural regeneration. These processes involve not only neurons but also supportive cells such as Schwann cells and oligodendrocytes as well as phagocytic cells such as macrophages and microglia. Injuries to axons in the PNS lead to their degeneration, which triggers the reprogramming and dedifferentiation of Schwann cells into repair Schwan cells and disruption of the blood–nerve barrier along the entire length of the injured axon. Repair Schwann cells play a major part in the initial phase of myelin degradation and clearance. About 50% of the myelin is degraded during this phase. Dismantling of the blood–nerve barrier allows massive infiltration of monocyte-derived macrophages, which phagocytose myelin debris. Rapid clearance of myelin debris allows for axon regeneration and subsequent restoration of the blood–nerve barrier. In the CNS, limited disruption of the blood–brain barrier restricts infiltration of monocyte-derived macrophages, dramatically slowing the process of myelin

removal. Myelin is primarily removed by reactive microglia and secondarily by reactive astrocytes. In addition, apoptosis of oligodendrocytes, inefficient phagocytic activity of microglia, and the formation of an astrocyte-derived scar lead to failure of nerve regeneration in the CNS.

In the CNS, inefficient clearance of myelin debris due to limited access of monocyte-derived macrophages, the inefficient phagocytic activity of microglia, and the formation of an astrocyte-derived scar severely restricts nerve regeneration.

A key difference in the **CNS response to axonal injury** relates to the fact that the blood–brain barrier (see pages 424-425) is disrupted only at the site of injury and not along the entire length of the injured axon (see Fig. 12.38). This limits infiltration of monocyte-derived macrophages to the CNS and dramatically slows the process of myelin removal, which can take months or even years. Although the number of microglial cells increases at the sites of CNS injury, these **reactive microglia cells** do not possess the full phagocytotic capabilities of migrating macrophages. As discussed earlier (see page 410), astrocytic phagocytosis also plays a role in nerve tissue remodeling after brain injury. The inefficient **clearance of myelin debris** is a major factor in the failure of nerve regeneration in the CNS. Another factor that affects nerve regeneration is the formation of a **glial (astrocyte-derived) scar** that fills the empty space left by degenerated axons. Scar formation is discussed in Folder 12.3; cognitive impairments after COVID-19 infection are discussed in Folder 12.4.

FOLDER 12.3

CLINICAL CORRELATION: REACTIVE GLIOSIS: SCAR FORMATION IN THE CENTRAL NERVOUS SYSTEM

When a region of the central nervous system (CNS) is injured, astrocytes near the lesion become activated. They divide and undergo marked hypertrophy with a visible increase in the number of their cytoplasmic processes. In time, the processes become densely packed with **glial fibrillary acidic protein (GFAP) intermediate filaments**. Eventually, scar tissue is formed. This process is referred to as **reactive gliosis**, whereas the resulting permanent scar is most often called a **plaque**. Reactive gliosis varies widely in duration, degree of hyperplasia, and time course of expression of GFAP immunostaining.

Several biological mechanisms for induction and maintenance of reactive gliosis have been proposed. The type of glial cell that responds during reactive gliosis depends on the brain structure that is damaged. In addition, activation of the microglial cell population occurs almost

immediately after any kind of injury to the CNS. These reactive microglial cells migrate toward the site of injury and exhibit marked phagocytic activity. However, their phagocytic activity and ability to remove myelin debris are much less than that of monocyte-derived macrophages. Gliosis is a prominent feature of many diseases of the CNS, including stroke, neurotoxic damage, genetic diseases, inflammatory demyelination, and neurodegenerative disorders, such as multiple sclerosis. Much of the research in CNS regeneration is focused on preventing or inhibiting glial scar formation.

FOLDER 12.4

CLINICAL CORRELATION: COGNITIVE IMPAIRMENTS AFTER COVID-19 INFECTIONS

The **COVID-19** (coronavirus disease 2019) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in over 550 million documented COVID cases worldwide and 6.3 million deaths (mid-2022 data). Individuals with COVID-19 experience symptoms ranging from mild respiratory symptoms to severe multiorgan illnesses. Recent studies indicate that in both humans and animal models, even mild COVID infection can result in detrimental **neuroinflammatory responses**. These are marked by elevation of neurotoxic cytokines and chemokines such as IFN-γ, IL6, TNF-α, CXCL10, CCL7, CCL2, CCL11, GMCSF, BAFF, and others that characteristically react against **white matter microglial cells**. In a mouse model of mild respiratory COVID-19 infection, researchers discovered hippocampal changes that included a decreased number of oligodendrocytes with subsequent myelin loss. These changes were accompanied by elevated levels of cerebrospinal fluid (CSF) chemokines, including **CCL11** (also known as *eosinophil chemotactic protein* or *eotaxin-1*), which is associated with the cognitive impairments seen in aging. Similarly, individuals that recovered from COVID-19 experience persistent neurologic symptoms resembling **cancer therapy–related cognitive impairment (CRCI)**. Certain drugs used in chemotherapy treatment (e.g., methotrexate) activate a distinct subpopulation of microglia that reside in white matter. Activated (reactive) microglia impair the ongoing differentiation of myelin-forming oligodendrocytes (loss of myelin), inhibit new neuron formation (neurogenesis) in the hippocampus, and cause elevation of CCL11. The cognitive impairments experienced by individuals with CRCI syndrome are often referred to as "**chemo fog**." Recent studies indicate that COVID-19 survivors experience similar neurologic symptoms called "**COVID fog**," which represent post-COVID cognitive impairments. These include **impaired attention, decreased concentration,**

slowed information processing speed, memory problems, as well as other impairments of executive function. As a result of these impairments, individuals who recovered from COVID-19 may present in the clinic with increased rates of **anxiety, depression, disordered sleep**, and **fatigue**. These symptoms of post–COVID-19 cognitive impairments represent a major public health crisis preventing people from returning to their previous level of occupational activity.

Traumatic degeneration occurs in the proximal part of the injured nerve.

Some retrograde degeneration also occurs in the proximal axon and is called **traumatic degeneration**. This process appears to be histologically similar to anterograde (Wallerian) degeneration. The extent of traumatic degeneration depends on the severity of the injury and usually extends to only one or a few internodal segments. Sometimes, traumatic degeneration extends more proximally than one or a few nodes of Ranvier and may result in death of the cell body. When a motor fiber is cut, the muscle innervated by that fiber undergoes atrophy (Fig. 12.37c).

Retrograde signaling to the cell body of an injured nerve causes a change in gene expression that initiates reorganization of the perinuclear cytoplasm.

Axonal injury also initiates retrograde signaling to the nerve cell body, leading to the upregulation of a gene called **c-jun**. C-jun transcription factor is involved in the early as well as later stages of nerve regeneration. Reorganization of the perinuclear cytoplasm and organelles starts within a few days. The cell body of the injured nerve swells, and its nucleus moves peripherally. Initially, Nissl bodies disappear from the center of the neuron and move to the periphery of the neuron in a process called **chromatolysis**. Chromatolysis is first observed within 1–2 days after injury and reaches a peak at about 2 weeks (see Fig. 12.37b). The changes in the cell body are proportional to the amount of axoplasm destroyed by the injury; extensive loss of axoplasm can lead to the death of the cell.

Before the development of modern dyes and radioisotope tracer techniques, Wallerian degeneration and chromatolysis were used as research tools. These tools allowed researchers to trace the pathways and destination of axons and the localization of the cell bodies of experimentally injured nerves.

Regeneration

In the PNS, repair Schwann cells divide and develop cellular bands that bridge a newly formed scar and direct growth of new nerve processes.

