*Neurology is the greatest and, I think, the most important, unexplored field in the whole of science. Certainly, our ignorance and the amount that is to be learned is just as vast as that of outer space. And certainly too, what we learn in this field of neurology is more important to man. The secrets of the brain and the mind are hidden still. The interrelationship of brain and mind are perhaps something we shall never be quite sure of, but something toward which scientists and doctors will always struggle.*

Wilder Penfield (1891–1976)
(From the Penfield papers, Montreal Neurological Institute,
with permission of the literary executors,
Theodore Rasmussen and William Feindel)

# CHAPTER 1

# Introduction to the Nervous System

The human nervous system is a specialized complex of excitable cells, called **neurons**. There are many functions associated with neurons, including (1) reception of stimuli, (2) transformation of these stimuli into nerve impulses, (3) conduction of nerve impulses, (4) neuron to neuron communication at points of functional contact between neurons called **synapses**, and (5) the integration, association, correlation, and interpretation of impulses such that the nervous system may act on, or respond to, these impulses. The nervous system resembles a well-organized and extremely complex communicational system designed to receive information from the external and internal environment, and assimilate, record, and use such information as a basis for immediate and intended behavior. The ability of neurons to communicate with one another is one way in which neurons differ from other cells in the body. Such communication between neurons often involves chemical messengers called **neurotransmitters**.

The human nervous system consists of the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS, surrounded and protected by bones of the skull and **vertebral column**, consists of the brain and **spinal cord**. The term "brain" refers to the following structures: brain stem, cerebellum, diencephalon, and the cerebral hemispheres. The PNS includes all cranial, spinal, and autonomic nerves and also their ganglia, and associated sensory and motor endings.

## 1.1 NEURONS

The structural unit of the nervous system is the **neuron** with its neuronal cell body (or soma) and numerous, elaborate neuronal processes. There are many contacts between neurons through these processes. The volume of cytoplasm in the processes of a neuron greatly exceeds that found in its cell

body. A collection of neuronal cell bodies in the PNS is a ganglion; a population of neuronal cell bodies in the CNS is a nucleus. An example of the former is a spinal ganglion and of the latter is the dorsal vagal nucleus – a collection of neuronal cell bodies in the brain stem whose processes contribute to the formation of the vagal nerve [X].

## 1.1.1 Neuronal cell body (soma)

The central part of a neuron without its many processes is the **neuronal cell body** (Fig. 1.1). It has a prominent, central nucleus (with a large nucleolus), various organelles, and inclusions such as the chromatophil (Nissl) substance, neurofibrils (aggregates of neurofilaments), microtubules, and actin filaments (microfilaments). The neuronal cell body contains the complex machinery needed for continuous protein synthesis – a characteristic feature of neurons. It also has an area devoid of chromatophil substance that corresponds to the point of origin of the axon called the **axon hillock** (Fig. 1.1). With proper staining and then examined microscopically, the chromatophil substance appears as intensely basophil aggregates of rough endoplasmic reticulum. There is an age-related increase of the endogenous pigment **lipofuscin**, a marker of cellular aging often termed "age pigment," in lysosomes of postmitotic neurons and in some glial cells of the human brain. Lipofuscin consists of a pigment matrix in association with varying amounts of lipid droplets. Another age pigment, **neuromelanin** makes its appearance by 11–12 months of life in the human locus coeruleus and by about 3 years of life in the human substantia nigra. This brownish to black pigment
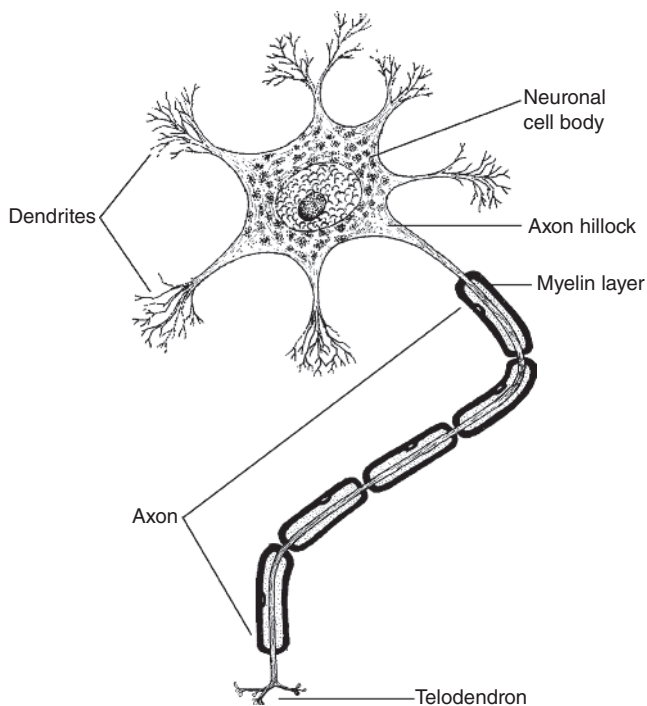
**Figure 1.1** ● Component parts of a neuron.

undergoes age-related reduction in both these nuclear groups and is marker for catecholaminergic neurons.

### Neuronal cytoskeleton

Neurofibrils, microtubules, and actin filaments in the neuronal cell body make up the **neuronal cytoskeleton** that supports and organizes organelles and inclusions, determines cell shape, and generates mechanical forces in the cytoplasm. Injury to the neuronal cell body or its processes due to genetic causes, mechanical damage, or exposure to toxic substances will disrupt the neuronal cytoskeleton. Neurofibrils, identifiable with a light microscope as linear fibrillary structures, are aggregates of neurofilaments when viewed with the electron microscope. Neurofilaments are slender, tubular structures 8–14 nm in diameter occurring only in neurons. Neurofilaments help maintain the radius of larger axons. Microtubules are longer, with a hollow-core, and have an outside diameter of about 22–25 nm. Their protein subunit is composed of α-and β-tubulin. They form paths or "streets" through the center of the axoplasm that are traveled by substances transported from the neuronal cell body and destined for the axon terminal. In the terminal, such substances may participate in the renewal of axonal membranes and for making synaptic vesicles. Actin filaments (microfilaments, F-actin) are in the neuronal cell body where they measure about 7 nm in diameter. The protein actin is the subunit of these neuronal actin filaments.

### Neurofibrillary degenerations

Neurofilaments increase in number, thicken, or become tangled during normal aging and in certain diseases such as Alzheimer disease and Down syndrome. These diseases are termed **neurofibrillary degenerations** because of the involvement of neurofilaments. Alzheimer disease is the sixth leading cause of death in the United States and the fifth leading cause of death for those aged 65 years and older. Approximately 5.2 million Americans have Alzheimer disease. By 2050, the number of people living with Alzheimer disease in the United States is likely to reach about 13.8 million. This is an irreversible degenerative disease with an insidious onset, inexorable progression, and fatal outcome. Alzheimer disease involves loss of memory and independent living skills, confusion, disorientation, language disturbances, and a generalized intellectual deficit involving personality changes that ultimately result in the loss of identity ("Mr. Jones is no longer the same person"). Progression of symptoms occurs over an average of 5–15 years. Eventually, patients with Alzheimer disease become confused and disoriented, lose control of voluntary motor activity, become bedridden and incontinent, and cannot feed themselves.

*Neuritic plaques, neurofibrillary tangles, and neuropil threads*

Small numbers of plaques and tangles characterize the brain of normal individuals 65 years of age and over. **Neuritic plaques**, **neurofibrillary tangles**, and **neuropil threads**,

however, are structural changes characteristic of the brains of patients with Alzheimer disease. These structural changes may occur in neuronal populations in various parts of the human brain. Other elements such as 10 and 15 nm straight neurofilaments, various-sized dense granules, and microtubule-associated proteins, especially the tau protein, also occur in this disease. Neurofibrillary tangles occur in the neuronal cytoplasm and have a paired helical structure that consists of pairs of 14–18 nm neurofilaments linked by thin cross-bridging filaments that coil around each other at regular 70–90 nm intervals. These paired helical filaments, unlike any neuronal organelle and unique to the human brain, are formed by one or more modified polypeptides that have unusual solubility properties but originate from neurofilament or other normal cytoskeletal proteins. Antibodies raised against the microtubule-associated protein, tau, are a useful marker that recognizes the presence of this protein in these neurofibrillary tangles. The tau protein helps organize and stabilize the neuronal cytoskeleton. Proponents of the "tau theory" of Alzheimer disease suggest that the phosphorylated form of this protein is a central mediator of the disease as it loses its ability to maintain the neuronal cytoskeleton, eventually aggregating into neurofibrillary tangles. Neuropil threads (curly fibers) are fine, extensively altered neurites in the cerebral cortex consisting of paired helical filaments or nonhelical straight filaments with no neurofilaments. They occur primarily in dendrites.

