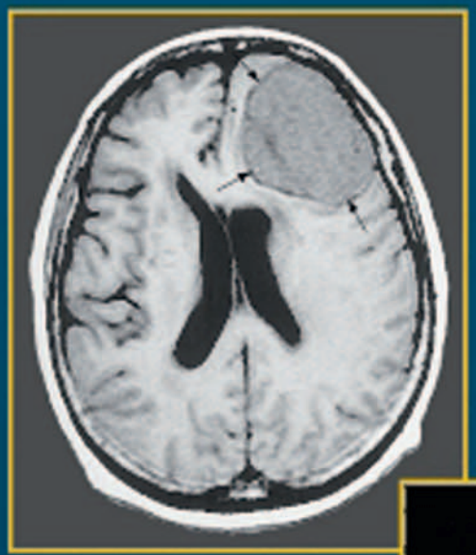
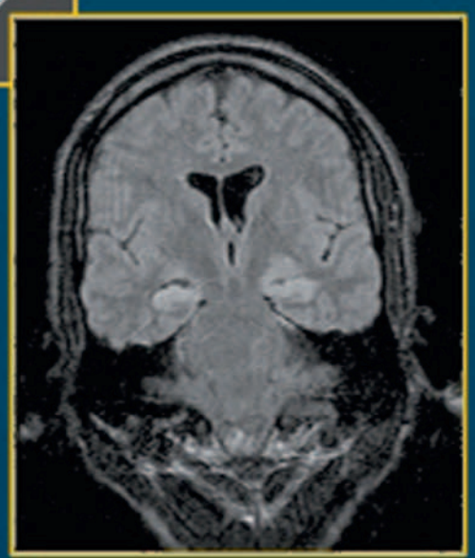
FIFTH EDITION

FUNDAMENTAL NEUROSCIENCE

for Basic and Clinical Applications





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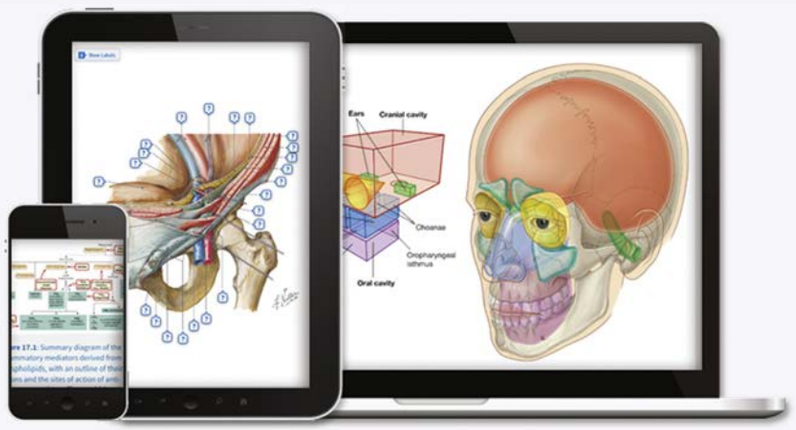

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As seen in this unretouched photograph of a small myelinated axon, mitochondria may assume a variety of sizes, shapes, and orientations.

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for Basic and Clinical Applications

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FUNDAMENTAL NEUROSCIENCE FOR BASIC AND CLINICAL APPLICATIONS, FIFTH EDITION

ISBN: 978-0-323-39632-5

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Spanish Translation (2003) of the Second English (2002)
Spanish Translation (2014) of the Fourth English (2013)

Previous editions copyrighted 2013, 2006, 2002, and 1997.

Library of Congress Cataloging-in-Publication Data

Names: Haines, Duane E., editor. | Mihailoff, Gregory A., editor.
Title: Fundamental neuroscience for basic and clinical applications / [edited by] Duane E. Haines, Gregory A. Mihailoff ; medical illustrator, W.K. Cunningham and M.P. Schenk ; photographer, G.W. Armstrong ; computer graphics, C.P. Runyan.
Description: Fifth edition. | Philadelphia, PA : Elsevier, [2018] | Includes bibliographical references and index.
Identifiers: LCCN 2017024153 | ISBN 9780323396325 (hardcover : alk. paper)
Subjects: | MESH: Central Nervous System--physiology | Neurons | Neuroimaging--methods
Classification: LCC QP355.2 | NLM WL 300 | DDC 612.8/22--dc23 LC record available at https://lccn.loc.gov/2017024153

Content Strategist: Marybeth Thiel
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Design Direction: Ryan Cook

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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Preface

The significant changes in the fifth edition of *Fundamental Neuroscience for Basic and Clinical Applications* take into consideration (1) new discoveries in the basic neurosciences, (2) how these may be applied to educating students in the clinical setting, (3) new observations in the clinical neurosciences, and of particular importance (4) how this information may be used to understand and diagnose the neurologically compromised patient. These concepts recognize two important points essential to medical education. First, the contemporary approach allows educators to integrate basic and clinical science information, rather than to just teach anatomy or connections within the nervous system for their own sake. The clinical observation is a springboard for students to understand and apply basic science concepts to a neurologically compromised patient. Second, accrediting and licensing bodies that govern the various branches of medicine, dentistry, and allied health have clearly indicated that the integration of basic science and clinical information is an integral part of the contemporary educational experience.

The significant changes and additions to *Fundamental Neuroscience* (both great and small) emphasize the intimate interaction between the basic and clinical neurosciences. The main goals are to introduce additional and relevant clinical information, to integrate clinical and basic science information in a seamless fashion, and to introduce new anatomic information when it enhances the understanding of clinical concepts. The emphasis is clearly shifted to an even more clinically oriented approach. Of particular note is the fact that of the approximate 598 illustrations in this new edition, about 48%, are new/revised (artwork, CT, MRI): labels have been changed, artwork was modified, and many drawings were recast so as to now appear in color.

In addition, about 275 general Review Questions with explanatory answers are available online on the Student Consult website (www.studentconsult.com) for review, practice, or assessment.

It is not possible to describe each individual change, modification, or addition; only the more significant are mentioned here.

First, key words, phrases, and concepts appear in boldface. This expedites quick and easy access.

Second, the presentation, or availability, of anatomic information in a "clinical orientation" is an essential feature of contemporary neuroscience education; it prepares the student for the significant realities of the clinical environment where viewing the central nervous system in MRI and CT in a "clinical orientation" is the established standard. This is especially true for images such as stained sections or artwork of the spinal cord or brainstem, when they are presented in an axial plane. For example, in an axial MRI of the midbrain, its dorsal aspect (the colliculi) is "down" in the image, and its ventral portion (the crus and interpeduncular fossa) is "up" in the image. This is opposite the "anatomic orientation." Because the MRI/clinical orientation is opposite the anatomic orientation (commonly used in the instructional setting), a method is incorporated into this edition that allows the reader to easily flip selected images from the anatomic orientation to the clinical orientation and thereby view the anatomy as it is presented in MRI and CT. Images that are identified by a flip

symbol in the figure description within the book can be viewed in either anatomic or clinical orientation with online resources at www.studentconsult.com. The availability of this feature accommodates a wide variety of educational approaches and review opportunities but especially prepares the user for the expectations and requirements of the clinical experience.

Third, the relevance of clinical information and its integration with basic neuroscience concepts is an absolutely essential component of the contemporary educational process. To this end, all clinical information, including reflexes, appears in a light blue highlight throughout the book. This approach allows the clinical correlations to remain in their proper textual context within the natural flow of structural and functional information. At the same time, it also allows the reader to immediately identify what text on any given page is clinical in nature.

Fourth, new clinical and anatomic terminology is introduced that reflects a contemporary, and more correct, usage of classic terms. This also has allowed existing concepts and interpretations to be clarified and corrected.

Fifth, new clinical information in the form of MRI and CT, clinical examples, line drawings, and related information is introduced. A special effort has been made to fully integrate this information with existing text and new basic neuroscience data.

Sixth, throughout the book, a significant number of anatomic and clinical drawings are corrected; modified to increase their clarity; replaced with new artwork; correlated with clinical images such as MRI, CT, and angiograms; or otherwise improved.

This edition follows the official international list of anatomic terms for neuroanatomy (*Terminologia Anatomica*, Thieme, 1998) or draws on recent publications that provide particular clarity. We have made a concerted effort to include the most current and most correct terminology; if some terms have eluded us, these will be corrected in future printings.

To further improve this work, the editor and contributors welcome comments, corrections, and suggestions from students, our colleagues, and any other readers of this book.

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Acknowledgments

This fifth edition of *Fundamental Neuroscience for Basic and Clinical Applications* is the result of helpful input from many individuals. We express our sincere thanks to our students for their probing interest and insightful comments that have allowed us to better address their present, and future, educational needs.

A special thanks is extended to those many colleagues who have provided valuable input to this, and earlier, editions, including Drs. V.K. Anand, D.E. Angelaki, R.H. Baisden, M. Behari, A.J. (Tony) Castro, S.C. Crawford, J.L. Culberson, E. Dietrichs, J.T. Ericksen, W.C. Hall, R. Hoffman, J.S. King, W.M. King, S. Ledoux, G.R. Leichnetz, G.F. Martin, I.J. Miller, E. Mugnaini, R. Nieuwenhuys, R.S. Nowakowski, D.F. Peeler, A. Peters, J.D. Porter, J.A. Rafols, W.A. Roy, L.F. Schweitzer, D.L. Tolbert, and M.L. Woodruff. The MRI of nasal polyps in Chapter 23 was generously provided by Dr. Vinod Anand, Baptist Medical Center, Jackson, MS. The photographs of Golgi-stained material in Chapters 26 and 27 are from the Clement A. Fox Collection at Wayne State University and through the courtesy of Dr. Rafols. The photograph of the unipolar brush cell in Chapter 27 was generously provided by Dr. Enrico Mugnaini, Northwestern University Institute for Neuroscience, and Dr. Madhuri Behari, All India Institute of Medical Sciences, generously supplied the MRI image of a Wilson patient in Chapter 26. Dr. Richard Miller, The University of Mississippi Medical Center (UMMC), kindly provided the images of congenital megacolon in Chapters 5 and 29. The photograph on the half-title page was provided by Drs. Ross Kosinski and Greg Mihailoff.

We especially wish to thank our colleagues for their willingness to assume authorship, or co-authorship, of several chapters in this fifth edition: Dr. Terry Dwyer (Chapters 3 and 4), Dr. Wade Grow (Chapters 5 and 32), Dr. Bucky Jones and Dr. Jason Kaufman (Chapters 19 and 29), and Dr. Jian Chen (Chapter 33). In addition, Dr. Quang Vu, Wake Forest, Department of Neurology; and Dr. Jian Chen, UMMC, Department of Neurology, have generously given of their time to collect MRI and CT images for this edition. We greatly appreciate their help.

We also extend our sincere thanks to Professor Roy R. Weller, University of Southampton, School of Medicine, for his review of new material included in this edition on an alternate route for the return of CSF to the venous system. This particular system has important clinical implications, and we appreciate his insights and suggestions.

The Review Questions that are available on Student Consult for Chapters 1-2 and 5-33 are from a book written by D.E. Haines and J.A. Lancon, *Review of Neuroscience* ©2003, and questions for Chapters 3 and 4 were prepared by Dr. Terry M. Dwyer.

Our colleagues at UMMC have been most cooperative in the giving of their time and energy as the fifth edition was in preparation. We want to thank all my colleagues in the Department of Neurobiology and Anatomical Sciences, particularly Drs. Ard, Lin, Lynch, May, Moore, Naftel, Simpson, and Warren; in the Department of Neurology, especially Drs. Auchus, Corbett, Herndon, Uschmann, and Wolf; and the residents, particularly Drs. Ali, Bradley, Hussaini, Sinclair, Sapkota, and Willis; in the Department of Neurosurgery, particularly Drs. Gaspard, Harkey, Luzardo, Marks, and Parent; and the residents, particularly Drs. Johnson, Orozco, and Rey-Dios; and in the Department of Radiology, especially Drs. Buciuc, Kahn, and McCowan.

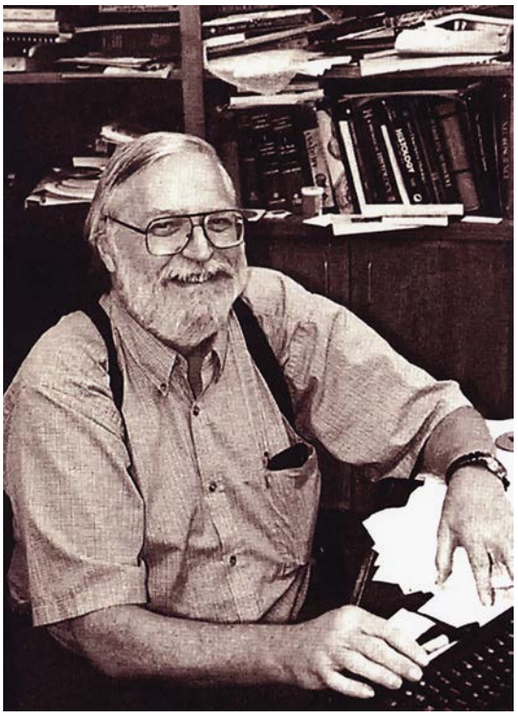
The following individuals have participated in past editions of this work: Drs. March Ard, Jim Bloedel, Paul Brown, Robert Chronister, Owen (Bev) Evans, Jonathan Fratkin, Patrick Hardy, James Hutchins, John Lancon, James Lynch, John Naftel, Frank Raila, Rob Rockhold, Maria Santiago, and Robert Sweazey. Most are not participating due to life changes such as retirement. Their participation was most gratefully acknowledged.

All the artwork and photography (but not including specifically acknowledged photographs) were provided in the Department of Biomedical Illustration Services at UMMC. The authors are indebted to Mr. Michael P. Schenk (former Director of the Department, now retired) and his colleagues, Mr. W.K. Cunningham, Mr. G.W. Armstrong, and Mr. C.P. Runyan, for their exemplary efforts. All photography was undertaken by Mr. Armstrong; Mr. Runyan scanned images and cleaned those as needed. We are enormously appreciative of their patience and cooperation in getting the best quality artwork and photographs.

For this fifth edition the vast majority of the artwork (corrections, new images, revising for color, labeling, and many other essential tasks) was completed by Mr. W.K. (Kyle) Cunningham, who now works as a freelance medical illustrator. His high-quality work, excellent cooperation, insights into what qualifies as an excellent result, and numerous suggestions were absolutely essential to the completion of the fifth edition. We are very grateful for his outstanding cooperation and participation.