As mentioned previously, at the site of the injury, cells are reprogrammed to generate specialized **repair Schwann cells** to promote tissue repair. Division of repair Schwann cells is the first step in the regeneration of a severed or crushed peripheral nerve. Initially, these cells arrange themselves in a series of cylinders called **endoneurial tubes**. Removal of myelin and axonal debris inside the tubes eventually causes them to collapse. Proliferating repair Schwann cells elongate, extending long, parallel processes, and organize themselves into cellular bands resembling longitudinal columns called regeneration tracks or **bands of Büngner** (Fig. 12.39). These cellular bands guide the growth of new nerve processes (**neurites** or **sprouts**) of regenerating axons. Once the bands are in place, large numbers of sprouts begin to grow from the proximal stump (see Fig. 12.37c). A **growth cone** develops in the distal portion of each sprout that consists of filopodia rich in actin filaments. The tips of the filopodia establish a direction for the advancement of the growth cone. They preferentially interact with proteins of the extracellular matrix such as fibronectin and laminin found within the external lamina of the repair Schwann cell. Thus, if a sprout associates itself with a band of Büngner, it regenerates between the layers of external lamina of the repair Schwann cell. This sprout will grow along the band at a rate of about **3 mm/day**. Although many new sprouts do not make contact with cellular bands and degenerate, their large number increases the probability of reestablishing sensory and motor connections. After crossing the site of injury, sprouts enter the surviving cellular bands in the distal stump. These bands then guide the neurites to their destination as well as provide a suitable microenvironment for continued growth (Fig. 12.37d). Axonal regeneration leads to Schwann cell redifferentiation, which occurs in a proximal-to-distal direction. In addition, redifferentiated Schwann cells upregulate genes for myelin-specific proteins and downregulate **c-Jun transcription factor**, which is central to the reprogramming of myelinating and nonmyelinating Remak Schwann cells to repair Schwann cells after injury.

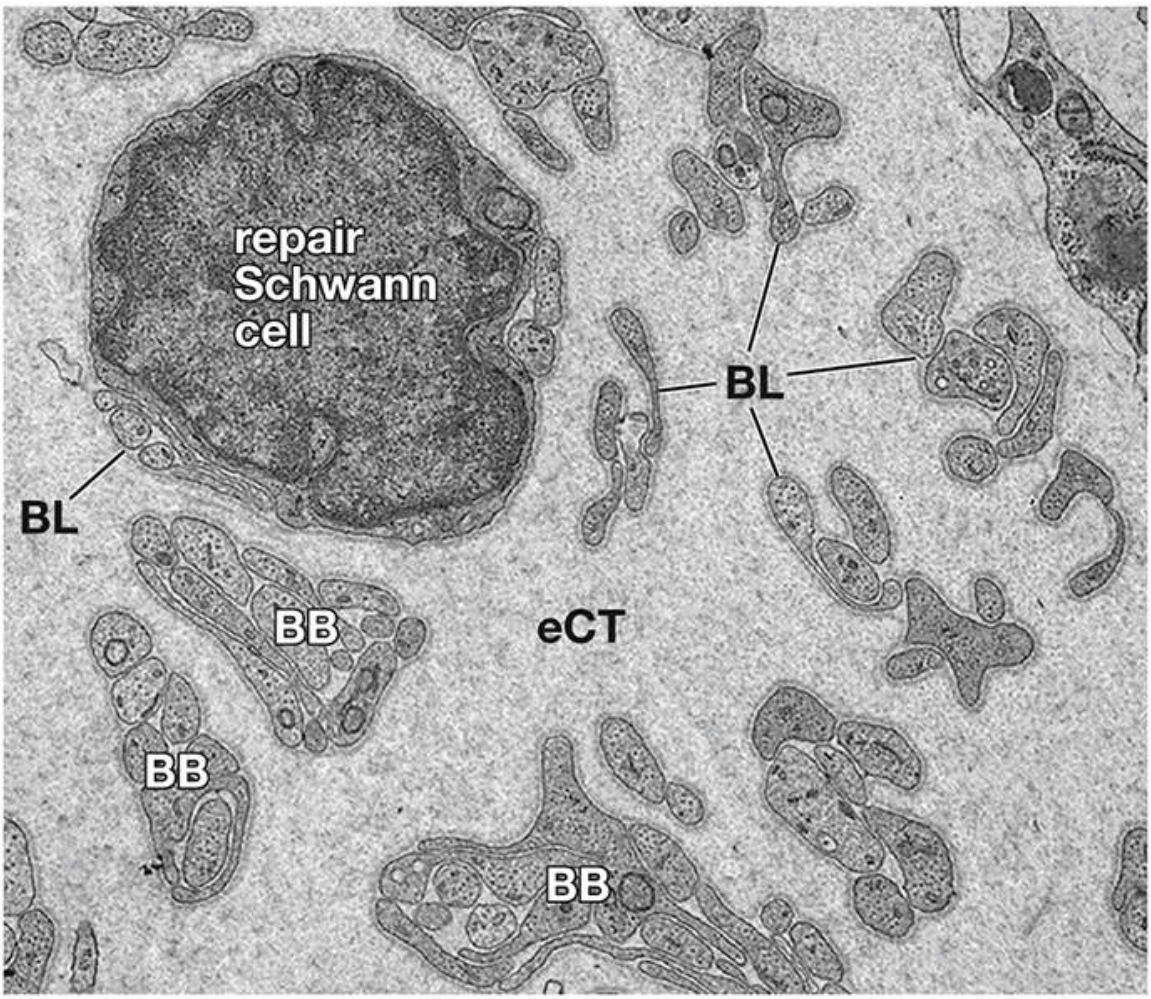


FIGURE 12.39. Electron micrograph of a distal stump of regenerating nerve. This image shows a cross section through the distal stump of the mouse tibial nerve 4 weeks after transection. A repair Schwann cell with a large nucleus and a thin rim of cytoplasm is enclosed by the basal (external) lamina (*BL*). Several cross sections of Büngner bands (*BB*) are embedded in the endoneurial connective tissue (*eCT*). They contain elongated parts of repair Schwann cells and their parallel processes. Note that every band and their components are also surrounded by the basal laminae. The cell in the *right upper corner* represents connective tissue cell (lack of basal lamina), and it may represent part of fibroblast or macrophage. × 65,000. (Courtesy of Dr. Kristjan R. Jessen, University College London, London, UK).

If physical contact is reestablished between a motor neuron and its muscle, function is usually reestablished.

Microsurgical techniques that rapidly reestablish intimate apposition of severed nerve and vessel ends have made reattachment of severed limbs and digits, with subsequent reestablishment of function, a relatively common procedure. If the axonal sprouts do not reestablish contact with the appropriate Schwann cells, then the sprouts grow in a disorganized

manner, resulting in a mass of tangled axonal processes known as a **traumatic neuroma** or **amputation neuroma**. Clinically, a traumatic neuroma usually appears as a freely movable nodule at the site of nerve injury and is characterized by pain, particularly on palpation. Formation of a traumatic neuroma of the injured motor nerve prevents reinnervation of the affected muscle.

NERVE TISSUE

OVERVIEW OF THE NERVOUS SYSTEM

- The **nervous system** enables the body to respond to changes in its external environment and controls the functions of internal organs and systems.
- Anatomically, the nervous system is divided into the **central nervous system** (CNS; (brain and spinal cord) and the **peripheral nervous system** (PNS; peripheral and cranial nerves and ganglia).
- Functionally, the nervous system is divided into the **somatic nervous system** (SNS; under conscious voluntary control) and the **autonomic nervous system** (ANS; under involuntary control).
- The ANS is further subdivided into **sympathetic**, **parasympathetic**, and **enteric divisions**. The enteric division serves the alimentary canal and regulates the function of internal organs by innervating smooth and cardiac muscle cells as well as glandular epithelium.

SUPPORTING CELLS OF THE NERVOUS SYSTEM: NEUROGLIA

- **Peripheral neuroglia** includes Schwann cells and satellite cells.
- In **myelinated** nerves, **Schwann cells** produce the **myelin sheath** from compacted layers of their own cell membranes that are wrapped concentrically around the nerve cell process.
- The junction between two adjacent Schwann cells, the **node of Ranvier**, is the site where the electrical impulse is regenerated for

high-speed propagation along the axon.

- In **unmyelinated** nerves, nerve processes are enveloped in the cytoplasm of **Remak Schwann cells**.
- **Satellite cells** maintain a controlled microenvironment around the nerve cell bodies in ganglia of the PNS.
- There are four types of **central neuroglia**: **astrocytes** (provide physical and metabolic support for neurons of the CNS), **oligodendrocytes** (produce and maintain the myelin sheath in the CNS), **microglia** (possess phagocytotic properties and mediate neuroimmune reactions), and **ependymal cells** (form the epithelial-like lining of the ventricles of the brain and spinal canal).

