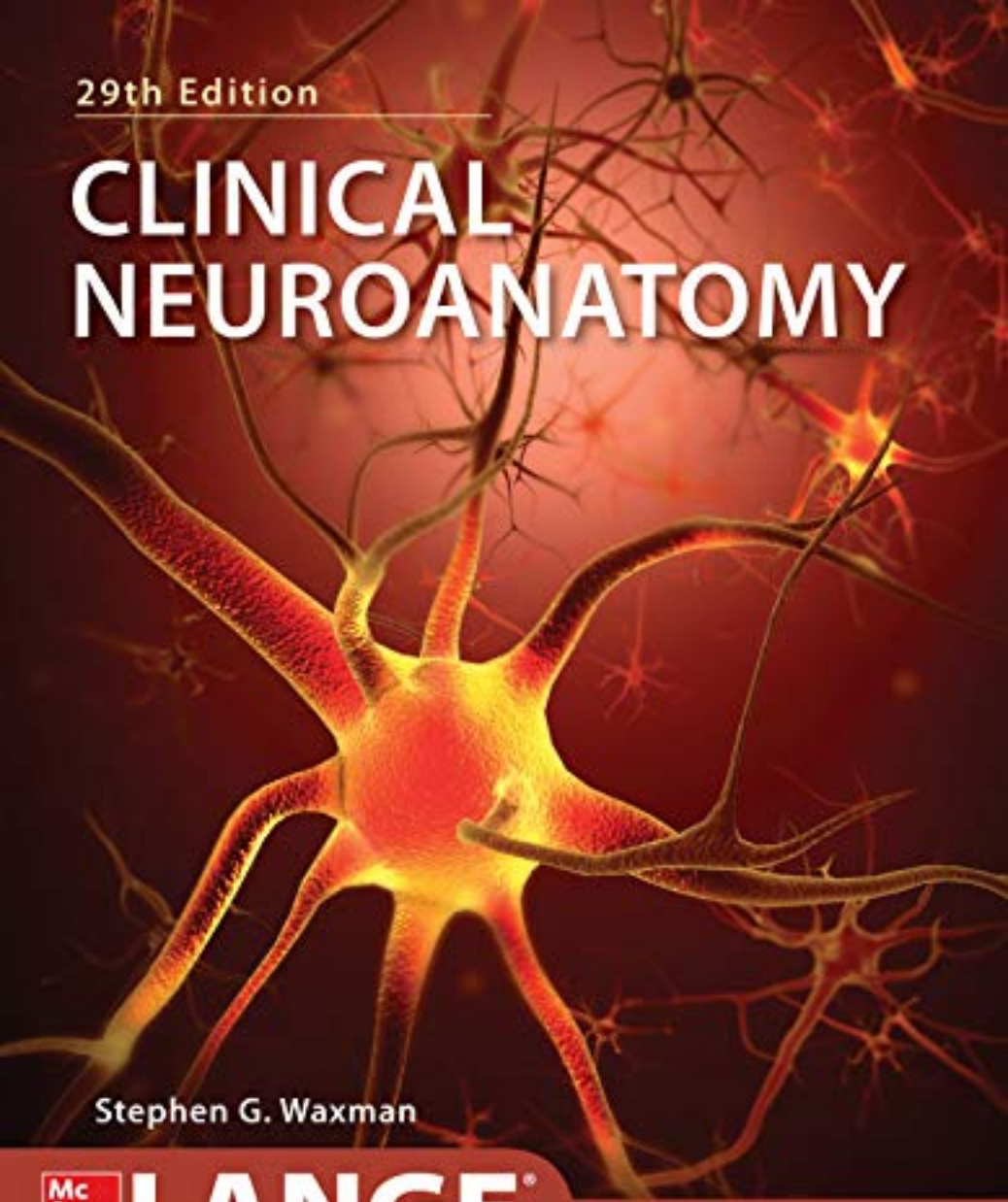
29th Edition

CLINICAL NEUROANATOMY



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Chapter 1: Fundamentals of the Nervous System

INTRODUCTION

A good working knowledge of neuroanatomy is essential to every clinician in every specialty. More than any other organ, the nervous system makes human beings special. The human central nervous system (CNS) is the most complex and elegant computing device that exists. It receives and interprets an immense array of sensory information, controls a variety of simple and complex motor behaviors, and engages in deductive and inductive logic. The brain can imagine, plan ahead, make complex decisions, think creatively, and feel emotions. It can *generalize* and possesses an elegant ability to recognize that cannot be reproduced by even advanced computers. The human nervous system, for example, can immediately identify a familiar face regardless of the angle at which it is presented. It can carry out many of these demanding tasks in a nearly simultaneous manner.

The complexity of the nervous system's actions is reflected by a rich and intricate structure—in a sense, the nervous system can be viewed as a complex and dynamic network of interlinked computers. Nevertheless, the anatomy of the nervous system *can* be readily learned and understood. Since different parts of the brain and spinal cord subserve different functions, the astute clinician can often make relatively accurate predictions about the site(s) of dysfunction on the basis of the clinical history and careful neurological examination. Clinical neuroanatomy (ie, the structure of the nervous system, considered in the context of disorders of the nervous system) is essential for an understanding of disorders of the nervous system.

OVER-ALL PLAN OF THE NERVOUS SYSTEM

Main Divisions

A. Anatomy

The human nervous system consists of two subdivisions.

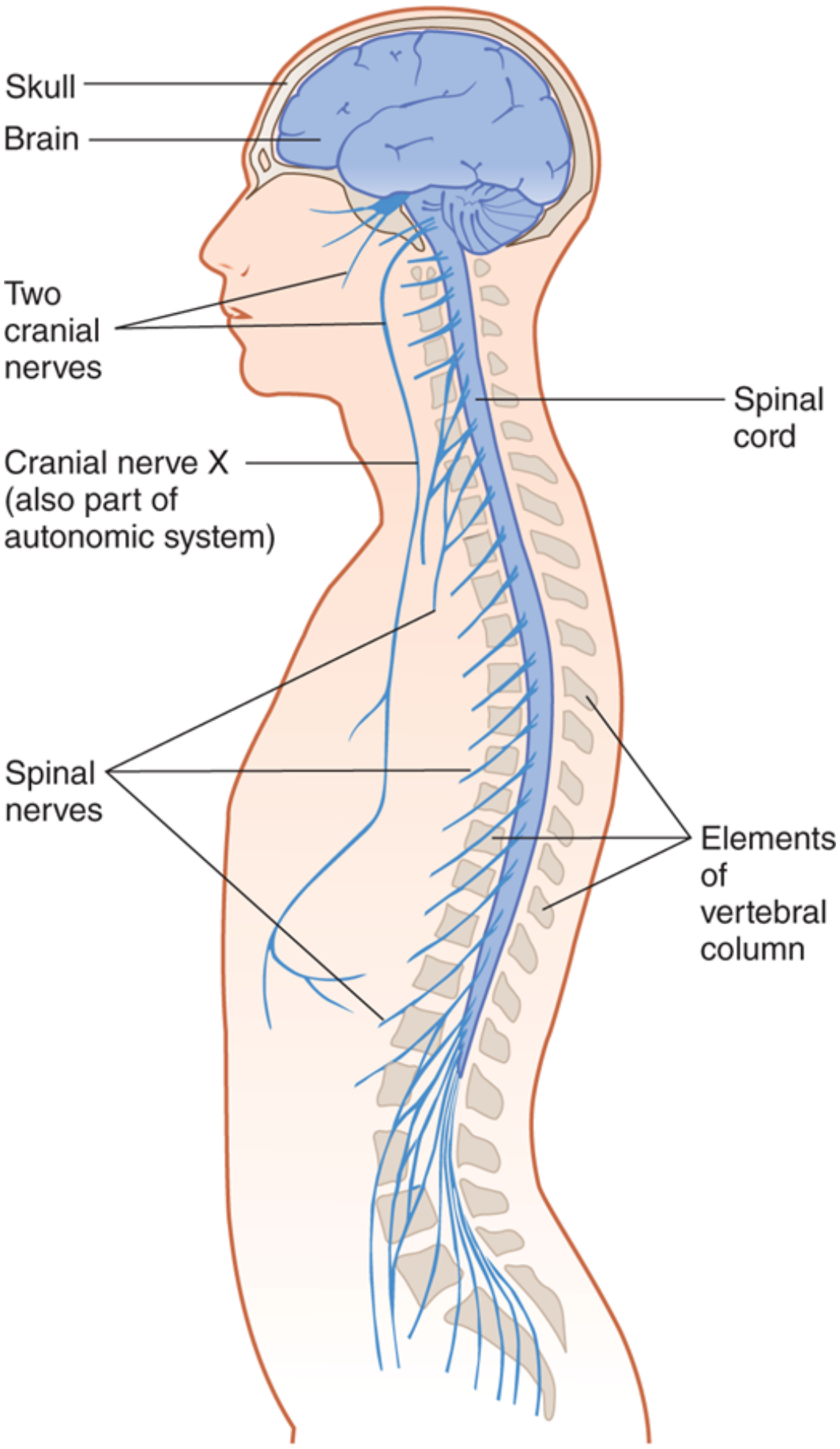
1. CNS

The CNS, comprising the brain and spinal cord, is enclosed in bone and wrapped in protective coverings (meninges) and fluid-filled spaces.

2. Peripheral nervous system (PNS)

The PNS is formed by the cranial and spinal nerves (Fig 1–1).

FIGURE 1–1
The structure of the central nervous system and the peripheral nervous system, showing the relationship between the central nervous system and its bony coverings.



B. Function

Functionally, the nervous system is divided into two systems.

1. Somatic nervous system

This innervates the structures of the body wall (muscles, skin, and mucous membranes).

2. Autonomic (visceral) nervous system (ANS)

The ANS contains portions of the central and peripheral systems. It controls the activities of the smooth muscles and glands of the internal organs (viscera) and the blood vessels and returns sensory information from these organs to the brain.

Structural Units and Overall Organization

The central portion of the nervous system consists of the **brain** and the **spinal cord** (Fig 1–2 and Table 1–1). The brain has a tiered structure and, from a gross point of view, can be subdivided into the cerebrum, the brain stem, and the cerebellum.

FIGURE 1–2
The two major divisions of the central nervous system, the brain, and the spinal cord, as seen in the midsagittal plane.

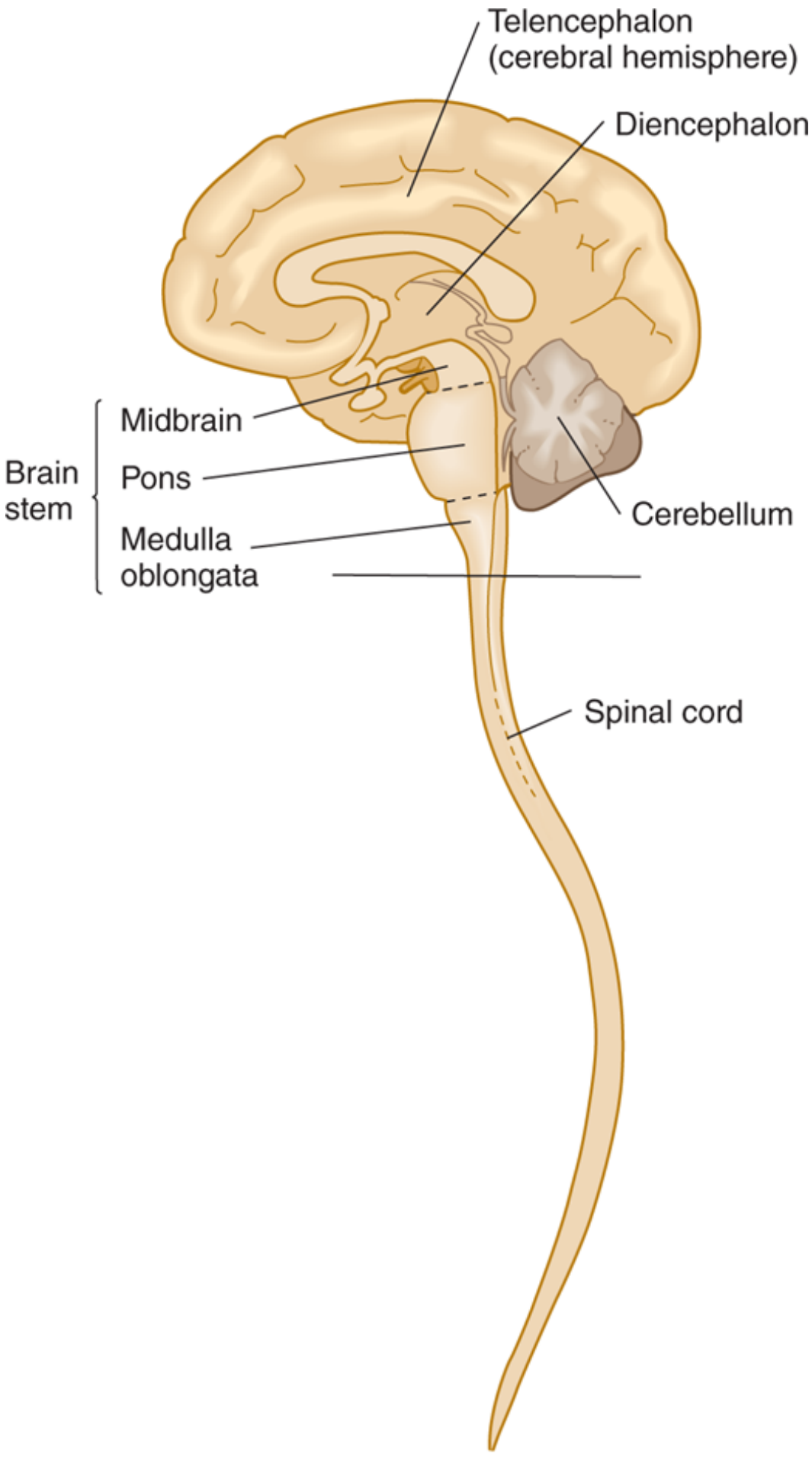


TABLE 1–1

Major Divisions of the Central Nervous System.

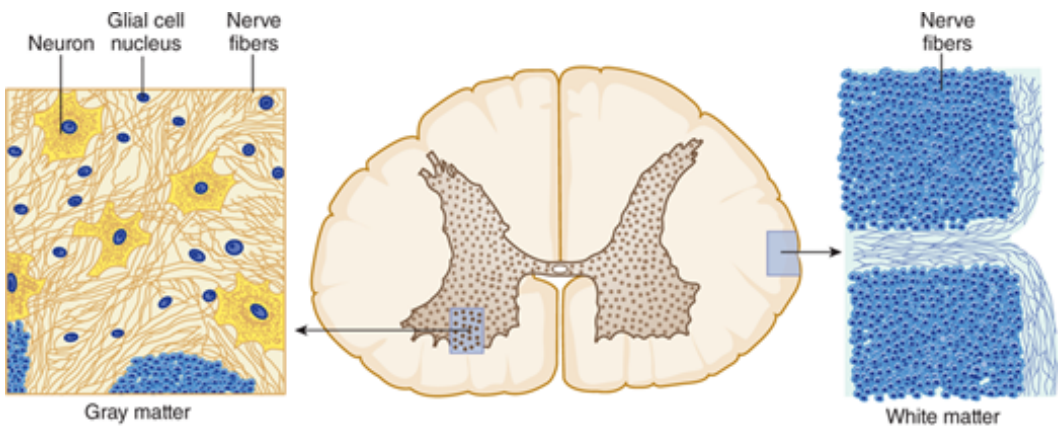
Brain (encephalon)	Cerebrum (forebrain)	Telencephalon	Cerebral cortex Subcortical white matter Commissures Basal ganglia
		Diencephalon	Thalamus Hypothalamus Epithalamus Subthalamus
	Cerebellum		Cerebellar cortex Cerebellar nuclei
	Brain stem		Midbrain (mesencephalon) Pons Medulla oblongata
Spinal cord	White matter		Dorsal columns Lateral columns Anterior columns
	Gray matter		

The most rostral part of the nervous system (cerebrum, or forebrain) is the most phylogenetically advanced and is responsible for the most complex functions (eg, cognition). The brain stem, medulla, and spinal cord serve less advanced, but essential, functions.

The **cerebrum (forebrain)** consists of the **telencephalon** and the **diencephalon**; the telencephalon includes the cerebral cortex (the most highly evolved part of the brain, sometimes called “gray matter”), subcortical white matter, and the basal ganglia, which are gray masses deep within the cerebral hemispheres. The **white matter** carries that name because, in a freshly sectioned brain, it has a glistening appearance as a result of its high lipid-rich myelin content; the white matter consists of myelinated fibers and does not contain neuronal cell bodies or synapses (Fig 1–3).

FIGURE 1–3

Cross section through the spinal cord, showing gray matter (which contains neuronal and glial cell bodies, axons, dendrites, and synapses) and white matter (which contains myelinated axons and associated glial cells). (Reproduced with permission from Junqueira LC, Carneiro J, Kelley RO: *Basic Histology: Text & Atlas*, 11th ed. New York, NY: McGraw-Hill Education; 2005.)



The major subdivisions of the diencephalon are the thalamus and hypothalamus. The **brain stem** consists of the **midbrain (mesencephalon), pons**, and **medulla oblongata**. The **cerebellum** includes the vermis and two lateral lobes. The brain, which is hollow, contains a system of spaces called **ventricles**; the spinal cord has a narrow central canal that is largely obliterated in adulthood. These spaces are filled with cerebrospinal fluid (CSF) (Figs 1–4 and 1–5; see also Chapter 11).

FIGURE 1–4

Photograph of a midsagittal section through the head and upper neck, showing the major divisions of the central nervous system. (Reproduced with permission from deGroot J: *Correlative Neuroanatomy of Computed Tomography and Magnetic Resonance Imagery*. 21st ed. New York, NY: Appleton & Lange; 1991.)