Production of this finely done and visually appealing book would not have been accomplished without Elsevier. We are very grateful to Ms. Lauren Willis (Associate Content Strategist) and Ms. Marybeth Thiel (Content Strategist) for their excellent cooperation and help, and for ensuring that everything went smoothly, Ms. Melissa Darling (Marketing Manager), Ms. Kristine Feeherty (Book Production Specialist), and Mr. Ryan Cook (Book Designer). We are especially indebted to Ms. Rae Robertson (Senior Content Development Specialist) for her wonderful cooperation and patience with us, in her ability to upload the manuscript, her deliberate review of every page, and her attention to the details that resulted in a finished book. D.E.H. expresses a special thanks to his wife, Gretchen (now Nana Gretchen, times 6); she was an absolutely essential element in getting everything done.

Dr. Robert Chronister (August 24, 1942–October 25, 2009) was a good friend of ours for many years and a fellow traveler along the neuroscience highway. Bob was enthusiastic about all things neuro, gracious and genuinely friendly, and always had a smile and a robust greeting when we saw each other at meetings. He was always interested in or had an opinion on almost any neuro topic that would come up in a conversation. For Editions 1, 2, and 3, Bob was senior author of *The Limbic System* and co-author of *The Hypothalamus*. We greatly appreciated his contributions and valued his friendship. He is missed.



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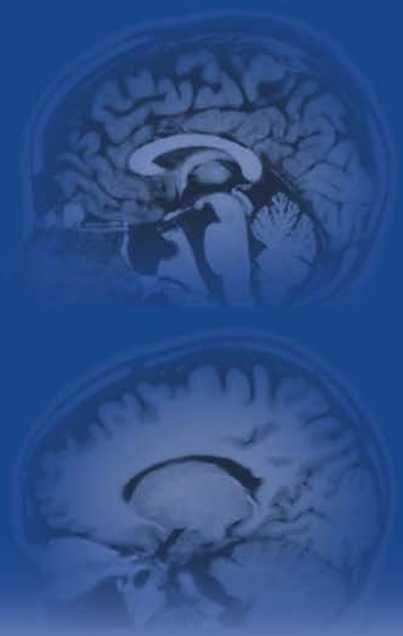

Section I

ESSENTIAL CONCEPTS

1-5

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Chapter 1
Orientation to the Structure and Imaging of the Central Nervous System

D.E. Haines and A.C. Terrell

Our nervous system makes us what we are. Personality, outlook, intellect, coordination, and the many other characteristics are the result of complex interactions within our nervous system. Information is received from the environment and transmitted into the brain or spinal cord. Once this sensory information is processed and integrated, an appropriate motor response is initiated.

The nervous system can be viewed as a scale of structural complexity. At the microscopic level, the individual structural and functional unit of the nervous system is the **neuron** (the cell body and its processes), or nerve cell. Interspersed among the neurons of the central nervous system are supportive elements called **glial cells.** At the macroscopic end of the scale are the large divisions (or parts) of the nervous system that can be handled and studied without magnification. These two extremes are not independent but form a continuum; functionally related neurons aggregate to form small structures that combine to form larger structures. Communication takes place at many different levels, the end result being a wide range of productive or life-sustaining nervous activities.

OVERVIEW

Central, Peripheral, and Visceromotor Nervous Systems

The human nervous system is divided into the **central nervous system** (CNS) and the **peripheral nervous system** (PNS) (Fig. 1.1*A*). The CNS consists of the brain and spinal cord. Because of their locations in the skull and vertebral column, these structures are the most protected in the body. The PNS is made up of nerves that connect the brain and spinal cord with peripheral structures. These nerves innervate muscle (skeletal, cardiac, smooth) and glandular epithelium and contain a variety of sensory fibers. These sensory fibers enter the spinal cord through the **posterior** (**dorsal**) root, and motor fibers exit through the **anterior** (**ventral**) root. The **spinal nerve** is formed by the joining of posterior (sensory) and anterior (motor) roots and is, consequently, a **mixed nerve** (Fig. 1.1*B*). In the case of **mixed cranial nerves,** the sensory and motor fibers are combined into a single root.

The **visceromotor nervous system** (also called **visceral motor**) is a functional division of the nervous system that has parts in both the CNS and the PNS (Fig. 1.1). It is made up of neurons that innervate **smooth muscle, cardiac muscle,** or **glandular epithelium** or **combinations of these tissues.** These individual **visceral tissues,** when combined, make up **visceral organs** such as the stomach and intestines. The visceromotor nervous system is also called the **autonomic nervous system** because it regulates visceral motor responses normally outside the realm of conscious control.

Neurons

At the histologic level, the nervous system is composed of **neurons** and **glial cells.** As the basic structural and functional units of the nervous system, neurons are specialized to receive information, to transmit electrical impulses, and to influence other neurons or effector tissues. In many areas of the nervous system, neurons are structurally modified to serve particular functions. At this point, we consider the neuron only as a general concept (see Chapter 2).

A **neuron** consists of a **cell body** (**perikaryon** or **soma**) and the processes that emanate from the cell body (Fig. 1.2*A*). Collectively, neuronal cell bodies constitute the **gray matter** of the CNS. Named and usually function-specific clusters of cell bodies in the CNS are called **nuclei** (singular, **nucleus**). Typically, **dendrites** are those processes that ramify in the vicinity of the cell body, whereas a single, longer process called the **axon** carries impulses to a more remote destination. The **white matter** of the CNS consists of bundles of axons that are wrapped in a sheath of insulating lipoprotein called **myelin.**

In general, there is a direct relationship between (1) the diameter of the axon, (2) the thickness of the myelin sheath, (3) the distance between the nodes of the myelin sheath (nodes of Ranvier), and (4) the conduction velocity of the nerve fiber. Axons with a large diameter have thick myelin sheaths with longer internodal distances and therefore exhibit faster conduction velocities. Likewise, axons with a thin diameter that have thin myelin sheaths with shorter internodal distances have slower conduction velocities. The axon terminates at specialized structures called **synapses** or, if they innervate muscles, **motor end plates** (**neuromuscular junctions**), which function much like synapses.

The generalized synapse (Fig. 1.2*A*) is the most common type seen in the CNS and is sometimes called an **electrochemical synapse.** It consists of a **presynaptic element,** which is part of an

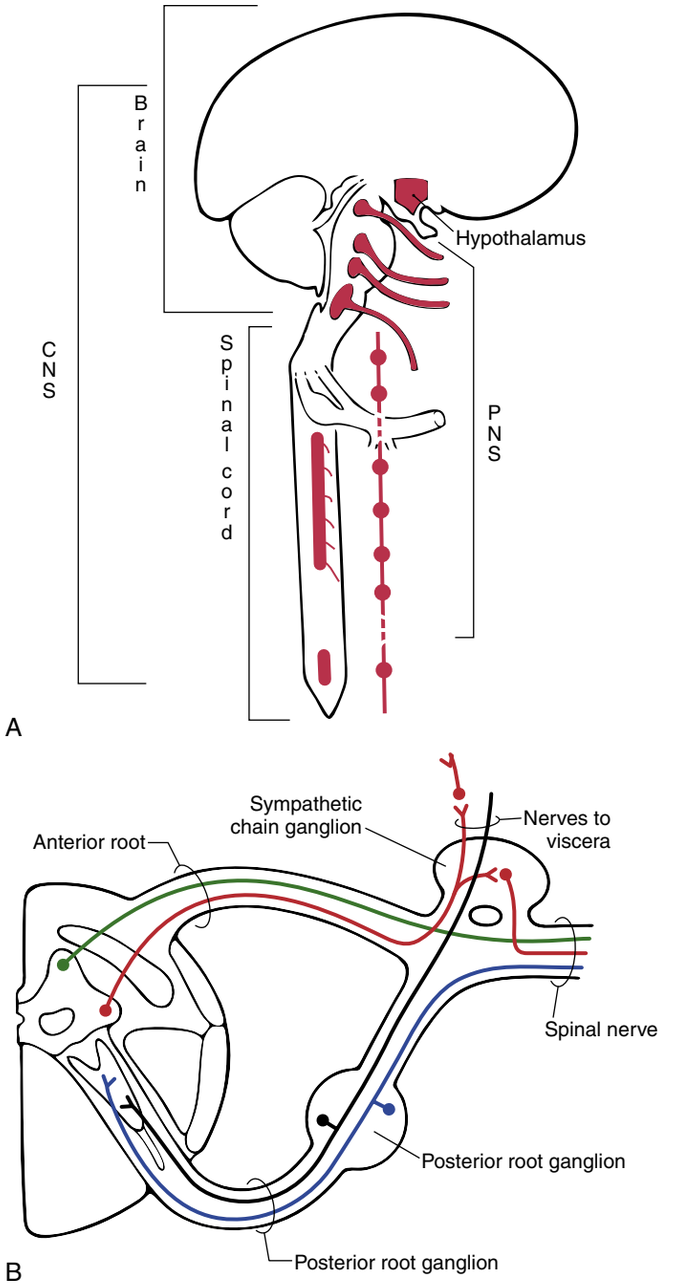

Fig. 1.1 **A,** General relationships of central (CNS), peripheral (PNS), and visceromotor nervous systems. Visceromotor regions of CNS and PNS are shown in red. **B,** A representation of the thoracic spinal cord in a clinical orientation showing the relationships of efferent (outgoing, motor) and afferent (incoming, sensory) fibers to spinal nerves and roots. Motor fibers are visceral efferent (visceromotor; *red*) and somatic efferent (*green*); sensory fibers are somatic afferent (*blue*) and visceral afferent (*black*).

axon, a gap called the **synaptic cleft,** and the **postsynaptic region** of the innervated neuron or effector structure. Communication across this synapse is accomplished as follows. An electrical impulse (the **action potential**) causes the release of a neuroactive substance (a **neurotransmitter, neuromodulator,** or **neuromediator**) from the presynaptic element into the synaptic cleft. This substance is stored in **synaptic vesicles** in the presynaptic element and is released into the synaptic space by the fusion of these vesicles with the presynaptic membrane (Fig. 1.2*A*).

The neurotransmitter diffuses rapidly across the synaptic space and binds to receptor sites on the postsynaptic membrane. On the basis of the action of the neurotransmitter at receptor sites, the postsynaptic neuron may be excited (lead to generation of an action potential) or inhibited (prevent generation of an action potential). Neurotransmitter residues in the synaptic cleft are rapidly inactivated by other chemicals found in this space. In this brief example, we see that (1) the neuron is structurally specialized to receive and propagate electrical signals, (2) this propagation is accomplished by a combination of electrical and chemical events, and (3) the transmission of signals across the synapse is in one direction (unidirectional), that is, from the presynaptic neuron to the postsynaptic neuron. There are a number of neurologic disorders, such as **myasthenia gravis, Lambert-Eaton syndrome,** or **botulism,** that represent a failure of neurotransmitter action at the presynaptic membrane, synapse, or at the receptors on the postsynaptic membrane.

Reflexes and Pathways

The function of the nervous system is based on the interactions between neurons. Fig. 1.2*B* illustrates one of the simplest types of neuronal circuits, a reflex arc composed of only two neurons. This is called a **monosynaptic reflex arc** because only one synapse is involved. In this example, the peripheral end of a sensory fiber responds to a particular type of input. The resulting action potential is conducted by the sensory fiber into the spinal cord, where it influences a motor neuron. The axon of the motor neuron conducts a signal from the spinal cord to the appropriate skeletal muscle, which responds by contracting. This is an example of a **muscle stretch reflex,** which is actually one of the more commonly tested reflexes in clinical medicine. **Reflexes are involuntary responses to a particular bit of sensory input.** For example, the physician taps on the patellar tendon, and the leg quickly extends at the knee without the patient consciously controlling the movement. The lack of a reflex (**areflexia**), an obviously weakened reflex (**hyporeflexia**), or an excessively active reflex (**hyperreflexia**) is usually indicative of a neurologic disorder.

By building on these summaries of the **neuron** and of the **basic reflex arc,** we shall briefly consider what neuronal elements constitute a **neural pathway**. If the patient bumps his or her knee and not only hits the patellar tendon but also damages the skin over the tendon, two things happen (Fig. 1.2C). First, impulses from receptors in the muscle stretched by the tendon travel through a reflex arc that causes the leg to extend (**knee jerk,** or **patellar reflex**). The synapse for this reflex arc is located in the lumbosacral spinal cord. Second, impulses from pain receptors in the damaged skin are transmitted in the lumbosacral cord to a second set of neurons that convey them via ascending axons to the forebrain (Fig. 1.2C). As can be seen in Fig. 1.2C, these axons cross the midline of the spinal cord and form an ascending tract on the contralateral side. In the forebrain, these signals are passed to a third group of neurons that distribute them to a region of the cerebral cortex specialized to interpret them as pain from the knee.

This three-neuron chain constitutes a **pathway,** a series of neurons designed to carry a specific type of information from one site to another (Fig. 1.2C). Some pathways carry information to a level of conscious perception (we not only recognize pain but know that it is coming from the knee), and others convey information that does not reach the conscious level. It is common to refer to all the neurons comprising a pathway and conducting a specific type of information as a **system.** For example, the **anterolateral system** conducts pain and thermal information, whereas the **posterior column–medial lemniscus system** conducts body position and vibratory sense, and the **corticospinal system** conducts descending information from the cerebral cortex to spinal cord motor neurons.