Degenerating neuronal processes along with an extracellular glycoprotein called **amyloid precursor protein** or β-amyloid protein (β-AP) form neuritic plaques. These plaques are of three types: primitive plaques composed of distorted neuronal processes with a few reactive cells, classical plaques of neuritic processes around an amyloid core, and end-stage plaques with a central amyloid core surrounded by few or no processes. Proponents of the "amyloid hypothesis" of Alzheimer disease regard the production and accumulation of β-amyloid protein in the brain and its consequent neuronal toxicity as a key event in this disease. In addition to the amyloid hypothesis and the "tau theory," other possible causes of Alzheimer disease include inflammation and vascular factors.

## 1.1.2 Axon hillock

The **axon hillock** (Fig. 1.1), a small prominence or elevation of the neuronal cell body, gives origin to the initial segment of an axon. Chromatophil substance is scattered throughout the neuronal cell body but reduced in the axon hillock, appearing as a pale region on one side of the neuronal cell body.

## 1.1.3 Neuronal processes – axons and dendrites

Since most stains do not mark them, neuronal processes often go unrecognized. Two types of processes characteristic of neurons are **axons** and **dendrites** (Fig. 1.1). Axons transmit impulses away from the neuronal cell body whereas dendrites transmit impulses to it. The term axon applies to any long peripheral process extending from the spinal cord regardless of direction of impulse conduction.

### Axons

The axon hillock (Fig. 1.1) arises from the neuronal cell body, tapers into an axon initial segment, and then continues as an axon that remains near the cell body or extends for a considerable distance before ending as a telodendron [Greek: end tree] (Fig. 1.1). A "considerable distance" might involve an axon leaving the spinal cord and passing to a limb to activate the fingers or toes. In a 7 ft. tall professional basketball player, the distance from the spinal cord to the tip of the fingers would certainly be "a considerable distance." Long axons usually give off collateral branches arising at right-angles to the axon.

Beyond the initial segment, axonal cytoplasm lacks chromatophil substance but has various microtubule-associated proteins (MAPs), actin filaments, neurofilaments, and microtubules that provide support and assist in the transport of substances along the entire length of the axon. The structural component of axoplasm, the axoplasmic matrix, is distinguishable by the presence of abundant microtubules and neurofilaments that form distinct bundles in the center of the axon.

### Myelin

Concentric layers of plasma membranes may insulate axons. These layers of lipoprotein wrapping material, called **myelin**, increase the efficiency and speed of saltatory conduction of impulses along the axon. Oligodendrocytes, a type of supporting cell in the nervous system called **neuroglial cells**, are myelin-forming cells in the CNS whereas neurilemmal (Schwann) cells produce myelin in the PNS. Each myelin layer (Fig. 1.1) around an axon has periodic interruptions at nerve fiber nodes (of Ranvier). These nodes bound individual internodal segments of myelin layers.

A radiating process from a myelin-forming cell forms an internodal segment. The distal part of such a process forms a concentric spiral of lipid-rich surface membrane, the myelin lamella, around the axon. Multiple processes from a single oligodendrocyte form as many as 40 internodal segments in the CNS whereas in the PNS a single neurilemmal cell forms only one internodal segment. In certain demyelinating diseases, such as multiple sclerosis (MS), myelin layers, although normally formed, are disturbed or destroyed perhaps by anti-myelin antibodies. Impulses attempting to travel along disrupted or destroyed myelin layers are erratic, inefficient, or absent.

### Dendrites

Although neurons have only one axon, they have many **dendrites** (Fig. 1.1). On leaving the neuronal cell body, dendrites taper, twist, and ramify in a tree-like manner. Dendritic trees grow continuously in adulthood. Dendrites

are usually short and branching but rarely myelinated, with smooth proximal surfaces and branchlets covered by innumerable dendritic spines that give dendrites a surface area far greater than that of the neuronal cell body. With these innumerable spines, dendrites form a major receptive area of a neuron. Dendrites have few neurofilaments but many microtubules. Larger dendrites, but never axons, contain chromatophil substance. Dendrites in the PNS may have specialized receptors at their peripheral termination that respond selectively to stimuli and convert them into impulses, evoking sensations such as pain, touch, or temperature. Chapter 6 provides additional information on these specialized endings.

## 1.2 CLASSIFICATION OF NEURONS

### 1.2.1 Neuronal classification by function

Based on function, there are three neuronal types: motor, sensory, and interneurons. Motor neurons carry impulses that influence the contraction of nonstriated and skeletal muscle or cause a gland to secrete. Ventral horn neurons of the spinal cord are examples of motor neurons. Sensory neurons such as dorsal horn neurons carry impulses that yield a variety of sensations such as pain, temperature, touch, and pressure. Interneurons relate motor and sensory neurons by transmitting information from one neuronal type to another.

### 1.2.2 Neuronal classification by number of processes

Based on the number of processes, there are four neuronal types: unipolar, bipolar, pseudounipolar, and multipolar. Unipolar neurons occur during development but are rare in the adult brain. Bipolar neurons (Fig. 1.2C) have two separate processes, one from each pole of the neuronal cell body. One process is an axon and the other a dendrite. Bipolar neurons are in the retina, olfactory epithelium, and ganglia of the vestibulocochlear nerve [VIII].

The term pseudounipolar neuron (Fig. 1.2A) refers to adult neurons that during development were bipolar but their two processes eventually came together and fused to form a single, short stem. Thus, they have a single T-shaped process that bifurcates, sending one branch to a peripheral tissue and the other branch into the spinal cord or brain stem. The peripheral branch functions as a dendrite and the central branch as an axon. Pseudounipolar neurons are sensory and in all spinal ganglia, the trigeminal ganglion, geniculate ganglion [VII], glossopharyngeal, and vagal ganglia. Both branches of a spinal ganglionic neuron have similar diameters and the same density of microtubules and neurofilaments. These organelles remain independent as they pass from the neuronal cell body and out into each branch. A special collection of pseudounipolar neurons in the CNS is the trigeminal mesencephalic nucleus.

Most neurons are multipolar neurons in that they have more than two processes – a single axon and numerous dendrites (Fig. 1.1). Examples include motor neurons and numerous small interneurons of the spinal cord, pyramidal neurons in the cerebral cortex, and Purkinje cells of the cerebellar cortex. Multipolar neurons are divisible into two groups according to the length of their axon. Long-axon multipolar (Golgi type I) neurons have axons that pass from their neuronal cell body and extend for a considerable distance before ending (Fig. 1.3A). These long axons form commissures, association, and projection fibers of the CNS. Short-axon multipolar (Golgi type II) neurons have short axons that remain near their cell body of origin (Fig. 1.3B). Such neurons are numerous in the cerebral cortex, cerebellar cortex, and spinal cord.
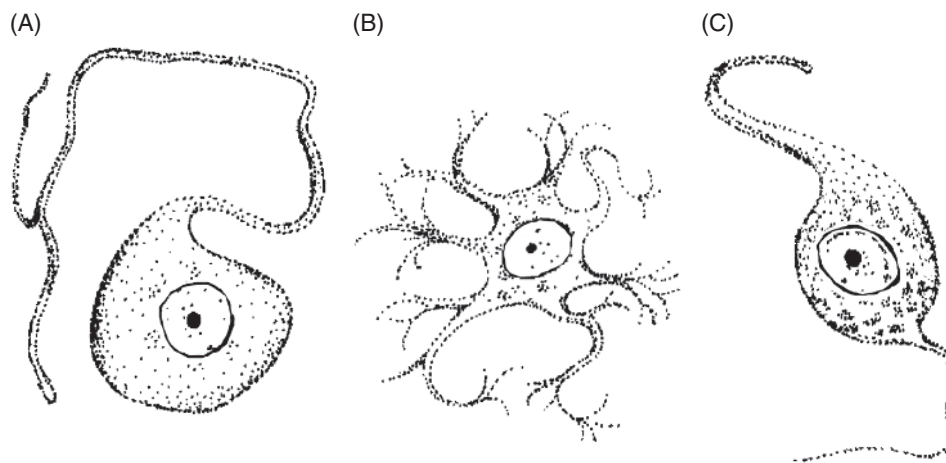