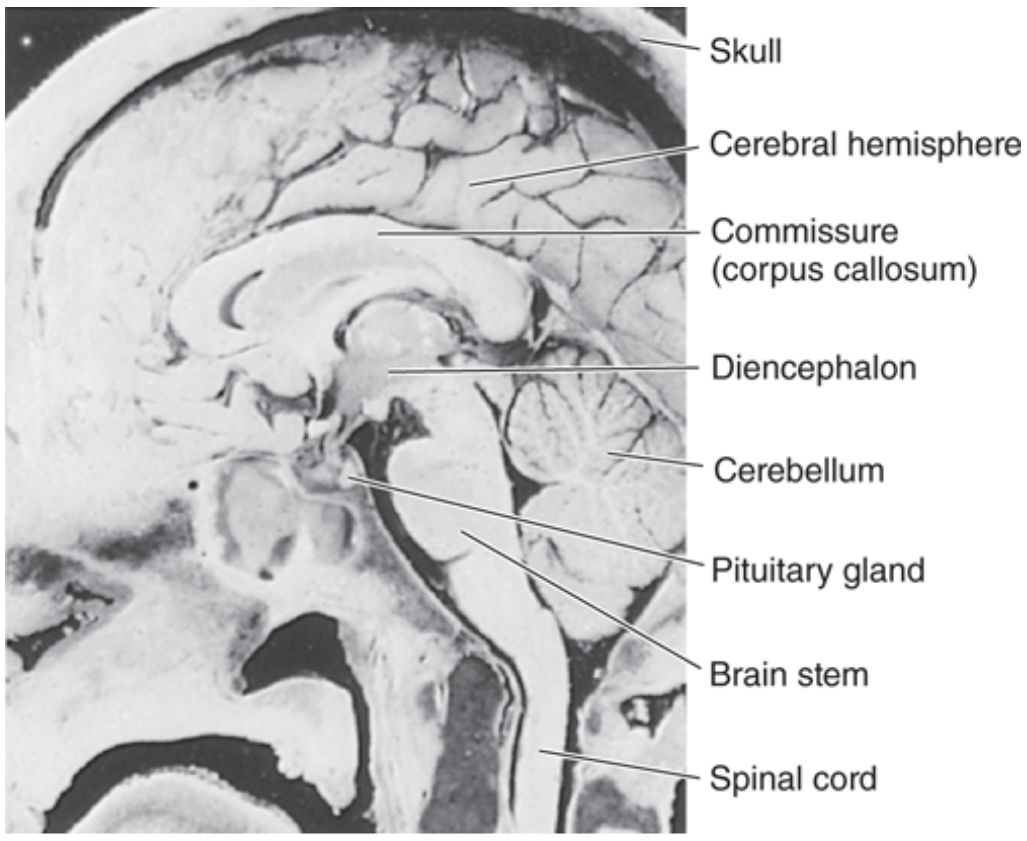
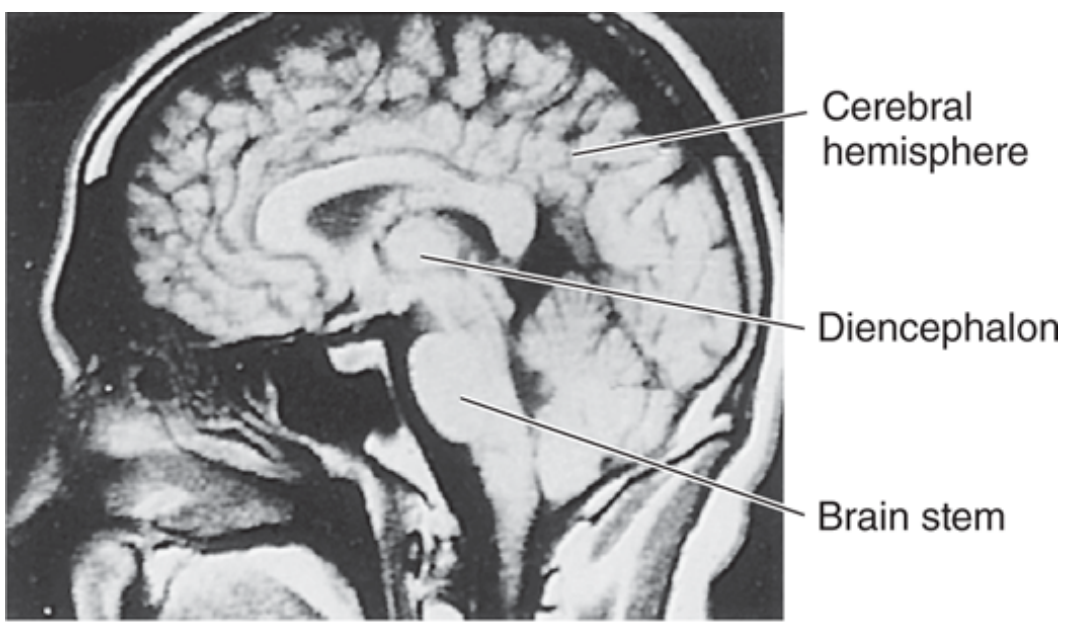


FIGURE 1–5

Magnetic resonance image of a midsagittal section through the head (short time sequence; see Chapter 22). Compare with Figure 1–2.



Functional Units

The brain, which accounts for about 2% of the body's weight, contains many billions (perhaps even a trillion) of neurons and glial cells (see Chapter 2). **Neurons**, or nerve cells, are specialized cells that receive and send signals to other cells through their extensions (nerve fibers, or **axons)**. The information is processed and encoded in a sequence of electrical or chemical steps that occur, in most cases, very rapidly (in milliseconds). Many neurons have relatively large cell bodies and long axons that transmit impulses quickly over a considerable distance. Interneurons, on the other hand, have small cell bodies and short axons and transmit impulses locally. Nerve cells serving a common function, often with a common target, are frequently grouped together into clusters called **nuclei**. Nerve cells with common form, function, and connections that are grouped together outside the CNS are called **ganglia**.

Other cellular elements that support the activity of the neurons are the **glial cells**, of which there are several types. Glial cells within the brain and spinal cord outnumber neurons 10:1.

Information Processing in the Nervous System

Nerve cells convey signals to one another at **synapses** (see Chapters 2 and 3). Chemical transmitters are associated with the function of the synapse: excitation or inhibition. A neuron may receive thousands of synapses, which bring it information from many sources. By integrating the excitatory and inhibitory inputs from these diverse sources and producing its own message, each neuron acts as an information-processing device.

Some very primitive behaviors (eg, the reflex and unconscious contraction of the muscles around the knee in response to percussion of the patellar tendon) are mediated by a simple **monosynaptic** chain of two neurons connected by a **synapse**. More complex behaviors, however, require larger **polysynaptic** neural circuits in which many neurons, interconnected by synapses, are involved.

Tracts and Commissures

The connections, or pathways, between groups of neurons in the CNS are in the form of fiber bundles, or tracts (**fasciculi**). Aggregates of tracts, as seen in the spinal cord, are referred to as **columns (funiculi)**. Tracts may **descend** (eg, from the cerebrum to the brain stem or spinal cord) or **ascend** (eg, from the spinal cord to the cerebrum). These pathways are vertical pathways that in their course may cross (**decussate**) from one side of the CNS to the other. Horizontal (lateral) connections are called **commissures**.

Symmetry in the Nervous System

A general theme in neuroanatomy is that, to a first approximation, the nervous system is constructed with **bilateral symmetry**. This is most apparent in the cerebrum and cerebellum, which are organized into right and left **hemispheres**. Some higher cortical functions such as language are represented more strongly in one hemisphere than in the other, but to gross inspection, the hemispheres have a similar structure. Even in more caudal structures, such as the brain stem and spinal cord, which are not organized into hemispheres, there is bilateral symmetry.

Crossed Representation

Another general theme in the construction of the nervous system is **decussation and crossed representation**: Neuroanatomists use the term "decussation" to describe the crossing of a fiber tract from one side of the nervous system (right or left) to the other. *The right side of the brain receives information about, and controls motor function pertaining to, the left side of the world and vice versa*. Visual information about the right side of the world is processed in the visual cortex on the left. Similarly, sensation of touch, sensation of heat or cold, and joint position sense from the body's right side are processed in the somatosensory cortex in the left cerebral hemisphere. In terms of motor control, the motor cortex in the left cerebral hemisphere controls body movements that pertain to the right side of the external world. This includes, control of the muscles of the right arm and leg, such as the biceps, triceps, hand muscles, and gastrocnemius. There are occasional exceptions to this pattern of "crossed innervation": For example, the *left* sternocleidomastoid muscle is controlled by the *left* cerebral cortex. However, even this exception makes functional sense: As a result of its unusual biomechanics, contraction of the left sternocleidomastoid rotates the neck to the *right*. Even for this anomalous muscle, then, control of movements relevant to the right side of the world originates in the contralateral left cerebral hemisphere, as predicted by the principle of crossed representation.

There is one major exception to the rule of crossed motor control: As a result of the organization of cerebellar inputs and outputs, each cerebellar hemisphere controls coordination and muscle tone on the *ipsilateral* side of the body (see Chapter 7).

Maps of the World Within the Brain

An important design feature of the nervous system is that, at each of many levels, the brain maps (contain a representation of) various aspects of the outside world. For example, consider the dorsal columns (which carry sensory information, particularly with respect to touch and vibration, from sensory endings on the body surface upward within the spinal cord). Axons within the dorsal columns are arranged in an orderly manner, with fibers from the arm, trunk, and leg forming a map that preserves the spatial relationship of these body parts. Within the cerebral cortex, there is also a sensory map (which has the form of a small man and is, therefore, called a homunculus) within the sensory cortex. There are multiple maps of the visual world within the occipital lobes and within the temporal and parietal lobes. These maps are called retinotopic because they preserve the geometrical relationships between objects imaged on the retina and thus provide spatial representations of the visual environment within the brain.

The existence of these maps within the brain is important to clinicians. Focal lesions of the brain may interfere with function of only part of the map, thus producing signs and symptoms (such as loss of vision in only part of the visual world) that can help to localize the lesions.

Development

The earliest tracts of nerve fibers appear at about the second month of fetal life; major descending motor tracts appear at about the fifth month. **Myelination** (sheathing with myelin) of the spinal cord's nerve fibers begins about the middle of fetal life; some tracts are not completely myelinated for 20 years. The oldest tracts (those common to all animals) myelinate first; the corticospinal tracts myelinate largely during the first and second years after birth.

Growing axons are guided to the correct targets during development of the nervous system by extracellular **guidance molecules** (including the **netrins** and **semaphorins**). Some of these act as attractants for growing axons, guiding them toward a particular target. Others act as repellants.

There are many types of guidance molecules, probably each specific for a particular type of axon, and they are laid down in gradients of varying concentration. In many parts of the developing nervous system, there is initially an overabundance of young axons, and those that do not reach the correct targets are subsequently lost by a process of pruning.

PERIPHERAL NERVOUS SYSTEM

The **peripheral nervous system (PNS)** consists of spinal nerves, cranial nerves, and their associated ganglia (groups of nerve cells outside the CNS). The nerves contain nerve fibers that conduct information to (afferent) or from (efferent) the CNS. Peripheral nerves are connected to the spinal cord via **dorsal** (sensory) and **ventral** (motor) **roots**. In general, **efferent** fibers are involved in motor functions, such as the contraction of muscles or secretion of glands; **afferent** fibers usually convey sensory stimuli from the skin, mucous membranes, and deeper structures.

Individual nerves can be injured by compression or physical trauma, resulting in a motor and sensory deficit in the part of the body innervated by that particular nerve. Some systemic illnesses such as diabetes, or exposure to toxins or drugs that are neurotoxic can injure nerves throughout the body, producing a peripheral polyneuropathy; in these cases the longest nerves (those innervating the feet) are affected first.

Appendices B and C show the pattern of innervation of the body for each spinal root and for each peripheral nerve.

PLANES AND NEUROANATOMIC TERMS

Neuroanatomists tend to think of the brain and spinal cord in terms of how they appear in slices, or sections. It is important for every clinician to understand. The planes of section and terms used in neuroanatomy, which are shown in Figure 1–6 and Table 1–2.

FIGURE 1–6

Planes (coronal, horizontal, transverse) and directions (rostral, caudal, etc.) frequently used in the description of the brain and spinal cord. The plane of the drawing is the midsagittal.

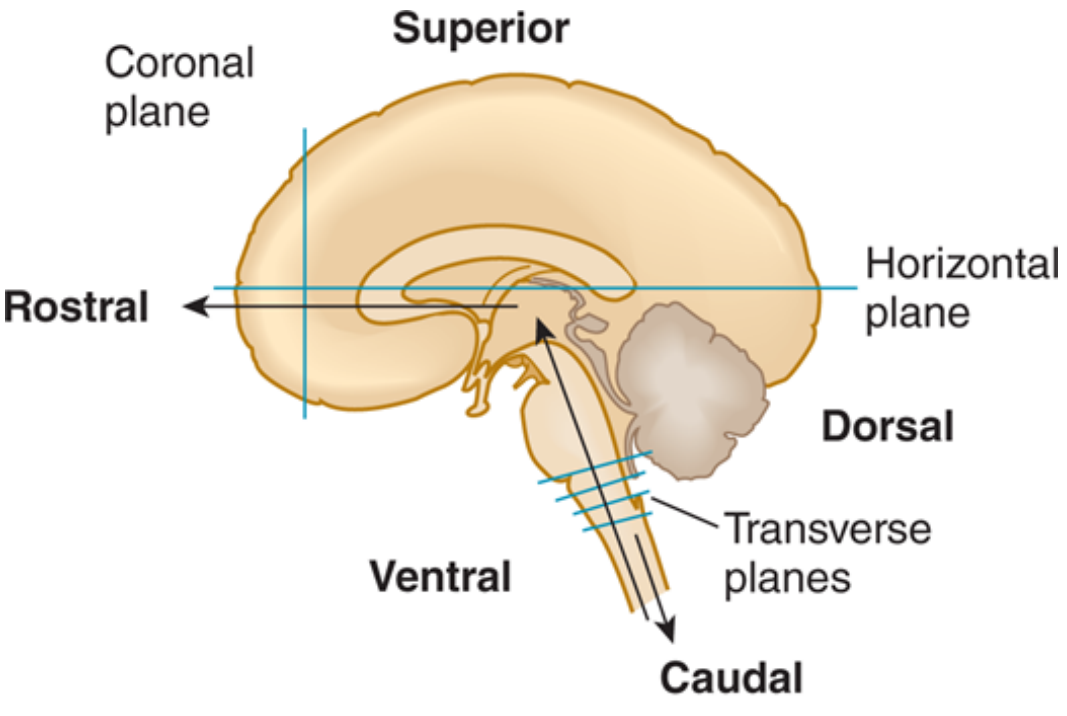


TABLE 1–2

Terms Used in Neuroanatomy.

Ventral, anterior	On the front (belly) side
Dorsal, posterior	On the back side
Superior, cranial	On the top (skull) side
Inferior	On the lower side
Caudal	In the lowermost position (at the tail end)
Rostral	On the forward side (at the nose end)
Medial	Close to or toward the middle
Median	In the middle, the midplane (midsagittal)
Lateral	Toward the side (away from the middle)
Ipsilateral	On the same side
Contralateral	On the opposite side
Bilateral	On both sides

BOX 1–1

Essentials for the Clinical Neuroanatomist

After reading and digesting this chapter, you should know and understand:

The main divisions of the nervous system

The functional (cellular) units of the nervous system; different functions of neurons and glial cells

Principles of symmetry and crossed representation within the brain

The principle of decussations

The principle of maps within the brain

The meaning of “afferent” versus “efferent”

The planes used by neuroanatomists and neuroimagers: coronal, horizontal, transverse (Fig. 1–6)

Terminology, including “rostral” and “caudal,” “dorsal” and “ventral”; see Table 1–2

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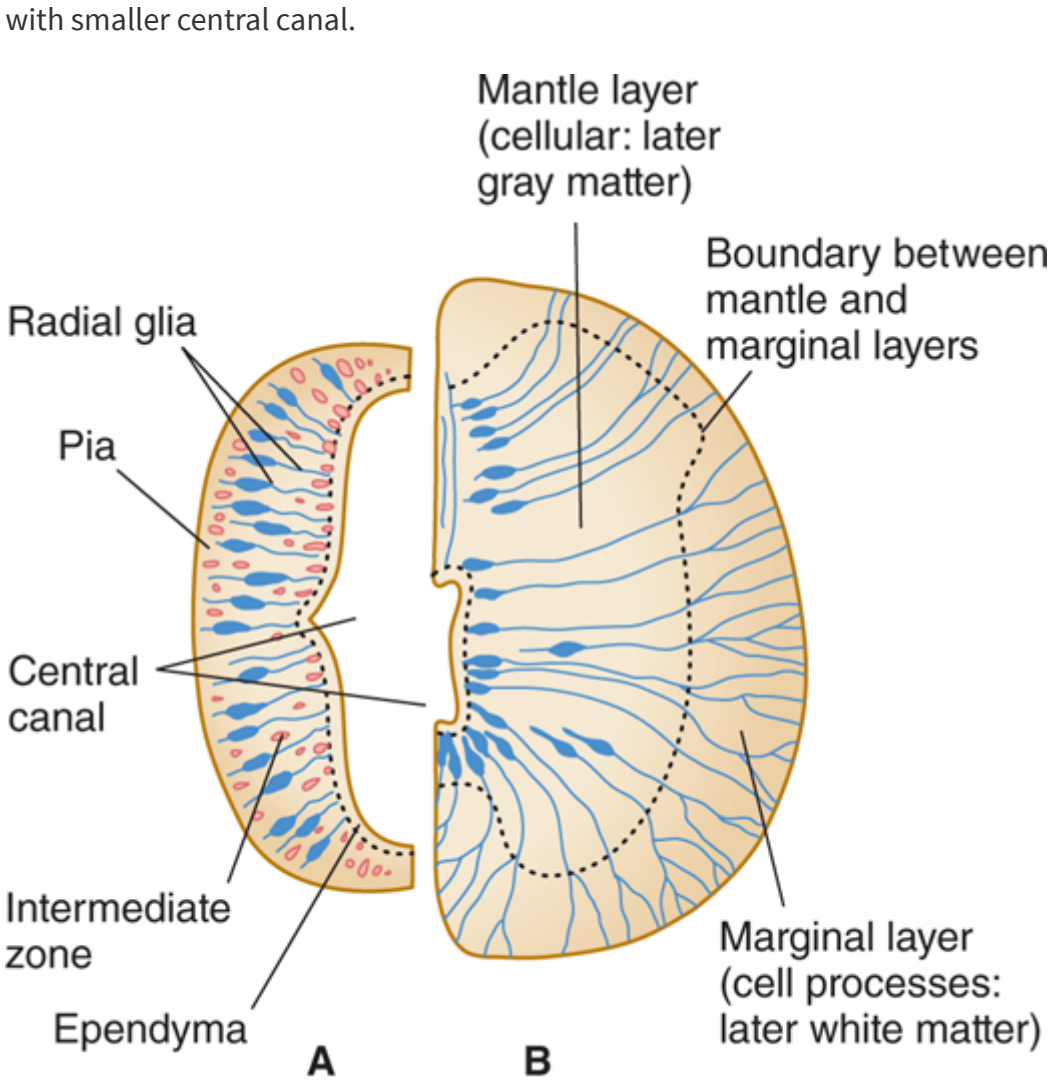
NEURAL DEVELOPMENT

Early in the development of the nervous system, a hollow tube of ectodermal neural tissue forms at the embryo's dorsal midline. The cellular elements of the tube appear undifferentiated at first, but they later develop into various types of neurons and supporting glial cells.