REGIONS OF THE CENTRAL NERVOUS SYSTEM

Spinal Cord

The spinal cord is located inside the vertebral canal and is rostrally continuous with the medulla oblongata of the brain (Fig. 1.3). An essential link between the PNS and the brain, it conveys sensory information originating from the body wall, extremities,

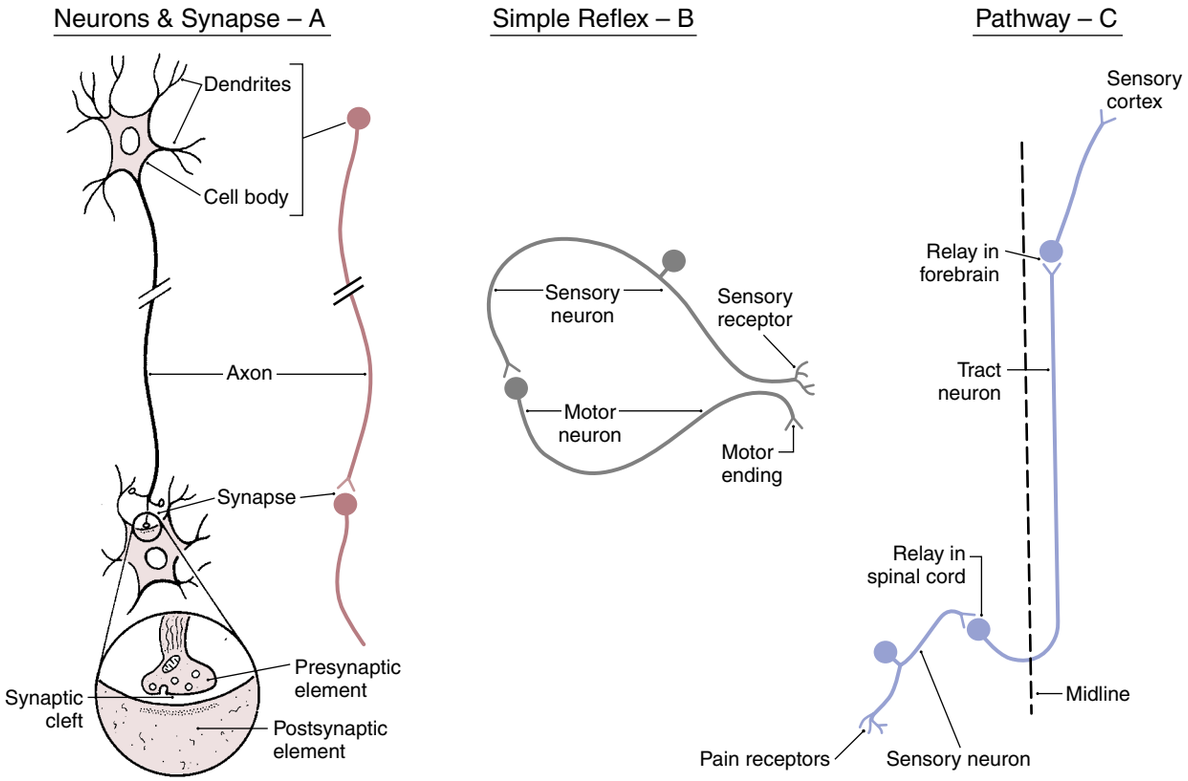

Fig. 1.2 A representative neuron and synapse (**A**), a simple (monosynaptic) reflex (**B**), and a pathway (**C**). Many pathways share the feature of being crossed (a decussation or commissure) at some point in their trajectory.

and gut and distributes motor impulses to these areas. Impulses enter and leave the spinal cord through the 31 pairs of spinal nerves (Fig. 1.1; see also Fig. 9.2). The spinal cord contains sensory fibers and motor neurons involved in reflex activity and ascending and descending **pathways** or **tracts** that link spinal centers with other parts of the CNS. Ascending pathways convey sensory information to higher centers, whereas descending pathways influence neurons in the spinal cord or brainstem.

Medulla Oblongata

At the level of the foramen magnum, the spinal cord is continuous with the most caudal part of the brain, the **medulla oblongata,** commonly called the **medulla** (Fig. 1.3). The medulla consists of (1) neurons that perform functions associated with the medulla and (2) ascending (generally sensory) and descending (generally motor) tracts that pass through the medulla on their way from or to the spinal cord. Some of the neuronal cell bodies of the medulla are organized into nuclei associated with specific cranial nerves. The medulla contains the nuclei for the glossopharyngeal (cranial nerve IX), vagus (X), and hypoglossal (XII) nerves as well as portions of the nuclei for the trigeminal (V) and vestibulocochlear (VIII) nerves; the nucleus of the accessory nerve (XI) is located in cervical levels of the spinal cord. It also contains important relay centers and nuclei that are essential to the regulation of respiration, heart rate, and various visceral functions.

Pons and Cerebellum

The pons and cerebellum originate embryologically from the same segment of the developing neural tube. However, in the adult, the pons forms part of the **brainstem** (the other parts being the **midbrain** and **medulla**) and the cerebellum is a **supra-segmental** structure because it is located posterior (dorsal) to the brainstem (Fig. 1.3).

Like the medulla, the pons contains many neuronal cell bodies, some of which are organized into cranial nerve nuclei, and it is traversed by ascending and descending tracts. The pons contains the nuclei of the abducens (VI) and facial (VII) nerves and portions of the nuclei for the trigeminal (V) and vestibulocochlear (VIII) nerves. The anterior (ventral) part of the pons contains large populations of neurons (**pontine nuclei**) that form a relay station between the cerebral cortex and cerebellum and descending motor fibers that travel to all spinal levels.

The cerebellum is connected with diverse regions of the CNS and is considered part of the motor system. It serves to coordinate the activity of individual muscle groups to produce smooth, purposeful, synergistic movements.

Midbrain

Rostrally, the pons is continuous with the midbrain (Fig. 1.3). This part of the brain is, quite literally, the link between the brainstem and the forebrain. Ascending or descending pathways to or from the forebrain must traverse the midbrain. The nuclei for the oculomotor (III) and trochlear (IV) cranial nerves as well as part of the trigeminal (V) complex are found in the midbrain. Other midbrain centers are concerned with visual and auditory reflex pathways, motor function, transmission of pain, and visceral functions.

Thalamus

The forebrain consists of the **cerebral hemispheres,** large groups of neurons that comprise the **basal nuclei,** and the **thalamus** (Fig. 1.3). We shall see later that the thalamus actually consists of several regions—for example, the hypothalamus, subthalamus, epithalamus, and dorsal thalamus. The thalamus is also commonly called the **diencephalon,** a term that reflects its embryologic origin.

The thalamus is rostral to the midbrain and almost completely surrounded by elements of the cerebral hemisphere. Individual parts of the thalamus can be seen in detail only when the brain is cut in coronal or axial planes.

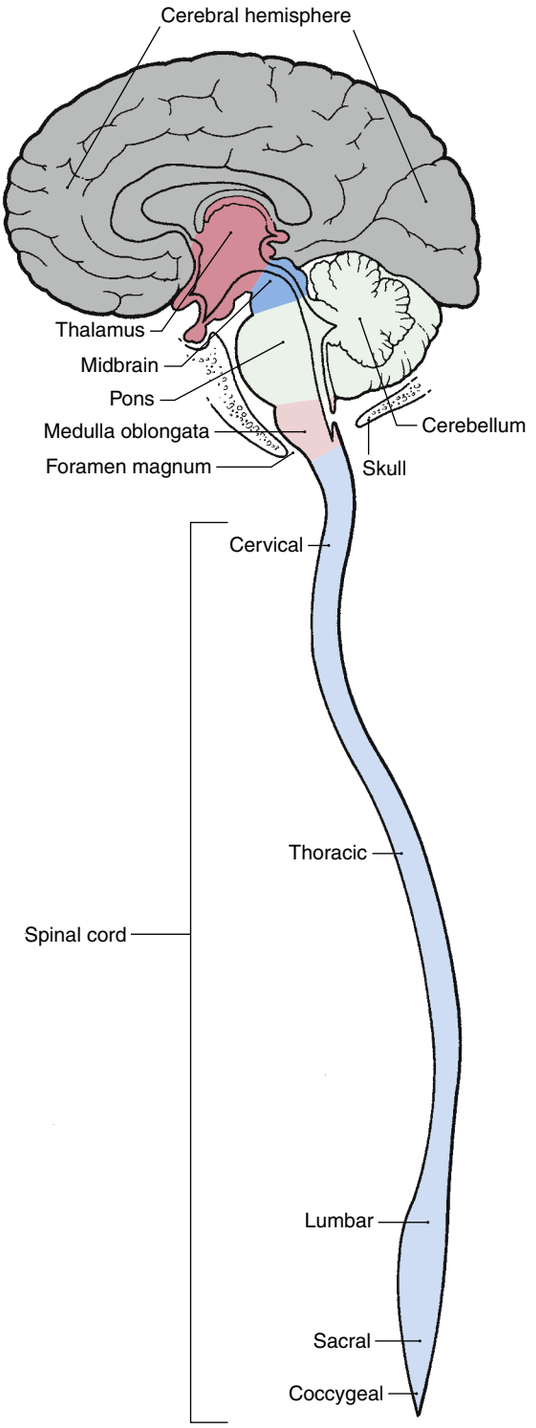

Fig. 1.3 The basic divisions of the central nervous system.

With the exception of olfaction (sense of smell), all sensory information that eventually reaches the cerebral cortex must synapse in the thalamus. One function of the thalamus, therefore, is to receive sensory information of many sorts and to distribute it to the specific regions in the cerebral cortex that are specialized to decode it. Other areas of the thalamus receive input from pathways conveying information on, for example, position sense or the tension in a tendon or muscle. This input is relayed to areas of the cerebral cortex that function to generate smooth, purposeful movements.

Although it is small, the hypothalamus functions in sexual behavior, feeding, hormonal output of the pituitary gland, body temperature regulation, and a wide range of visceromotor functions. Through descending connections, the hypothalamus influences visceral centers in the brainstem and spinal cord.

Cerebral Hemispheres

The largest and most obvious parts of the human brain are the two cerebral hemispheres. Each hemisphere is composed of three major subdivisions. First, the **cerebral cortex** is a layer of neuronal cell bodies about 0.5 cm thick that covers the entire surface of the hemisphere. This layer of cells is thrown into elevations or peaks called **gyri** (singular, **gyrus**) separated by valleys called **sulci** (singular, **sulcus**).

The second major part of the hemisphere is the **subcortical white matter,** which is made up of myelinated axons that carry information to or from the cerebral cortex. The largest and most organized part of the white matter is the **internal capsule.** This bundle contains fibers passing to and from the cerebral cortex, such as **corticospinal** and **thalamocortical** fibers.

The third major component of the hemisphere is a prominent group of neuronal cell bodies collectively called the **basal nuclei.** These prominent forebrain centers are involved in motor function. **Parkinson disease,** a neurologic disorder associated with the basal nuclei, is characterized by a progressive impairment of movements and in many cases eventual dementia.

The gyri and sulci that make up the cerebral cortex are named, and many are associated with particular functions. Some gyri receive sensory input from thalamic relay nuclei, whereas descending fibers from these gyri may influence centers in the brainstem or spinal cord. The cerebral cortex also includes association areas that are essential for analysis and cognitive thought.

FUNCTIONAL SYSTEMS AND REGIONS

A **functional system** is a set of neurons linked together to convey a particular block of information or to accomplish a particular task. In this respect, **systems** and **pathways,** in some cases, may be similar, and their meanings may frequently overlap.

Anatomic parts of the CNS, such as the medulla and pons, are commonly called **regions.** The study of their structure and function, called **regional neurobiology,** is the focus of the second section of this book. **Systems** and **pathways,** however, generally traverse more than one region. The system of neurons and axons that allows you to feel the edge of this page, for example, crosses every region of the nervous system between your fingers and the somatosensory cortex of the cerebral hemisphere. The study of functional systems, called **systems neurobiology,** is the focus of the third section of this text. It is important to remember that the **functional characteristics of regions coexist with those of systems.**

Let us consider an example of how the interrelation of systems and regions can be important clinically. The signals that influence movements of the hand originate in the cerebral cortex. Neurons in the hand area of the motor cortex send their axons to cervical levels of the spinal cord, where they influence spinal motor neurons that innervate the muscles of the upper extremity. These are called **corticospinal fibers** because their cell bodies are in the cerebral cortex (**cortico-**) and their axons end in the spinal cord (**-spinal**). These fibers pass through the subcortical white matter, the entire brainstem, and the upper levels of the cervical spinal cord. En route, they pass near nuclei and fiber tracts that are specific to that particular region (Fig. 1.4). In the midbrain, for example, they pass near fibers of the oculomotor nerve, which originate in the midbrain and control certain extraocular muscles. In the medulla, they pass near fibers that originate in the medulla and innervate the musculature of the tongue. An injury to the midbrain could therefore cause motor problems in the hand (**systems damage**) combined with partial paralysis of eye movement (**regional damage**). In similar fashion, an injury to the medulla could cause the same hand problem but now in association with partial paralysis of the tongue rather than of eye movements. **Successful diagnosis of patients with neurologic disorders will**

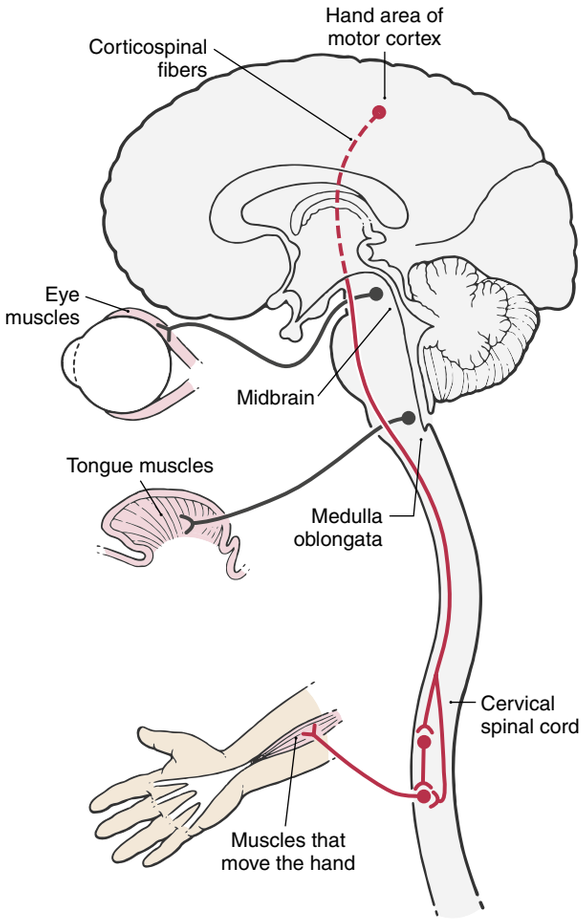

Fig. 1.4 An example of the relation of systems to regions. Fibers of the motor system that control hand movement descend from the motor cortex to the cervical spinal cord. In the cord, these fibers influence motor neurons that control hand and forearm muscles. Injury at any point along the way can damage fibers of the system and structures specific to the region. For example, injury to the midbrain could damage both fibers to the hand and fibers to the eye muscles, whereas injury to the medulla could damage both fibers to the hand and fibers to the tongue musculature. In cases of damage to a long tract (motor or sensory) and to a cranial nerve (root or nucleus), the cranial nerve deficits are usually the best localizing signs.

depend on, among other things, a good understanding of both regional and systems neurobiology.