**Figure 1.2** ● Neurons classified by the number of processes extending from the soma. (A) Pseudounipolar neuron in the spinal ganglia; (B) multipolar neuron in the ventral horn of the spinal cord; (C) bipolar neuron typically in the retina, olfactory epithelium, and ganglia of the vestibulocochlear nerve [VIII].
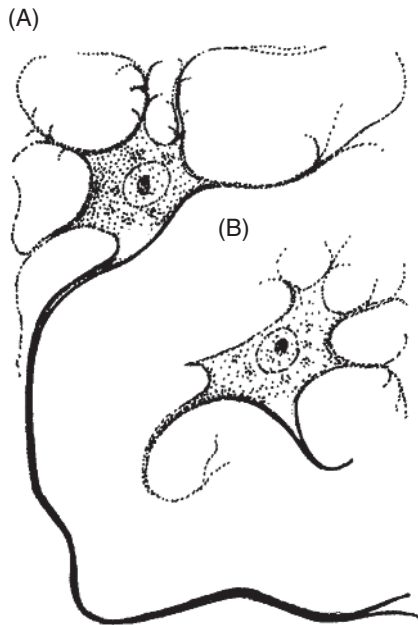
Figure 1.3 ● Multipolar neurons classified by the length of their axon. (A) Long-axon multipolar (Golgi type I) neurons have extremely long axons; (B) short-axon (Golgi type II) multipolar neurons have short axons that end near their somal origin.

## 1.3 THE SYNAPSE

Under normal conditions, the dendrites of a neuron receive impulses, carry them to its cell body, and then transmit those impulses away from the cell body via the neuronal axon to a muscle or gland, causing movement or yielding a secretion. Because of this unidirectional flow of impulses (dendrite to cell body to axon), neurons are said to be polarized. Impulses also travel from one neuron to another through points of functional contact between neurons called **synapses** (Fig. 1.4). Such junctions are points of functional contact between two neurons for purposes of transmitting impulses. Simply put, the nervous system consists of chains of neurons linked together at synapses. Impulses travel from one neuron to the next through synapses. Since synapses occur between component parts of two adjacent neurons, the following terms describe most synapses: axodendritic, axosomatic, axoaxonic, somatodendritic, somatosomatic, and dendrodendritic. Axons may form symmetric or asymmetric synapses. Asymmetric synapses contain round or spherical vesicles and are distinguishable by a thickened, postsynaptic density. They are presumably excitatory in function. Symmetric synapses contain flattened or elongated vesicles, pre- and postsynaptic membranes that are parallel to one another but lack a thickened postsynaptic density. Symmetric synapses are presumably inhibitory in function.

### 1.3.1 Components of a synapse

Most synapses have a **presynaptic part** (Fig. 1.4A), an intervening measurable space or **synaptic cleft** of about 20–30 nm, and a **postsynaptic part** (Fig. 1.4B). The presynaptic part has
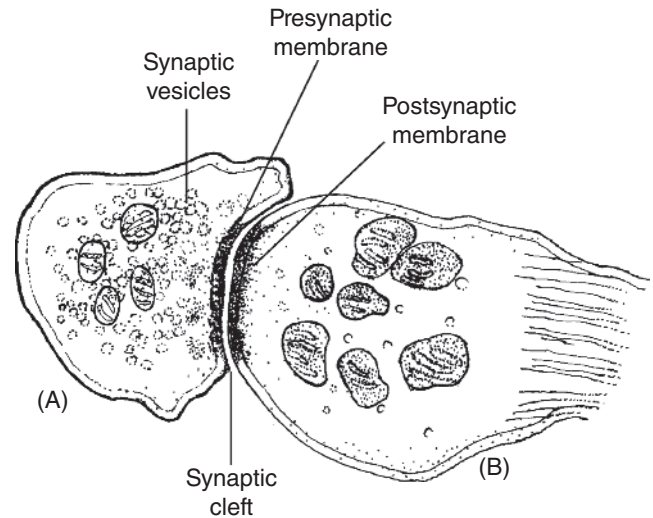


Figure 1.4 ● Ultrastructural appearance of an interneuronal synapse in the central nervous system with presynaptic (A) and postsynaptic (B) parts.

a presynaptic membrane (Fig. 1.4) – the plasmalemma of a neuronal cell body or that of one of its processes, associated cytoplasm with mitochondria, neurofilaments, synaptic vesicles (Fig. 1.4), cisterns, vacuoles, and a presynaptic vesicular grid consisting of trigonally arranged dense projections that form a grid. Visualized at the ultrastructural level, presynaptic vesicles are either dense or clear in appearance, and occupy spaces in the grid. The grid with vesicles is a characteristic ultrastructural feature of central synapses.

Chemical substances or **neurotransmitters** synthesized in the neuronal cell body are stored in presynaptic vesicles. Upon arrival of a nerve impulse at the presynaptic membrane, there is the release of small quantities (quantal emission) of a neurotransmitter through the presynaptic membrane by a process of exocytosis. Released neurotransmitter diffuses across the synaptic cleft to activate the postsynaptic membrane (Fig. 1.4) on the postsynaptic side of the synapse, thus bringing about changes in postsynaptic activity. The postsynaptic part has a thickened postsynaptic membrane and some associated synaptic web material, collectively called the **postsynaptic density**, consisting of various proteins and other components plus certain polypeptides.

### 1.3.2 Neurotransmitters and neuromodulators

Over 50 chemical substances are identifiable as **neurotransmitters**. Chemical substances that do not fit the classical definition of a neurotransmitter are termed **neuromodulators**. Acetylcholine (ACh), histamine, serotonin (5-HT), the catecholamines (dopamine, norepinephrine, and epinephrine), and certain amino acids (aspartate, glutamate, γ-aminobutyric acid, and glycine) are examples of neurotransmitters. Neuropeptides are derivatives of larger polypeptides that encompass more than three dozen substances. Cholecystokinin (CCK), neuropeptide Y (NPY), somatostatin (SOM), substance P, and

vasoactive intestinal polypeptide (VIP) are neurotransmitters. Classical neurotransmitters coexist in some neurons with a neuropeptide. Almost all of these neurotransmitters are in the human brain. On the one hand, neurological disease may alter certain neurotransmitters while on the other hand their alteration may lead to certain neurological disorders. Neurotransmitter deficiencies occur in Alzheimer disease where there is a cholinergic and a noradrenergic deficit, perhaps a dopaminergic deficit, a loss of serotonergic activity, a possible deficit in glutamate, and a reduction in somatostatin and substance P.

### 1.3.3 Neuronal plasticity

A unique feature of the human brain is its **neuronal plasticity**. As our nervous system grows and develops, neurons are always forming, changing, and remodeling. Because of its enormous potential to undergo such changes, the nervous system has the quality of being "plastic." Changes continue to occur in the mature nervous system at the synaptic level as we learn, create, store and recall memories, as we forget, and as we age. Alterations in synaptic function, the development of new synapses, and the modification or elimination of those already existing are examples of synaptic plasticity. With experience and stimulation, the nervous system is able to organize and reorganize synaptic connections. Age-related synaptic loss occurs in the primary visual cortex, hippocampal formation, and cerebellar cortex in humans.

Another aspect of synaptic plasticity involves changes accompanying defective development and some neurological diseases. Defective development may result in spine loss and alterations in dendritic spine geometry in specific neuronal populations. A decrease in neuronal number, lower density of synapses, atrophy of the dendritic tree, abnormal dendritic spines, loss of dendritic spines, and the presence of long, thin spines occur in the brains of children with mental retardation. Deterioration of intellectual function seen in Alzheimer disease may be due to neuronal loss and a distorted or reduced dendritic plasticity – the inability of dendrites of affected neurons to respond to, or compensate for, loss of inputs, loss of adjacent neurons, or other changes in the microenvironment.

**Fetal alcohol syndrome**

Prenatal exposure to alcohol, as would occur in an infant born to a chronic alcoholic mother, may result in **fetal alcohol syndrome**. Decreased numbers of dendritic spines and a predominance of spines with long, thin pedicles characterize this condition. The significance of these dendritic alterations in mental retardation, Alzheimer disease, fetal alcohol syndrome, and other neurological diseases awaits further study.

### 1.3.4 The neuropil

The precisely organized gray matter of the nervous system where most synaptic junctions and innumerable functional interconnections between neurons and their processes occur is termed the **neuropil**. The neuropil is the matrix or background of the nervous system.