The Neural Tube

The embryonic neural tube has three layers (Fig 2–1): the **ventricular zone**, later called the **ependyma**, around the lumen (central canal) of the tube; the **intermediate zone**, which is formed by the dividing cells of the ventricular zone (including the earliest radial glial cell type) and stretches between the ventricular surface and the outer (pial) layer; and the external **marginal zone**, which is formed later by processes of the nerve cells in the intermediate zone (Fig 2–1B).

FIGURE 2–1
Two stages in the development of the neural tube (only half of each cross section is shown). A: Early stage with large central canal. **B:** Later stage with smaller central canal.



The intermediate zone, or mantle layer, increases in cellularity and becomes gray matter. The nerve cell processes in the marginal zone, as well as other cell processes, become white matter when myelinated.

Cell Differentiation and Migration

The largest neurons, which are mostly motor neurons, differentiate first. Sensory and small neurons, and most of the glial cells, appear later, up to the time of birth. Newly formed neurons may migrate extensively through regions of previously formed neurons. When glial cells appear, they can act as a framework that guides growing neurons to the correct target areas. Because the axonal process of a neuron may begin growing toward its target during cell migration, nerve processes in the adult brain are often curved rather than straight.

NEURONS

Neurons vary in size and complexity. Motor neurons are usually larger than sensory neurons. Nerve cells with long processes (eg, dorsal root ganglion cells) are larger than those with short processes (Figs 2–2 and 2–3).

FIGURE 2–2
Schematic illustration of nerve cell types. A: Central nervous system cells: (1) motor neuron projecting to striated muscle, (2) special sensory neuron, and (3) general sensory neuron from skin. **B:** Autonomic cells to smooth muscle. Notice how the position of the cell body with respect to the axon varies.

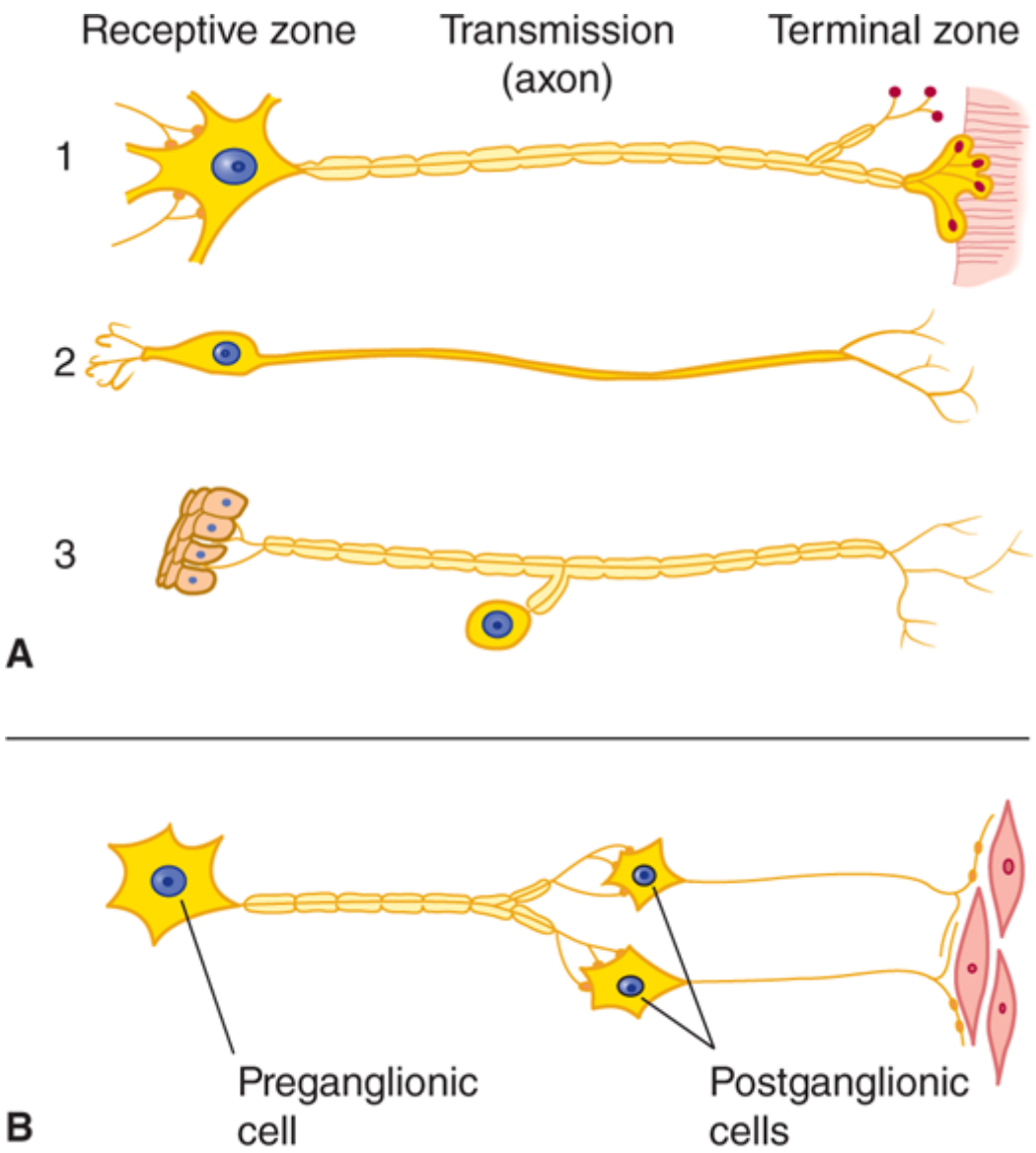
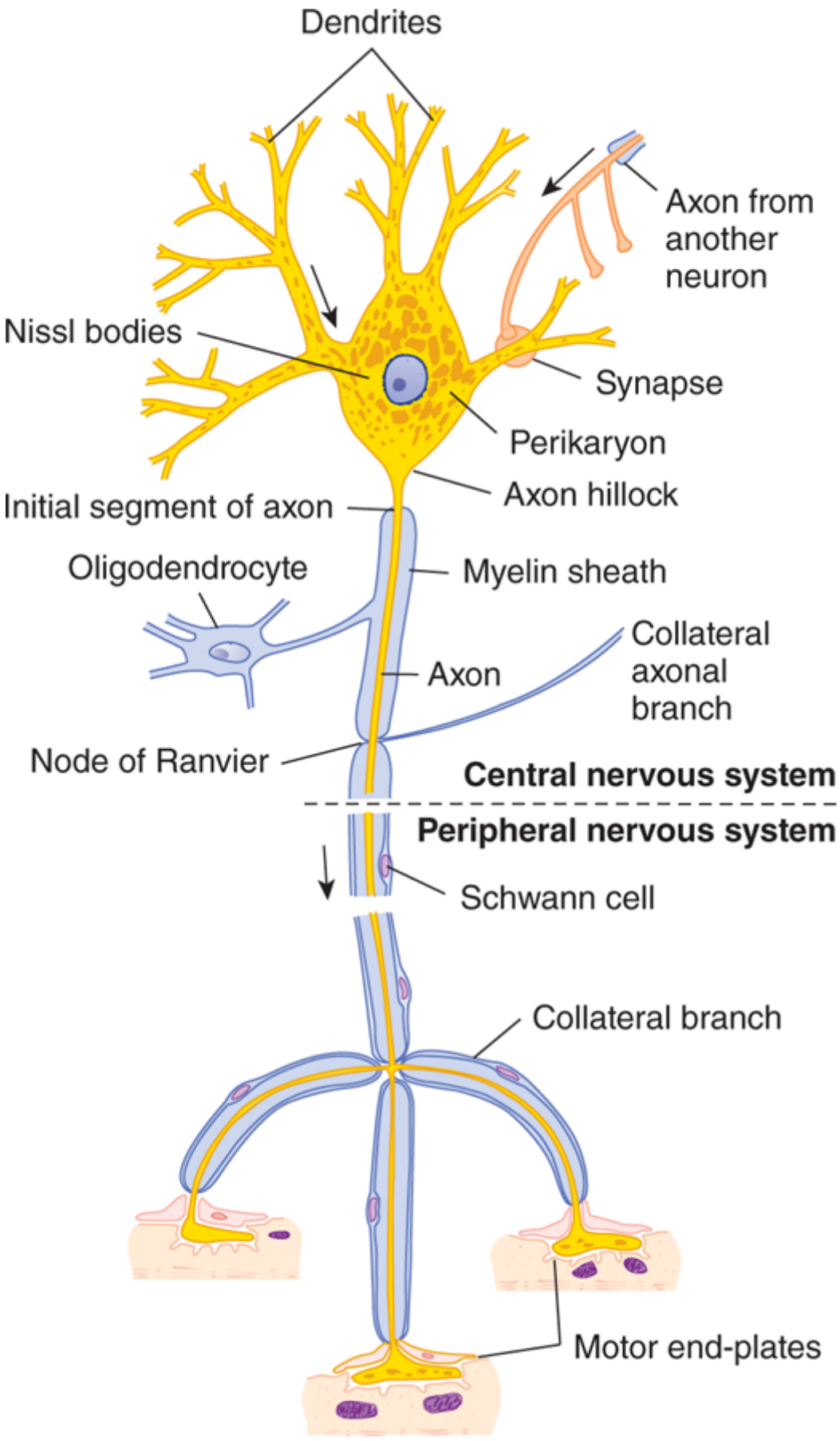


FIGURE 2–3

Schematic drawing of a motor neuron. Note that the neuron gives rise to many dendrites, of to one axon. The myelin sheath which covers the axon is produced by oligodendrocytes in the central nervous system and by Schwann cells in the peripheral nervous system. Note the three motor end-plates, which transmit the nerve impulses to striated skeletal muscle fibers. **Arrows** show the direction of the nerve impulse. (Reproduced with permission from Junqueira LC, Carneiro J, Kelley RO: *Basic Histology: Text & Atlas*, 11th ed. New York, NY: McGraw-Hill Education; 2005.)



Some neurons project from the cerebral cortex to the lower spinal cord, a distance of 3 ft or more in adults; others have very short processes, reaching, for example, only from cell to cell in the cerebral cortex. These small neurons, with short axons that terminate locally, are called **interneurons**.

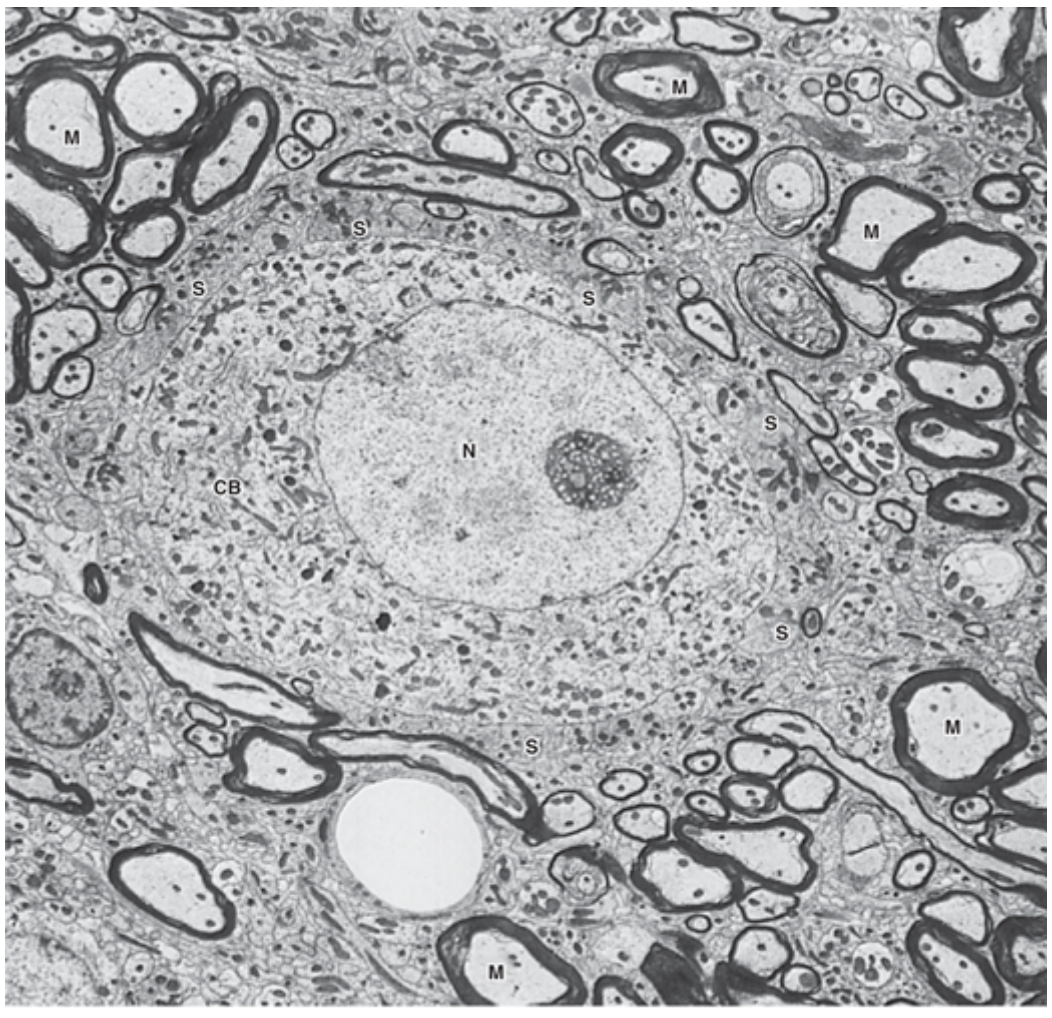
Extending from the nerve cell body are usually a number of processes called the **axon** and **dendrites**. Most neurons give rise to a single axon (which branches along its course) and many dendrites (which also divide and subdivide, like the branches of a tree). The receptive part of the neuron is the **dendritic zone** (see Dendrites section). The conducting (propagating or transmitting) part is the axon, which may have one or more collateral branches. The downstream end of the axon is called the **synaptic terminal**, or **arborization**. The neuron's cell body is called the **soma**, or **perikaryon**.

The Neuronal Cell Body (Soma)

The cell body is the metabolic and genetic center of a neuron (see Fig 2–3). Although its size varies greatly in different neuron types, the cell body makes up only a small part of the neuron's total volume.

The cell body and dendrites constitute the receptive pole of the neuron. Synapses from other cells or glial processes tend to cover the surface of a cell body (Fig 2–4).

FIGURE 2–4
Electron micrograph of a nerve cell body (CB) surrounded by nerve processes. The neuronal surface is completely covered by either synaptic endings of other neurons (S) or processes of glial cells. Many other processes around this cell are myelinated axons (M). CB, neuronal cell body; N, nucleus, ×5,000. (Used with permission from Dr. DM McDonald.)



Dendrites

Dendrites are branches of neurons that extend from the cell body; they receive incoming synaptic information and thus, together with the cell body, provide the receptive pole of the neuron. Most neurons have many dendrites (see Figs 2–2, 2–3, and 2–5).

FIGURE 2–5
Dendrite from pyramidal neuron in the motor cortex. Note the spines on the main dendrite and on its smaller branches. Scale = 10 µm. (Used with permission from Dr. Andrew Tan, Yale University.)

Source: Stephen G. Waxman: *Clinical Neuroanatomy*, 29e

Because most dendrites are long and thin, they act as resistors, isolating electrical events, such as postsynaptic potentials, from one another (see Chapter 3). The branching pattern of the dendrites can be complex and determines how the neuron integrates synaptic inputs from various sources. Some dendrites give rise to **dendritic spines**, which are small mushroom-shaped projections that act as fine dendritic branches and receive synaptic inputs (Fig 2–5). Dendritic spines are currently of great interest to researchers. The shape of a spine regulates the strength of the synaptic signal that it receives. A synapse onto the tip of a spine with a thin "neck" will have a smaller influence than a synapse onto a spine with a thick neck. Dendritic spines are dynamic, and their shape can change. Changes in dendritic spine shape can strengthen synaptic connections so as to contribute to learning and memory. Maladaptive changes in spines may contribute to altered function of the nervous system after injury.