NEURONS

- **Nerve tissue** consists of two principal types of cells: **neurons** (specialized cells that conduct impulses) and **supporting cells** (nonconducting cells in close proximity to nerve cells and their processes).
- The neuron is the structural and functional unit of the nervous system.
- **Neurons** do not divide; however, in certain regions of the brain, **neural stem cells** may divide and differentiate into new neurons.
- Neurons are grouped into three categories: **sensory neurons** (carry impulses from receptors to the CNS), **motor neurons** (carry impulses from the CNS or ganglia to effector cells), and **interneurons** (communicate between sensory and motor neurons).
- Each neuron consists of a **cell body** or **perikaryon** (contains the nucleus, Nissl bodies, and other organelles), an **axon** (usually the longest process of the cell body; transmits impulses away from the cell body), and several **dendrites** (shorter processes that transmit impulses toward the cell body).
- Neurons communicate with other neurons and with effector cells by specialized junctions called **synapses**.
- **Chemical synapses** are the most common type of synapse. Each has a **presynaptic element** containing vesicles filled with neurotransmitter, a **synaptic cleft** into which neurotransmitter is released from the presynaptic vesicles, and a **postsynaptic membrane** containing receptors to which the neurotransmitter binds.
- **Electrical synapses** are less common and are represented by **gap junctions**.
- The chemical structure of a **neurotransmitter** determines either an **excitatory** (e.g., acetylcholine, glutamine) or **inhibitory** (e.g., GABA, glycine) response from the postsynaptic membrane.

ORIGIN OF NERVE TISSUE CELLS

- CNS neurons and central glia (except microglial cells) are derived from neuroectodermal cells of the **neural tube**. Microglial cells represent population of resident macrophages derived from erythro-myeloid progenitor cells in the **yolk sac**.
- PNS ganglion cells and peripheral glia are derived from the **neural crest**.

ORGANIZATION OF THE PERIPHERAL NERVOUS SYSTEM

- The PNS consists of **peripheral nerves** with specialized nerve endings (synapses) and **ganglia**-containing nerve cell bodies.
- **Motor neuron cell bodies** of the PNS lie in the CNS, and **sensory neuron cell bodies** are located in the dorsal root ganglia.
- Individual nerve fibers are held together by connective tissue organized into **endoneurium** (surrounds each individual nerve fiber and associated Schwann cell), **perineurium** (surrounds each nerve fascicle), and **epineurium** (surrounds a peripheral nerve and fills the spaces between nerve fascicles).
- **Perineurial cells** are connected by tight junctions and contribute to the formation of the **blood–nerve barrier**.

ORGANIZATION OF THE CENTRAL NERVOUS SYSTEM

- The CNS consists of the **brain** and **spinal cord**. It is protected by the skull and vertebrae and is surrounded by three connective tissue membranes called **meninges** (**dura matter**, **arachnoid**, and **pia matter**).
- The **cerebrospinal fluid (CSF)** produced by the choroid plexus in the brain ventricles occupies the **subarachnoid space** located between arachnoid and pia matter. CSF surrounds and protects the CNS within the cranial cavity and the vertebral column.
- In the brain, the **gray matter** forms an outer layer of the cerebral cortex, whereas the **white matter** forms the inner core that is composed of axons, associated glial cells, and blood vessels.

- In the **spinal cord**, gray matter exhibits a butterfly-shaped inner substance, whereas the white matter occupies the periphery.
- The **cerebral cortex** contains nerve cell bodies, axons, dendrites, and central glial cells.
- The **blood–brain barrier** protects the CNS from fluctuating levels of electrolytes, hormones, and tissue metabolites circulating in the blood.

ORGANIZATION OF THE AUTONOMIC NERVOUS SYSTEM

- The **ANS** controls and regulates the body's internal environment. Its neural pathways are organized in a chain of two neurons (**presynaptic** and **postsynaptic neurons**) that convey impulses from the CNS to the visceral effectors.
- The ANS is subdivided into sympathetic, parasympathetic, and enteric divisions.
- **Presynaptic neurons** of the **sympathetic division** are located in the thoracolumbar portion of the spinal cord, whereas the **presynaptic neurons** of the **parasympathetic division** are located in the brainstem and sacral spinal cord.
- The **enteric division** of the ANS consists of ganglia and their processes that innervate the alimentary canal.

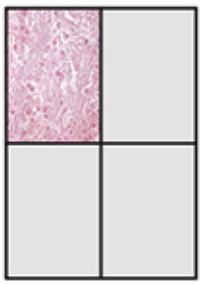
RESPONSE OF NEURONS TO INJURY

- Injured axons in the PNS usually regenerate, whereas axons severed in the CNS do not regenerate. This difference is related to the inability of microglial cells and astrocytes to efficiently phagocytose myelin debris.
- In the PNS, neuronal injury initially induces complete degeneration of an axon distal to the site of injury (**Wallerian degeneration**).
- **Traumatic degeneration** occurs in the proximal part of the injured nerve, followed by **neural regeneration**, in which repair Schwann cells divide and develop cellular bands that guide the growing axonal sprouts to the effector site.

PLATE 12.1 ■ SYMPATHETIC AND DORSAL ROOT GANGLIA

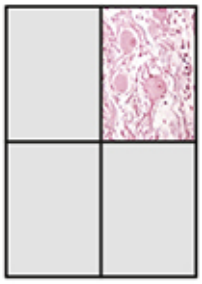
Ganglia are clusters of neuronal cell bodies located outside the *central nervous system* (CNS); nerve fibers lead to and from them. Sensory ganglia lie just outside the CNS and contain the cell bodies of sensory nerves that carry impulses into the CNS. Autonomic ganglia are peripheral motor ganglia of the *autonomic nervous system* (ANS) and contain the cell bodies of postsynaptic neurons that conduct nerve impulses to smooth muscle, cardiac muscle, and glands. Synapses between presynaptic neurons (all of which have their cell bodies in the CNS) and postsynaptic neurons occur in autonomic ganglia. *Sympathetic ganglia* constitute a major subclass of autonomic ganglia; *parasympathetic ganglia* and *enteric ganglia* constitute the other subclasses.

Sympathetic ganglia are located in the sympathetic chain (**paravertebral ganglia**) and on the anterior surface of the aorta (**prevertebral ganglia**). They send long postsynaptic axons to the viscera. **Parasympathetic ganglia (terminal ganglia)** are located in, or close to, the organs innervated by their postsynaptic neurons. The **enteric ganglia** are located in the *submucosal plexus* and the *myenteric plexus* of the alimentary canal. They receive parasympathetic presynaptic input as well as intrinsic input from other enteric ganglia and innervate smooth muscle of the gut wall.



Sympathetic ganglion, human, silver and hematoxylin and eosin (H&E) stains ×160.

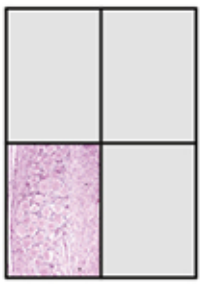
This micrograph shows a sympathetic ganglion stained with silver and counterstained with H&E is illustrated here. Shown to advantage are several discrete bundles of nerve fibers (*NF*) and numerous large circular structures, namely, the cell bodies (*CB*) of the postsynaptic neurons. Random patterns of nerve fibers are also seen. Moreover, careful examination of the cell bodies shows that some display several processes joined to them. Thus, these are multipolar neurons (one contained within the *rectangle* is shown at higher magnification). Generally, the connective tissue is not conspicuous in a silver preparation, although it can be identified by virtue of its location around the larger blood vessels (*BV*), particularly in the *upper part* of this figure.



Sympathetic ganglion, human, silver and H&E stains ×500.

The cell bodies of the sympathetic ganglion are typically large, and the one labeled here shows several processes (*P*). In addition, the cell body contains a large, pale-staining spherical nucleus (*N*); this, in turn, contains a spherical, intensely staining nucleolus (*NL*). These features, namely, a large pale-staining nucleus (indicating much-extended chromatin) and a large nucleolus, reflect a cell active in

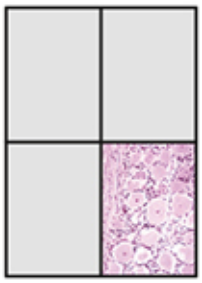
protein synthesis. Also shown in the cell body are accumulations of lipofuscin (*L*), a yellow pigment that is darkened by silver. Because of the large size of the cell body, the nucleus is not always included in the section; in that case, the cell body appears as a rounded cytoplasmic mass.



Dorsal root ganglion, cat, H&E ×160.

Dorsal root ganglia differ from autonomic ganglia in a number of ways. Whereas the latter contain multipolar neurons and have synaptic connections, dorsal root ganglia contain pseudounipolar sensory neurons and have no synaptic connections in the ganglion.