## 1.4 NEUROGLIAL CELLS

Although the nervous system may include as many as $10^{12}$ neurons (estimates range between 10 billion and 1 trillion; the latter seems more likely), it has an even larger number of supporting cells termed **neuroglial cells**. Neuroglial cells are in both the CNS and PNS. Ependymocytes, astrocytes, oligodendrocytes, and microglia are examples of central glia; neurilemmal cells and satellite cells are examples of peripheral glia. Satellite cells surround the cell bodies of neurons.

Although astrocytes and oligodendrocytes arise from ectoderm, microglial cells arise from mesodermal elements (blood monocytes) that invade the brain in perinatal stages and after brain injury. In the developing cerebral hemispheres of humans, the appearance of microglial elements goes hand in hand with the appearance of vascularization.

### 1.4.1 Neuroglial cells differ from neurons

Neuroglial cells differ from neurons in a number of ways: (1) neuroglial cells have only one kind of process; (2) neuroglial cells are separated from neurons by an intercellular space of about 150–200 Å and from each other by gap junctions across which they communicate; (3) neuroglial cells cannot generate impulses but display uniform intracellular recordings and have a potassium-rich cytoplasm; and (4) astrocytes and oligodendrocytes retain the ability to divide, especially after injury to the nervous system. Virchow, who coined the term "neuroglia," thought that these supporting cells represented the interstitial connective tissue of brain – a kind of "nerve glue" ("Nervenkitt") in which neuronal elements are dispersed. An aqueous extracellular space separates neurons and neuroglial cells and accounts for about 20% of total brain volume. Neuroglial processes passing between the innumerable axons and dendrites in the neuropil serve to compartmentalize the glycoprotein matrix of the extracellular space of the brain.

### 1.4.2 Identification of neuroglia

Identifying neuroglial cells in sections stained by routine methods such as hematoxylin and eosin is difficult. Their identification requires special methods such as metallic impregnation, histochemical, and immunocytochemical methods. Astrocytes are identifiable using the gold chloride sublimate technique of Cajal, microglia by the silver carbonate technique of del Rio-Hortega, and oligodendrocytes by silver impregnation methods. Immunocytochemical methods are available for the visualization of astrocytes using the intermediate filament cytoskeletal protein glial fibrillary acidic protein (GFAP). Various antibodies are available for

the identification of oligodendrocytes and microglia. Microglial cells are identifiable in the normal human brain with a specific histochemical marker (lectin *Ricinus communis* agglutinin-1) or are identified under various pathological conditions with a monoclonal antibody (AMC30).

### Astrocytes

Two kinds of **astrocytes** – protoplasmic (Fig. 1.5A) and fibrous (Fig. 1.5B), are recognized. Astrocytes have a light homogeneous cytoplasm and nucleoplasm less dense than that in oligodendrocytes. Astrocytes are stellate with the usual cytoplasmic organelles and long, fine, perikaryal filaments and particulate glycogen as distinctive characteristics. These astroglial filaments are intermediate in size (7–11 nm) and composed of glial fibrillary acidic protein. Their radiating and tapering processes, with characteristic filaments and particles, often extend to the surface of blood vessels as vascular processes or underlie the pial covering on the surface of the brain as pial processes.

Protoplasmic astrocytes occur in areas of gray matter and have fewer fibrils than fibrous astrocytes. Fibrous astrocytes have numerous glial filaments and occur in white matter where their vascular processes expand in a sheet-like manner to cover the entire surface of nearby blood vessels, forming a perivascular glial limiting membrane. Processes of fibrous astrocytes completely cover and separate the cerebral cortex from the pia-arachnoid as a superficial glial limiting membrane, whereas along the ventricular surfaces they form the periventricular glial limiting membrane. Astrocytic processes cover the surfaces of neuronal cell bodies and their dendrites. These glial processes also surround certain synapses, and

separate bundles of axons in the central white matter. Fibrous astrocytes with abnormally thickened and beaded processes occur in epileptogenic foci removed during neurosurgical procedures.

### Oligodendrocytes

The most numerous glial element in adults, called **oligodendrocytes** (Fig. 1.5C), are small myelin-forming cells ranging in diameter from 10 to 20 μm, with a dense nucleus and cytoplasm. This nuclear density results from a substantial amount of heterochromatin in the nuclear periphery. A thin rim of cytoplasm surrounds the nucleus and densely packed organelles balloon out on one side. Oligodendrocytes lack the perikaryal fibrils and particulate glycogen characteristic of astrocytes. Their cytoplasm is uniformly dark with abundant free ribosomes, ribosomal rosettes, and randomly arranged microtubules, 25 nm in diameter, that extend into the oligodendrocyte processes and become aligned parallel to each other. Accumulations of abnormal microtubules in the cytoplasm and processes of oligodendrocytes, called **oligodendroglial microtubular masses**, are present in brain tissue from patients with neurodegenerative diseases such as Alzheimer or Pick disease.

Oligodendrocytes are identifiable in various parts of the brain. Interfascicular oligodendrocytes accumulate in the deeper layers of the human cerebral cortex in rows parallel to bundles of myelinated and nonmyelinated fibers. Perineuronal oligodendrocytes form neuronal satellites in close association with neuronal cell bodies. The cell bodies of these perineuronal oligodendrocytes contact each other yet maintain their myelin-forming potential, especially during
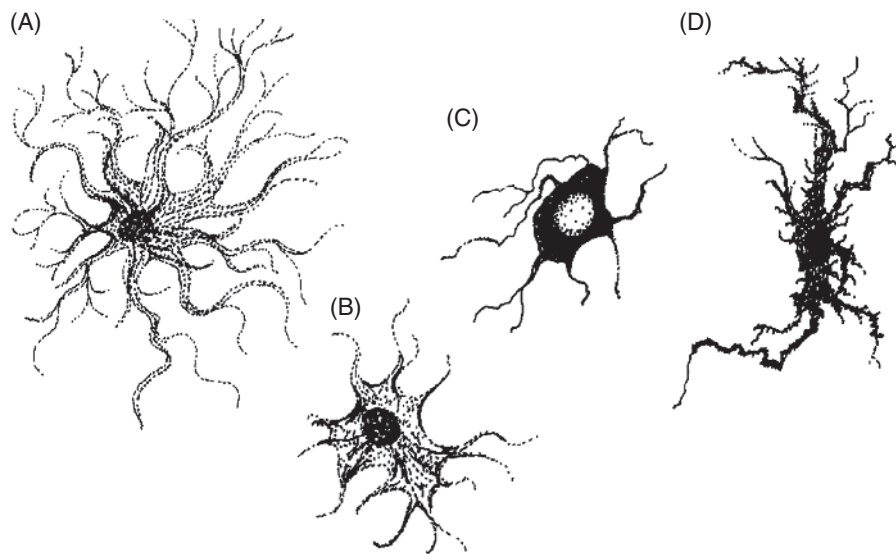


**Figure 1.5** ● Types of neuroglial cells in humans. (A) Protoplasmic astrocyte in the cerebral gray matter stained by Cajal's gold chloride sublimate method. (B) Fibrous astrocyte in the cerebral white matter stained by Cajal's gold chloride sublimate method. This gliocyte usually has vascular processes extending to nearby blood vessels or to the cortical or ventricular surface. (C) Oligodendrocyte revealed by the silver impregnation method. This small cell (10–20 μm in diameter) is in the deep layers of the cerebral cortex. (D) Microglial cell revealed by the del Rio-Hortega silver carbonate method. Microglia are evenly and abundantly distributed throughout the cerebral cortex.

remyelination of the CNS. Perineuronal oligodendrocytes are the most metabolically active of the neuroglia. Associated with capillaries are the perivascular oligodendrocytes.

**Microglial cells**

**Microglial cells** are rod shaped with irregular processes arising at nearly right-angles from the cell body (Fig.1.5D). They have elongated, dark nuclei and dense clumps of chromatophil substance around a nuclear envelope. The cytoplasmic density varies, with few mitochondria (often with dense granules), little endoplasmic reticulum, and occasional vacuoles. Microglia are often indented or impinged on by adjacent cellular processes and are evenly and abundantly distributed throughout the cerebral cortex. In certain diseases, microglial cells are transformable into different shapes, elongating and appearing as rod cells or collecting in clusters forming microglial nodules. Microglial cells are CNS-adapted macrophages derived from mesodermal elements (blood monocytes).