Axons

A single **axon** or nerve fiber arises from most neurons. The axon is a long extension arising from the neuron, cylindrical tube of cytoplasm covered by a membrane, the **axolemma**. A **cytoskeleton** consisting of **neurofilaments** and **microtubules** runs through the axon. The microtubules provide a framework for fast axonal transport (see Axonal Transport section). Specialized molecular motors (**kinesin** molecules) bind to vesicles containing molecules (eg, neurotransmitters) destined for transport via a series of adenosine triphosphate (ATP)-consuming steps along the microtubules.

The axon conducts electrical signals (action potentials) from the initial segment (the proximal part of the axon, near the cell body) to the synaptic terminals. The **initial segment** has distinctive morphological features; it differs from both cell body and axon. The axolemma of the initial segment contains a high density of sodium channels, which permit the initial segment to act as a **trigger zone**. In this zone, action potentials are generated so that they can travel along the axon, finally invading the terminal axonal branches and triggering synaptic activity, which impinges on other neurons. The initial segment does not contain Nissl substance (see Fig 2–3). In large neurons, the initial segment arises conspicuously from the **axon hillock**, a cone-shaped portion of the cell body. Axons range in length from a few microns (in interneurons) to well over a meter (ie, in a lumbar motor neuron that projects from the spinal cord to the muscles of the foot) and in diameter from 0.1 µm to more than 20 µm.

A. Myelin

Many axons are covered by **myelin**. The myelin consists of multiple concentric layers of lipid-rich membrane produced by Schwann cells in the peripheral nervous system (PNS) and by oligodendrocytes (a type of glial cell) in the central nervous system (CNS) (Figs 2–6 to 2–10). The myelin sheath is divided into segments about 1 mm long separated by small gaps (1 µm long) where myelin is absent; these are the **nodes of Ranvier**. The smallest axons are unmyelinated. As noted in Chapter 3, myelin functions as an insulator. In general, myelination serves to increase the speed of impulse conduction along the axon.

FIGURE 2–6

Diagrammatic view, in three dimensions, of a prototypic neuron. Dendrites (1) radiate from the neuronal cell body, which contains the nucleus (3). The axon arises from the cell body at the initial segment (2). Axodendritic (4) and axosomatic (5) synapses impinge on the dendrites and cell body. Myelin sheaths (6) are present around some axons.

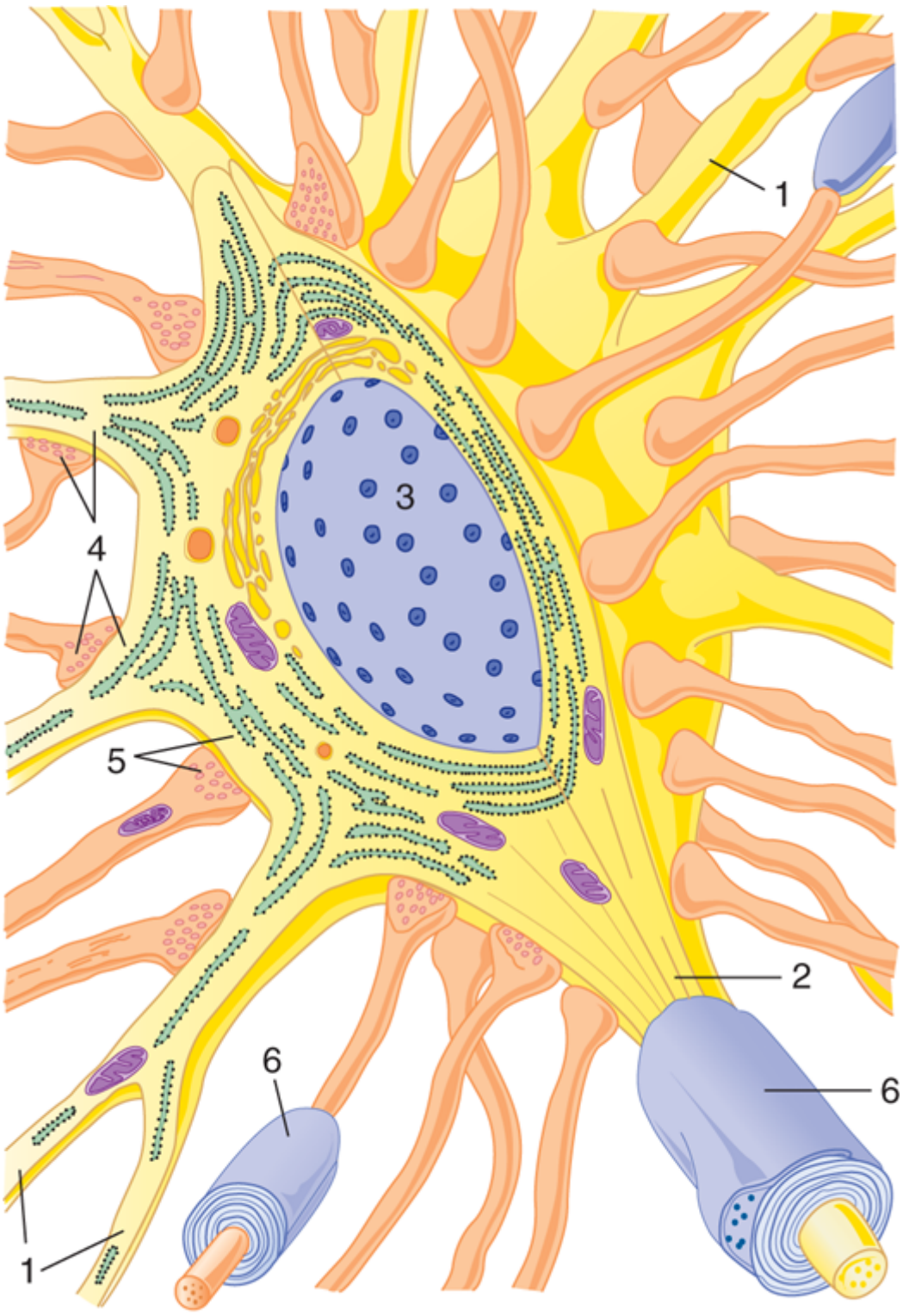


FIGURE 2–7

Schwann cells and their relationships with axons. A: In the peripheral nervous system (PNS), unmyelinated axons are located within grooves on the surface of Schwann cells. These axons are not, however, insulated by a myelin sheath. **B:** Myelinated PNS fibers are surrounded by a myelin sheath that is formed by a spiral wrapping of the axon by a Schwann cell. Panels 1–4 show four consecutive phases of myelin formation in peripheral nerve fibers. (Reproduced with permission from Junqueira LC, Carneiro J, Kelley RO: *Basic Histology*: Text & Atlas, 11th ed. New York, NY: McGraw-Hill Education; 2005.)

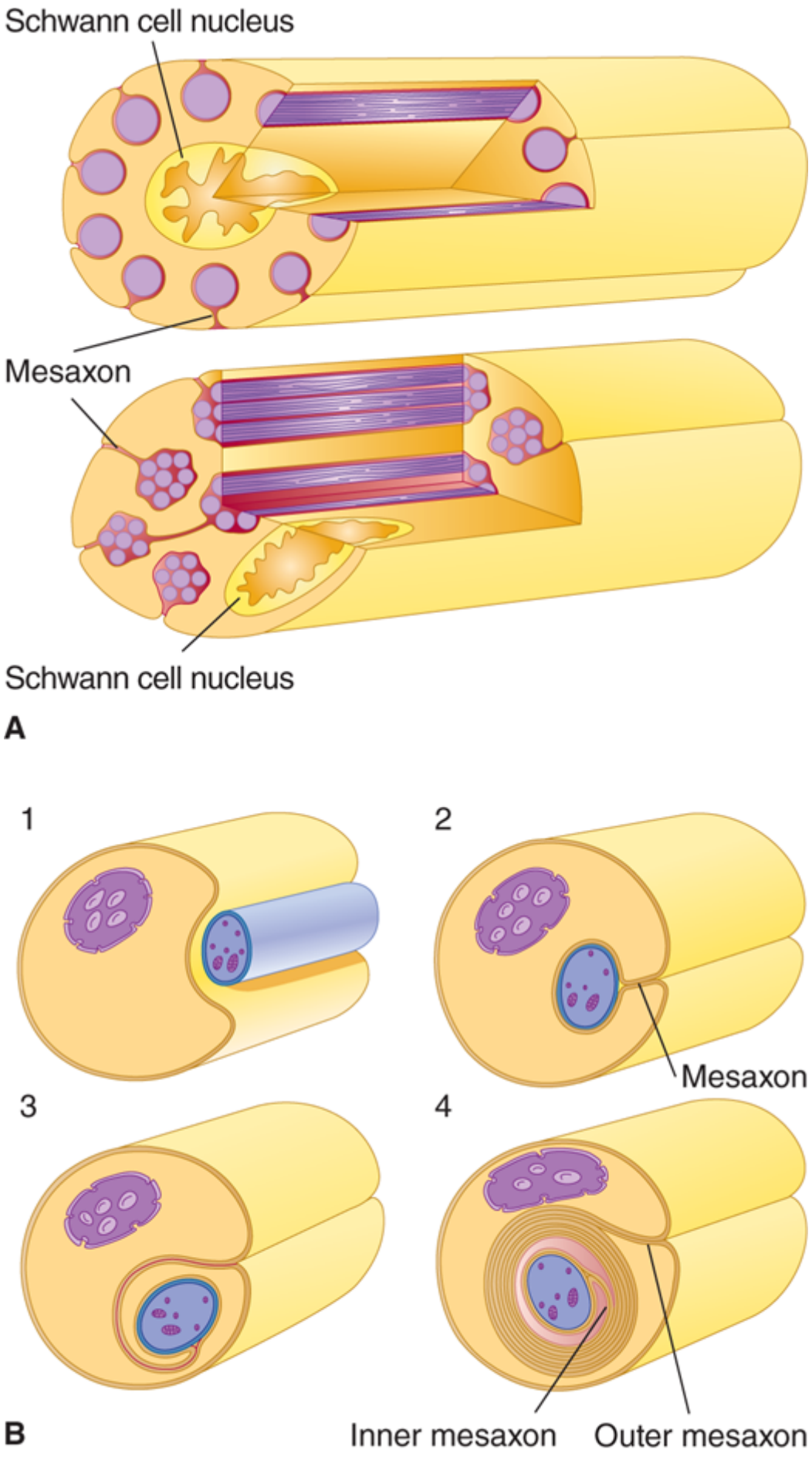


FIGURE 2–8

Electron micrograph of myelinated (M) and unmyelinated (U) axons of a peripheral nerve. Schwann cells (S) may surround one myelinated or several unmyelinated axons. ×16,000. (Used with permission from Dr. DM McDonald.)

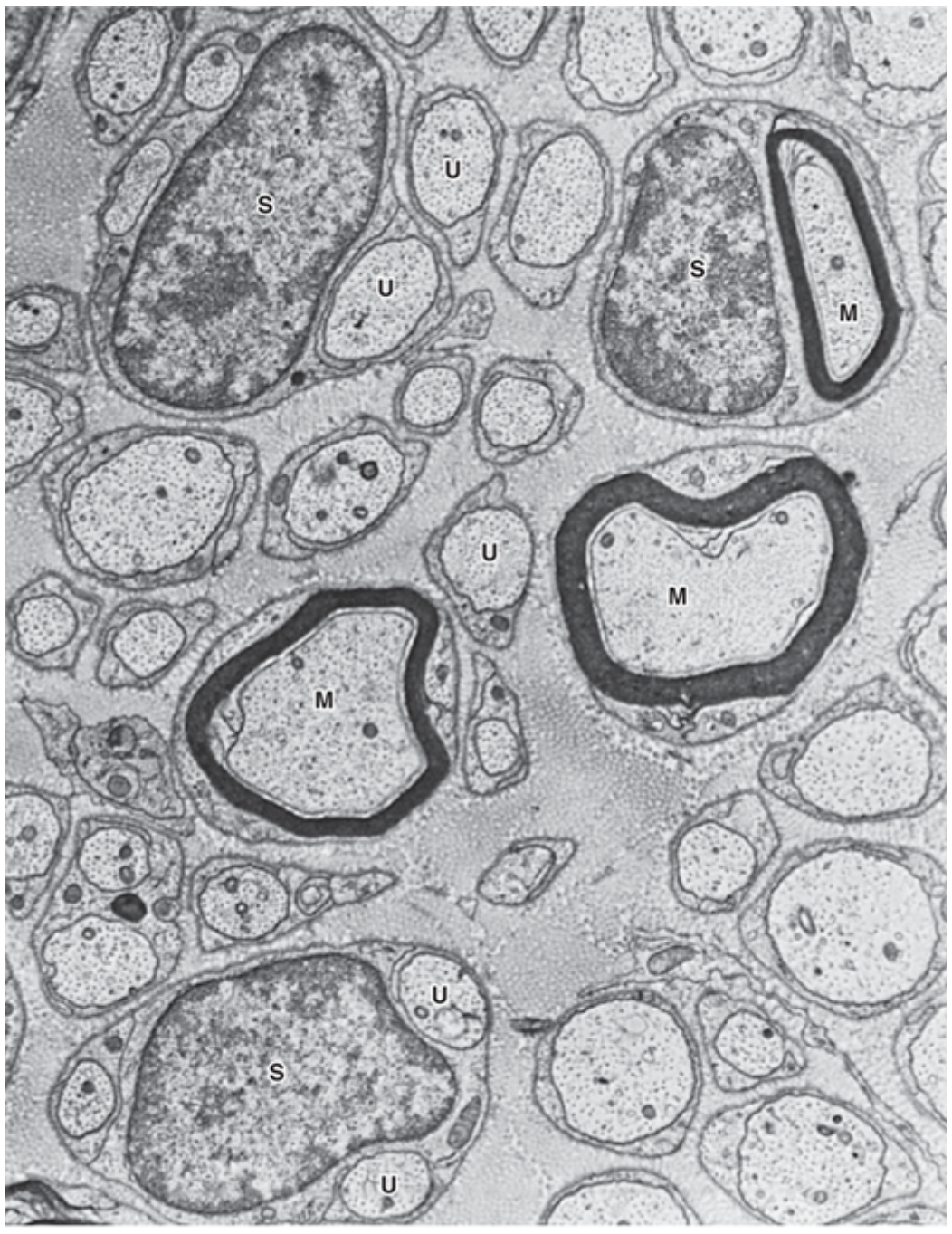


FIGURE 2–9

Oligodendrocytes form myelin in the central nervous system (CNS). A single oligodendrocyte myelinates an entire family of axons (2–50). There is little oligodendrocyte cytoplasm (Cyt) in the oligodendrocyte processes that spiral around the axon to form myelin, and the myelin sheaths are connected to their parent oligodendrocyte cell body by only thin tongues of cytoplasm. This may account, at least in part, for the paucity of remyelination after damage to the myelin in the CNS. The myelin is periodically interrupted at nodes of Ranvier, where the axon (A) is exposed to the extracellular space (ES). (Reproduced with permission from Bunge M, Bunge R, Pappas G: Ultrastructural study of remyelination in an experimental lesion in adult cat spinal cord, *J Biophys Biochem Cytol*. 1961 May;10:67–94.)