Part of a dorsal root ganglion stained with H&E is shown in this figure. The specimen includes the edge of the ganglion, where it is covered with connective tissue (*CT*). The dorsal root ganglion contains large cell bodies (*CB*) that are typically arranged as closely packed clusters. Also, between and around the cell clusters, there are bundles of nerve fibers (*NF*). Most of the fiber bundles indicated by the label have been sectioned longitudinally.



Dorsal root ganglion, cat, H&E ×350.

At higher magnification of the same ganglion, the constituents of the nerve fiber show their characteristic structure, namely, a centrally located axon (*A*) surrounded by an empty space after myelin was washed out during slide preparation (not labeled), which, in turn, is bounded on its outer border by the thin cytoplasmic strand of the neurilemma (*arrowheads*).

The cell bodies of the sensory neurons display large, pale-staining spherical nuclei (*N*) and intensely staining nucleoli (*NL*). Also seen in this H&E preparation are the nuclei of satellite cells (*Sat C*) that completely surround the cell body and are continuous with the Schwann cells that invest the axon. Note how much smaller these cells are compared with the neurons. Clusters of cells (*asterisks*) within the ganglion that have an epithelioid appearance are en-face views of satellite cells where the section tangentially includes the satellite cells but barely grazes the adjacent cell body.

A, axon
BV, blood vessels
CB, cell body of neuron
CT, connective tissue
L, lipofuscin
N, nucleus of nerve cell

NF, nerve fibers
NL, nucleolus
P, processes of nerve cell body
Sat C, satellite cells
arrowheads, neurilemma
asterisks, clusters of satellite cells

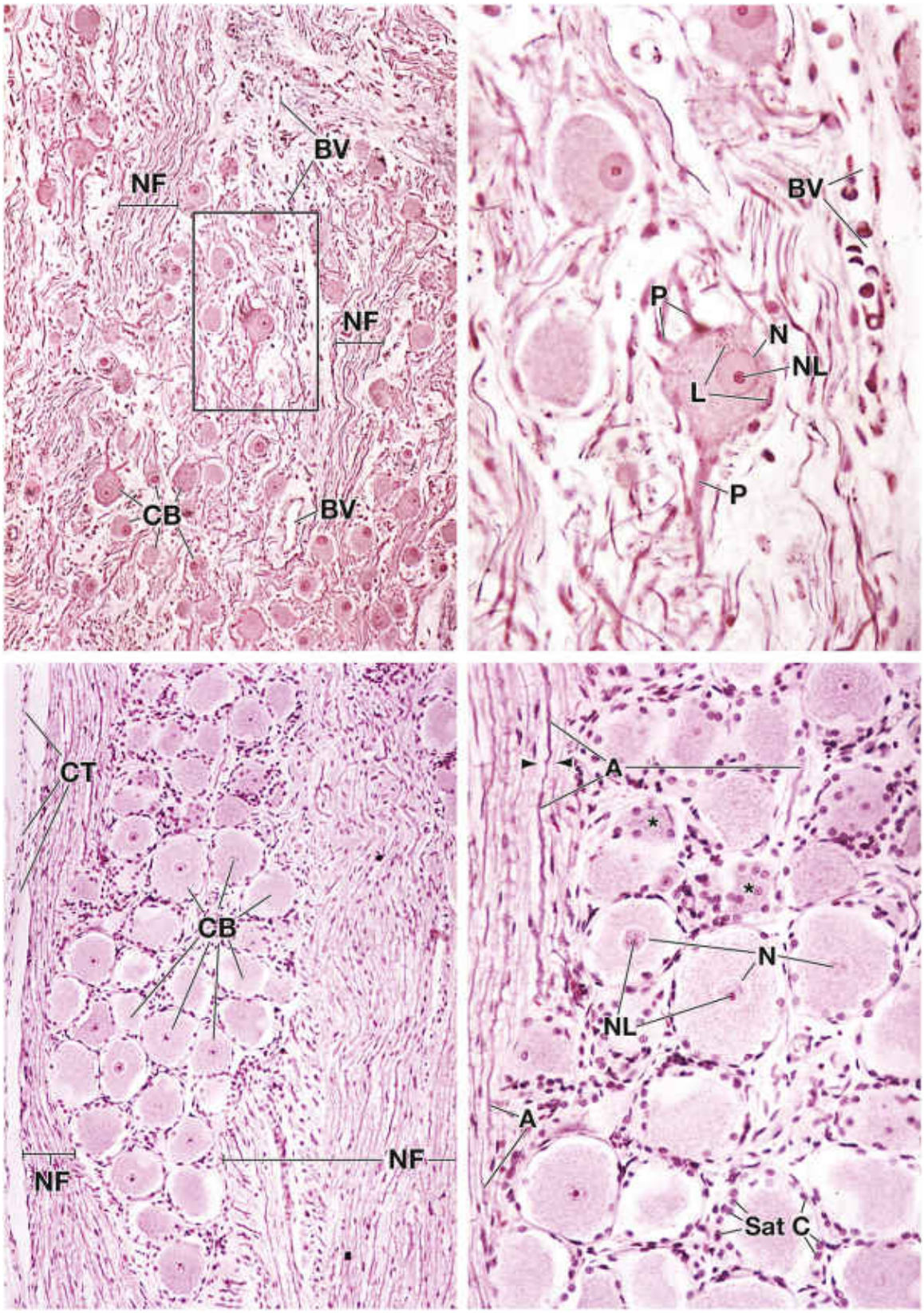
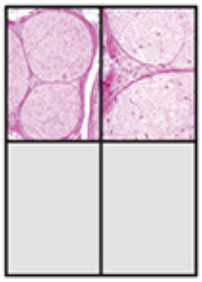


PLATE 12.2 ■ PERIPHERAL NERVE

Peripheral nerves are composed of bundles of nerve fibers held together by connective tissue and a specialized layer (or layers) of cells, the **perineurium**. The connective tissue consists of an outer layer, the **epineurium**, surrounding the whole nerve; the perineurium, surrounding bundles of nerve fibers; and the **endoneurium**, associated with individual nerve fibers. Each nerve fiber consists of an axon that is surrounded by a cellular investment called the **neurilemma** or the sheath of Schwann. The fiber may be myelinated or unmyelinated. The myelin, if present, is immediately around the axon and is formed by the concentric wrapping of the Schwann cell around the axon. This, in turn, is surrounded by the major portion of the cytoplasm of the Schwann cell, forming the neurilemma. Unmyelinated axons rest in grooves in the Remak Schwann cell.



Peripheral nerve, cross section, femoral nerve, hematoxylin and eosin (H&E) ×200 and ×640.

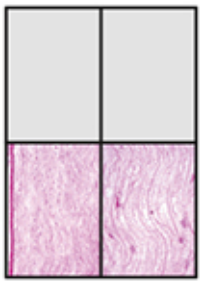
This cross section shows several bundles of nerve fibers (*BNF*). The external cover for the entire nerve is the **epineurium** (*Epn*), the layer of dense connective tissue that one touches when a nerve has been exposed during a dissection. The epineurium may also serve as part of the outermost cover of individual bundles. It contains blood vessels (*BV*) and may contain some fat cells. Typically, adipose tissue (*AT*) surrounds the nerve.

The figure on the *right* shows, at higher magnification, the perineurial septum (marked with *arrows* on the *left* image, which is now rotated and vertically disposed).

The layer beneath the epineurium that directly surrounds the bundle of nerve fibers is the **perineurium** (*Pn*). As seen in the cross section through the nerve, the nuclei of the perineurial cells appear flat and elongated; they are actually being viewed on edge and belong to flat cells that are also being viewed on edge. Again, as noted by the distribution of nuclei, it can be ascertained that the perineurium is only a few cells thick. The perineurium is a specialized layer of cells and extracellular material whose arrangement is not evident in H&E sections. The perineurium (*Pn*) and epineurium (*Epn*) are readily distinguished in the *triangular area* formed by the diverging perineurium of the two adjacent nerve bundles.

The nerve fibers included in the figure on the *right* are mostly myelinated, and because the nerve is cross-sectioned, the nerve fibers are also seen in this plane. They have a characteristic cross-sectional profile. Each nerve fiber shows a centrally placed axon (*A*); this is surrounded by a myelin space (*M*) in which some radially disposed precipitate may be retained, as in this specimen. External to the myelin space is a thin cytoplasmic rim representing the **neurilemma**. On occasion, a Schwann cell's nucleus (*SS*) appears to be perched on the neurilemma. The *upper*

edge of the nuclear crescent appears to occupy the same plane as that occupied by the neurilemma (*NI*). These features enable one to identify the nucleus as belonging to a Schwann (neurilemma) cell. Other nuclei are not related to the neurilemma but, rather, appear to be located between the nerve fibers. Such nuclei belong to the rare fibroblasts (*F*) of the endoneurium. The latter is the delicate connective tissue between the individual nerve fibers; it is extremely sparse and contains the capillaries (*C*) of the nerve bundle.