**Ependymal cells**

A fourth type of neuroglial cells are the **ependymal cells** that line the ventricles of the brain and the central canal of the spinal cord. The ependyma is nonciliated in adults. In the ventricles, vascular fringes of pia mater, known as the tela choroidea, invaginate their covering of modified ependyma and project into the ventricular cavities. The combination of vascular tela and cuboidal ependyma protruding into the ventricular cavities is termed the **choroid plexus**. The plexuses are invaginated into the cavities of both lateral and the third and fourth ventricles; they are concerned with the formation of cerebrospinal fluid.

The term "blood–cerebrospinal fluid barrier" refers to the tissues that intervene between the blood and the cerebrospinal fluid, including the capillary endothelium, several homogeneous and fibrillary layers (identified by electron microscopy), and the ependyma of the choroid plexus. The chief elements in the barrier are tight junctions between the ependymal cells.

## 1.4.3 Neuroglial function

Neuroglial cells are partners with neurons in the structure and function of the nervous system in that they support, protect, insulate, and isolate neurons. Neuroglial cells help maintain conditions favorable for neuronal excitability by maintaining ion homeostasis (external chloride, bicarbonate, and proton homeostasis and regulation of extracellular $K^+$ and $Ca^{2+}$) while preventing the haphazard flow of impulses. Impairment of neuroglial control of neuronal excitability may be a cause of epilepsy (also called **focal seizures**) in humans. About 2.7 million people in the United States are afflicted with focal seizures consisting of sudden, excessive, rapid, and localized electrical discharge by small groups of neurons in the brain. Every year a further 181 000 people develop this disorder.

Neuroglial cells control neuronal metabolism by regulating substances reaching neurons such as glucose and lipid precursors, and by serving as a dumping ground for waste products of metabolism. They are continually communicating with neurons serving as a metabolic interface between them and the extracellular fluid, releasing and transferring macromolecules, and altering the ionic composition of the microenvironment. They also supply necessary metabolites to axons. Neuroglial cells terminate synaptic transmission by removing chemical substances involved in synaptic transmission from synapses.

Astrocytes are involved in the response to injury involving the CNS. A glial scar (astrocytic gliosis) forms by proliferation of fibrous astrocytes. As neurons degenerate during the process of aging, astrocytes proliferate and occupy the vacant spaces. The brains of patients more than 70 years old may show increased numbers of fibrous astrocytes.

The intimate relationship between neurons and astrocytes in the developing nervous system has led to the suggestion that this relationship is significant in normal development and that astrocytes are involved in neuronal migration and differentiation. Astrocytes in tissue culture are active in the metabolism and regulation of glutamate (an excitatory amino acid) and γ-aminobutyric acid (GABA) (an inhibitory amino acid). Astrocytes remove potential synaptic transmitter substances such as adenosine and excess extracellular potassium.

Astrocytes may regulate local blood flow to and from neurons. A small number of substance P-immunoreactive astrocytes occur in relation to blood vessels of the human brain (especially in the deep white matter and deep gray matter in the cerebral hemispheres). Such astrocytes may cause an increase in blood flow in response to local metabolic changes. Astrocytes in tissue culture act as vehicles for the translocation of macromolecules from one cell to another.

Oligodendrocytes are the myelin-forming cells in the CNS and are equivalent to neurilemmal cells in the PNS. Each internodal segment of myelin originates from a single oligodendrocyte process, yet a single oligodendrocyte may contribute as many as 40 internodal segments as it gives off numerous sheet-like processes. A substantial number of oligodendrocytes in the white matter do not connect to myelin segments. Pathological processes involving oligodendrocytes may result in demyelination. Oligodendrocytes related to capillaries likely mediate iron mobilization and storage in the human brain based on the immunocytochemical localization in human oligodendrocytes of transferrin (the major iron binding and transport protein), ferritin (an iron storage protein), and iron.

Microglia are evident after indirect neural trauma such as transection of a peripheral nerve, in which case they interpose themselves between synaptic endings and the surface of injured neurons (a phenomenon called **synaptic stripping**). Microglial cells are also involved in pinocytosis, perhaps to prevent the spread of exogenous proteins in the CNS extracellular space. They are dynamic elements in a variety of neurological conditions such as infections, autoimmune

disease, and degeneration and regeneration. Microglial cells are likely antigen-presenting cells in the development of inflammatory lesions of the human brain such as multiple sclerosis.

Proliferation and accumulation of microglia occur near degenerating neuronal processes and in close association with amyloid deposits in the cerebral and cerebellar cortices in Alzheimer disease. Microglia may process neuronal amyloid precursor protein in these degenerating neurons, leading to the formation and deposition of a polypeptide called **β-amyloid** in neuritic plaques. Hence microglial cells are likely involved in the pathogenesis of amyloid deposition in Alzheimer disease.

Based on their structure, distribution, and macrophage-like behavior, and the observation that they can be induced to express major histocompatibility complex (MHC) antigens, microglia are thought to form a network of immune competent cells in the CNS. Microglial cells (and invading macrophages) are among the cellular targets for the human immunodeficiency virus-1 (HIV-1) known to cause acquired immunodeficiency syndrome (AIDS). Infected microglia presumably function to release toxic substances capable of disrupting and perhaps destroying neurons, leading to the neurological impairments associated with AIDS. Another possibility is that destruction of the microglia causes an altered immune-mediated reaction to the AIDS virus and other pathogens in these patients.

### 1.4.4 Neuroglial cells and aging

Oligodendrocytes show few signs of aging, but astrocytes and microglia may accumulate lipofuscin with age. There is a generalized, age-related increase in the number of microglia throughout the brain. Age-related astrocytic proliferation and hypertrophy are associated with neuronal loss. A demonstrated decrease in oligodendrocytes remains unexplained. Future studies of aging are sure to address the issue of neuroglial cell changes and their effect on neurons.

### 1.4.5 Neuroglial cells and brain tumors

Primary brain tumors begin in the brain, tend to remain in the brain, and occur in people of all ages, but they are statistically more frequent in children and older adults. Metastatic brain tumors begin outside the brain, spread to the brain, and are more common in adults than in children. The most common types of cancer that may spread to the brain include cancer of the breast, colon, kidney, or lung and also melanoma (skin cancer). Most primary brain tumors are gliomas, including astrocytomas, oligodendrogliomas, and ependymomas. As their names suggest, these gliomas are derived from neuroglial cells – astrocytes, oligodendrocytes, and ependymal cells. Gliomas, a broad term that includes all tumors arising from neuroglial cells, represent 30% of all brain tumors and 80% of all malignant tumors (American Brain Tumor Association, 2014).

## 1.5 AXONAL TRANSPORT

Neuronal processes grow, regenerate, and replenish their complex machinery. They are able to do this because proteins synthesized in the neuronal cell body readily reach the neuronal processes. **Axonal transport** is the continuous flow (in axons and dendrites) of a range of membranous organelles, proteins, and enzymes at different rates and along the entire length of the neuronal process. A universal property of neurons, axonal transport, is ATP dependent and oxygen and temperature dependent, requires calcium, and probably involves calmodulin and the contractile proteins actin and myosin in association with microtubules. Axonal transport takes place from the periphery to the neuronal cell body (retrograde transport) and from the neuronal cell body to the terminal ending (anterograde transport).

Rapid or **fast axonal transport**, with a velocity of 50–400 mm per day, carries membranous organelles. Slow axonal transport, characterized by two subcomponents with different velocities, carries structural proteins, glycolytic enzymes, and proteins that regulate polymerization of structural proteins. The slower subcomponent (SCa) of slow axonal transport, with a velocity of 1–2 mm per day, carries assembled neurofilaments and microtubules. The faster subcomponent of slow axonal transport, with a velocity of 2–8 mm per day, carries proteins that help maintain the cytoskeleton such as actin (the protein subunit of actin filaments), clathrin, fodrin, and calmodulin and also tubulin (the protein subunit of microtubules), and glycolytic enzymes. The size of a neuronal process does not influence the pattern or rate of axonal transport.

### 1.5.1 Functions of axonal transport

Anterograde transport plays a vital role in the normal maintenance, nutrition, and growth of neuronal processes supplying the terminal endings with synaptic transmitters, certain synthetic and degradative enzymes, and membrane constituents. One function of retrograde transport is to recirculate substances delivered by anterograde transport that are in excess of local needs. Structures in the neuronal cell body may degrade or resynthesize these excess substances as needed. Half the protein delivered to the distal process returns to the neuronal cell body. Retrograde transport, occurring at a rate of 150–200 mm per day, permits the transfer of worn-out organelles and membrane constituents to lysosomes in the neuronal cell body for digestion and disposal. Survival or neurotrophic factors, such as nerve growth factor (NGF), reach their neuronal target by this route. Tetanus toxin, the poliomyelitis virus, and herpes simplex virus gain access to neuronal cell bodies by retrograde transport. Retrograde axonal transport can thus convey both essential and harmful or noxious substances to the neuronal cell body.