Localizing Signs and Localization

The example (Fig. 1.4) of corticospinal fibers that innervate spinal motor neurons serving the hand coupled with neuron cell bodies in the midbrain that innervate eye muscles via the oculomotor nerve also illustrates the concept of **localizing signs.** Brain injury that results in only a weakness or paralysis of the upper extremity generally localizes the lesion only to one cerebral hemisphere or perhaps to one side of the brainstem. The clinical examination does not tell us which region of the brain is injured (internal capsule, midbrain, pons, or medulla) or, for that matter, even whether the lesion is in the upper portions of the cervical spinal cord. However, if the paralysis of the upper extremity is coupled with a partial paralysis of eye movement, the lesion can be **specifically localized to the midbrain.** In this example, the lesion in the midbrain damages the fibers of the oculomotor nerve that are specific to this level, whereas the corticospinal fibers are injured as they traverse the midbrain (Fig. 1.4). In general, cranial nerve signs are more helpful than long tract signs in localizing the lesion; that is, they are better **localizing signs.**

Another general concept of **localization** states that certain combinations of neurologic deficits may indicate involvement of one of three general locations of the CNS. First, deficits (motor or sensory) located on the same side of the head and body frequently signify lesions in the cerebral hemisphere. Second, deficits on one side of the head and on the opposite side of the body generally indicate a lesion in the brainstem. Such deficits are called **crossed (alternating,** or **alternate) deficits.** Third, deficits of the body only usually suggest a lesion in the spinal cord. Although there are exceptions to these general rules, we shall see that they hold true in many clinical situations.

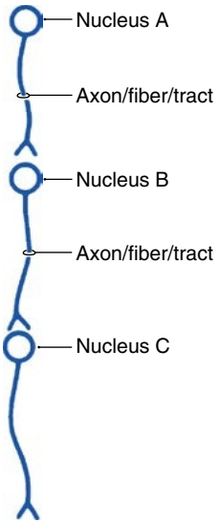

Fig. 1.5 Diagrammatic representation of the use of the terms **afferent** and **efferent** to describe information conducted toward or away from a particular reference point.

CONCEPT OF AFFERENT AND EFFERENT

The terms **afferent** and **efferent** are used to describe a variety of structures in the human body, such as nerve fibers, small vessels, and lymphatics. **Afferent** refers to conduction (of an impulse on a nerve or fluid in a vessel) toward a structure; this is an incoming bit of information. **Efferent** refers to conduction (of an impulse or fluid) away from a structure; this is an outgoing bit of information.

In this respect, the posterior root of the spinal nerve is **afferent** because it conducts **sensory** impulses toward the spinal cord, whereas the anterior root is **efferent** because it conducts **motor** impulses away from the spinal cord (Figs. 1.1 and 1.2). This has given rise to the widely held but incorrect view that afferent nerve fibers are always sensory and efferent nerve fibers are always motor. Although this may be true for the restricted examples of spinal and cranial nerves, the terms **afferent** and **efferent** can also be used to designate bundles of fibers (axons) traveling toward or away from a specific nucleus (Fig. 1.5).

Whether a bundle of axons is afferent or efferent, in relation to a specific nucleus, depends on what **reference point is selected to define the bundle and its relationships.** For example, the neuron cell body in nucleus A in Fig. 1.5 gives rise to an axon that is an **efferent of nucleus A** (conducting away from), but at the same time, this axon is an **afferent of nucleus B** (coming toward). If nucleus B is chosen as the reference point, it would be described as receiving afferent input from nucleus A and sending efferent impulses to nucleus C (Fig. 1.5). The use of these terms is commonplace in describing connections within the nervous system. For example, as described in the previous section, corticospinal fibers are **efferents** of the cerebral cortex and, at the same time, **afferents** to the spinal cord.

POSTERIOR (DORSAL), ANTERIOR (VENTRAL), AND OTHER DIRECTIONS IN THE CENTRAL NERVOUS SYSTEM

By convention, directions in the human CNS—such as **posterior** (**dorsal**) and **anterior** (**ventral**), **medial** (toward or at the midline) and **lateral** (away from the midline), **rostral** (or **rostrad,** a direction toward the nose), and **caudal** (or **caudad,** a direction toward the tail)—are absolute with respect to the central axis of the brain and spinal cord. In a similar manner, the anatomic orientation of the body in space is related to its central axis. For example, if the patient is lying on his or her stomach, the posterior surface of the trunk is up and its anterior surface is down (Fig. 1.6). If the patient rolls over, the back remains the posterior surface of the patient's body even though it now faces down.

As shown in Fig. 1.7, the spinal cord and the brainstem (medulla, pons, and midbrain) form a nearly straight line that is roughly parallel with the superoinferior axis of the body. Therefore anatomic directions in these regions of the CNS coincide roughly with those of the body as a whole.

During embryonic development, the forebrain rotates (at the cephalic flexure) relative to the midbrain until its rostrocaudal axis corresponds to a line drawn from the forehead to the occiput (from the frontal to the occipital poles of the cerebral hemispheres). This rotation creates a sharp angle in the long axis of the CNS at the midbrain-thalamus junction. Consequently, the long axis of the CNS bends at the midbrain-thalamus junction, and the directions posterior and anterior follow accordingly (Fig. 1.7).

In the cerebral hemisphere (forebrain), **posterior** (**dorsal**) is toward the top of the brain, **anterior** (**ventral**) is toward the base of the brain, **rostral** is toward the frontal pole, and **caudal** is toward the occipital pole. Anatomic directions in the forebrain relate to its long axis; therefore the posterior side of the forebrain structures faces the vertex of the head, and the anterior aspect of the forebrain faces the base of the skull (Fig. 1.7). **Posterior** and **dorsal** and **anterior** and **ventral** are considered synonymous and **are commonly and frequently used interchangeably.**

These directional terms are extremely valuable in the description of the relative position of a structure within the brain or spinal cord or the relative positions of two structures to each other. For example, the midbrain is **rostral to the pons but caudal to the thalamus** (Fig. 1.3). The midbrain is selected as the reference point and adjacent structures are described in relation to it. Also, directional terms, such as **posterior** and **lateral,** can be combined to describe a structure that occupies an intermediate position. For example, the nuclei in the spinal cord transmitting sensory information can be described as **posterolateral** to the central canal.

SYMPTOM OR SIGN?

These terms are used literally every day in countless clinical settings and serve to form an essential and important part of the physician-patient relationship—that is, the communication of information that will result in proper and successful medical treatment. It is useful to establish what constitutes a **symptom** versus a **sign** at this point. These concepts and definitions are revisited throughout subsequent chapters.

Symptom

A **symptom** is a departure from any normal state of structure or function that is **experienced by the patient.** In other words, something is wrong and the patient knows it. Symptoms may develop slowly, almost imperceptibly, as in a slow-growing tumor or as part of the aging process, or appear suddenly, as in hemorrhage or trauma. A symptom such as pain may be clear to the patient (a symptom) but difficult for the attending physician to evaluate. A symptom is a **subjective indicator** of a presumably abnormal process.

Sign

A **sign** is a departure from any normal state of structure or function that is **discovered, observed, and evaluated by a health care professional on examination of the patient.** In this situation, the clinical problem (be it great or small) is seen and can be evaluated by the physician. It is possible that a patient may have signs of a disease process, seen during the examination, that he or she is unaware of; the patient has **signs but no symptoms.** A sign is an **objective indicator** of a presumably abnormal process.

CLINICAL IMAGES OF THE BRAIN AND SKULL

The most routinely used methods to image the brain and skull are computed tomography (CT) and magnetic resonance imaging (MRI) (Fig. 1.8). As we shall see, CT is especially useful in visualizing the skull and the brain in the early stages of subarachnoid hemorrhage. On the other hand, MRI, by use of T1-weighted or T2-weighted techniques, shows brain anatomy in elegant detail,

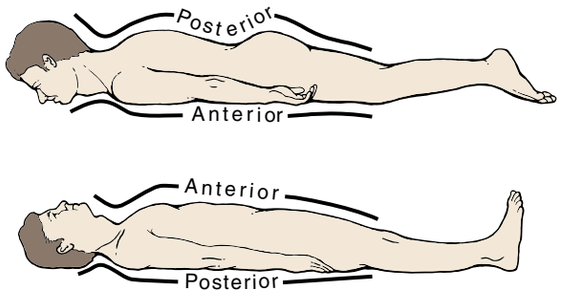

Fig. 1.6 The anatomic directions of the body are absolute with respect to the axes of the body, not with respect to the position of the body in space.

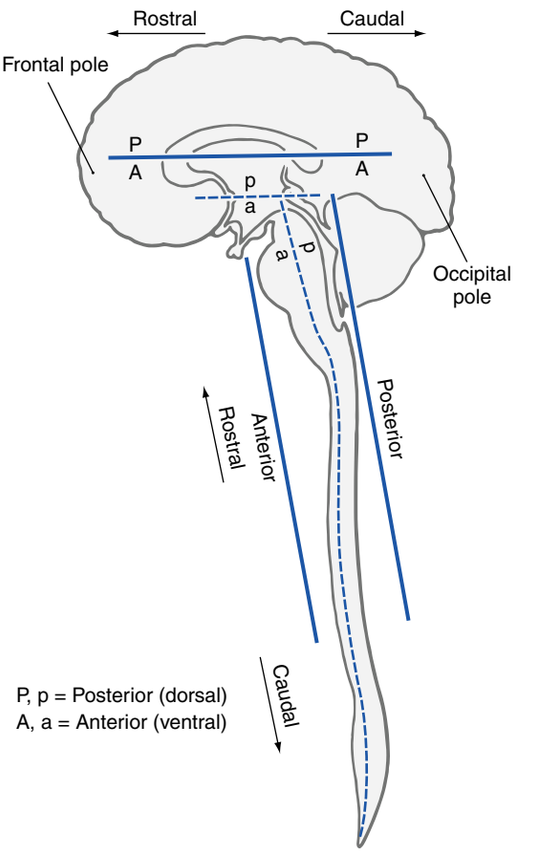

Fig. 1.7 The central axis and anatomic directions of the central nervous system (CNS). The dashed line shows the long (rostrocaudal) axis of the CNS. The long axis of the spinal cord and brainstem forms a sharp angle with the long axis of the forebrain. Posterior (dorsal) and anterior (ventral) orientations are also shown.

cisternal relationships, cranial nerves, and a wide variety of clinical abnormalities.

Magnetic resonance angiography (MRA) visualizes arteries and veins by measuring the velocity of flow in these structures (Fig. 1.9*A*). The resultant images show detail of vascular structures that, in some situations, may be superior to that seen on angiograms. Arterial structures may be selectively imaged, or combinations of arterial and venous structures or only venous structures can be visualized. Clinicians refer to these images of venous structures as MRVs (magnetic resonance venograms).

Computed tomography angiography (CTA, Fig. 1.9*B*) visualizes arteries with use of an injectable radiopaque substance (such as ioversol, Optiray 300) that can be infused through superficial veins on the upper extremity. When x-rays are passed through the patient, the infused vessels appear clearly more white than the surrounding brain (they are **hyperdense**). As with MRA, arterial and venous structures may be imaged in great detail, and in certain clinical situations, CTA offers advantages over standard angiography.

Computed Tomography

CT is an x-ray imaging technique that measures the effects that tissue density and the various types of atoms in the tissue have on x-rays passing through that tissue (Table 1.1; see also Fig. 1.8*A, B*). Changes in the emerging x-ray beam are measured by detectors.

The higher the atomic number, the greater the ability of the atom to attenuate, or stop, x-rays. These attenuation transmission intensities emerging from the tissue are transformed by a computer into numbers that represent values found in all the points located in the volume of the tissue slice. These values are expressed in Hounsfield units (HUs). HU values, also known as CT numbers, are used in an arbitrary scale in which bone is specified as +1000 (and is very white; Fig. 1.8*A, B*), water as zero, and air as −1000 (and is very black). With use of this scale, the HU values, or CT numbers, represent specific shades of gray for each of the various points located in the slice (Table 1.1; see also Fig. 1.8*A, B*).

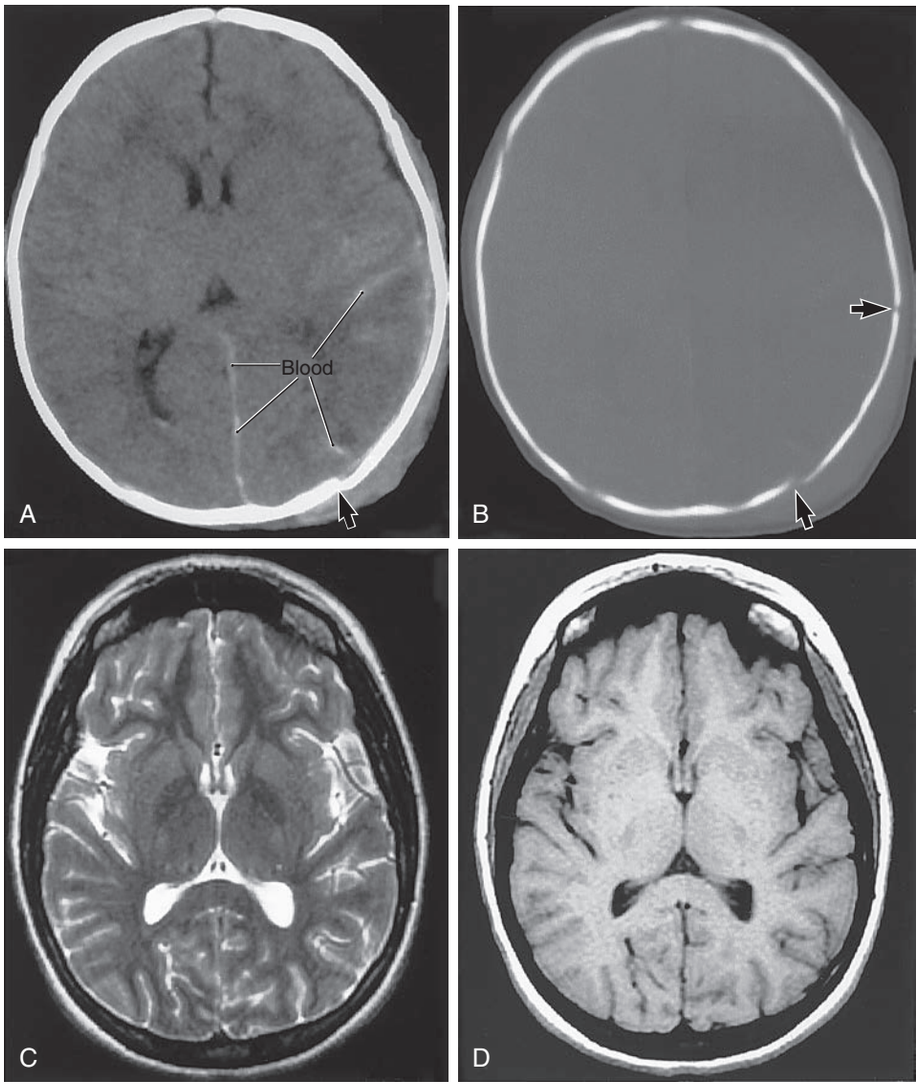

Fig. 1.8 CT scans (**A** and **B**) of a 2-month-old infant who was a victim of the shaken baby syndrome and MR images (**C** and **D**) of a normal 20-year-old woman. On the CT study, note that brain detail is less than on the MR images but that the presence of blood (**A,** in the interhemispheric fissure between the hemisphere and in the brain substance) is obvious. In the same patient, the bone window (**B**) clearly illustrates the outline of the skull but also clearly shows skull fractures (*arrows* in **A** and **B**). In this infant, the ventricles on the left are largely compressed, and the gyri have largely disappeared because of pressure from bleeding into the hemisphere. This is evidence of increased intracranial pressure, potential compromised brain function, and possible brain herniation. The pressure results in the effacement of the sulci and gyri on the left side. In the T2-weighted image (**C**), cerebrospinal fluid is white, internal brain structures are seen in excellent detail, and vessels are obvious. In the T1-weighted image (**D**), cerebrospinal fluid is dark and internal structures of the brain are somewhat less obvious.