Peripheral nerve, longitudinal section, femoral nerve, H&E ×200 and ×640.

The edge of a longitudinally sectioned nerve bundle is shown on the *left*; a portion of the same nerve bundle is shown at higher magnification on the *right*. The boundary between the epineurium (*Epn*) and perineurium is ill-defined. Within the nerve bundle, the nerve fibers show a characteristic wavy pattern. Included among the wavy nerve fibers are nuclei belonging to **Schwann cells** and cells within the endoneurium. Higher magnification allows one to identify certain specific components of the nerve. Note that the nerve fibers (*NF*) are now shown in longitudinal profile. Moreover, each myelinated nerve fiber shows a centrally positioned axon (*A*) surrounded by a myelin space (*M*), which, in turn, is bordered on its outer edge by the thin cytoplasmic band of the neurilemma (*NI*). Another diagnostic feature of myelinated nerve fibers is also seen in longitudinal section, namely, the **node of Ranvier** (*NR*). This is the site at which the ends of the two Schwann cells meet. Histologically, the node appears as a constriction of the neurilemma, and sometimes, the constriction is marked by a cross-band, as in the figure on the *right*. It is difficult to determine whether the nuclei (*N*) shown here belong to Schwann cells or endoneurial fibroblasts.

A, axon
AT, adipose tissue
BNF, bundle of nerve fibers
BV, blood vessels
C, capillary
Epn, epineurium
F, fibroblast
M, myelin
N, nucleus of Schwann cell
NF, nerve fiber
NI, neurilemma
NR, node of Ranvier

Pn, perineurium
SS, Schwann cell nucleus
arrows, septum formed by perineurium

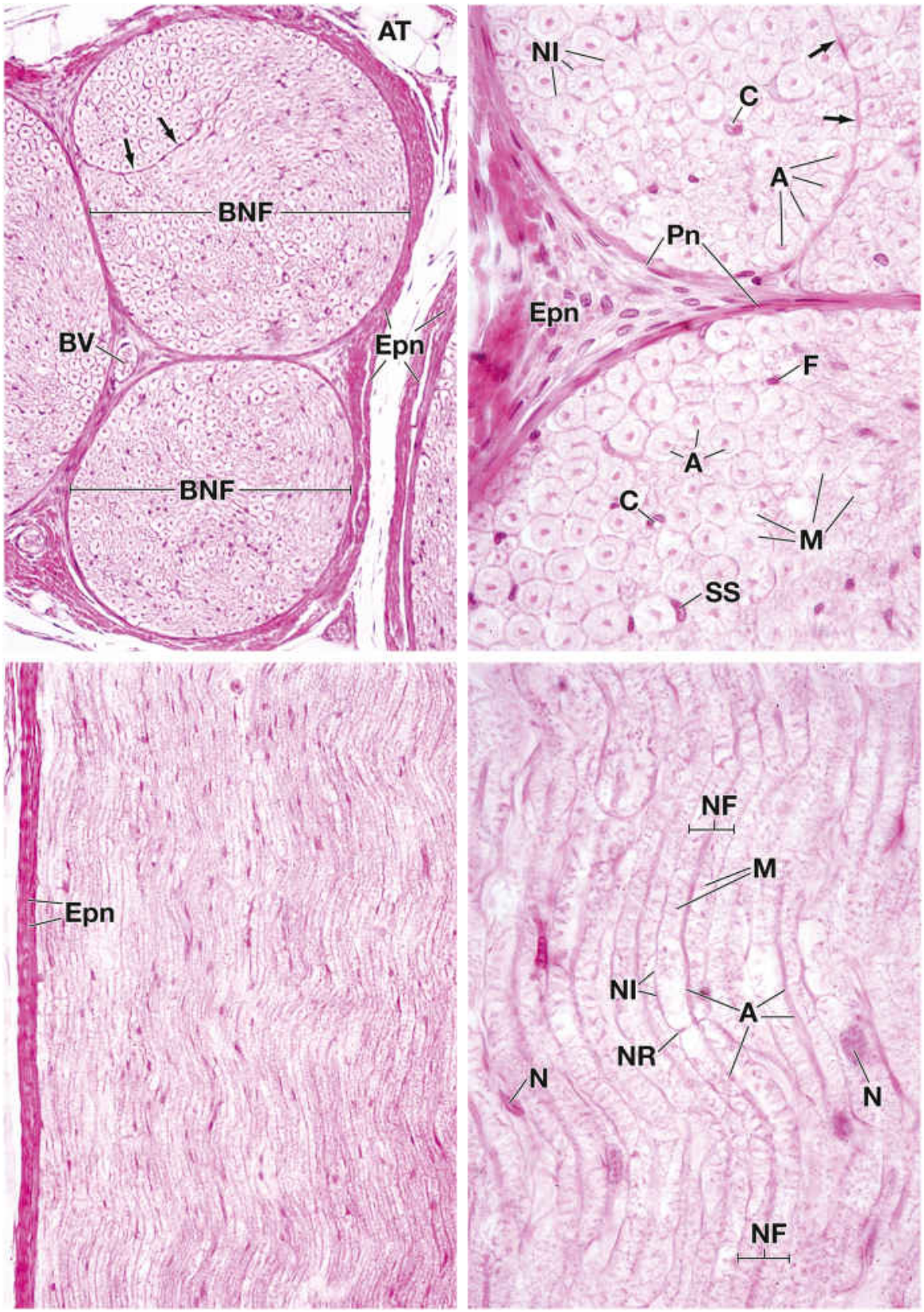
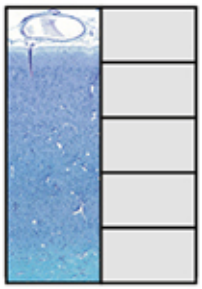


PLATE 12.3 ■ CEREBRUM

The cerebrum is the principal portion of the brain and contains the cell bodies of nerves that receive and store sensory information, nerves that control voluntary motor activity, and nerves that integrate and coordinate the activity of other nerves as well as the nerves and neural pathways that constitute memory.



Cerebral cortex, brain, human, Luxol fast blue—(Periodic acid–Schiff) PAS ×65.

This micrograph shows a low-magnification view of the cerebral cortex (*CC*). It includes the full thickness of the gray matter and a small amount of white matter at the bottom of the micrograph (*WM*). The white matter contains considerably fewer cells per unit area; these are neuroglial cells rather than nerve cell bodies that are present in the cortex. Covering the cortex is the pia mater (*PM*). A vein (*V*) can be seen enclosed by the pia mater. Also, a smaller blood vessel (*BV*) can be seen entering the substance of the cortex. The six layers of the cortex are marked by *dashed lines*, which represent only an approximation of the boundaries. Each layer is distinguished on the basis of predominant cell types and fiber (axon and dendrite) arrangement. Unless the fibers are specifically stained, they cannot be utilized to further aid in the identification of the layers. Rather, the delineation of the layers, as they are identified here, is based on cell types and more specifically, the shape and appearance of the cells.

The six layers of the cortex are named and described as follows:

I. The **plexiform layer** (or molecular layer) consists largely of fibers, most of which travel parallel to the surface, and relatively few cells, mostly neuroglial cells and occasional horizontal cells of Cajal.

II. The **small pyramidal cell layer** (or outer granular layer) consists mainly of small pyramidal cells and granule cells, also called *stellate cells*.

III. The **layer of medium pyramidal cells** (or layer of outer pyramidal cells) is not sharply demarcated from layer II. However, the pyramidal cells are somewhat larger and possess a typical pyramidal shape.

IV. The **granular layer** (or inner granular layer) is characterized by the presence of many small granule cells (stellate cells).

V. The **layer of large pyramidal cells** (or inner layer of pyramidal cells) contains pyramidal cells that, in many parts of the cerebrum, are smaller than

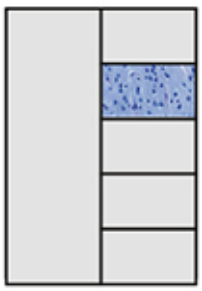
the pyramidal cells of layer III but, in the motor area, are extremely large and are called *Betz cells*.

VI. The **layer of polymorphic cells** contains cells with diverse shapes, many of which have a spindle of fusiform shape. These cells are called *fusiform cells*.