### 1.5.2 Defective axonal transport

The phenomenon of defective axonal transport may cause disease in peripheral nerves, muscle, or neurons. Mechanical

and vascular blockage of axonal transport in the human **optic nerve** [II] causes swelling of the optic disk (papilledema). Senile muscular atrophy may result from age-related adverse effects on axoplasmic transport. Certain genetic disorders (Charcot–Marie–Tooth disease and Déjerine–Sottas disease), viral infections (herpes zoster, herpes simplex, and poliomyelitis), and metabolic disorders (diabetes and uremia) manifest a reduction in the average velocity of axonal transport. Accumulation of transported materials in the axon terminal may lead to terminal overloading and axonal breakdown causing degeneration and denervation. Interference with axonal transport of neurofilaments may be a mechanism underlying the structural changes in Alzheimer disease (neurofibrillary tangles and neuritic plaques) and other degenerative diseases of the CNS. In the future, retrograde transport may prove useful in the treatment of injured or diseased neurons by applying drugs to terminal processes for eventual transport back to the injured or diseased neuronal cell body.

Neurons are polarized transmitters of nerve impulses and active chemical processors with bidirectional communication through various small molecules, peptides, and proteins. Information exchange involving a chemical circuit is as essential as that exchanged by electrical conduction. These chemical and electrical circuits work in a complementary manner to achieve the extraordinary degree of complex functioning characteristic of the human nervous system.

## 1.6 DEGENERATION AND REGENERATION

After becoming committed to an adult class or population and synthesizing a neurotransmitter, most neurons lose the capacity for DNA synthesis and cell division. Hence, once destroyed, most mature neurons in the human CNS die; new neurons do not then take their place. The implications of this are devastating for those who have suffered CNS injury. About 222 000–285 000 people in the United States are living with spinal cord injuries, with nearly 11 000 new cases every year. An additional 4860 individuals die each year before reaching the hospital. A further 2 000 000 patients have suffered brain trauma or other injury to the head, with over 800 000 new cases each year. Hence the inability of the adult nervous system to add neurons or replace damaged neurons as needed is a serious problem for those afflicted with CNS injury.

Curtis *et al.* (2007) reported that in neurologically normal human brains, neuroblasts migrating via a lateral ventricular extension become neurons in the olfactory bulb. However, it is possible that this represents normal migration of neural progenitors from their site of birth to their final destination in the developing brain (Middeldorp *et al.*, 2010) rather than a source of progenitor cells with migratory characteristics involved in adult neurogenesis. Unlike rodents and nonhuman primates, in which neurogenesis in the adult cerebral cortex is unclear, studies in humans did not reveal any evidence for the occurrence of neurogenesis in the adult human cerebral cortex (Zhao *et al.*, 2008). Zhao *et al.* noted the complexity of this process and that both intracellular and extracellular factors are major regulators in adult neurogenesis, including extracellular growth factors, neurotrophins, cytokines, and hormones and also intracellular cell-cycle regulators, transcription factors, and epigenetic factors.

### 1.6.1 Axon or retrograde reaction

Degeneration of neurons is similar in the CNS and PNS. One exception is the difference in the myelin-forming oligodendrocytes in the CNS in contrast to the myelin-forming neurilemmal cells of the PNS. Only hours after injury to a neuronal process, perhaps because of a signal conveyed by retrograde axonal transport, a genetically programmed and predictable series of changes occur in a normal neuronal cell body (Fig. 1.6A). These collective changes in the neuronal cell body are termed the **axon or retrograde reaction**. By 1–3 days after the initial injury, the neuronal cell body swells and becomes rounded (Fig. 1.6B), the cell wall appears to thicken, and the nucleolus enlarges. These events are followed by displacement of the nucleus to an eccentric position (Fig. 1.6C), widening of the rough endoplasmic reticulum, and mitochondrial swelling. Chromatophil substance at this time undergoes conspicuous rearrangement – a process referred to as chromatolysis, involving fragmentation and loss of concentration of chromatophil substance causing loss of basophil staining by injured neurons (Fig. 1.6D). Chromatolysis is prominent about 15–20 days after injury.

Along with the axon reaction, alterations in protein and carbohydrate synthesis occur in the chromatolytic neuron. DNA-dependent RNA synthesis seems to play a key role in this process. As the axon reaction continues, there is increased production of free polyribosomes, rough endoplasmic reticulum, and neurofilaments, and an increase in the size and number of lysosomes. The axon reaction includes a dramatic proliferation of perineuronal microglia, leading to displacement of synaptic terminals on the neuronal cell body and stem dendrites, causing electrophysiological disturbances.

The sequence of events characteristic of an axon reaction depends, in part, on the neuronal system and age and also the severity and exact site of injury. If left unchecked, the axon reaction leads to neuronal dissolution and death. If the initial injury is not severe, the neuronal nucleus returns to a central position, the chromatophil substance becomes concentrated, and the neuronal cell body returns to normal size.

Initial descriptions of chromatolysis suggested that it was a degenerative process caused by neuronal injury. Recent work suggests that chromatolysis represents neuronal reorganization leading to a regenerative process. As part of the axon reaction, the neuronal cell body shifts from production of neurotransmitters and high-energy ATP to the production of lipids and nucleotides needed for repair of cell membranes. Hence chromatolysis may be the initial event in a series of metabolic changes involving the conservation of energy and leading to neuronal restoration.
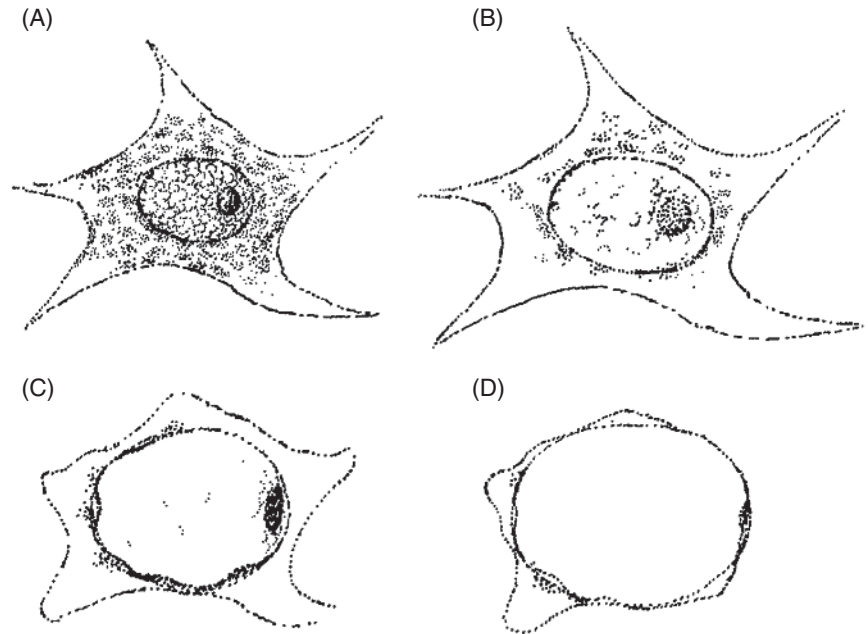
**Figure 1.6** ● Changes in the neuronal cell body during the axon reaction. (A) Normal cell; (B) swollen soma and nucleus with disruption of the chromatophil substance; (C, D) additional swelling of the cell body and nucleus with eccentricity of the nucleus and loss of concentration of the chromatophil substance.

## 1.6.2 Anterograde degeneration

Transection of a peripheral nerve, such as traumatic section of the ulnar nerve at the elbow, yields proximal and distal segments of the transected nerve. Changes taking place throughout the entire length of the distal segment (Fig. 1.7) are termed **anterograde degeneration** – first described in 1850 by Augustus Waller (therefore also termed Wallerian degeneration) in sectioned frog glossopharyngeal and hypoglossal nerves. Minutes after injury, swelling and retraction of neurilemmal cells occur at the nerve fiber nodal regions. By 24 h after injury, the myelin layer loosens. During the next 2–3 days, the myelin layer swells and fragments, globules form, and then the myelin layer disrupts by about day 4. Disappearance of myelin layers by phagocytosis takes about 6 months. A significant aspect of this process is that the endoneurial tubes and basement membranes of the distal segment collapse and fold but maintain their continuity. About 6 weeks after injury there is fragmentation and breakdown of the cytoplasm of the distal segment.