Present-generation CT scanners, known as helical (spiral) scanners, image a continuous spiral slice through a preselected body region very quickly. Computer software converts this information into contiguous slices of a chosen thickness. This technique eliminates movement artifacts and enables reconstruction of soft tissues, bone, or contrast medium–enhanced vessels into three-dimensional images that can be manipulated in any plane.

CT is a fast and accurate method of detecting recent subarachnoid hemorrhage (Table 1.2; see also Fig. 1.8*A*). An acute subarachnoid hemorrhage in a noncontrast CT scan appears hyperdense (white) in contrast to the subarachnoid spaces and cisterns, which normally are hypodense (dark).

Enhanced CT is a technique using an iodinated contrast material injected intravenously followed by CT examination. Iodine has a large atomic number and attenuates x-rays. As a result, vasculature is visualized as hyperdense (white) structures. This contrast material may also enhance neoplasms or areas of inflammation because the contrast agent leaks from the vessels into the cellular spaces owing to a breakdown of the blood-brain barrier. Imaged in this way, the tumor, inflamed meninges, or brain parenchyma will show varying degrees of enhancement or hyperdensity (varying degrees of whiteness).

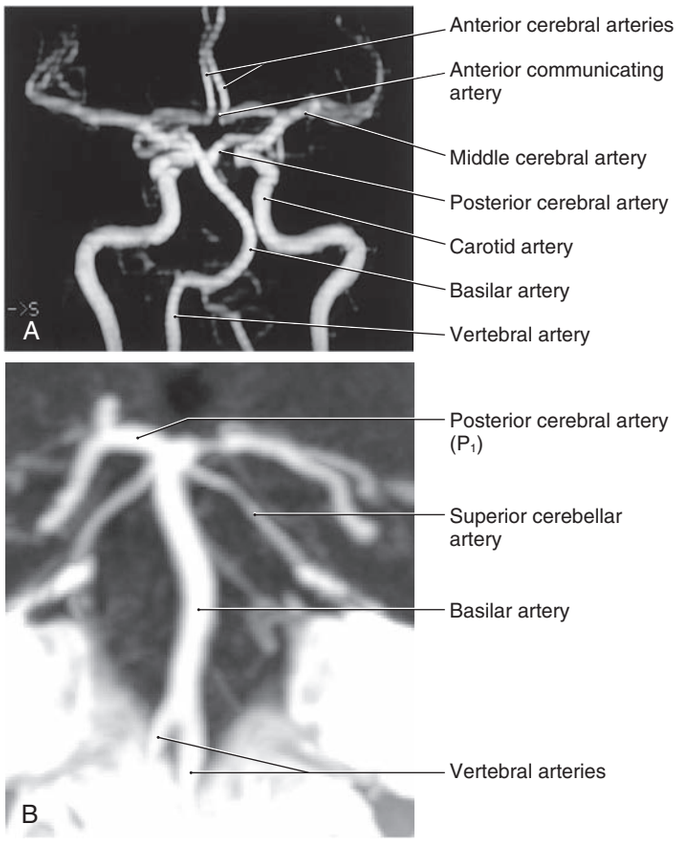

Fig. 1.9 **A,** MR angiography (MRA) of portions of the internal carotid artery and vertebrobasilar system. **B,** CT angiography (CTA) of a corresponding view of the vertebrobasilar system. Note that in the CTA image, the initial segment of the posterior cerebral artery (P_1) is constricted in this patient.

Magnetic Resonance Imaging

Protons (hydrogen) constitute a large proportion of body tissue. These atoms have a nucleus and a shell of electrons and a north and a south pole, and they spin around an angulated axis like small planets. As the electrons move with the spinning atom, they induce an electrical current that creates a magnetic field. These atoms function somewhat like little spinning bar magnets. They are aligned randomly because of the changing magnetic effects on each other. When these protons are exposed to a powerful magnet, they stop pointing randomly and align themselves parallel to the external magnetic field but at different energy levels. The stronger the external magnetic field, the faster the frequency of the spin at that angle. When undergoing an MRI examination, the patient becomes a magnet, with all the protons aligning along the external magnetic field and spinning at an angle with a certain frequency.

A radio wave is an electromagnetic wave. When a radio wave is sent as a short burst into the magnet containing the patient, it is known as a radiofrequency (RF) pulse. This RF pulse can vary in frequency strength. Only when the frequency strength of the RF pulse matches the frequency strength of the angulated spinning proton will the proton absorb energy from the radio wave. This phenomenon is called resonance and is the "resonance" in "magnetic resonance imaging." This results in a twofold effect: it cancels out the magnetic effects of certain protons, and it raises the energy levels and magnetic effects of another group of protons. When the radio wave is turned off, the canceled-out protons gradually return to their original state and strength of magnetization, which is called **relaxation** and is described by a time constant known as T1 (Fig. 1.8*D*). The protons that aligned themselves at a higher energy level and magnetization also start to lose their energy (relaxation), and this time constant is known as T2 (Fig. 1.8C). The T1 relaxation time is longer than the T2 relaxation time. The "de-excited" or relaxed protons release their energy as an "echo" of radio waves. A receiver coil (antenna) absorbs this information, and a computer determines the characteristics of the emitted radio waves from all the specific points in that section of the body. The MR image is then constructed and transferred to a computer monitor or recorded on film. T1-weighted or T2-weighted images can be obtained by use of varying times to receive the echoes (TE).

Table 1.1 Appearance of Tissues Imaged by CT and MRI

	Tissue						
MODALITY	**BONE**	**CSF**	**GRAY MATTER**	**WHITE MATTER**	**FAT**	**AIR**	**MUSCLE**
CT*	↑↑↑	↓↓	↓	↓↓	↓	↓↓↓	↑↑
MRI/T1†	↓↓↓	↓↓↓	↓↓	↓	↑↑	↓↓↓	↓↓
MRI/T2†	↓↓↓	↑↑↑	↓↓	↓↓↓	↑	↓↓↓	↓↓–↓↓↓

*Measures tissue density.
†Measures tissue signal.
↑↑↑–↑ represents very white to light gray:

↓–↓↓↓ represents light gray to very black:

CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

Conventional **spin-echo** sequences generate images that may be T1-weighted or T2-weighted according to the time interval in milliseconds between each exciting radio wave. This is called **repetition time** (TR). The time interval, in milliseconds, required to collect these radio waves from the relaxing protons is called **echo time** (TE). With spin-echo pulse sequences, the shorter the TR and TE, the more the image is considered T1-weighted. The longer the TR and TE, the more the image is considered T2-weighted.

The contrast material used to enhance tumors and blood vessels is the paramagnetic rare earth gadolinium. It is used in solution for intravenous injection. The gadolinium causes an increase in signal by shortening the relaxation time for T1. Owing to a breakdown of the blood-brain barrier, intravascular gadolinium enters the pericellular spaces, where it increases the relaxation state of water protons and generates a bright signal on T1-weighted images (Table 1.1).

Acute subarachnoid hemorrhage is poorly imaged by MRI on T1-weighted images but well imaged by CT (Table 1.2). Some MRI sequences are sensitive for detection of acute bleeding, but other factors may limit this method of examination. Special MRI techniques can also determine if a brain infarct or ischemia is acute (about 1 to 3 hours old) or subacute (about 4 hours old or more). Contraindications to MRI are cardiac pacemakers, cochlear implants, implantable cardioverter-defibrillators, ferromagnetic foreign bodies in the eye, and certain aneurysm clips. Large metallic implants or ferromagnetic foreign bodies in the body may heat up. The general appearance of the brain and adjacent structures in health and disease on MRI and CT is summarized in Tables 1.1 and 1.2.

Image Density and Intensity

As described before, a CT scan is produced when the patient is placed between a source of x-rays and detectors; the degree to which the tissues of the body attenuate these x-rays is a measure of its **density.** The various textures of gray seen in CT are a representation of this relative tissue density. **Hyperdense, hypodense,** and **isodense** are terms used in the clinical setting to specify various abnormal states in CT. Bone in CT greatly attenuates x-rays, has a high CT number, and appears white. Acute subarachnoid blood in CT is **hyperdense;** its appearance is shifted toward that of bone and is clearly whiter than the surrounding brain (Fig. 1.10*A*). On the other hand, air in CT poorly attenuates x-rays, has a low CT number, and appears black. An area of ischemia in CT is **hypodense;** its appearance is shifted toward that of air (or cerebrospinal fluid) and is darker than the surrounding brain (Fig. 1.10*B*, *arrows*). When the lesion, or tissue damage, appears basically the same as the surrounding brain, it is specified as **isodense** (Fig. 1.10C, *arrow*).

Also described before, an MR image is produced when the patient is exposed to a magnetic field, and the effects of this field on protons within the body are measured. Under the influence of an external magnet, these protons align themselves parallel to the source. When the external source is removed, the protons "relax"; those that relax more slowly from a lower energy level produce a T1-weighted image, whereas those that relax more rapidly from a higher energy level produce a T2-weighted image. **Hyperintense, hypointense,** and **isointense** specify various abnormal states in MRI in the clinical setting. In the normal patient, fat (T1) and cerebrospinal fluid (T2) appear distinctly more white. A lesion that is **hyperintense** in MRI appears whiter than the surrounding brain—for example, a meningioma and the surrounding edema (Fig. 1.10*D*). An example of a tumor that is **hypointense** is a medulloblastoma in the posterior fossa; this lesion appears darker than the surrounding brain (Fig. 1.10*E*, *arrows*). In between these extremes are lesions that are **isointense;** these lesions have basically the same appearance as the surrounding brain (Fig. 1.10*F, G*, *between arrows*).

Table 1.2 Differences in CT Density and MRI Signals in Representative Clinical Examples

CLINICAL PROBLEM	CT*	MRI T1†	MRI T2†
Acute SAH	↑↑↑	0	0
Subacute SAH	↑↑	0–↑	0
Tumor	0	0	↑–↑↑
Enhanced tumor	↑↑↑	↑↑↑	↑↑↑
Acute infarct	0	0–↑	↑–↑↑
Subacute infarct	0–↑	0–↓↓	↑↑–↑↑↑
Acute ischemia	0	0–↓	↑–↑↑
Subacute ischemia	0–↑	0–↓↓	↑↑–↑↑↑
Edema	0–↑	0–↓	↑–↑↑

*Measures tissue density.
†Measures tissue signal.
↑↑↑–↑ represents very white to light gray:

↓–↓↓↓ represents light gray to very black:

0 represents no change from normal.
CT, computed tomography; MRI, magnetic resonance imaging; SAH, subarachnoid hemorrhage.

Imaging of the Brain and Skull

Patients lie in the supine (face up) position for imaging of the brain or spinal cord and the surrounding bony structures (Fig. 1.11). In this position, the posterior (dorsal) surface of the brainstem and spinal cord and the caudal aspect (occipital pole) of the cerebral hemispheres face down. The anterior (ventral) surface of the brainstem and spinal cord and the frontal pole are face up (Fig. 1.11).

Images of the brain are commonly made in **coronal, axial** (horizontal), and **sagittal planes.** To illustrate the basic orientation of the CNS in situ, we shall look at examples of images in all three of these planes as they appear in the clinical setting (Figs. 1.11 and 1.12). Coronal imaging planes are oriented perpendicular to the rostrocaudal axis of the forebrain but are nearly parallel to the rostrocaudal axis of the brainstem and spinal cord. Therefore a coronal image obtained at a relatively rostral level of the cerebral hemispheres (Fig. 1.11*A*) will show only forebrain structures, and these structures will appear in cross section (perpendicular to their long axis). As the plane of imaging is moved caudally, brainstem structures enter the picture (Fig. 1.11*B*), but the brainstem is cut nearly parallel to its rostrocaudal axis.

Axial images, in contrast, are oriented parallel to the rostrocaudal axis of the cerebral hemispheres but nearly perpendicular to the long axis of the brainstem and spinal cord. Consequently, an axial image obtained midway through the cerebral hemispheres (Fig. 1.11*D*) will show only forebrain structures, with the rostral (frontal) end of the forebrain at the top of the image and the caudal (occipital) end at the bottom. As the plane of imaging is moved farther anteriorly (ventrally) relative to the forebrain, the brainstem appears (Fig. 1.11C). The brainstem, however, is cut nearly in cross section and is oriented with the anterior (ventral) surface "up" (toward the top of the image) and the posterior (dorsal) surface "down."