In addition to pyramidal cells, granule cells, and fusiform cells, two other cell types are also present in the cerebral cortex but are not recognizable in this preparation: the horizontal cells of Cajal, which are present only in layer I and send their processes laterally, and the cells of Martinotti, which send their axons toward the surface (opposite to that of pyramidal cells).

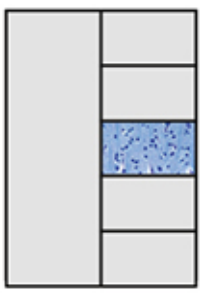
Layer I of cerebral cortex, brain, human, Luxol fast blue—PAS ×350.

This higher power micrograph shows layer I, the **plexiform layer**. It consists of nerve fibers, numerous neuroglial cells (*NN*), and occasional horizontal cells of Cajal. The neuroglial cells appear as naked nuclei, with the cytoplasm being indistinguishable from the nerve fibers that make up the bulk of this layer. Also present is a small capillary (*Cap*). The *pink* outline of the vessel is due to the PAS-staining reaction of its basement membrane.



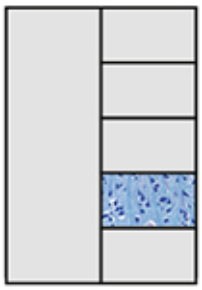
Layer II of cerebral cortex, brain, human, Luxol fast blue—PAS ×350.

This micrograph shows layer II, the **small pyramidal cell layer**. Many small pyramidal cells (*PC*) are present. Granule cells (*GC*) are also numerous, although difficult to identify here.



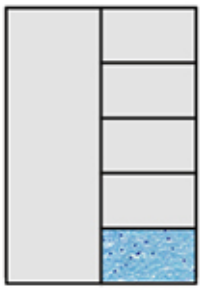
Layer IV of cerebral cortex, brain, human, Luxol fast blue—PAS ×350.

This micrograph shows layer IV, the **granular layer**. Many of the cells here are granule cells, but neuroglial cells are also prominent. The micrograph also reveals a number of capillaries. Note how they travel in various directions.



Layer VI of cerebral cortex, brain, human, Luxol fast blue—PAS ×350.

This micrograph shows layer VI, the **layer of polymorphic cells**, so named because of the diverse shape of the cells in this region. Pyramidal cells (*PC*) are readily recognized. Other cell types present include fusiform cells (*FC*), granule cells, and Martinotti cells.



White matter, brain, human, Luxol fast blue—PAS ×350.

This micrograph shows the outer portion of the **white matter**. The small round nuclei (*NN*) belong to neuroglial cells. As in the cortex, the cytoplasm of the cell is not distinguishable. Thus, they appear as naked nuclei in the bed of nerve processes. The neuropil is essentially a densely packed aggregation of nerve fibers and neuroglial cells.

BV, blood vessel
Cap, capillary
CC, cerebral cortex
FC, fusiform cells
GC, granule cells
NN, neuroglial nuclei
PC, pyramidal cells
PM, pia mater
V, vein
WM, white matter

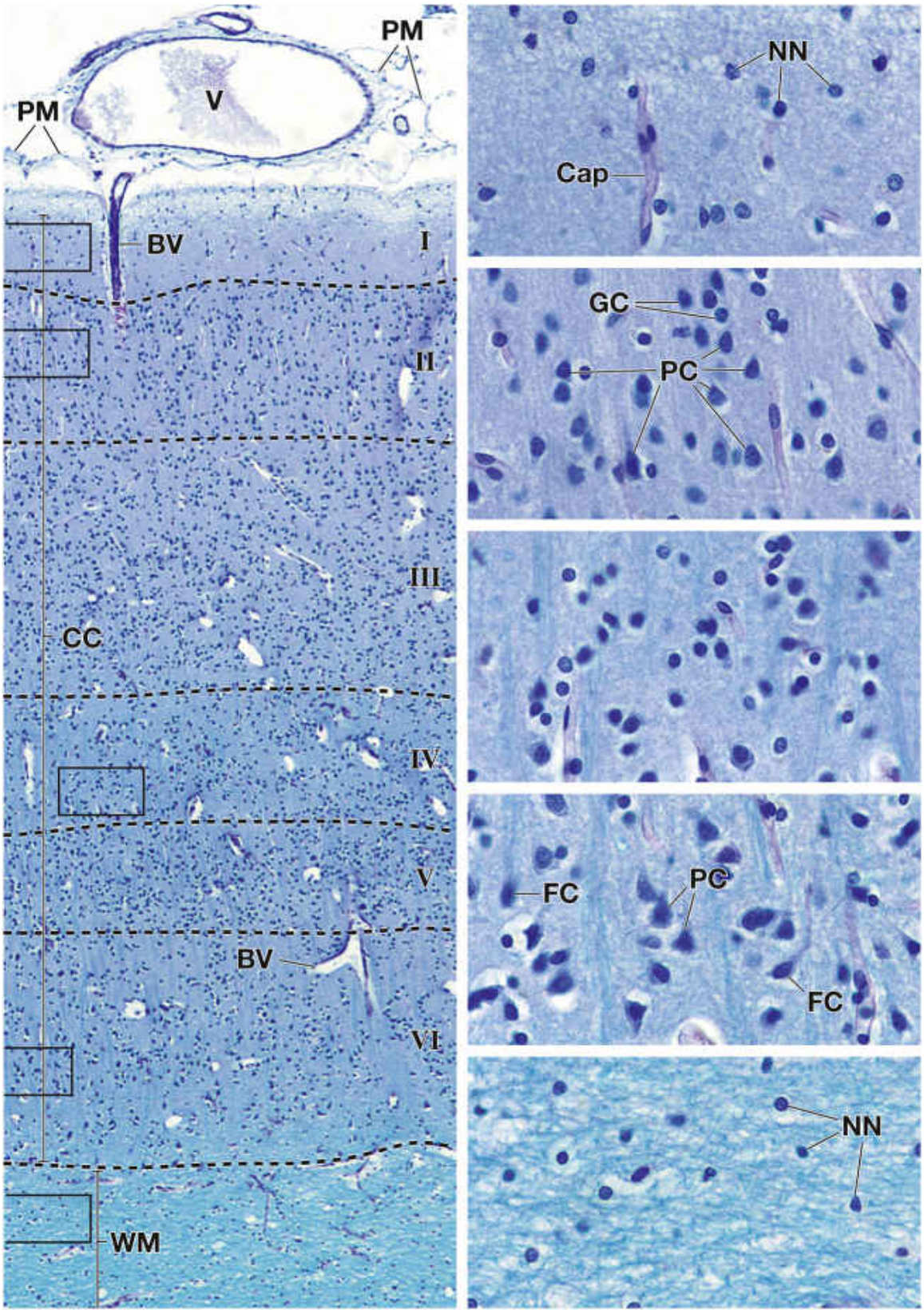
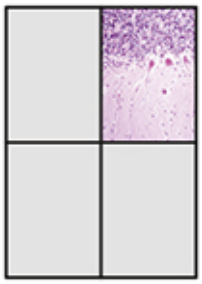


PLATE 12.4 ■ CEREBELLUM

The cerebellum is a portion of the brain lying behind and below the cerebrum; it serves to coordinate both voluntary movements and muscle function in the maintenance of normal posture.

Cerebellum, brain, human, hematoxylin and eosin (H&E) ×40.

The **cerebellar cortex** has the same appearance regardless of which region is examined. In this low-magnification view of the cerebellum, the outermost layer, the **molecular layer** (*Mol*), is lightly stained with eosin. Beneath this layer is the **granule cell layer** (*Gr*), which stains intensely with hematoxylin. Together, these two layers constitute the cortex of the cerebellum. Deep in the granule cell layer is another region that stains lightly with H&E and, except for location, shows no distinctive histologic features. This is the white matter (*WM*). As in the cerebrum, it contains nerve fibers, supporting neuroglial cells, and small blood vessels but no neuronal cell bodies. The fibrous cover on the cerebellar surface is the pia mater (*Pia*). Cerebellar blood vessels (*BV*) travel in this layer. (Shrinkage artifact has separated the pia mater from the cerebellar surface.) The *rectangular area* is shown at higher magnification in the figure on the *right*.



Cerebellum, brain, human, H&E ×400.