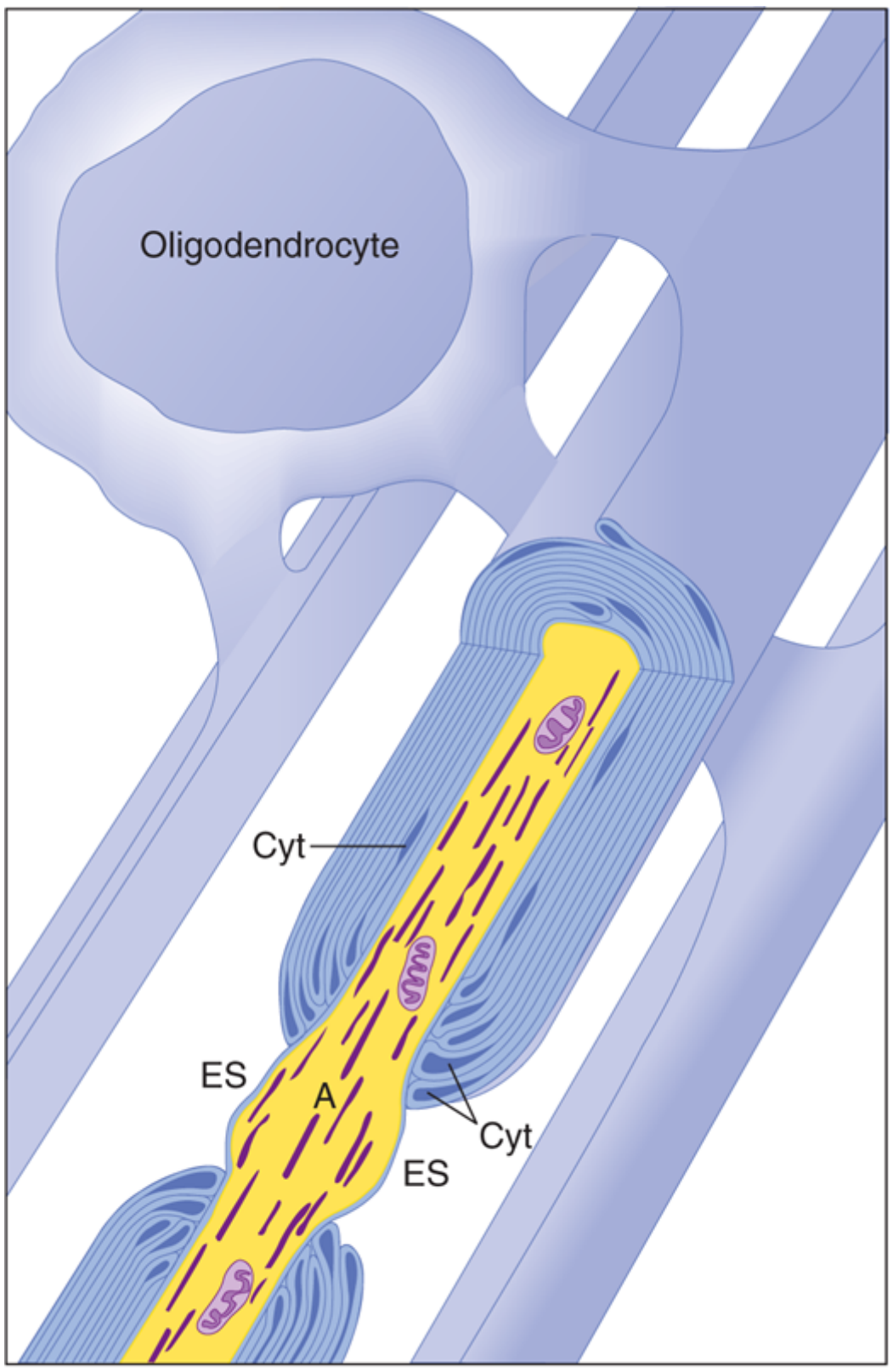
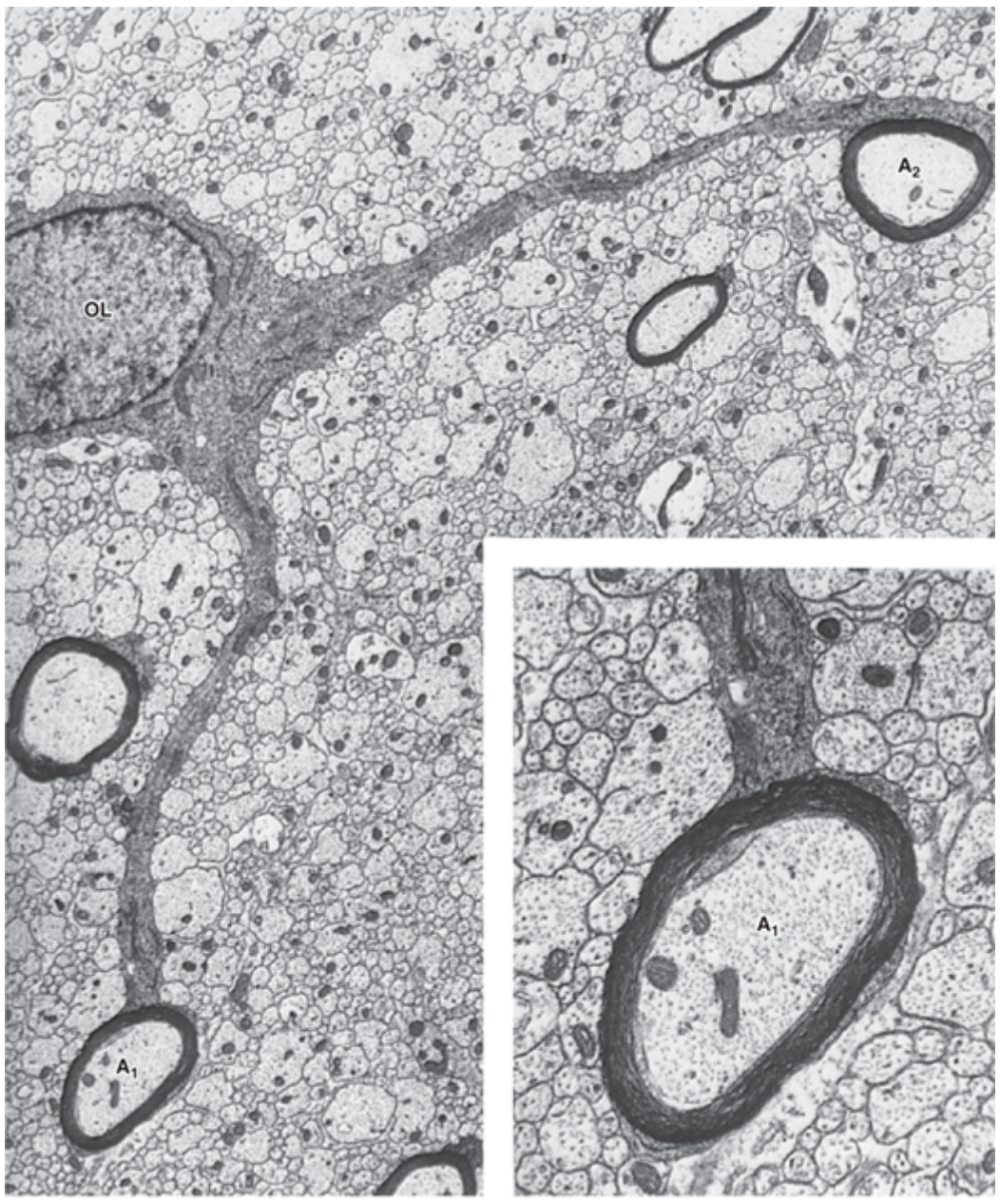


FIGURE 2–10

Electron micrograph showing oligodendrocyte (OL) in the spinal cord, which has myelinated two axons (A_1, A_2). ×6,600. The *inset* shows axon A_1 and its myelin sheath at higher magnification. The myelin is a spiral of oligodendrocyte membrane that surrounds the axon. Most of the oligodendrocyte cytoplasm is extruded from the myelin. Because the myelin is compact, it has a high electrical resistance and low capacitance so that it can function as an insulator around the axon. ×16,000.



B. Axonal Transport

In addition to conducting action potentials, axons transport materials from the cell body to the synaptic terminals (**anterograde transport**) and from the synaptic terminals to the cell body (**retrograde transport**). It is generally thought that ribosomes are not present in the axon, and this new protein must be synthesized and moved to the axon. This occurs via several types of axonal transport, which differ in terms of the rate and the material transported. Anterograde transport may be fast (up to 400 mm/d) or slow (about 1 mm/d). Retrograde transport is similar to rapid anterograde transport. Fast transport involves microtubules extending through the cytoplasm of the neuron.

An axon can be injured by being cut or severed, crushed, or compressed. After injury to the axon, the neuronal cell body responds by entering a phase called the **axon reaction**, or **chromatolysis**. In general, axons within peripheral nerves can regenerate quickly after they are severed, whereas those within the CNS do not tend to regenerate. The axon reaction and axonal regeneration are further discussed in Chapter 22.

Synapses

Transmission of information between neurons occurs at synapses. Communication between neurons usually occurs from the axon terminal of the transmitting neuron (presynaptic side) to the receptive region of the receiving neuron (postsynaptic side) (Figs 2–6 and 2–11). This specialized interneuronal complex is a **synapse**, or **synaptic junction**. As outlined in Table 2–1, some synapses are located between an axon and a dendrite (**axodendritic** synapses, which tend to be excitatory), or small dendritic spine which protrudes from the dendrite (Fig 2–12). Other synapses are located between an axon and a nerve cell body (**axosomatic** synapses, which tend to be inhibitory). Still other synapses are located between an axon terminal and another **axon**; these **axoaxonic** synapses modulate transmitter release by the postsynaptic axon. Synaptic transmission permits information from many presynaptic neurons to converge on a single postsynaptic neuron. Some neuronal large cell bodies receive several thousand synapses (see Fig 2–4).

FIGURE 2–11
Schematic drawing of a synaptic terminal. Vesicles fuse with the presynaptic membrane and release transmitter molecules into the synaptic cleft so that they can bind to receptors in the postsynaptic membrane.

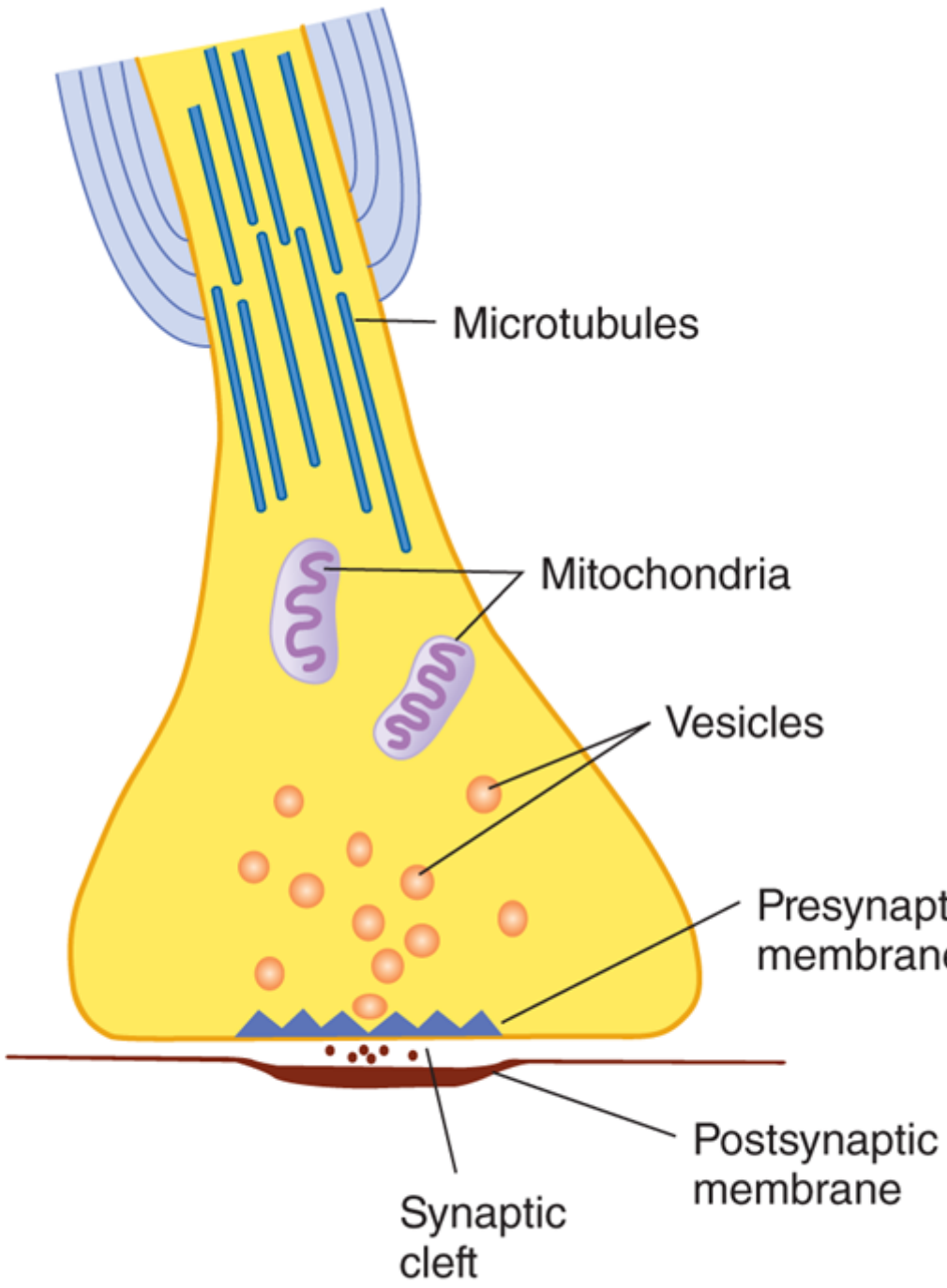


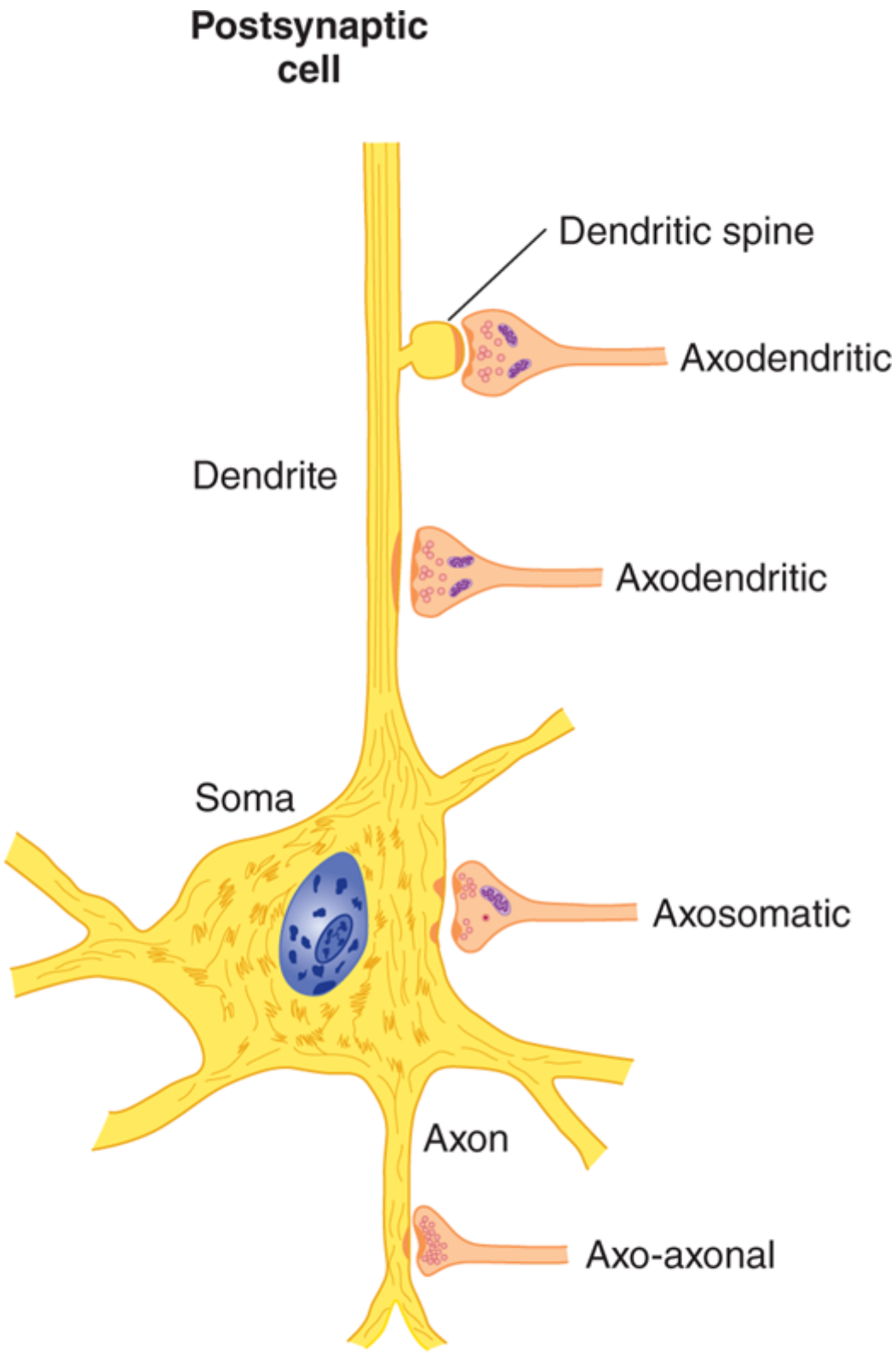
TABLE 2–1

Types of Synapses in the CNS.

Type	Presynaptic Element	Postsynaptic Element	Function
Axodendritic	Axon terminal	Dendrite	Usually excitatory
Axosomatic	Axon terminal	Cell body	Usually inhibitory
Axoaxonic	Axon terminal	Axon terminal	Presynaptic inhibition (modulates transmitter release in postsynaptic axon)
Dendrodendritic	Dendrite	Dendrite	Local interactions (may be excitatory or inhibitory) in axonless neurons, eg, in retina

FIGURE 2–12

Axodendritic synapses terminate on dendrities or mushroom-shaped "dendritic spines," and tend to be excitatory. Axosomatic synapses terminate on neuronal cell bodies and tend to be inhibitory. Axoaxonal synapses terminate on an axon, often close to synaptic terminals, and modulate the release of neurotransmitters. (Reproduced with permission from Ganong WF: *Review of Medical Physiology*, 22nd ed. New York, NY: McGraw-Hill Education; 2005.)



Impulse transmission at most synaptic sites involves the release of a chemical transmitter substance (see Chapter 3); at other sites, current passes directly from cell to cell through specialized junctions called **electrical synapses**, or **gap junctions**. Electrical synapses are most common in invertebrate nervous systems, although they are found in a small number of sites in the mammalian CNS. Chemical synapses have several distinctive characteristics: synaptic vesicles on the presynaptic side, a synaptic cleft, and a dense thickening of the cell membrane on both the receiving cell and the presynaptic side (see Fig 2–11). Synaptic vesicles contain neurotransmitters, and each vesicle contains a small packet, or **quanta**, of transmitter. When the synaptic terminal is depolarized (by an action potential in its parent axon), there is an influx of calcium. This calcium influx leads to phosphorylation of a class of proteins called **synapsins**. After phosphorylation of synapsins, synaptic vesicles dock at the presynaptic membrane facing the synaptic cleft, fuse with it, and release their transmitter (see Chapter 3).

Synapses are very diverse in their shapes and other properties. Some are inhibitory and some excitatory; in some, the transmitter is acetylcholine; in others, it is a catecholamine, amino acid, or other substance (see Chapter 3). Some synaptic vesicles are large, some small; some have a dense core, whereas others do not. Flat synaptic vesicles appear to contain an inhibitory mediator; dense-core vesicles contain catecholamines.