Images made in the sagittal plane are at, or parallel to, the midsagittal plane of the brain or spinal cord. This is the plane running through the middle (midline) of the head from rostral to caudal (along the frontal to occipital axis) or along the midline

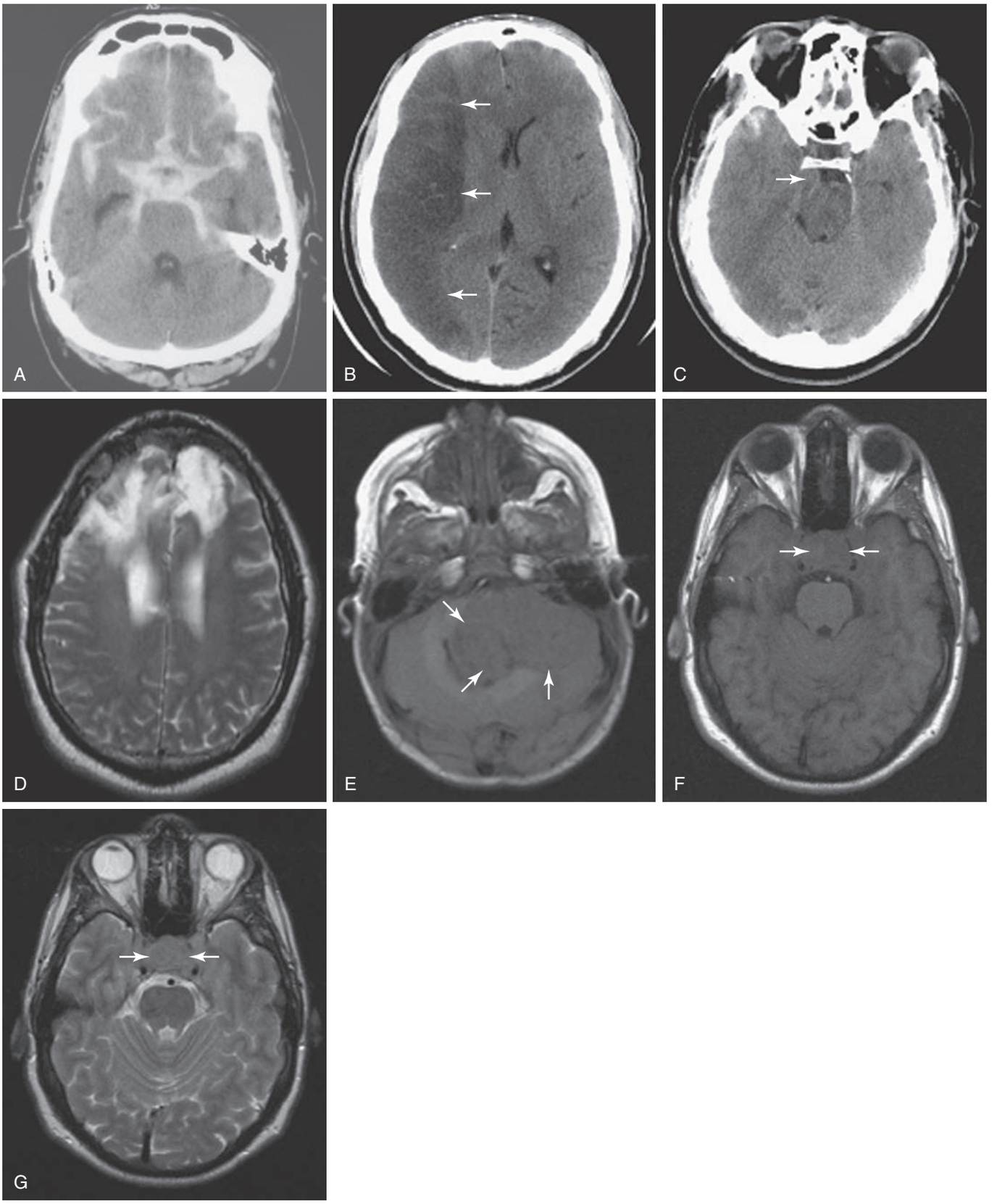

Fig. 1.10 Examples of density and intensity as seen in clinical images. In CT, subarachnoid blood is hyperdense (**A**), an area of infarct is hypodense (**B,** *arrows*), and a lesion causing herniation that appears the same texture as the brain is isodense (**C,** *at arrow*). In MRI, the edema surrounding a meningioma is hyperintense (**D,** T2-weighted), a nonenhanced medulloblastoma is hypointense (**E,** T1-weighted, *at arrows*), and a nonenhanced pituitary tumor that appears like the brain is isointense (**F,** T1-weighted; **G,** T2-weighted, *between arrows*).

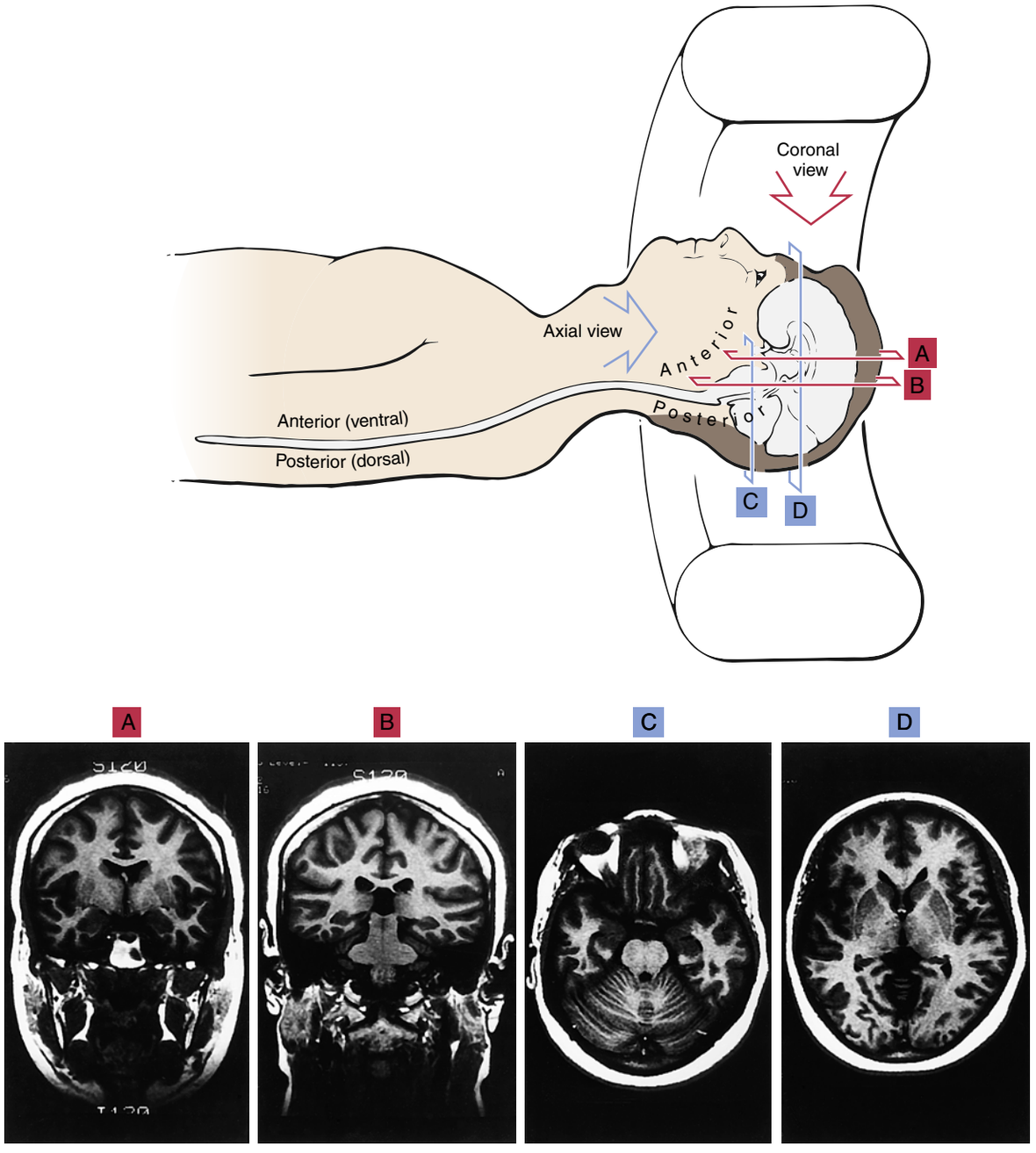

Fig. 1.11 The relation of imaging planes to the brain. The diagram shows the usual orientation of a patient in an MRI machine and the planes of the four scans (T1-weighted images) that are shown. **A** and **B,** Coronal scans. **C** and **D,** Axial scans.

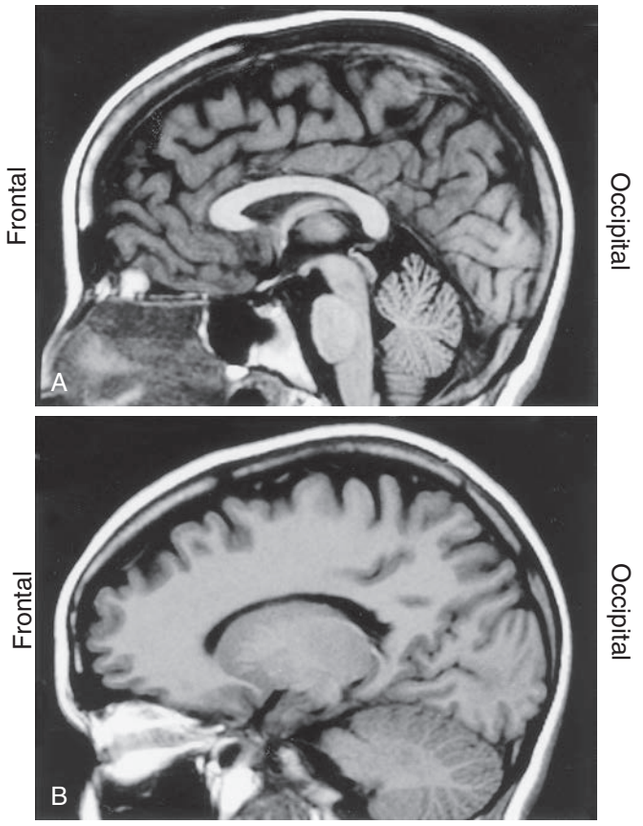

Fig. 1.12 MRI of the brain in the median sagittal plane (**A**) and in the sagittal plane but off the midline (**B**). The frontal lobe is to the left, and the occipital lobe is to the right. Other directions within the brain in this plane are appreciated by a comparison with Fig. 1.7.

of the spinal cord in a rostrocaudal axis. Sagittal images of the brain, be they at the midline (Fig. 1.12*A*) or off the midline (Fig. 1.12*B*), are oriented such that the frontal area is to the left and the occipital area is to the right. The various directions within the brain can be appreciated with a comparison of the midsagittal MR image with a drawing in the comparable orientation (compare Fig. 1.7*A* with Fig. 1.12).

A point also needs to be made about how the clinician views CT or MRI scans. Coronal scans are viewed as though the clinician is facing the patient, whereas axial scans are viewed as though the clinician is standing at the patient's feet looking up toward the patient's head from below as the patient lies supine in the machine. Axial scans, in other words, show the cerebral hemispheres from anterior (the more inferior portion of the hemisphere) to posterior (the more superior portion of the hemisphere), with the patient's frontal area and orbits at the top of the image and the occiput at the bottom. **In both coronal and axial views, the patient's left side is to the observer's right when viewing MRI and CT images.** This is an absolutely essential concept to remember as one examines MRI and CT scans and makes diagnostic judgments.

Sources and Additional Reading

The complete list is available online at www.studentconsult.com.

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Chapter 2
The Cell Biology of Neurons and Glia

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The number of cells in the adult human central nervous system (CNS) has been estimated at 100 billion. All arise from a relatively small population of precursors, yet a diversity of cell types is seen in the adult. Their most basic classification is as neurons and glia (glial cells).

OVERVIEW

Nerve cells (**neurons**) manipulate information. Doing so involves changes in the **bioelectrical** or **biochemical** properties of the cell, and these changes require a vast expenditure of energy for each cell. The nervous system, compared with other organs, is the greatest consumer of oxygen and glucose. These energy requirements arise directly from the metabolic demand placed on cells, which have large surface areas and concentrate biomolecules and ions against an energy gradient. Along with maintaining its metabolism, each neuron (1) **receives information** from either the environment or other nerve cells, (2) **processes information,** and (3) **sends information** to other neurons or effector tissues.

Glial cells control the CNS environment within which neurons function. They **shuttle nutritive molecules** from blood vessels to neurons, **remove waste** products, and **maintain the electrochemical** surroundings of neurons. **Glia** also communicate directly with nearby neurons through glial receptors and release mechanisms for certain neurotransmitters. During nervous system development, glia guide neuronal migration and promote synapse formation.

For neurons to carry out the three tasks of receiving, processing, and sending information, they must have specialized structures that contribute to each of these functions. The main components of a neuron are shown in Fig. 2.1. In addition, specialized mechanisms and structures are required to solve some special problems specific to neuron function. Two such problems are immediately apparent. First, the mix of ions inside neurons is different from the mix outside the cell. Maintaining this difference requires extraordinary amounts of energy because ions must be pumped against electrical and diffusion gradients. The large surface area of neurons compounds this problem. Second, those neurons that send information over long distances must have a way to supply these distant sites with macromolecules and energy. For the cell biology of neurons to be fully appreciated, it is important to see the biochemical, anatomic, and physiologic properties of neurons as part of an integrated whole, the machinery that permits the neuron to do its specialized functions. In the following sections, we examine how specializations in neuronal architecture and chemistry contribute to meeting these special demands.

STRUCTURE OF NEURONS

Although the architecture of neurons is especially diverse, our focus will be on the characteristic features of an archetypical neuron bounded by a continuous plasma membrane and consisting of a **cell body,** or **soma,** from which **dendrites** and an **axon** arise (Figs. 2.1 and 2.2). The cell body contains the nucleus surrounded by a mass of cytoplasm that includes the organelles necessary for protein synthesis and metabolic maintenance. Most neurons (**multipolar** neurons) have several dendrites extending from the cell body (Figs. 2.1 and 2.2). These are usually relatively short processes that taper from a thick base and, in doing so, branch extensively. In contrast, there is a single axon, which is a relatively long process (extending from a few millimeters to more than a meter) with a uniform diameter. The axon has few if any branches along most of its length, branching extensively only near the distal end (the **terminal arbor**) (Figs. 2.1 and 2.2). In most neurons, information normally flows from the dendrites to the cell body to the axon and its terminals, then to the next neuron or an effector tissue such as muscle. These components of the neuron are described in the order in which information is processed.