At the junction between the molecular and granule cell layers are the extremely large flask-shaped cell bodies of the **Purkinje cells** (*Pkj*). These cells are characteristic of the cerebellum. Each possesses numerous dendrites (*D*) that arborize in the molecular layer. The Purkinje cell has a single axon that is not usually evident in H&E sections. This nerve fiber represents the beginning of the outflow from the cerebellum.

The figure shows relatively few neuron cell bodies, those of the basket cells (*BC*), in the molecular layer; they are widely removed from each other and, at best, show only a small amount of cytoplasm surrounding the nucleus. In contrast, the granule cell layer presents an overall spotted-blue appearance due to the staining of numerous small nuclei with hematoxylin. These small neurons, called **granule cells**, receive incoming impulses from other parts of the CNS and send axons into the molecular layer, where they branch in the form of a T, so that the axons contact the dendrites of several Purkinje cells and basket cells. Incoming (mossy) fibers contact granule cells in the lightly stained areas called *glomeruli* (*arrows*). Careful examination of the granule cell layer where it meets the molecular layer will reveal a

group of nuclei (*G*) that are larger than the nuclei of granule cells. These belong to Golgi type II cells.

Cerebellum, brain, human, silver stain ×40.

The specimen in this figure has been stained with a silver procedure. Such procedures do not always color the specimen evenly, as does H&E. Note that the part of the molecular layer on the *right* is much darker than that on the *left*. A *rectangular area* on the *left* has been selected for examination at higher magnification in the *lower right* figure. Even at the relatively low magnification shown here, however, the Purkinje cells can be recognized in the silver preparation because of their large size, characteristic shape, and location between an outer molecular layer (*Mol*) and an inner granule cell layer (*Gr*). The main advantage of this silver preparation is that the **white matter** (*WM*) can be recognized as being composed of fibers; they have been blackened by the silver-staining procedure. The pia mater (*Pia*) and cerebellar blood vessels (*BV*) are also evident in the preparation.

Cerebellum, brain, human, silver stain ×400.

At higher magnification, the **Purkinje cell** bodies (*Pkj*) stand out as the most distinctive and conspicuous neuronal cell type of the cerebellum, and numerous dendritic branches (*D*) can be seen. Note, also, the blackened fibers within the granule cell layer (*Gr*), about the Purkinje cell bodies, and in the molecular layer (*Mol*) disposed in a horizontal direction (relative to the cerebellar surface). Basket cells (*BC*) are the most common neurons that are visible in the molecular layer. The *arrow* indicates a T-turn characteristic of the turn made by axons of granule cells. As these axonal branches travel horizontally, they make synaptic contact with numerous Purkinje cells.

BC, basket cells
BV, blood vessels
D, dendrites
G, Golgi type II cells
Gr, granule cell layer
Mol, molecular layer
Pia, pia mater
Pkj, Purkinje cells
WM, white matter

arrows, upper right figure, glomeruli; lower right figure, T branching of axon in molecular layer

rectangular area, areas shown at higher magnification

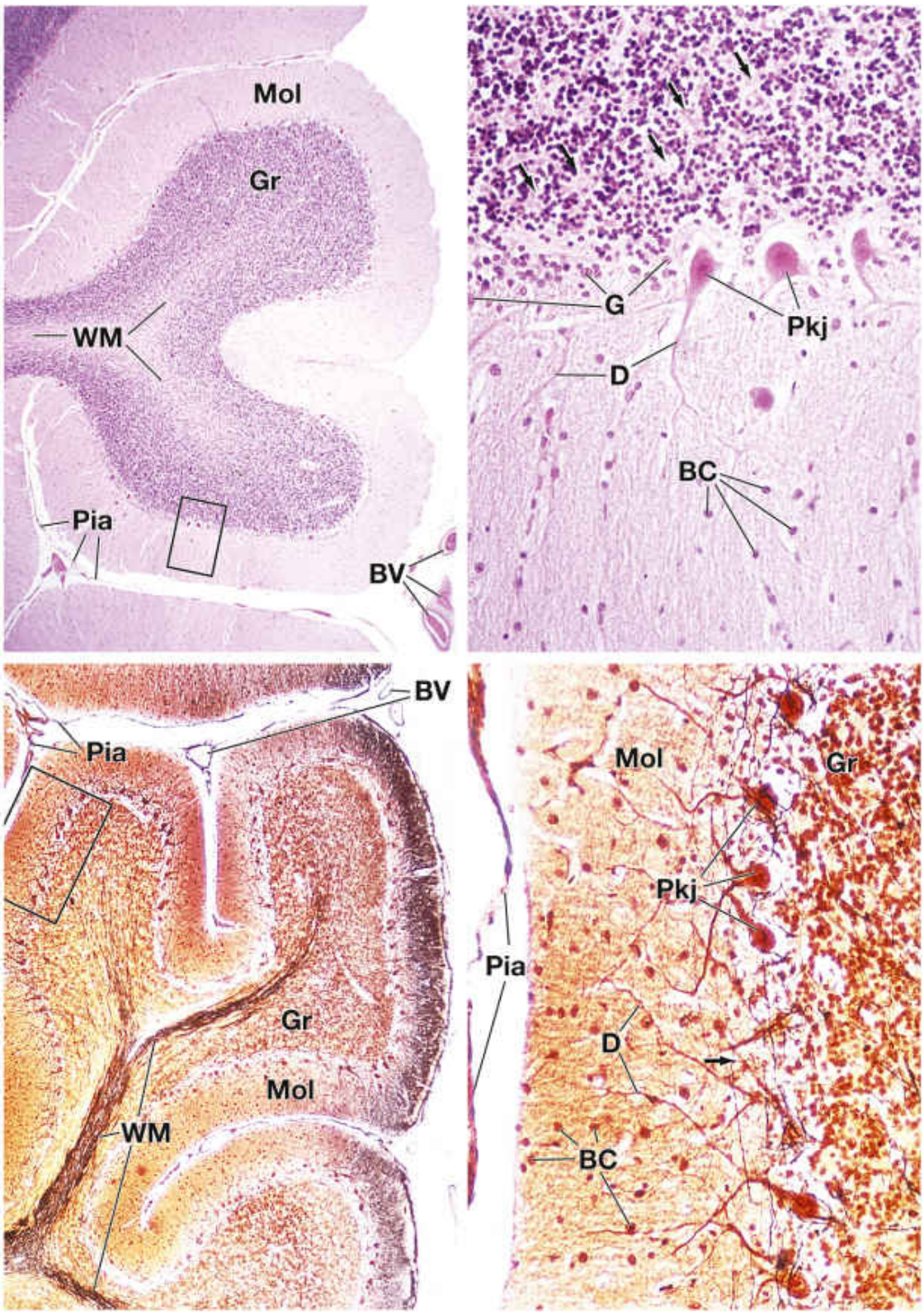


PLATE 12.5 ■ SPINAL CORD

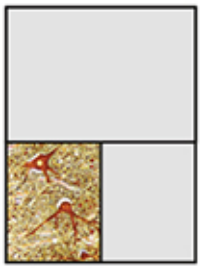
The spinal cord is organized into two discrete parts. The outer part, called the **white matter** of the cord because of its appearance in unfixed specimens, contains ascending and descending nerve fibers. Some of the fibers go to and from the brain, whereas others connect different levels of the spinal cord. The inner part of the spinal cord, called the **gray matter** because of its appearance in unfixed specimens, contains the cell bodies of neurons as well as nerve fibers. The gray matter forms an H-or butterfly-shaped pattern surrounding the central canal. The gray matter is described as having **dorsal (posterior) horns** and **ventral (anterior) horns**. The ventral horns contain the large cell bodies of ventral motor neurons, whereas the dorsal horns contain neurons that receive, process, and retransmit information from the sensory neurons whose cell bodies are located in the dorsal root ganglia. The size of the gray matter (and, therefore, the size of the spinal cord) is different at different levels. Where the gray matter contains many large motor nerve cells that control the movement of the upper and lower limbs, the gray matter and the spinal cord are considerably larger than where the gray matter contains only the motor neurons for the muscle of the torso.

Spinal cord, human, silver stain ×16.

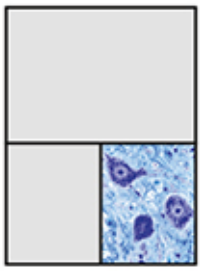
A cross section through the lower lumbar region of the spinal cord is shown here. The preparation is designed to stain the gray matter that is surrounded by the ascending and descending nerve fibers. Although the fibers that have common origins and destinations in the physiologic sense are arranged in tracts, these tracts cannot be distinguished unless they have been marked by special techniques, such as causing injury to the cell bodies from which they arise or by using special dyes or radioisotopes to label the axons.