In addition to calcium-dependent, vesicular neurotransmitter release, there is also a second, nonvesicular mode of neurotransmitter release that is not calcium-dependent. This mode of release depends on **transporter molecules**, which usually serve to take up transmitter from the synaptic cleft.

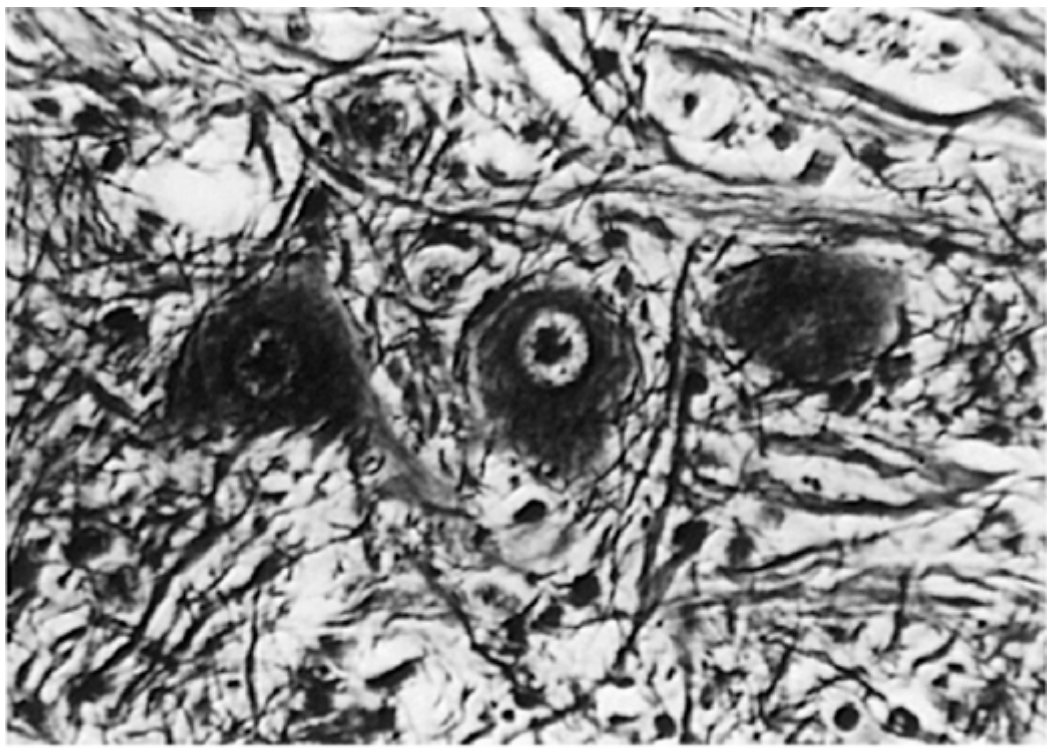
NEURONAL GROUPINGS AND CONNECTIONS

Nerve cell bodies are grouped characteristically in many parts of the nervous system. In the cerebral and cerebellar cortices, cell bodies aggregate to form layers called laminas. Nerve cell bodies in the spinal cord, brain stem, and cerebrum form compact groups, or **nuclei**. Each nucleus contains **projection neurons**, whose axons carry impulses to other parts of the nervous system, and **interneurons**, which act as short relays within the nucleus. In the peripheral nervous system, these compact groups of nerve cell bodies are called **ganglia**.

Groups of nerve cells are connected by pathways formed by bundles of axons. In some pathways, the axon bundles are sufficiently defined to be identified as **tracts**, or **fasciculi**; in others, there are no discrete bundles of axons. Aggregates of tracts in the spinal cord are referred to as **columns**, or **funiculi** (see Chapter 5). Within the brain, certain axon tracts are referred to as **lemnisci**. In some regions of the brain, axons are intermingled with dendrites and do not run in bundles so that pathways are difficult to identify. These web-like networks are called the **neuropil** (Fig 2–13).

FIGURE 2–13

Light micrograph of a small group of neurons (nucleus) in a network of fibers (neuropil). ×800. Bielschowsky silver stain.



GLIA

Neuroglial cells, commonly called glial cells, outnumber neurons in the brain and spinal cord 10:1. They do not form synapses. These cells appear to play a number of important roles, including myelin formation, guidance of developing neurons, maintenance of extracellular K^+ levels, and reuptake of transmitters after synaptic activity. There are two broad classes of glial cells, macroglia and microglia (Table 2–2).

TABLE 2–2

Nomenclature and Principal Functions of Glial Cells.

		Cell Type	Principal Functions
Glial cells	Macroglia	Oligodendrocytes	Myelin formation in CNS
		Astrocytes	Regulate ionic environment; reuptake of neurotransmitters; guidanc growing axons
	Microglia	Microglial cells	Immune surveillance of the CNS

Macroglia

The term **macroglia** refers to astrocytes and oligodendrocytes, both of which are derived from ectoderm. In contrast to neurons, these cells may have the capability, under some circumstances, to regenerate.

Astrocytes

There are two broad classes of astrocytes: **protoplasmic** and **fibrous**. Protoplasmic astrocytes are more delicate, and their many processes are branched. They occur in gray matter. Fibrous astrocytes are more fibrous, and their processes (containing glial fibrils) are seldom branched. Astrocytic processes radiate in all directions from a small cell body. They surround blood vessels in the nervous system, and they cover the exterior surface of the brain and spinal cord below the pia.

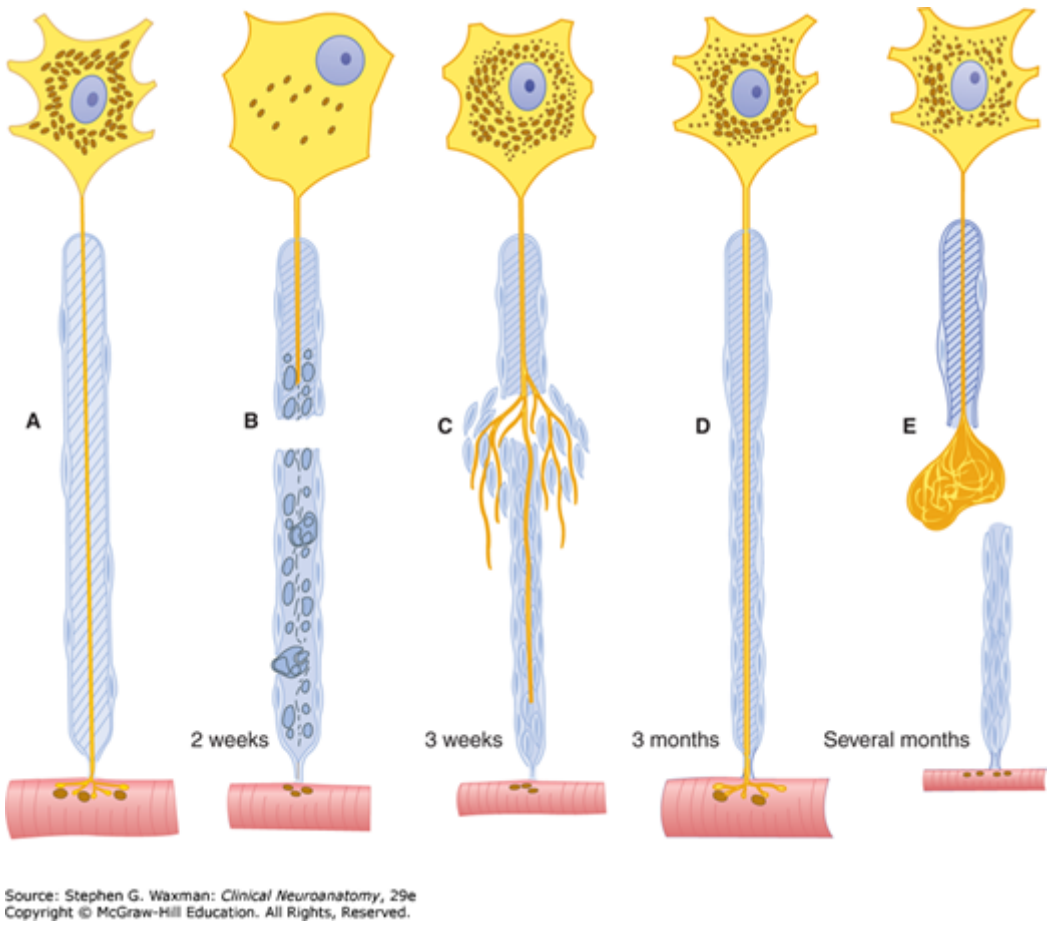
Astrocytes provide structural support to nervous tissue and act during development as guidewires that direct neuronal migration. They also maintain appropriate concentrations of ions such as K^+ within the extracellular space of the brain and spinal cord. Astrocytes may also play a role in synaptic transmission. Many synapses are closely invested by astrocytic processes, which appear to participate in the reuptake of neurotransmitters. Astrocytes also surround endothelial cells within the CNS, which are joined by tight junctions that impede the transport of molecules across the capillary epithelium, and contribute to the formation of the blood–brain barrier (see Chapter 11). Although astrocytic processes around capillaries do not form a functional barrier, they can selectively take up materials to provide an environment optimal for neuronal function.

Astrocytes form a covering on the entire CNS surface and proliferate within damaged neural tissue (Fig 2–14). These reactive astrocytes are larger, are more easily stained, and can be definitively identified in histological sections because they contain a characteristic, astrocyte-specific protein: **glial fibrillary acidic protein (GFAP)**. Chronic astrocytic proliferation leads to **gliosis**, sometimes called **glial scarring**. Whether glial scarring is beneficial, or inhibits regeneration of injured neurons, is currently being studied.

FIGURE 2–14

Changes in an injured nerve fiber. A: Normal nerve fiber, with its perikaryon and the effector cell (striated skeletal muscle). Notice the position of the neuron nucleus and the amount and distribution of Nissl bodies. **B:** When the fiber is injured, the neuronal nucleus moves to the cell

periphery, Nissl bodies become greatly reduced in number (chromatolysis), and the nerve fiber distal to the injury degenerates along with its myelin sheath. Debris is phagocytized by macrophages. **C:** The muscle fiber shows disuse atrophy. Schwann cells proliferate, forming a compact cord that is penetrated by the growing axon. The axon grows at a rate of 0.5 to 3 mm/d. **D:** In this example, the nerve fiber regeneration was successful, and the muscle fiber was also regenerated after receiving nerve stimuli. **E:** When the axon does not penetrate the cord of Schwann cells, its growth is not organized and successful regeneration does not occur. (Reproduced with permission from Willis RA, Willis AT: *The Principles of Pathology and Bacteriology*, 3rd ed. Philadelphia, PA: Butterworth; 1972.)



Oligodendrocytes

Oligodendrocytes predominate in white matter; they extend arm-like processes which wrap tightly around axons, extruding the oligodendroglial cytoplasm to form a compact sheath of myelin which acts as an insulator around axons in the CNS. Oligodendrocytes may also provide some nutritive support to the neurons they envelop. A single oligodendrocyte may wrap myelin sheaths around many (up to 30–40) axons (see Figs 2–9 and 2–10). In peripheral nerves, by contrast, each myelin sheath is formed by **Schwann cells**. Each Schwann cell myelinates a single axon, and remyelination can occur at a brisk pace after injury to the myelin in the peripheral nerves.

Microglia

Microglial cells are **macrophage-like cells,** or scavengers of the CNS. They constantly survey the brain and spinal cord, acting as sentries to detect, and destroy, invaders (such as bacteria). When an area of the brain or spinal cord is damaged or infected, microglia activate and migrate to the site of injury to remove cellular debris. Some microglia are always present in the brain, but when injury or infection occurs, others enter the brain from blood vessels. Microglia play an important role in protecting the nervous system from outside invaders such as bacteria. Their role after endogenous insults, including stroke or neurodegenerative diseases such as Alzheimer disease, is under investigation.

Extracellular Space

The fluid-filled space between the various cellular components of the CNS accounts for, under most circumstances, about 20% of the total volume of the brain and spinal cord. Because transmembrane gradients of ions, such as K^+ and Na^+, are important in electrical signaling in the nervous system (see Chapter 3), regulation of the levels of these ions in the extracellular compartment (**ionic homeostasis**) is an important function, which is, at least in part, performed by astrocytes. The capillaries within the CNS are completely invested by glial or neural processes. Moreover, capillary endothelial cells in the brain (in contrast to capillary endothelial cells in other organs) form **tight junctions**, which are impermeable to diffusion, thus creating a **blood–brain barrier**. This barrier isolates the brain extracellular space from the intravascular compartment.

Clinical Correlation

In **cerebral edema**, there is an increase in the bulk of the brain. Cerebral edema can be either vasogenic (primarily extracellular) or cytotoxic (primarily intracellular). Because of the limited size of the cranial vault within the skull, cerebral edema must be treated emergently.

DEGENERATION AND REGENERATION

The neuronal cell body maintains the functional and anatomic integrity of the axon (Fig 2–14). If the axon is cut, the part distal to the cut degenerates (**wallerian degeneration**), because materials for maintaining the axon (mostly proteins) are formed in the cell body and can no longer be transported down the axon (**axoplasmic transport**).

Distal to the level of axonal transection when a peripheral nerve is injured, Schwann cells dedifferentiate and divide. Together with macrophages, they phagocytize the remnants of the myelin sheaths, which lose their integrity as the axon degenerates.

After injury to its axon, the neuronal cell body exhibits a distinct set of histological changes (which have been termed the **axon reaction** or **chromatolysis**). The changes include swelling of the cell body and nucleus, which is usually displaced from the center of the cell to an eccentric location. The regular arrays of ribosome-studded endoplasmic reticulum, which characterize most neurons, are dispersed and replaced by polyribosomes. (The ribosome-studded endoplasmic reticulum, which had been termed the Nissl substance by classical neuroanatomists, normally stains densely with basic dyes. The loss of staining of the Nissl substance, as a result of dispersion of the endoplasmic reticulum during the axon reaction, led early scientists to use the term "chromatolysis.") In association with the axon reaction in some CNS neurons, there is detachment of afferent synapses, swelling of nearby astrocytes, and activation of microglia. Successful axonal regeneration does not commonly occur after injury to the CNS. It appears that this failure of CNS axons to regenerate is not due to an intrinsic inability of these cells to regrow, but rather to the presence, in the neighborhood of CNS axons, of factors that block of inhibit axonal regeneration. Many neurons appear to be dependent on connection with appropriate target cells; if the axon fails to regenerate and form a new synaptic connection with the correct postsynaptic cells, the axotomized neuron may become disorganized so that it functions impropriety, or die or atrophy.

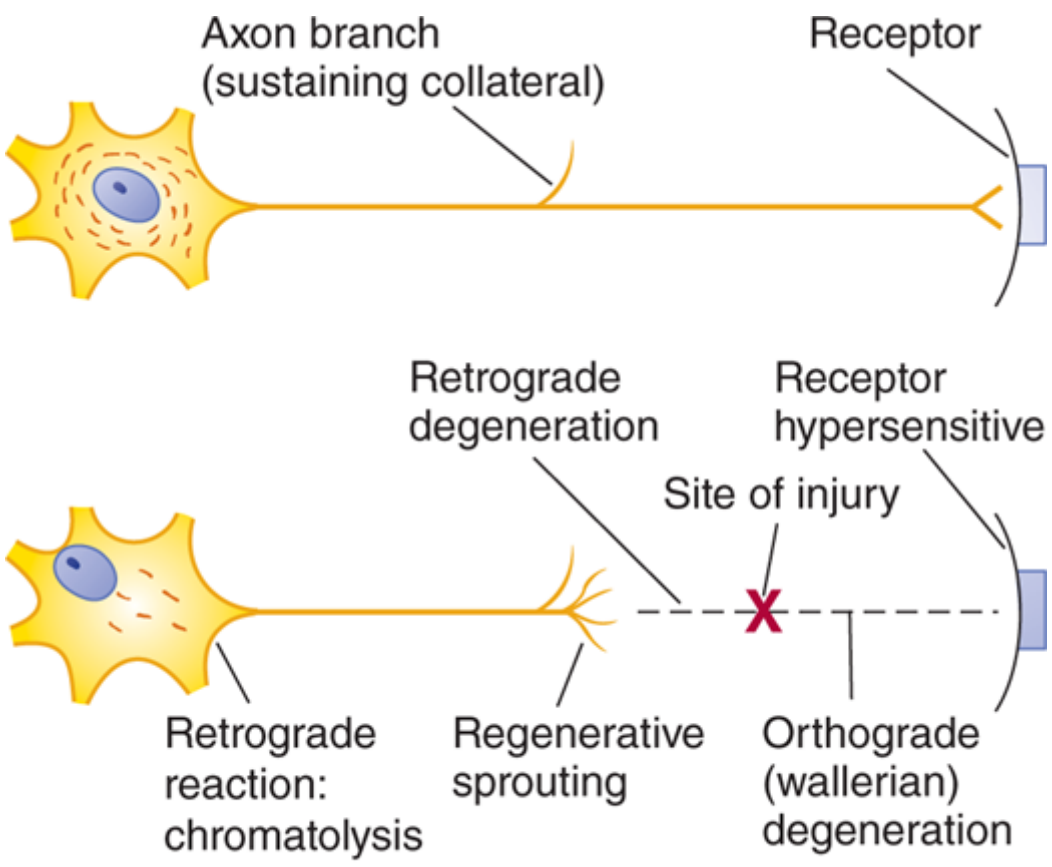
Regeneration

A. Peripheral Nerves

Regeneration denotes a nerve's ability to regrow to an appropriate target, including the reestablishment of functionally useful connections (see Figs 2–14 and 2–15). Shortly (1–3 days) after an axon is cut, the tips of the proximal stumps form enlargements, or growth cones. The growth cones send out exploratory pseudopodia that are similar to the axonal growth cones formed in normal development. Each axonal growth cone is capable of forming many branches that continue to advance away from the site of the original cut. If these branches can cross the scar tissue and enter the distal nerve stump, successful regeneration with restoration of function may occur.