## 1.6.3 Retrograde degeneration

Changes that occur in the proximal segment (Fig. 1.7) of a transected peripheral nerve are termed **retrograde degeneration**. One early event at the cut end of the proximal stump is the accumulation of proteins. As the stump seals, the axon retracts and a small knob or swelling develops. Firing stops as the injured neuron recovers its resting potential. Normal firing does not occur for several days. Other changes are similar to those taking place in the distal segment except that the process of retrograde degeneration in the proximal segment extends back only to the first or second nerve fiber node and does not reach the neuronal cell body (unless the initial injury is near the soma).

## 1.6.4 Regeneration of peripheral nerves

Although the degenerative processes are similar in the CNS and PNS, the processes of regeneration are not comparable. In neither system is there regeneration of neuronal cell bodies or processes if the cell body is seriously injured. Severance of the neuronal process near the cell body will lead to death of the soma and no regeneration. For the neuronal process to regenerate, the neuronal cell body must survive the injury. Only about 25% of those patients with surgically approximated severed peripheral nerves will experience useful functional recovery.

Many events occur during the regeneration of peripheral nerves. The timing and sequence of those events is unclear. Regenerating neurons shift their metabolic emphasis by decreasing the production of transmitter-related enzymes while increasing the production of substances necessary for the growth of a new cytoskeleton such as actin (the protein subunit of actin filaments) and tubulin (the protein subunit of microtubules). There is an increase in axonal transport of proteins and enzymes related to the hexose monophosphate shunt. Axonal sprouting from the proximal segment of a transected nerve during regeneration is a continuation of the process of cytoskeletal maintenance needed to sustain a neuronal process and its branches.

A tangible sign of regeneration, the proliferation of neurilemmal cells from the distal segment, takes place by about day 4 and continues for 3 weeks. A 13-fold increase in these myelin-forming cells occurs in the remains of the neurolemma, basal lamina, and the persisting endoneurial connective tissue.
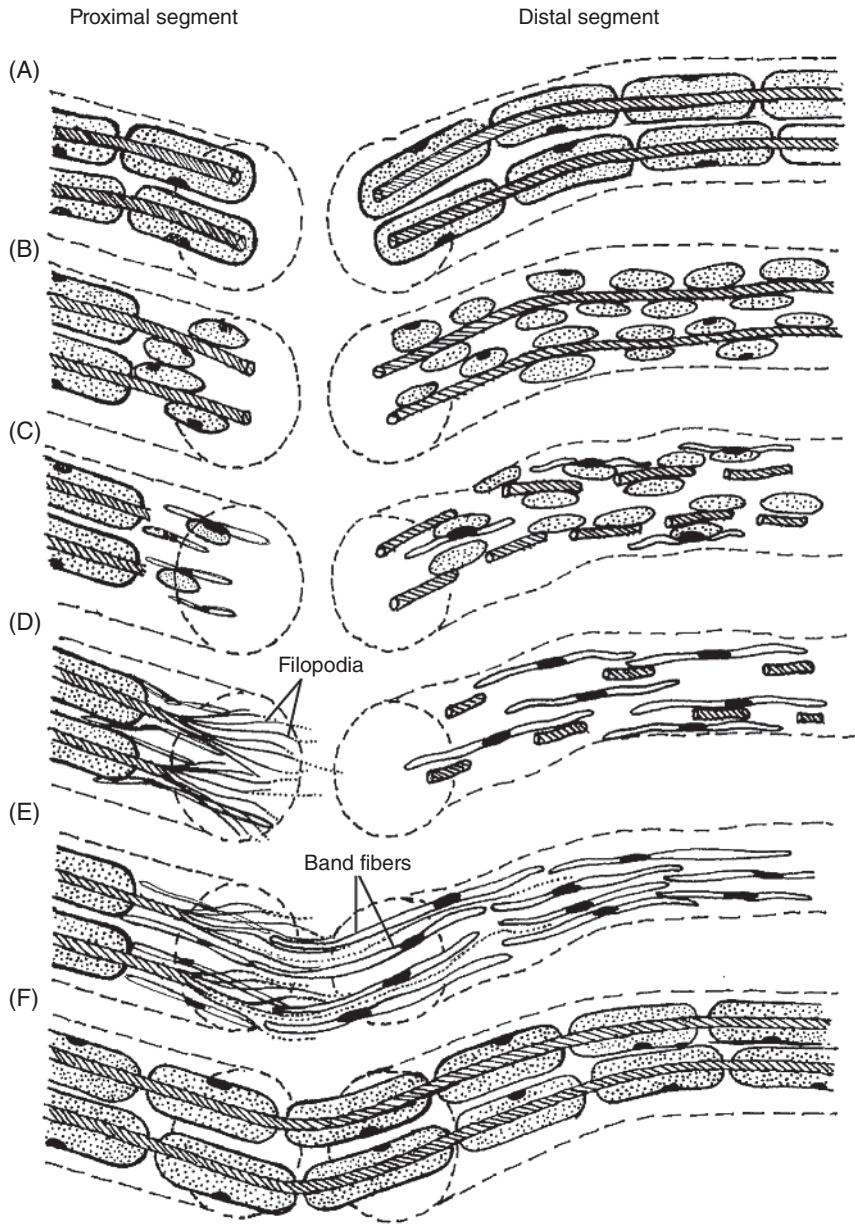
Proximal segment                    Distal segment

(A)

(B)

(C)

(D)

Filopodia

(E)

Band fibers

(F)

**Figure 1.7** ● Sequential steps (A–F) in the degeneration and regeneration in the proximal and distal segments of a transected neuronal process. In the proximal segment, degeneration extends back to the first or second nerve fiber node. Anterograde degeneration exists throughout the entire distal segment. Proliferation of neurolemmocytes from the distal segment forms a bridge across the transection, paving the way for an axonal sprout to find its way across the gap and eventually form a new process of normal diameter and length.

Mechanisms responsible for the induction of neurilemmal cell proliferation are unclear. Human neurilemmal cells maintained in cell culture will proliferate if they make contact with the exposed plasmalemma of demyelinated axons.

**Band fibers, growth cones, and filopodia**

Proliferating neurilemmal cells send out cytoplasmic processes called **band fibers** (Fig. 1.7E) that bridge the gap between the proximal and distal segments of a severed nerve. As the band fibers become arranged in longitudinal rows, they serve as guidelines for the **growth cone**s, bulbous and motile structures with a core of tubulin surrounded by actin that arise from the axonal sprouts of the proximal segment. Microtubules and neurofilaments, though rare in growth

cones, occur behind them and extend into the base of the growth cone, following the growth cones as they advance. Cytoskeletal proteins from the neuronal cell body such as actin and tubulin enter the growth cones by slow axonal transport 24 h after initial injury. The rate of construction of a new cytoskeleton behind the advancing growth cone limits the outgrowth of the regenerating process. Such construction depends on materials arriving by slow transport that are available at the time of axonal injury. The unstable surface of a parent growth cone yields two types of protrusions – many delicate, hair-like offspring called **filopodia** (or microspikes) and thin, flat lamellipodia (lamella), both of which contain densely packed actin filaments forming the motile region of the growth cone. Neuronal filopodia (Fig. 1.7D) are 10–30 μm long and 0.2 μm in diameter and evident at the transection

site extending from the proximal side and retracting as they try to find their way across the scaffold of neurilemmal cells. After they have made contact with their targets, extension of the filopodia ceases. There is successive addition of actin monomers at the apex of the growth cone with an ensuing rearward translocation of the assembled actin filaments. Both guidance and elongation of neuronal processes are essential features underlying successful regeneration. Such guidance is probably due to the presence of signaling molecules in the extracellular environment. In addition to their role in regeneration, growth cones play a role in the development of the nervous system, allowing neuronal processes to reach their appropriate targets.