The **gray matter** of the spinal cord appears roughly in the form of a butterfly. The anterior and posterior prongs are referred to as *ventral horns* (*VH*) and *dorsal horns* (*DH*), respectively. The connecting bar is called the *gray commissure* (*GC*). The neuron cell bodies that are within the ventral horns (ventral horn cells) are so large that they can be seen even at this extremely low magnification (*arrows*). The pale-staining fibrous material that surrounds the spinal cord is the **pia mater** (*Pia*). It follows the surface of the spinal cord intimately and dips into the large ventral fissure (*VF*) and the shallower sulci. Blood vessels (*BV*) are present in the pia mater. Some dorsal roots (*DR*) of the spinal nerves are included in the section.

Ventral horn, spinal cord, human, silver stain ×640.



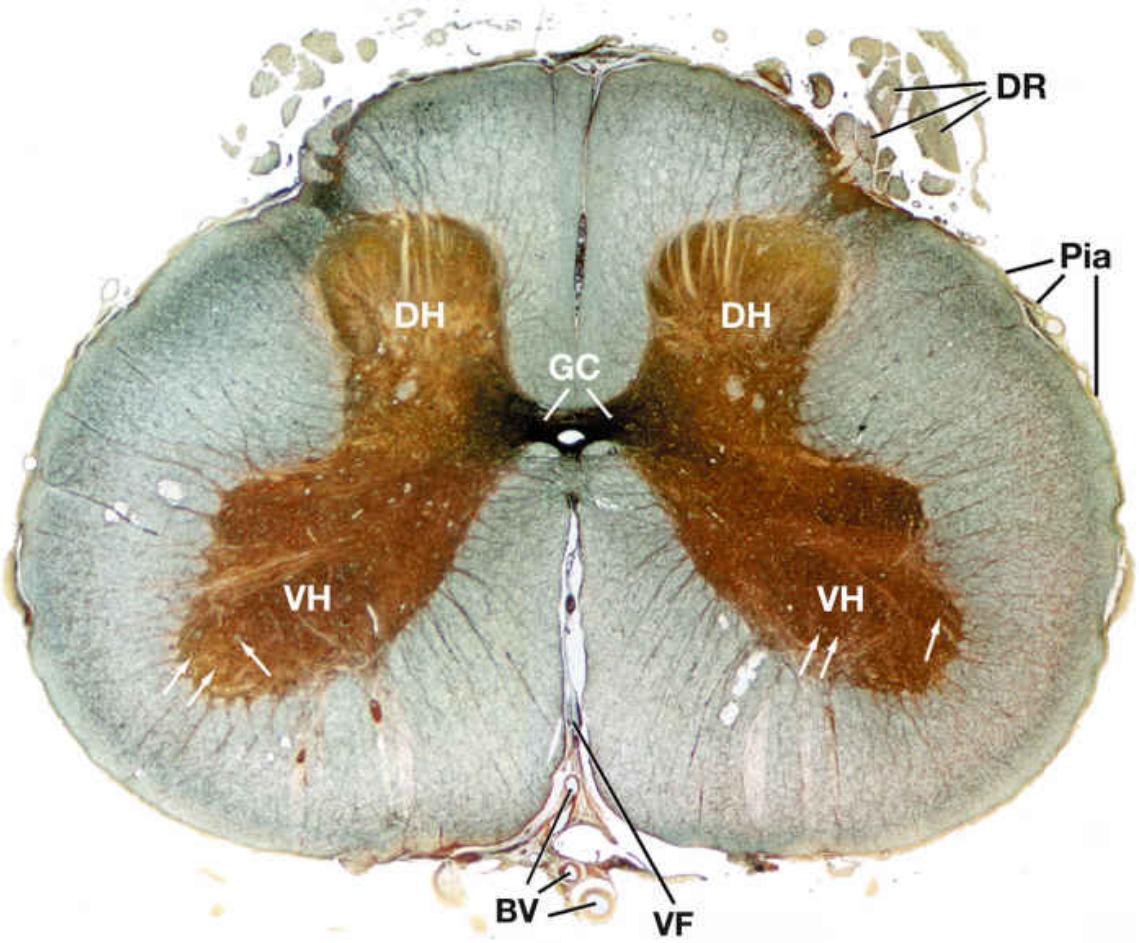
This preparation shows a region of a ventral horn. The nucleus (*N*) of the **ventral horn cell** (ventral motor neuron) is the large, spherical, pale-staining structure within the cell body. The ventral horn cell has many obvious processes. A number of other nuclei belong to neuroglial cells. The cytoplasm of these cells is not evident. The remainder of the field consists of nerve fibers and neuroglial cells whose organization is hard to interpret. This is called the neuropil (*Np*).

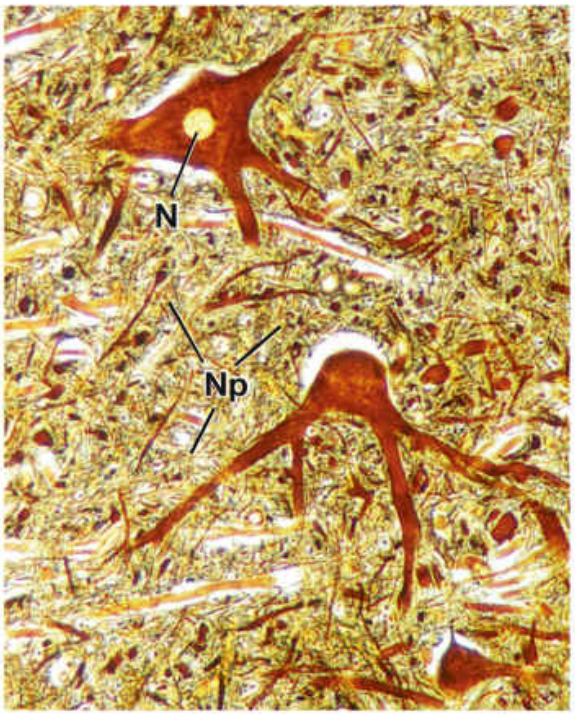


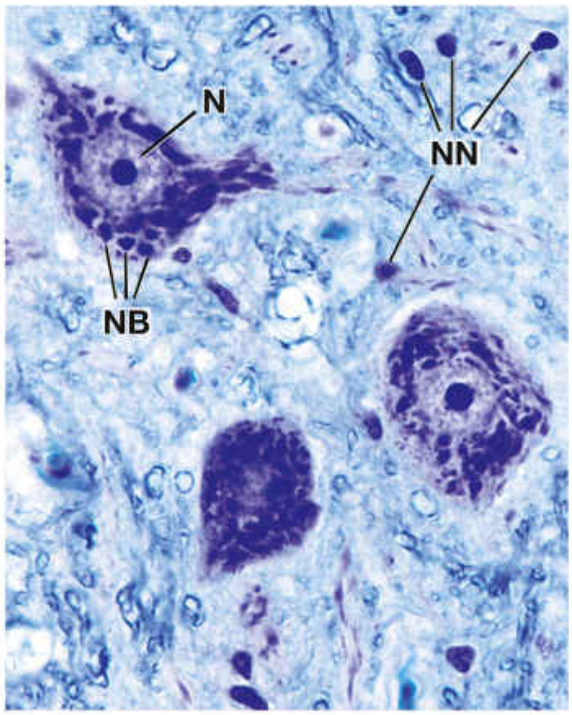
Ventral horn, spinal cord, human, toluidine blue ×640.

This preparation of the spinal cord is from an area comparable to the *left* image. Three ventral horn cells (ventral motor neurons) are visible. Owing to the plane of section, only two of them exhibit large pale-staining nuclei (*N*) with dark-staining nucleoli in the center. The toluidine blue reveals the **Nissl bodies** (*NB*) that appear as the large, dark-staining bodies in the cytoplasm. Nissl bodies do not extend into the axon hillock. The axon leaves the cell body at the axon hillock. The nuclei of neuroglial cells (*NN*) are also evident here.

BV, blood vessels
DH, dorsal horn
DR, dorsal root
GC, gray commissure
N, nucleus of ventral horn cell
NB, Nissl bodies
NN, nucleus of neuroglial cell
Np, neuropil
Pia, pia mater
VF, ventral fissure
VH, ventral horn
arrows, cell bodies of ventral horn cell


DR
Pia
DH
DH
GC
VH
VH
BV
VF


N
Np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