FIGURE 2–15

Summary of changes occurring in a neuron and the structure it innervates when its axon is crushed or cut at the point marked X. (Reproduced with permission from Ganong WF: *Review of Medical Physiology*, 22nd ed. New York, NY: McGraw-Hill Education; 2005.)



The importance of axonal regeneration through the Schwann cell tubes surrounded by basal lamina (Büngner's bands) in the distal stump explains the different degrees of regeneration that are seen after *nerve crush* compared with *nerve transection*. After a crush injury to a peripheral nerve, the axons may be severed, but the Schwann cells, surrounding basal lamina, and perineurium maintain continuity through the lesion, facilitating regeneration of axons through the injured nerve. In contrast, if the nerve is cut, the continuity of these pathways is disrupted. Even with meticulous surgery, it can be difficult to align the proximal and distal parts of each axon's pathway; successful regeneration is, therefore, less likely.

B. Central Nervous System

Axonal regeneration is typically abortive in the CNS. The reasons for regeneration failure are not yet entirely clear. Classical neuropathologists suggested that the glial scar, which is largely formed by astrocytic processes, may be partly responsible. The properties of the oligodendroglial cells (in contrast to those of the Schwann cells of peripheral nerves) may also account for the difference in regenerative capacity. An inhibitory factor produced by oligodendrocytes, CNS myelin, or both may interfere with regeneration of axons through the CNS. It is now appreciated that molecules such as NoGo act as "stop signs" that inhibit regeneration of axons within the brain and spinal cord. Neutralization of NoGo has been shown to promote the regeneration of axons within the spinal cord in experimental animals. When confronted with a permissive environment (eg, when the transected axons of CNS neurons are permitted to regrow into a peripheral nerve, or transplanted into the CNS as a "bridge"), CNS axons can regenerate for at least a few centimeters. Some of the regenerated axons can establish synaptic connections with appropriate target cells.

C. Remyelination

In some disorders of the peripheral nervous system (such as the Guillain–Barré syndrome), demyelination, interferes with conduction (see Chapter 3). This condition is often followed by remyelination by Schwann cells, which are capable of elaborating new myelin sheaths. In contrast, remyelination occurs much more slowly (if at all) in the CNS. Little remyelination occurs within demyelinated plaques within the brain and spinal cord in multiple sclerosis. A different form of plasticity (ie, molecular reorganization of the axon membrane that acquires sodium channels in demyelinated zones) appears to underlie clinical remissions (in which there is neurological improvement) in patients with multiple sclerosis.

D. Collateral Sprouting

This phenomenon has been demonstrated in the CNS as well as in the peripheral nervous system (see Fig 2–13). It occurs when an innervated structure has been partially denervated. The remaining axons then form new collaterals that reinnervate the denervated part of the end organ. This kind of regeneration demonstrates that there is considerable plasticity in the nervous system and that one axon can take over the synaptic sites formerly occupied by another.

NEUROGENESIS

It has classically been believed that neurogenesis—the capability for production of neurons from undifferentiated, proliferative progenitor cells—is confined to the development period that precedes birth in mammals. According to this traditional view, after pathological insults that result in neuronal death, the number of neurons is permanently reduced. However, some recent evidence suggests that a small number of neuronal precursor cells, capable of dividing and then differentiating into neurons, may exist in the forebrain of adult mammals, including humans. These rare precursor cells reside in the subventricular zone. For example, there is some evidence for postnatal neurogenesis in the dentate gyrus of the hippocampus, and it has been suggested that the rate of generation of new neurons in this critical region can be accelerated in an enriched environment. While the number of new neurons that can be produced within the adult human brain is still being debated, the existence of these precursor cells may suggest strategies for restoring function after injury to the CNS. This is an area of intense research.

BOX 2–1

Essentials for the Clinical Neuroanatomist

After reading and digesting this chapter, you should know and understand:

The main components of the neuron (cell body, axon, dendrites) and their functions

Synapses: types and functions

Glial cells (astrocytes, oligodendrocytes, microglia) and their functions; myelination in peripheral nerve (Schwann cells) versus myelination in CNS (oligodendrocytes)

Principle of axonal degeneration and regeneration

The principle of neurogenesis

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Chapter 3: Signaling in the Nervous System

INTRODUCTION

For the nervous system to function properly, nervous must communicate with each other. Along with muscle cells, neurons are unique in that they are **excitable**; that is, they respond to stimuli by generating electrical impulses. Electrical responses of neurons (modifications of the electrical potential across their membranes) may be **local** (restricted to the place that received the stimulus) or **propagated** (may travel through the neuron and its axon). Propagated electrical impulses (nerve impulses) are termed **action potentials**. Neurons communicate with each other at **synapses** by a process called **synaptic transmission**.

MEMBRANE POTENTIAL

The membranes of nerve cells are structured so that a difference in electrical potential exists between the inside (negative) and the outside (positive). This results in a **resting potential** across the cell membrane, which is normally about −70 mV (70 one-thousandths of a volt).

The electrical potential across the neuronal cell membrane is the result of its selective permeability to charged ions. Cell membranes are highly permeable to most inorganic ions, but they are almost impermeable to proteins and many other organic ions. The difference (**gradient**) in ion composition inside and outside the cell membrane is maintained by **ion pumps** in the membrane, which maintain a nearly constant concentration of inorganic ions within the cell (Fig 3–1 and Table 3–1). The pump that maintains Na^+ and K^+ gradients across the membrane is Na, K-ATPase; this specialized protein molecule extrudes Na^+ from the intracellular compartment, moving it to the extracellular space, and imports K^+ from the extracellular space, carrying it across the membrane into the cell. In carrying out this essential activity, the pump consumes adenosine triphosphate (**ATP**).

FIGURE 3–1

Na^+ and K^+ flux through the resting nerve cell membrane. Notice that the Na^+/K^+ pump (Na^+/K^+-ATPase) is fueled by ATP and tends to extrude Na^+ from the interior of the cell, but it carries K^+ ions inward. (Eccles, John C.. *The Physiology of Nerve Cells.* pp. 26 Figure 8. © 1957 Johns Hopkins University Press. Reprinted with permission of Johns Hopkins University Press.)

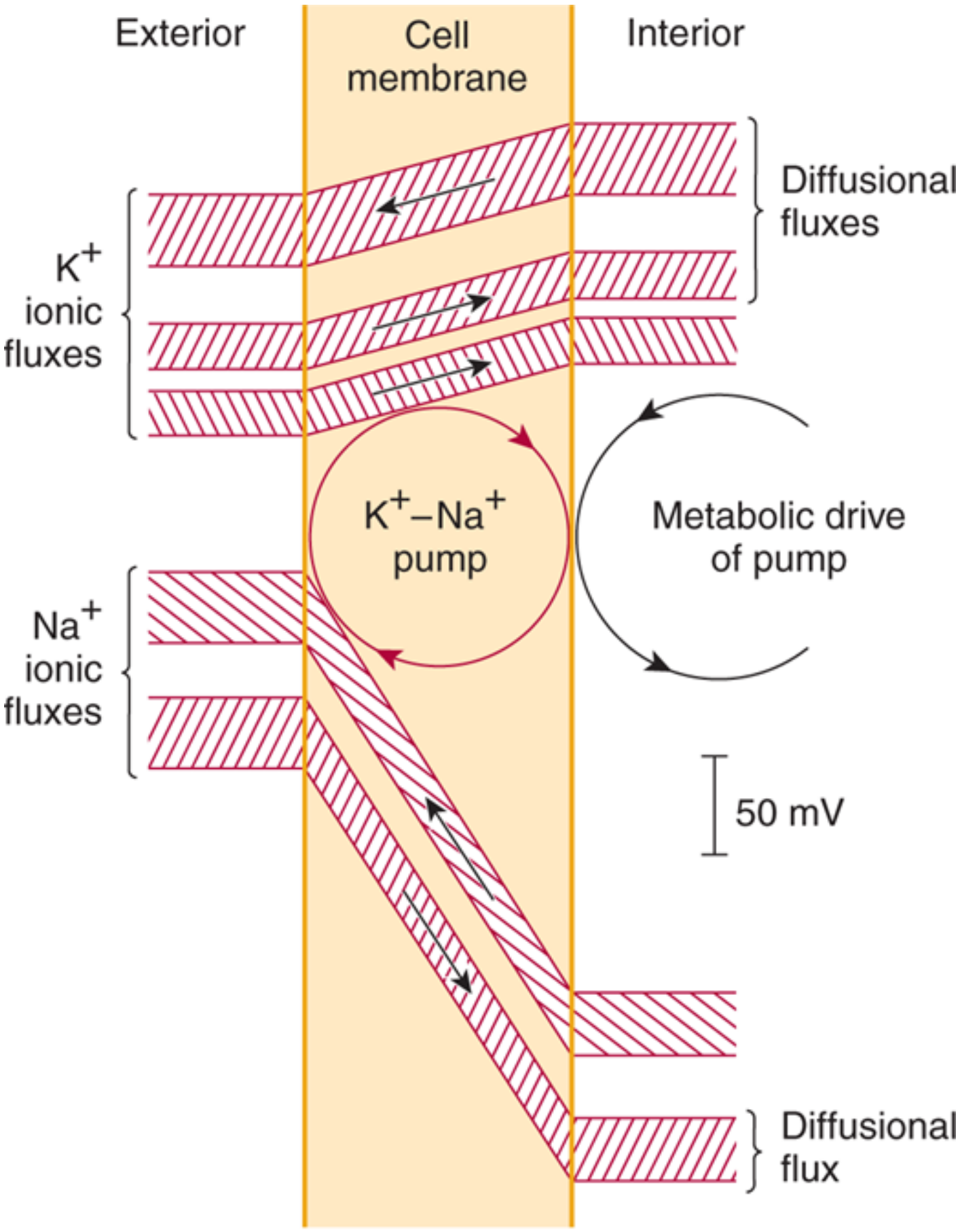


TABLE 3–1

Concentration of Ions Inside and Outside Mammalian Spinal Motor Neurons.

Concentration (mmol/L H_2O)			
Ion	**Inside Cell**	**Outside Cell**	**Equilibrium Potential (mV)**
Na^+	15.0	150.0	+60
K^+	150.0	5.5	−90
Cl^-	9.0	125.0	−70

Resting membrane potential = −70 mV.

Data from Ross G: *Essentials of Human Physiology*. Philadelphia, PA: Year Book; 1978.

Two types of passive forces maintain an equilibrium of Na^+ and K^+ across the membrane: A chemical force tends to move Na^+ inward and K^+ outward, from the compartment containing high concentration to the compartment containing low concentration, and an electrical force (the membrane potential) tends to move Na^+ and K^+ inward. When the chemical and electrical forces are equally strong, an **equilibrium potential** exists.

For an idealized membrane that is permeable to only K^+, the **Nernst equation**, which describes the relationship between these forces, is used to calculate the equilibrium potential (ie, the membrane potential at which equilibrium exists). Normally, there is a much higher concentration of K^+ inside the cell ($[K^+]_i$) than outside the cell ($[K^+]_o$) (see Table 3–1). The Nernst equation, which is used to determine membrane potential across a membrane permeable only to K^+ ions, is as follows:

$$E_K \frac{RT}{nF} \log_{10} \frac{\left[K^+\right]_o}{\left[K^+\right]_i}$$

where

E = equilibrium potential (no net flow across the membrane)

K = potassium

T = temperature

R = gas constant

F = Faraday constant (relates charge in coulombs to concentration in moles)

N = valence (for potassium, valence = 1)

$[K^+]_i$ = concentration of potassium inside cell

$[K^+]_o$ = concentration of potassium outside cell

At physiologic temperatures

$$E_K = 58 \log \frac{\left[K^+\right]_o}{\left[K^+\right]_i}$$

The equilibrium potential (E_{Na}) for sodium can be found by substituting $[Na^+]_i$ and $[Na^+]_o$ in the Nernst equation; this potential would be found across a membrane that was permeable only to sodium. In reality, most cell membranes are permeable to *several* ionic species. For these membranes, potential is the *weighted average* of the equilibrium potentials for each permeable ion, with the contribution for each ion weighted to reflect its contribution to total membrane permeability. This is described mathematically, for a membrane that is permeable to Na^+ and K^+, by the Goldman–Hodgkin–Katz equation (also known as the constant field equation):

$$V_m = 58 \log \frac{P_K\left[K^+\right]_o + P_{Na}\left[Na^+\right]_o}{P_K\left[K^+\right]_i + P_{Na}\left[Na^+\right]_i}$$

where

$[Na]_i$ = concentration of sodium inside cell

$[Na]_o$ = concentration of sodium outside cell

P_{Na} = membrane permeability to sodium

P_K = membrane permeability to potassium

As seen in this equation, membrane potential is affected by the **relative permeability** to each ion. If permeability to a certain ion increases (eg, by the opening of pores or channels specifically permeable to that ion), membrane potential moves *closer* to the equilibrium potential for that ion. Conversely, if permeability to that ion decreases (eg, by closing of pores or channels permeable to that ion), membrane potential moves *away* from the equilibrium potential for that ion.

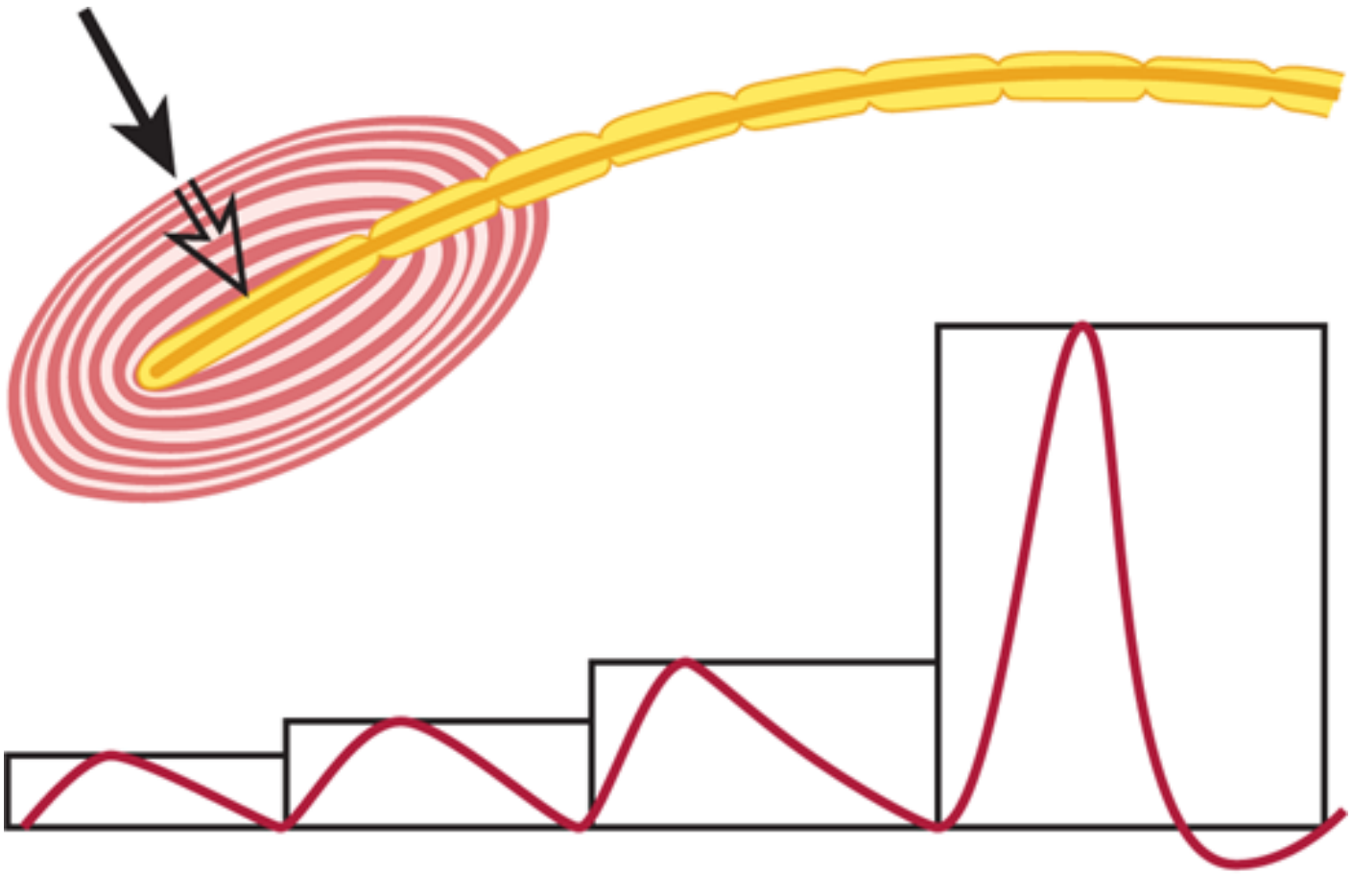
In the membrane of resting neurons, K^+ permeability is much higher (~20-fold) than Na^+ permeability; that is, the P_K–P_{Na} ratio is approximately 20:1. Thus, when a neuron is inactive (resting), the Goldman–Hodgkin–Katz equation is dominated by K^+ permeability so that membrane potential is close to the equilibrium potential for K (E_K). This accounts for the resting potential of approximately −70 mV.