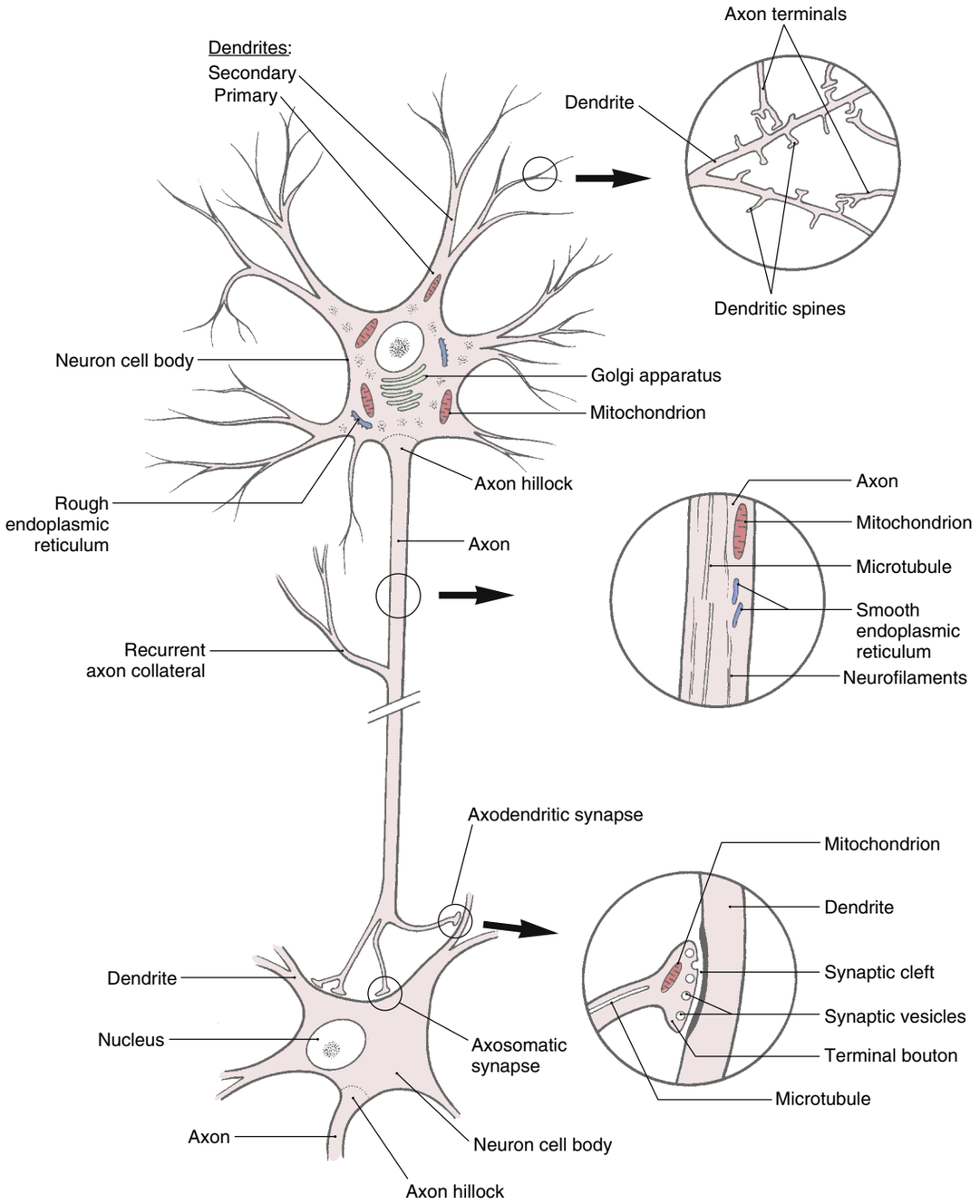

Fig. 2.1 Diagrammatic representation of a typical multipolar neuron. Dendrites, with their variety of spines (*top inset*), branch in the immediate vicinity of the cell body, whereas the single axon, with its occasional recurrent collaterals, may travel great distances to the next neuron. The cell body contains the organelles essential for neuronal function. Microtubules (*middle and bottom insets*) are important structures for the transport of substances within the axon. The axon ends as a terminal arbor that forms many terminal boutons (*bottom inset*), each containing the necessary machinery for synaptic transmission.

Dendrites

Dendrites receive signals either from other neurons through axonal contacts (**synapses**) formed on their surfaces (Figs. 2.1 and 2.3*D*). Dendrites usually branch extensively in the vicinity of the cell body, giving the appearance of a tree or bush (Figs. 2.1 to 2.3*A*). Small bud-like extensions (**dendritic spines,** Fig. 2.3C) of a variety of shapes are frequently seen on the more distal dendrites (Figs. 2.1 and 2.3*B, C*). These are sites of **synaptic contacts** (discussed later). The branches of dendrites increase in thickness as they coalesce and approach the cell body.

Observed in thin distal dendrites are sparse numbers of microtubules and neurofilaments along with small triangular-shaped clusters of agranular reticulum and ribosomes at some branch points. These structures are believed to be sites of protein synthesis and associated with memory formation. Often the distinction between the smallest dendrites and axons is difficult to discern. However, as dendrites begin to coalesce and become thicker, the number and type of organelles present increases until the cytoplasm of proximal (primary) dendrites appears no different from that observed in the soma (Figs. 2.3*D, E* and 2.4). Numerous types of endoplasmic reticulum, vesicles, mitochondria, microtubules, neurofilaments, Nissl bodies, polyribosomes, and free ribosomes can be seen in the primary dendrites.

Cell Body

The cell body of a neuron is also called the **soma** (plural, **somata**) or **perikaryon** (plural, **perikarya**) (Figs. 2.2 and 2.4). The perikaryon is the **metabolic center** of the nerve cell. Abundant mitochondria reflect the high energy consumption of the cell. Active protein synthesis is indicated by the large size of the nucleus and

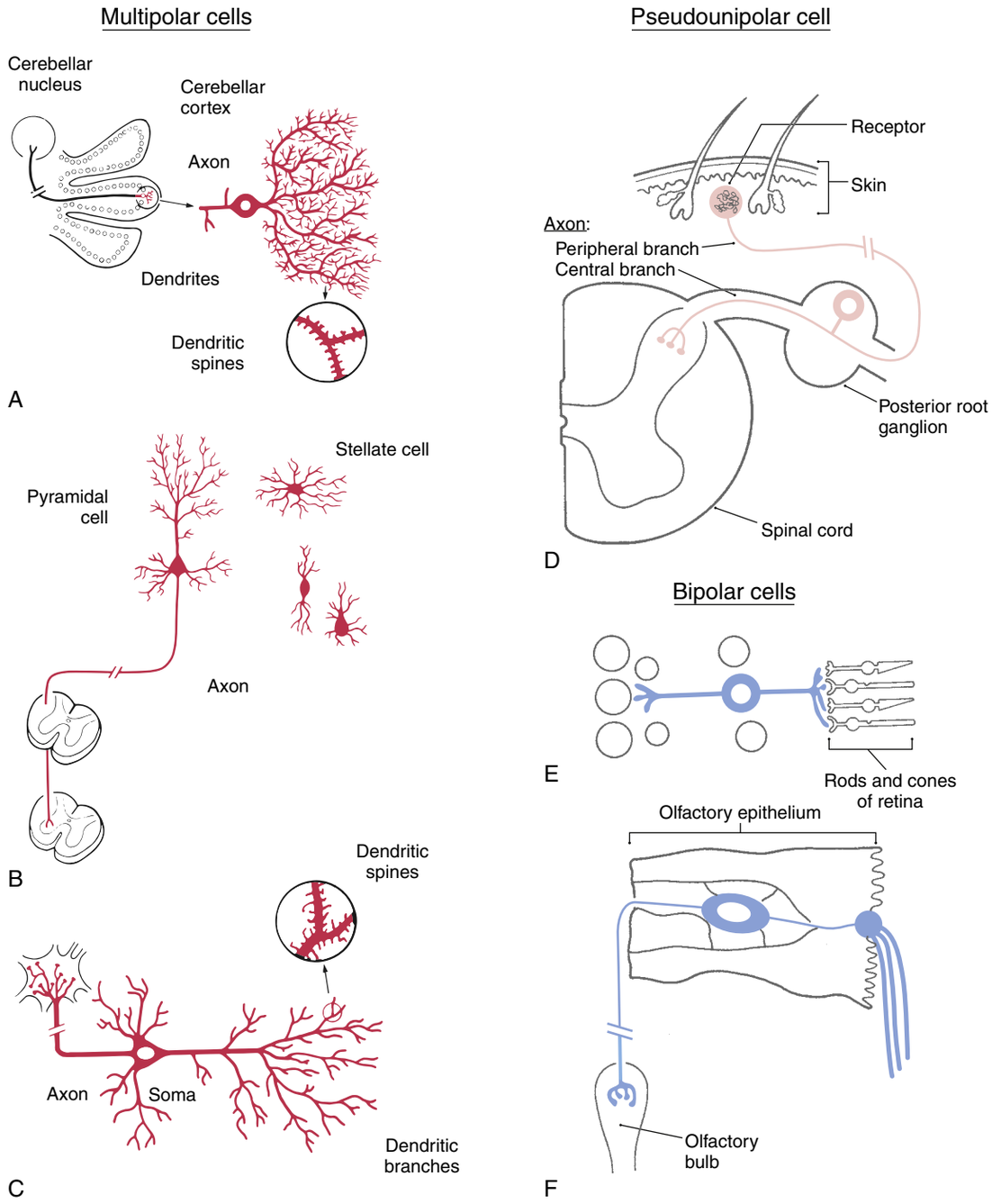

Fig. 2.2 Examples of various types of neurons showing the dendrites, somata, and axons of multipolar cells from the cerebellar cortex (**A**) and from the cerebral cortex (**B** and **C**). Compare these with a pseudounipolar cell of the posterior root ganglion (**D**) and with bipolar cells from the retina (**E**) and olfactory epithelium (**F**).

its content of diffuse chromatin (euchromatin) and at least one prominent nucleolus (the site of ribosomal RNA synthesis). In the cytoplasm, **ribosomes** are abundant, and the **rough endoplasmic reticulum** (rER) and **Golgi complex** are extensive (Fig. 2.1). The rER is basophilic (binds basic dyes) as a result of the large amount of ribosomal RNA attached to the endoplasmic membrane. These extensive, stacked layers of rER are seen as patches of basophilic staining (called **Nissl substance**) in histologic preparations of nerve cells.

Neurons are classified into three general types on the basis of the shape of the cell body and the pattern of processes emerging from it. These types are the multipolar, pseudounipolar, and bipolar cells (Table 2.1; see also Fig. 2.2).

The cell bodies of **multipolar** neurons vary widely in shape, so their profiles in tissue sections may appear fusiform, flask shaped, triangular, polygonal, or stellate (Fig. 2.2*A*-*C*). Variations of a stellate polygon are most common. This shape results from the presence of multiple, tapering dendrites that emerge from the soma. Typically the cell body also emits a single axon that generally appears thin relative to the cell's dendrites. More than 99% of all neurons are multipolar neurons, and the different kinds of these have characteristic patterns of processes, some of which are listed in Table 2.1.

The **pseudounipolar** (or **unipolar**) neuron has a spherical cell body with a centrally placed (concentric) nucleus. The cell body emits a single process that courses only a short distance before bifurcating into a long peripheral branch and a long central branch (Fig. 2.2*D*). The peripheral branch courses as part of a peripheral nerve to convey sensory information from a somatic or visceral structure, such as the skin, skeletal muscle, or wall of intestine. The distal end of the peripheral process is dendrite-like in the sense that its terminal branches receive information

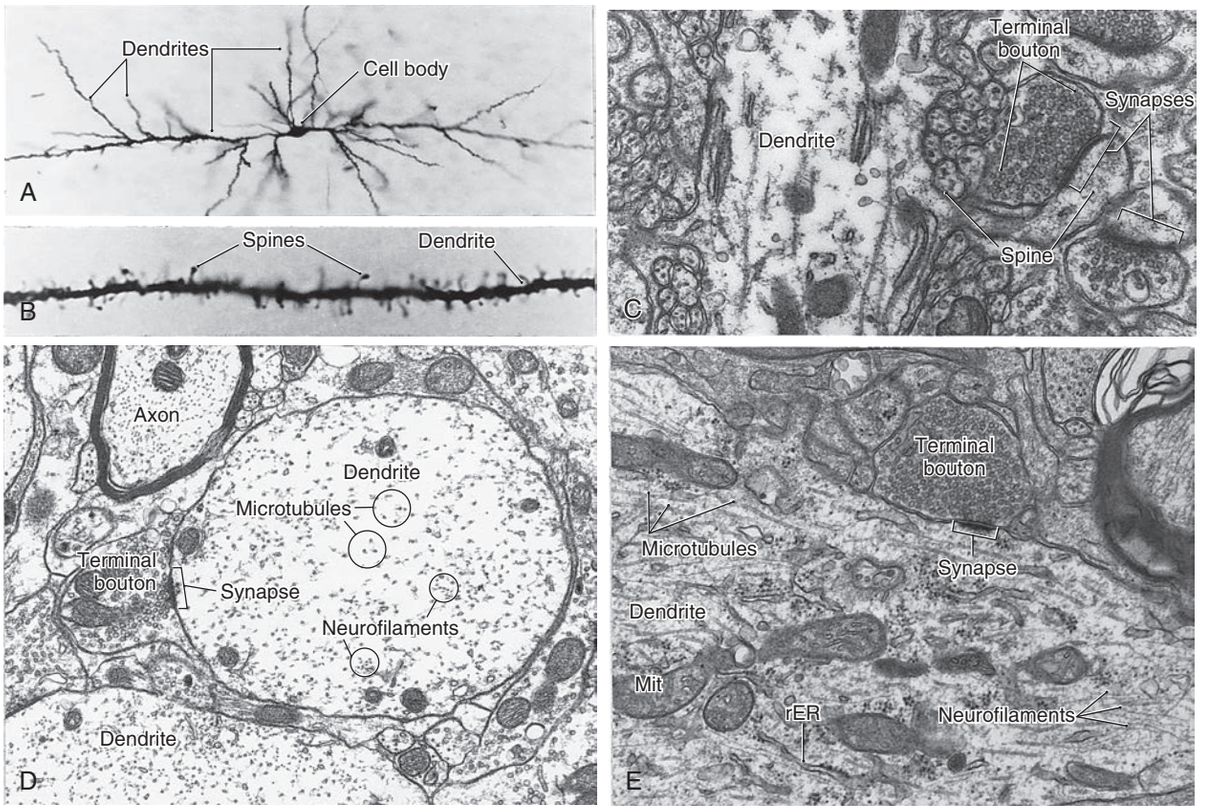

Fig. 2.3 Elements of dendrite structure. Dendritic tree of a multipolar neuron (**A**) and dendritic spines (**B**), both in Golgi-stained cortical tissue. Ultrastructural features of dendrites, showing an axonal terminal bouton synapsing on a dendritic spine (**C**), a cross section of a dendrite with characteristic cytoskeletal elements and organelles (**D**), and a longitudinal section of a dendrite in the anterior horn of the spinal cord (**E**). *MIT,* mitochondrion; *rER,* rough endoplasmic reticulum.