At the transection site, growth cones progress at the rate of about 0.25 mm per day. If the distance between the proximal and distal stumps is not greater than 1.0–1.5 mm, the axonal sprouts from the proximal side eventually link up with the distal stump. As noted earlier, the endoneurial tubes and basement membranes of the distal segment collapse and fold but maintain their continuity. Growth cones invade the persisting endoneurial tubes and advance at a rate of about 1.0–1.5 mm per day. A general rule for the growth of peripheral nerves in humans is 1 in per month. After transection of the median nerve in the axilla, 9 months may be required before motor function returns in the muscles innervated by that nerve and 15 months before sensory function returns in the hand. After injury to a major nerve to the lower limb, a period of 9–18 months is required before motor function returns. When a motor nerve enters a sensory endoneurial tube or vice versa, the process of regeneration will cease. If one kind of sensory fiber (one that carries painful impulses) enters the endoneurial tube of another kind of sensory fiber (one that carries tactile impulses), then abnormal sensations called **paresthesias** (numbness, tingling, or prickling) may appear in the absence of specific stimulation.

After a regenerated process has crossed the transection site and entered the appropriate endoneurial tube, regeneration is still incomplete. The new process must be of normal diameter and length, remyelination must occur, and the original site of termination must be identified with eventual re-establishment of appropriate connections. If the regenerating nerve is a motor nerve, it must find the muscle that it originally innervated. A regenerating sensory nerve must innervate an appropriate peripheral receptor. Reduced sensitivity and poor tactile discrimination with peripheral nerve injuries are a result of misguidance of regenerating fibers and poor reinnervation. Regrowing fibers may end in deeper tissues and in the palm rather than in the fingertips – the site of discriminative tactile receptors. Poor motor coordination for fine movements observed in muscles of the human hand after peripheral nerve section and repair may be the result of misdirection of regenerating motor axons.

#### Collateral sprouting

**Collateral sprouts** may arise from the main axonal shaft of uninjured axons remaining in a denervated area. Such collateral sprouting, representing an attempt by uninjured axons to innervate an adjacent area that has lost its innervation, is often confused with axonal sprouts that originate from the proximal segment of injured or transected neuronal processes. Collateral sprouting from adjacent uninjured axons may lead to invasion of a denervated area and restoration of sensation in the absence of regeneration by injured axons, thus leading to recovery of sensation.

#### Neuromas

If the distance between the severed ends of a transected process is too great to re-establish continuity, the growing fibers from the proximal side continue to proliferate, forming a tangled mass of endings. The resulting swollen, overgrown mass of disorganized fibers and connective tissue is termed a **traumatic neuroma** or **nerve tumor**. A neuroma is usually firm, the size of a pea, and forms in about 3 weeks. When superficial, incorporated in a dense scar, and subject to compression and movement, a neuroma may be the source of considerable pain and paresthesias. Neuromas form in the brain stem or spinal cord or on peripheral nerves. In most peripheral nerve injuries, the nerve is incompletely severed and function is only partially lost. Blunt or contusive lacerations, crushing injuries, fractures near nerves, stretching or traction on nerves, repeated concussion of a nerve, and gunshot wounds may produce neuromas in continuity. Indeed, in about 60% of such cases, neuromas in continuity develop. A common example is metatarsalgia of Morton – an interdigital neuroma in continuity along the plantar digital nerves as they cross the transverse metatarsal ligament. Wearing ill-fitting high-heeled shoes stretches these nerves, bringing them into contact with the ligament. Other examples are intraoral neuromas that form on the branches of the inferior alveolar nerve (inferior dental branches and the mental nerve) or on branches of the maxillary nerve (superior dental plexus), amputation neuromas in those who have had limbs amputated, and bowler's thumb, which results from repetitive trauma to a digital nerve.

### 1.6.5 Regeneration and neurotrophic factors

Regeneration of a peripheral nerve requires an appropriate microenvironment (a stable neuropil, sufficient capillaries, and neurilemmal cells), and the presence of certain **neurotrophic factors** such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), or neurotrophin-3. Absorption of these factors by the axonal tip and their retrograde transport will influence the metabolic state of the neuronal cell body and support neuronal survival and neurite growth. Other substances attract the tip of the growth cone or axonal sprout, thus determining the direction of growth.

### 1.6.6 Regeneration in the central nervous system

Regeneration of axons occurs in certain nonmyelinated parts of the mammalian CNS such as the neurohypophysis

(posterior lobe of the pituitary gland) in the dog, retinal ganglionic cell axons and olfactory nerves in mice, and the corticospinal tract of neonatal hamsters. However, the process of CNS regeneration leading to restoration of function is invariably unsuccessful in humans. Several theories have attempted to explain this situation. The barrier hypothesis suggests that mechanical obstruction and compression due to formation of a dense glial scar at the injury site impede the process of axonal growth in the human CNS. Such dense scar formation or astrocytic gliosis is the result of the elaboration of astrocytes in response to injury. This glial scar forms an insurmountable barrier to effective regeneration in the CNS. Remyelination, accompanied by astrocytic gliosis, takes place in the CNS if axonal continuity is preserved. Myelin, in the process of degeneration, releases active peptides such as axonal growth inhibitory factors (AGIFs) and fibroblast growth factors (FGFs). AGIFs may lead to abortive growth of most axons whereas the FGFs are apparently responsible for the deposition of a collagenous scar. The observation that the breakdown of myelin in the PNS is unaccompanied by elaboration of AGIFs seems to strengthen this hypothesis. The presence of these growth-promoting and growth-inhibiting molecules along with the formation of glial scars offers a great challenge to those seeking therapeutic methods to aid persons with CNS injury.

Efforts are under way to determine if neurons of the CNS are missing the capability of activating necessary mechanisms to increase the production of ribosomal RNA. Other attempts at restoring function in the injured spinal cord involve removing the injured cord region and then replacing it with tissue from the PNS.

Inherent neuronal abilities and the properties of the environment (neuropil, local capillaries, and the presence of repulsive substrates or inhibitors of neurite outgrowth) are responsible for the limited capacity for CNS regeneration. Neuroglial cells, by virtue of their ability to produce trophic and regulatory substances, plus their ability to proliferate, forming a physical barrier to regeneration, also play an essential role in regeneration. A minimum balance exists between the capacity of axons to regenerate and the ability of the environment to support regeneration. CNS regeneration in humans is an enigma awaiting innovative thinking and extensive research. Success in this endeavor will bring joy to millions of victims of CNS injury and their families.

## 1.7  NEURAL TRANSPLANTATION

In light of the absence of CNS regeneration leading to restoration of function in humans, there is a great deal of interest in the possibility of neural transplantation as a means of improving neurological impairment due to injury, aging, or disease. Sources of donor material for neural transplants are neural precursor cells from human embryonic stem cells, adult cells, or umbilical cords, ganglia from the PNS (spinal and autonomic ganglia and adrenal medullary tissue), and cultured neurons. Other sources are genetically modified cell lines capable of secreting neurotrophic factors or neurotransmitters.

Focal brain injuries, diseases of well-circumscribed chemically defined neuronal populations, identifiable high-density terminal fields, areas without highly specific point-to-point connections, or regions where simple one-way connections from the transplant would be functionally effective are likely to profit from neural transplantation. Neurological diseases such as Alzheimer and Parkinson disease involve a complex set of signs and symptoms with damage to more than one region and more than one neurotransmitter involved, such that individuals suffering from these diseases might not benefit from a single neural transplant but may require dissimilar transplants in different locations. Because these diseases are also progressive and degenerative, it is possible that the transplant itself will be subject to the same progressive and degenerative process. An equally disconcerting prospect is that with additional degeneration of the brain, the signs and symptoms ameliorated by the original transplant may disappear, replaced by a new set of signs and symptoms that might require a second transplant for their alleviation. Finally, because of the age of most patients with these diseases, it is likely that they will have other physical conditions that might necessitate selecting for treatment only those who do not have other underlying conditions or who have a very early stage of the disease.

Another approach to this problem that would circumvent the risks and ethical issues associated with neural transplantation would be to administer neurotrophic factors to support neuronal survival or promote the growth of functional processes. An exciting development in this regard is the isolation of a protein called **glial cell line-derived neurotrophic factor** (GDNF), which promotes the survival of dopamine-producing neurons in experimental animals. In Parkinson disease, there is restricted damage to a well-defined group of dopamine-producing neurons in the midbrain. Such a neurotrophic agent might prevent or reverse the signs and symptoms of this chronic, degenerative disease. An additional option would be to investigate the initial changes in the brain that lead to a particular neurological impairment and seek a means of preventing such changes. Much work remains before neural transplantation becomes a useful and practical form of therapy leading to complete functional recovery from neurological injuries, diseases, or age-related changes.

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