GENERATOR POTENTIALS

The **generator (receptor) potential** is a local, nonpropagated response that occurs in some sensory receptors (eg, muscle stretch receptors and pacinian corpuscles, which are touch-pressure receptors) where mechanical energy is converted into electric signals. The generator potential is produced in a small area of the sensory cell: the nonmyelinated nerve terminal. Most generator potentials are depolarizations, in which membrane potential becomes less negative. In contrast to action potentials (see the next section), which are all-or-none responses, generator potentials are **graded** (the larger the stimulus [stretch or pressure], the larger the depolarization) and **additive** (two small stimuli, close together in time, produce a generator potential larger than that made by a single small stimulus). Further increase in stimulation results in larger generator potentials (Fig 3–2). When the magnitude of the generator potential increases to about 10 mV, a propagated action potential (impulse) is generated in the sensory nerve.

FIGURE 3–2

Demonstration of a generator potential in a pacinian corpuscle. The electrical responses to a pressure (**black arrow**) of 1×, 2×, 3×, and 4× are shown. The strongest stimulus produced an action potential in the sensory nerve, originating in the center of the corpuscle (**open arrow**).

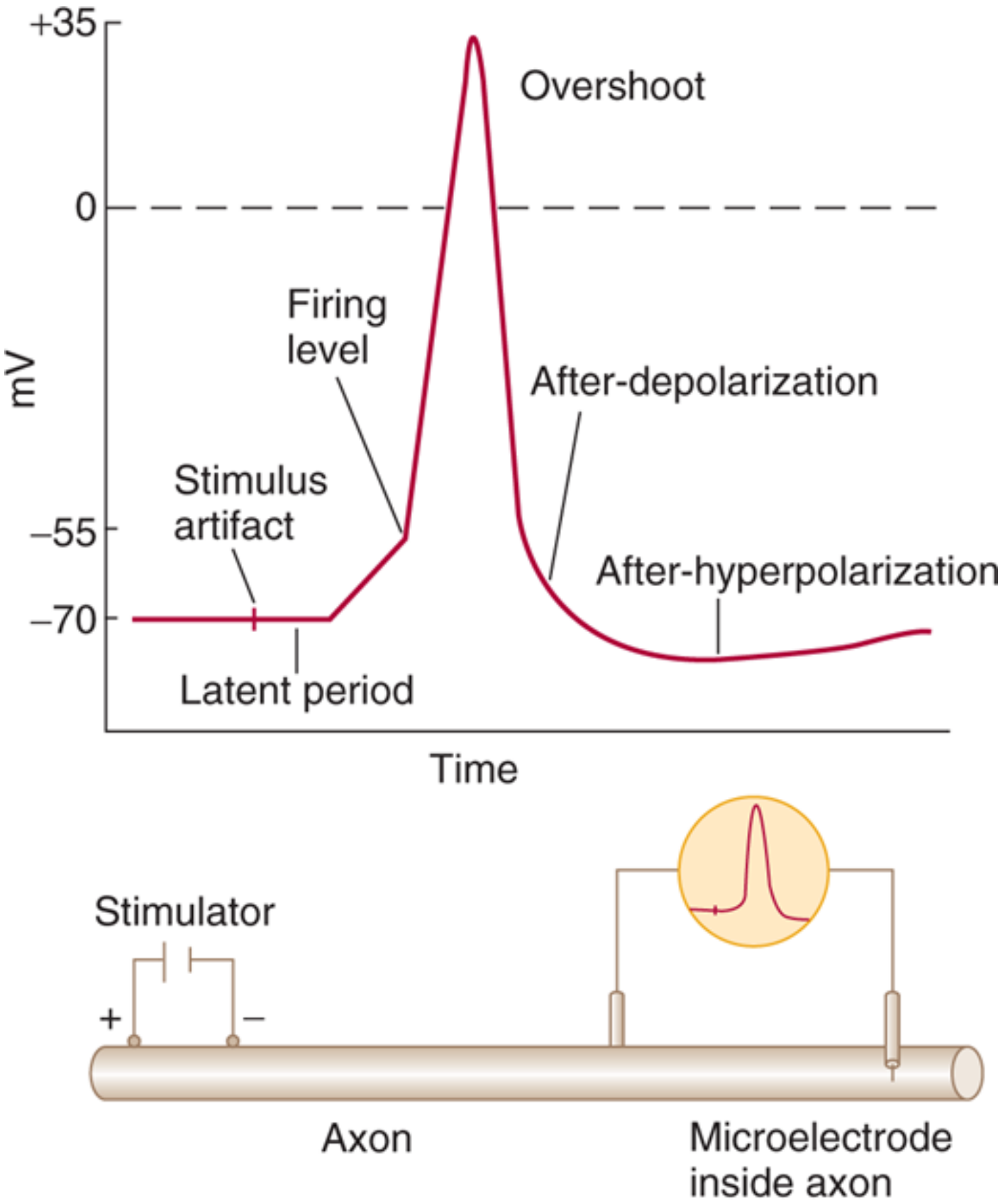


ACTION POTENTIALS

Neurons communicate by producing all-or-none electrical impulses called nerve impulses or **action potentials**. Action potentials are self-regenerative electrical signals that tend to propagate throughout a neuron and along its axon. The action potential is a depolarization of about 100 mV (a large signal for a neuron). The action potential is *all or none*. Its size is constant for each neuron. Because they look like spikes on a computer screen (Fig 3–3), action potentials are sometimes referred to as “spikes”.

FIGURE 3–3

Action potential (“spike”) recorded with an intracellular electrode inside cell. In the resting state, the membrane potential (resting potential) is about -70 mV. When the axon is stimulated, there is a small depolarization. If this depolarization reaches the firing level (threshold), there is an all-or-none depolarization (action potential). The action potential approaches E_{Na} and overshoots the 0-mV level. The action potential ends when the axon repolarizes, again settling at resting potential. (Reproduced with permission from Ganong WF: *Review of Medical Physiology*, 22nd ed. New York, NY: McGraw-Hill Education; 2005.)



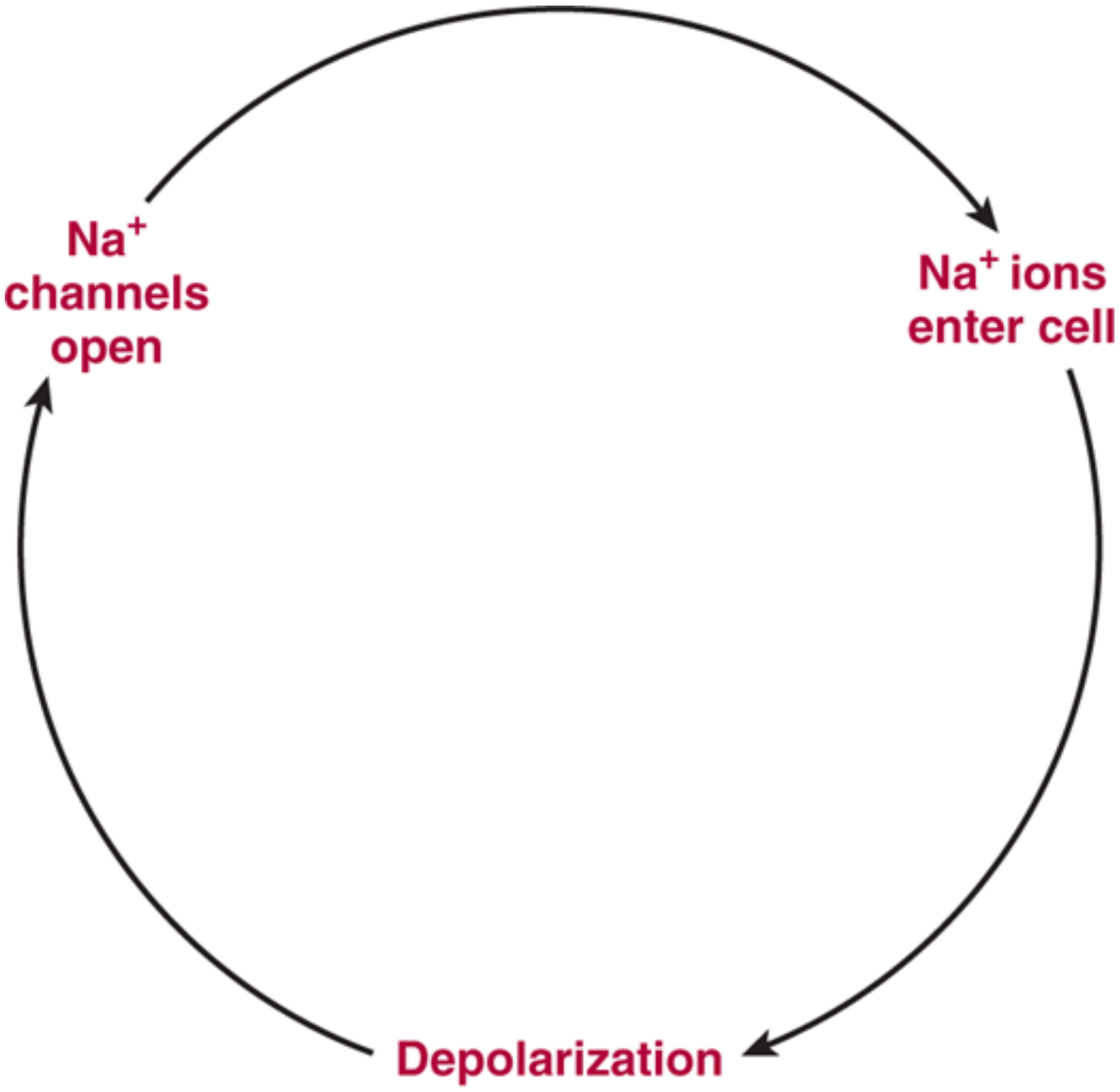
Neurons can generate action potentials because they contain specialized molecules, called sodium channels, that respond to depolarization by opening (activating). When this occurs, the relative permeability of the membrane to Na^+ increases, and the membrane moves closer to the equilibrium potential for Na^+, as predicted by the Goldman–Hodgkin Katz equation, thus causing further depolarization. When a depolarization (from a generator potential, synaptic potential, or oncoming action potential) impinges on a neuronal membrane, sodium channels activate and, as a result, the membrane begins to further **depolarize**. This action tends to activate still other sodium channels, which also open and cause depolarization. If a sufficient number of sodium channels are activated, there is a depolarization of about 15 mV, and threshold is reached so that the rate of depolarization increases sharply to produce an action potential (Fig 3–3). Thus, the membrane generates an explosive, all-or-none action potential. As the impulse passes, **repolarization** occurs rapidly at first and then more slowly. Membrane potential thus returns to resting potential. The action potential tends to last for a few milliseconds.

THE NERVE CELL MEMBRANE CONTAINS ION CHANNELS

Voltage-sensitive ion channels are specialized protein molecules that span the cell membrane. These doughnut-shaped molecules contain a **pore** that acts as a tunnel, permitting specific ions (eg, Na^+ or K^+), but not other ions, to permeate. The channel also possesses a **voltage sensor**, which, in response to changes in potential across the membrane, either opens (activates) or closes (inactivates) the channel.

The neuronal membrane has the ability to generate impulses because it contains **voltage-sensitive Na^+** channels, which are selectively permeable to Na^+ and tend to open when the membrane is depolarized. Because these channels open in response to depolarization, and because by opening they drive the membrane closer to Na^+ equilibrium potential (E_{Na}), they tend to further depolarize the membrane (Fig 3–4). If a sufficient number of these channels are opened, there is an explosive, all-or-none response, termed the action potential (see Fig 3–3). The degree of depolarization necessary to elicit the action potential is called the **threshold**.

FIGURE 3–4



Source: Stephen G. Waxman: *Clinical Neuroanatomy*, 29e

Ionic basis for the depolarization underlying the action potential. Voltage-sensitive Na^+ channels open when the membrane is depolarized. This action results in increased Na^+ permeability of the membrane, causing further ("regenerative") depolarization and the opening of still other Na^+ channels. When a sufficient number of Na^+ channels have opened, the membrane generates an explosive, all-or-none depolarization—the action potential.

Other voltage-sensitive ion channels (**voltage-sensitive K^+** channels) open (usually more slowly than Na^+ channels) in response to depolarization and are selectively permeable to K^+. When these channels open, the membrane potential is driven toward the K^+ equilibrium potential (E_K), leading to hyperpolarization.

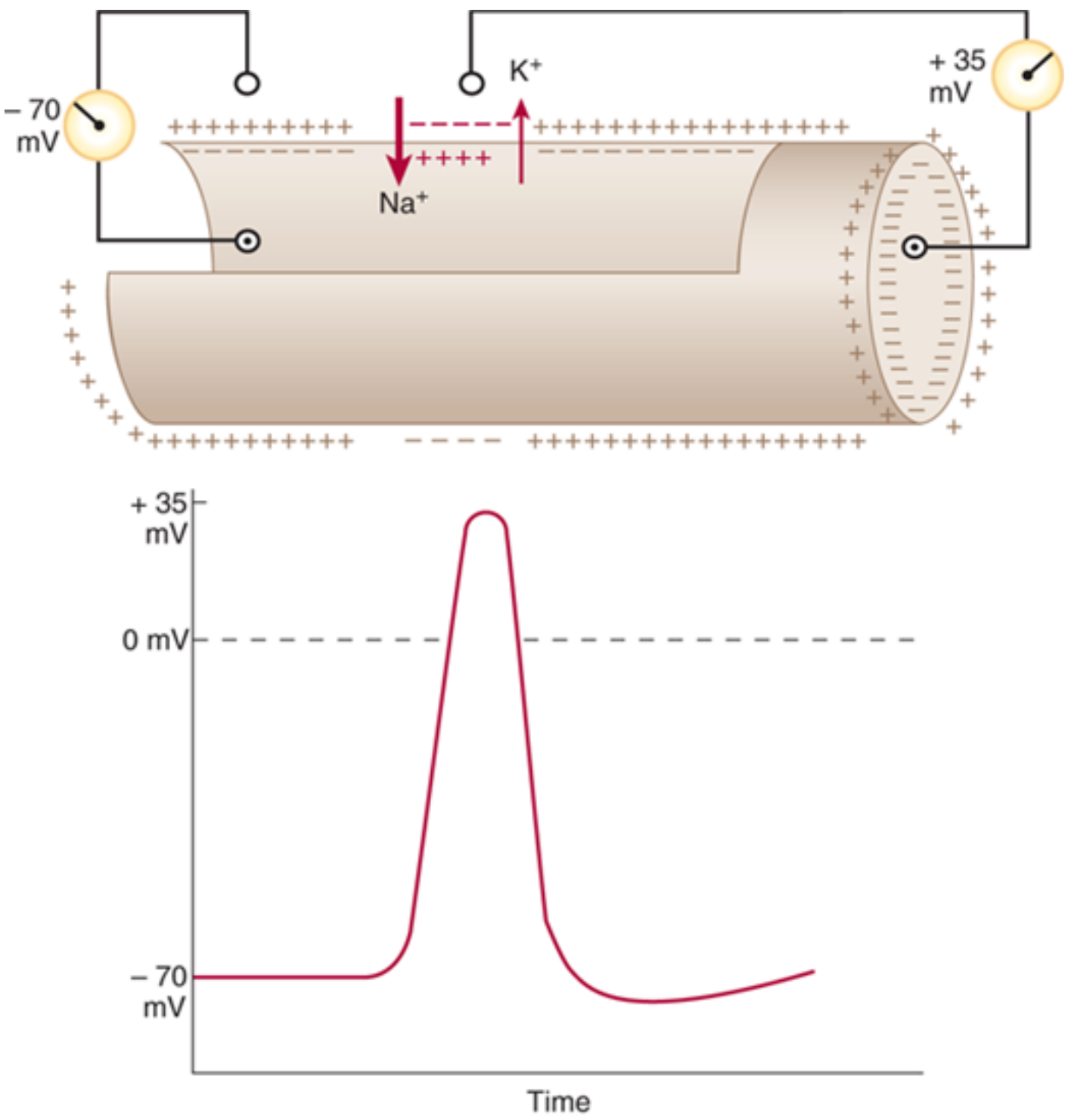
THE EFFECTS OF MYELINATION

Myelin is present around some axons within the peripheral nervous system (PNS) (where it is produced by S[illegible]vous system (CNS) (where it is produced by oligodendrocytes). Myelination has profound effects on the conduction of action potentials along the axon.

Nonmyelinated axons, in the mammalian PNS and CNS, generally have a small diameter (less than 1 µm in the PNS and less than 0.2 µm in the CNS). The action potential travels in a continuous manner along these axons because of a relatively uniform distribution of voltage-sensitive Na^+ and K^+ channels. As the action potential invades a given region of the axon, it depolarizes the region in front of it, so that the impulse crawls slowly and continuously along the entire length of the axon (Fig 3–5). In nonmyelinated axons, activation of Na^+ channels accounts for the depolarization phase of the action potential, and activation of K^+ channels produces repolarization.

FIGURE 3–5

Conduction of the nerve impulse through a nonmyelinated nerve fiber. In the resting axon, there is a difference of -70 mV between the interior of the axon and the outer surface of its membrane (resting potential). During the conduction of an action potential, Na^+ passes into the axon interior and subsequently K^+ migrates in the opposite direction. In consequence, the membrane polarity changes (the membrane becomes relatively positive on its inner surface), and the resting potential is replaced by an action potential (+35 mV here). (Reproduced with permission from Junqueira LC, Carneiro J, Kelley RO: *Basic Histology*, 7th ed. New York, NY: Appleton & Lange; 1992.)



Myelinated axons, in contrast, are covered by myelin sheaths. The myelin has a high electrical resistance and low capacitance, permitting it to act as an insulator. The myelin sheath is not continuous along the entire length of the axon. On the contrary, it is periodically interrupted by small gaps (approximately 1 µm long), called the **nodes of Ranvier**, where the axon is exposed. In mammalian myelinated fibers, the v[illegible] not distributed uniformly. Na^+ channels are clustered in high