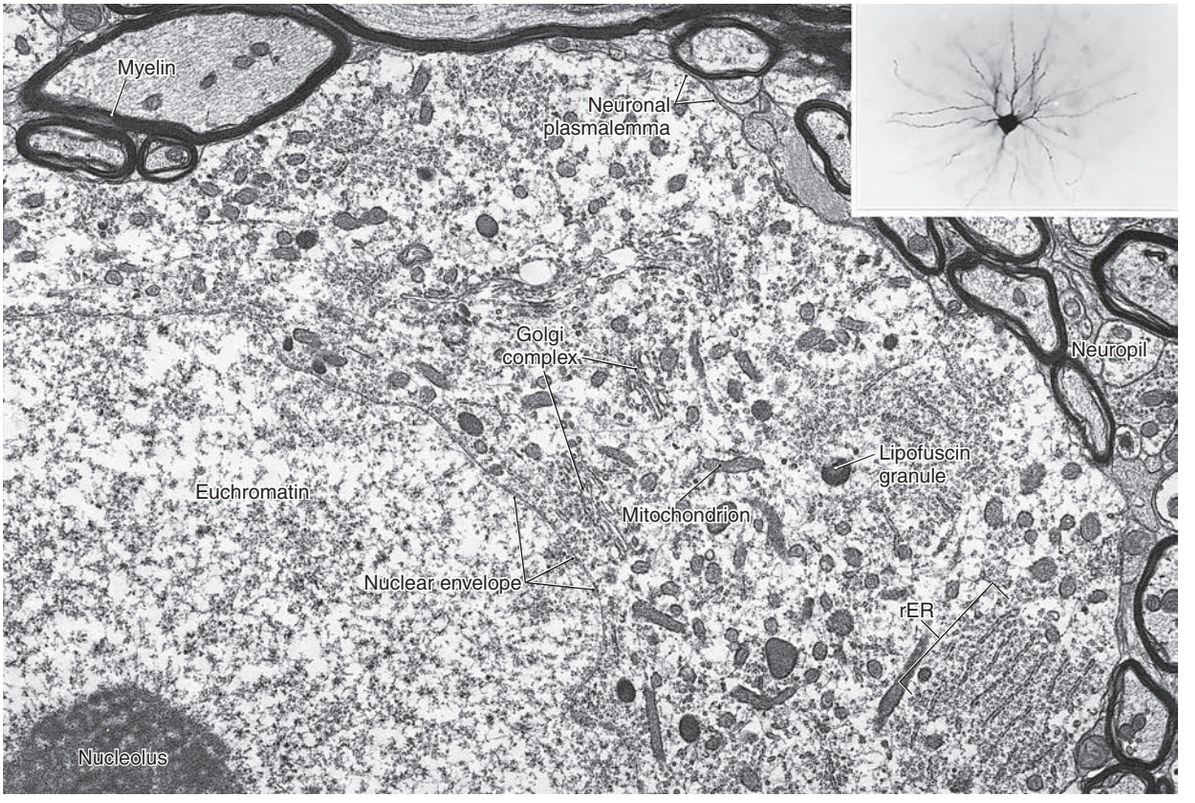

Fig. 2.4 The cell body of a multipolar neuron as seen on electron micrograph and in a Golgi-stained preparation (*inset*). *rER,* rough endoplasmic reticulum.

either by functioning as sensory receptors or by contacting other structures that function as receptors. The central branch courses as part of a nerve root to convey the sensory information to the CNS. In effect, the distal and central processes function together as a single axon. The cell bodies of pseudounipolar cells are found primarily in the sensory ganglia of cranial and spinal nerves.

Bipolar neurons have a round or oval perikaryon, with a single process emanating from each end of the cell body (Fig. 2.2*E, F*). They are commonly found in structures associated with the special senses. In the retina, bipolar cells are interposed between receptor cells and the neurons that send long axons from the retina to the thalamus (output cells). In the olfactory system, they function as both the receptors and the output neurons, with their axons projecting to the olfactory bulb; in the vestibular and auditory systems, they are the output cells that send information to the brainstem.

Unless special staining methods are used, the cell body of a neuron has the appearance of being the entire cell when it is viewed in histologic sections. However, the volume of the cell body of a neuron constitutes only a small fraction, often less than 1%, of the volume of the axon and dendrites even though the cell body synthesizes and continually replaces all structural molecules of these processes.

Table 2.1 A Few of the Neuronal Types Found in the Nervous System

TYPE OF NEURON	LOCATION OF CELL BODIES
Pseudounipolar	Posterior root or cranial nerve ganglion
Bipolar	Retina Olfactory epithelium Vestibular ganglion Auditory (spiral) ganglion
Multipolar	
Stellate (star shaped)	Many areas of CNS
Fusiform (spindle shaped)	Many areas of CNS
Pyriform (pear shaped)	Many areas of CNS
Pyramidal	Hippocampus; layers II, III, V, and VI of cerebral cortex
Purkinje	Cerebellar cortex
Mitral	Olfactory bulb
Chandelier	Visual areas of cerebral cortex
Granule	Cerebral and cerebellar cortex
Amacrine (axonless)	Retina

CNS, central nervous system.

Axons and Axon Terminals

The **axon** arises from the cell body at a small elevation called the **axon hillock.** The proximal part of the axon, adjacent to the axon hillock, is the **initial segment.** The cytoplasm of the axon (axoplasm) contains dense bundles of **microtubules** and **neurofilaments** (Figs. 2.1 and 2.5*A, B*). These function as structural elements, and the microtubules also play key roles in the transport of metabolites and organelles along the axon. Axons are typically devoid of ribosomes, a feature that distinguishes them from dendrites at the ultrastructural level.

In contrast to dendrites, axons may extend for long distances before branching and terminating. An example is the axon of a corticospinal tract neuron with a cell body in the motor cortex and an axon that reaches the caudal portion of the spinal cord. The axon of such a neuron accounts for approximately 99.8% of the total volume of the neuron. The surface area of an axon can be several thousand times the surface area of the parent cell body. Axons are sometimes referred to as **nerve fibers,** although strictly speaking, a nerve fiber includes both the axon and a sheath that is provided by support cells (described in a subsequent section).

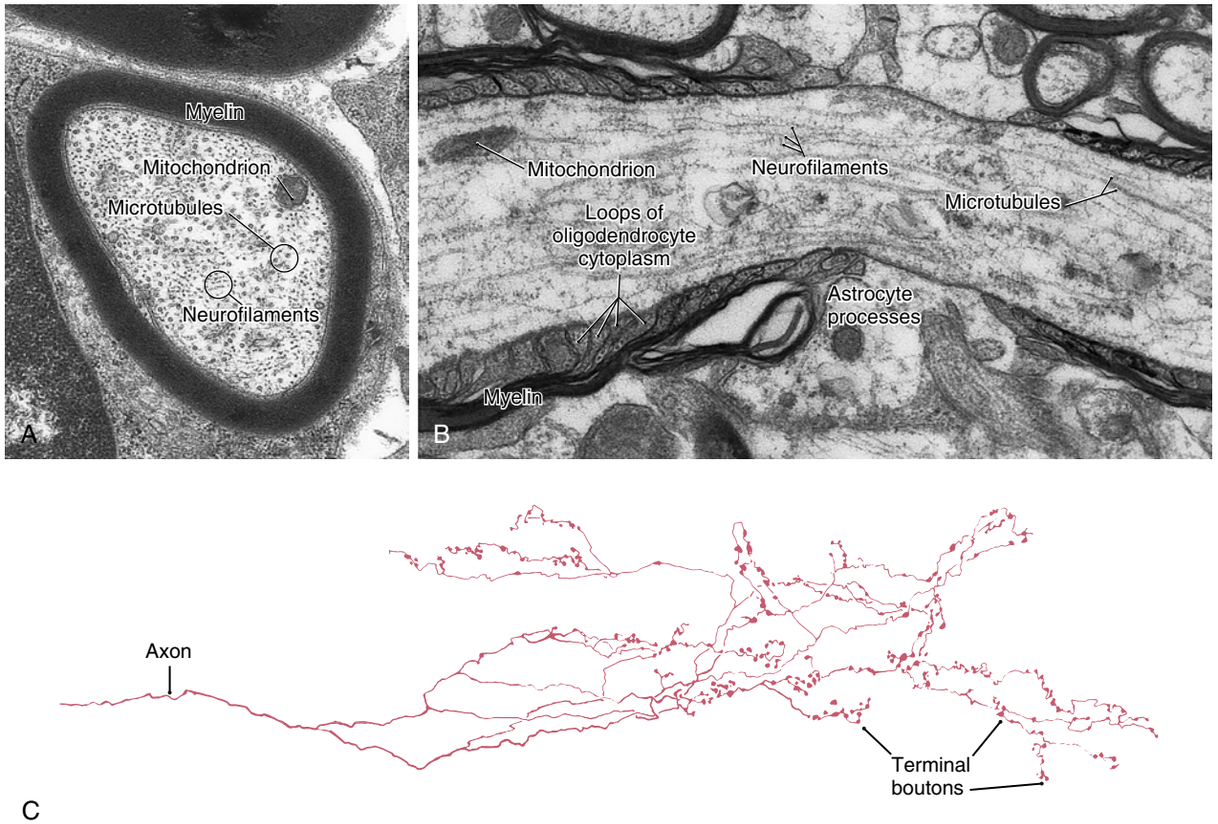

Fig. 2.5 Elements of axon structure. Ultrastructural features of a small myelinated axon in a cross section of a peripheral nerve (**A**) and a longitudinal view at a node of Ranvier of a myelinated axon in the central nervous system (**B**). Drawing of the complete terminal arbor of an axon in the thalamus reconstructed from serial sections (**C**).

Table 2.2 Characteristics of Axonal Transport

DIRECTION OF TRANSPORT	SPEED OF TRANSPORT	PROPOSED MECHANISM	SUBSTANCES CARRIED
Anterograde	Fast (100-400 mm/day)	Kinesin, microtubules Neurotransmitters in vesicles, mitochondria	Proteins in vesicles
	Slow (~1 mm/day)	Unknown	Cytoskeletal protein components (actin, myosin, tubulin) Neurotransmitter-related cytosolic enzymes
Retrograde	Fast (50-250 mm/day)	Dynein, microtubules	Macromolecules in vesicles, "old" mitochondria Pinocytotic vesicles from axon terminal

Axons in the CNS often end in fine branches known as **terminal arbors** (Fig. 2.5C). In most neurons, each axon terminal is capped with small **terminal boutons** (**boutons terminaux,** terminal buttons) (Figs. 2.1 and 2.3C, *E*). These correspond to functional points of contact (synapses) between nerve cells. In some cells, boutons are found along the length of the axon, where they are called **boutons en passant.** Other axons contain swellings, or **varicosities,** that are not button-like but still can represent points of cell-to-cell information transfer.

The site at which an axon terminal communicates with a second neuron, or with an effector tissue, is called a **synapse** (from the Greek word meaning "to clasp"). In general, the synapse can be defined as a contact between part of one neuron (usually its axon) and the dendrites, cell body, or axon of a second neuron. The contact can also be made with an effector cell such as a skeletal muscle fiber. Synapses are considered later in this chapter in the section Neurons as Information Transmitters.

Axonal Transport

Nerve cells have an elaborate transport system that moves organelles and macromolecules between the cell body and the axon and its terminals. Transport in the axon occurs in both directions (Table 2.2; Fig. 2.6). Axonal transport from the cell body toward the terminals is called **anterograde** or **orthograde;** transport from the terminals toward the cell body is called **retrograde.**

Anterograde axonal transport is classified into **fast** and **slow** components. Fast transport, at speeds of up to 400 mm/day, is based on the action of a protein called **kinesin.** Kinesin, an adenosine triphosphatase (ATPase), moves macromolecule-containing vesicles and mitochondria along microtubules in much the same manner as a small insect crawling along a straw. Slow transport carries important structural and metabolic components from the cell body to axon terminals; its mechanism is less well understood.

Retrograde axonal transport allows the neuron to respond to molecules, for example, growth factors, that are taken up near the axon terminal by either **pinocytosis** or **receptor-mediated endocytosis.** In addition, this form of transport functions in the continual recycling of components of the axon terminal. Retrograde transport along axonal microtubules is driven by the protein **dynein** rather than by kinesin.

Axonal transport is important in the pathogenesis of some human neurologic diseases. The **rabies virus** replicates in muscle tissue at the site of a bite by a rabid animal and is then transported in a retrograde direction to the cell bodies of neurons innervating the muscle. The neurons produce and shed copies of the rabies virus, which in turn are taken up by the terminals of adjacent cells. In this way, the infection becomes distributed throughout the CNS, causing the behavioral changes associated with this disease. From the CNS, the virus travels to the salivary glands by means of anterograde axonal transport in neurons innervating these glands. The infected salivary glands, in turn, shed the virus in the saliva.

The toxin produced by the bacterium *Clostridium tetani* is also transported in a retrograde direction in nerve cells whose axons terminate at the site of infection. **Tetanus toxin** is released from the nerve cell body and taken up by the terminals of neighboring neurons. However, unlike the rabies virus, which is replicated in the cell body, the tetanus toxin is diluted as it passes from cell to cell. In spite of this dilution effect, patients infected with C. *tetani* may have a range of neurologic deficits.

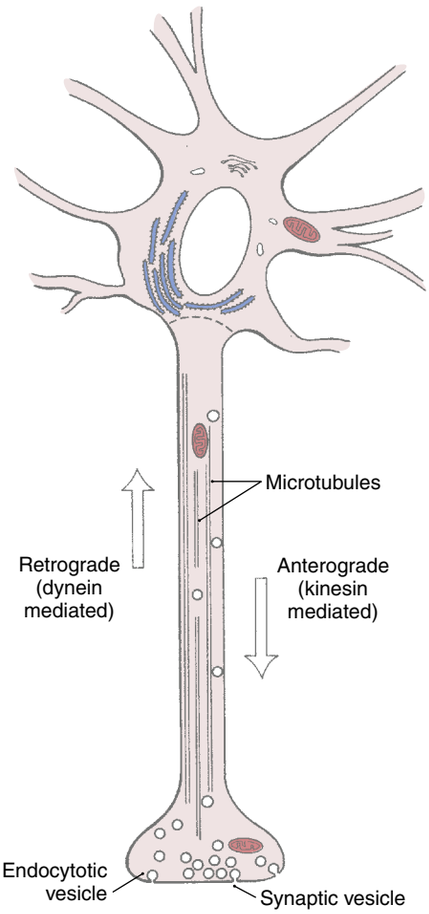

Fig. 2.6 Anterograde and retrograde axonal transport.

Axonal Transport as a Research Tool

The ability of neurons to transport intracellular materials is exploited in investigations of neuronal connections. For example, when the enzyme **horseradish peroxidase** (HRP) or a **fluorescent substance** is injected into regions containing axon terminals, it is taken up by these processes and transported in a retrograde direction to the cell body. After histologic preparation, the cell bodies containing these retrograde tracers can be visualized. The presence of the label in a cell body indicates that the neuron has axon terminals at the site of injection.

Tracer studies can also exploit the anterograde transport system of neurons. For example, if radioactively labeled amino acids are injected into a group of neuronal cell bodies, they will be incorporated into neuronal proteins and transported in an anterograde direction. The axons containing the labeled