

OVERVIEW

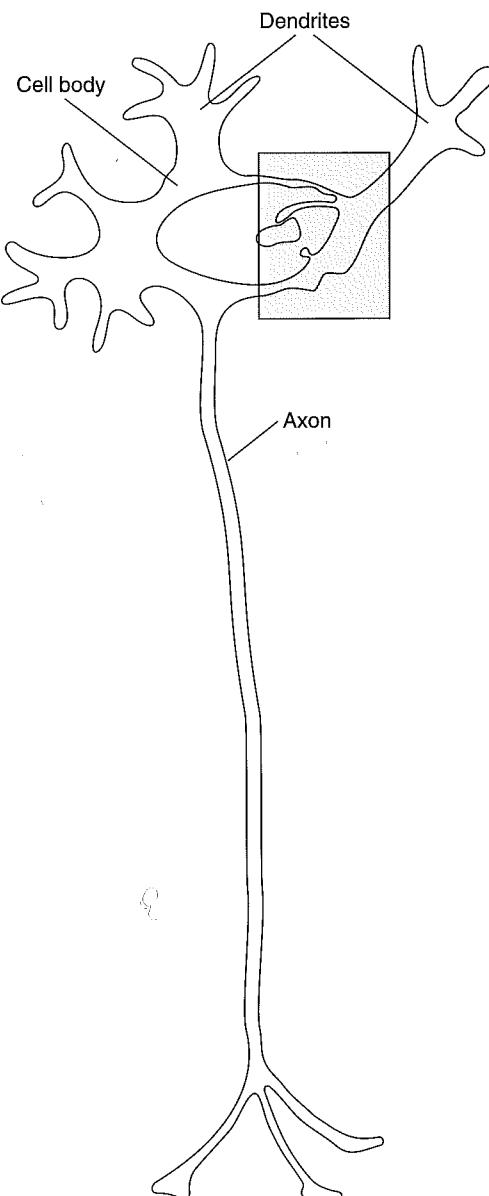
Most neurons consist of (1) a **cell body** with a large euchromatic nucleus and prominent nucleolus, (2) **dendrites**, thick, relatively short processes that carry signals to the cell body, and (3) the **axon**, a single long, thin process that carries signals away from the cell body. The size and shape of neurons vary considerably; however, within this diverse group most nerve cells retain this basic morphology.

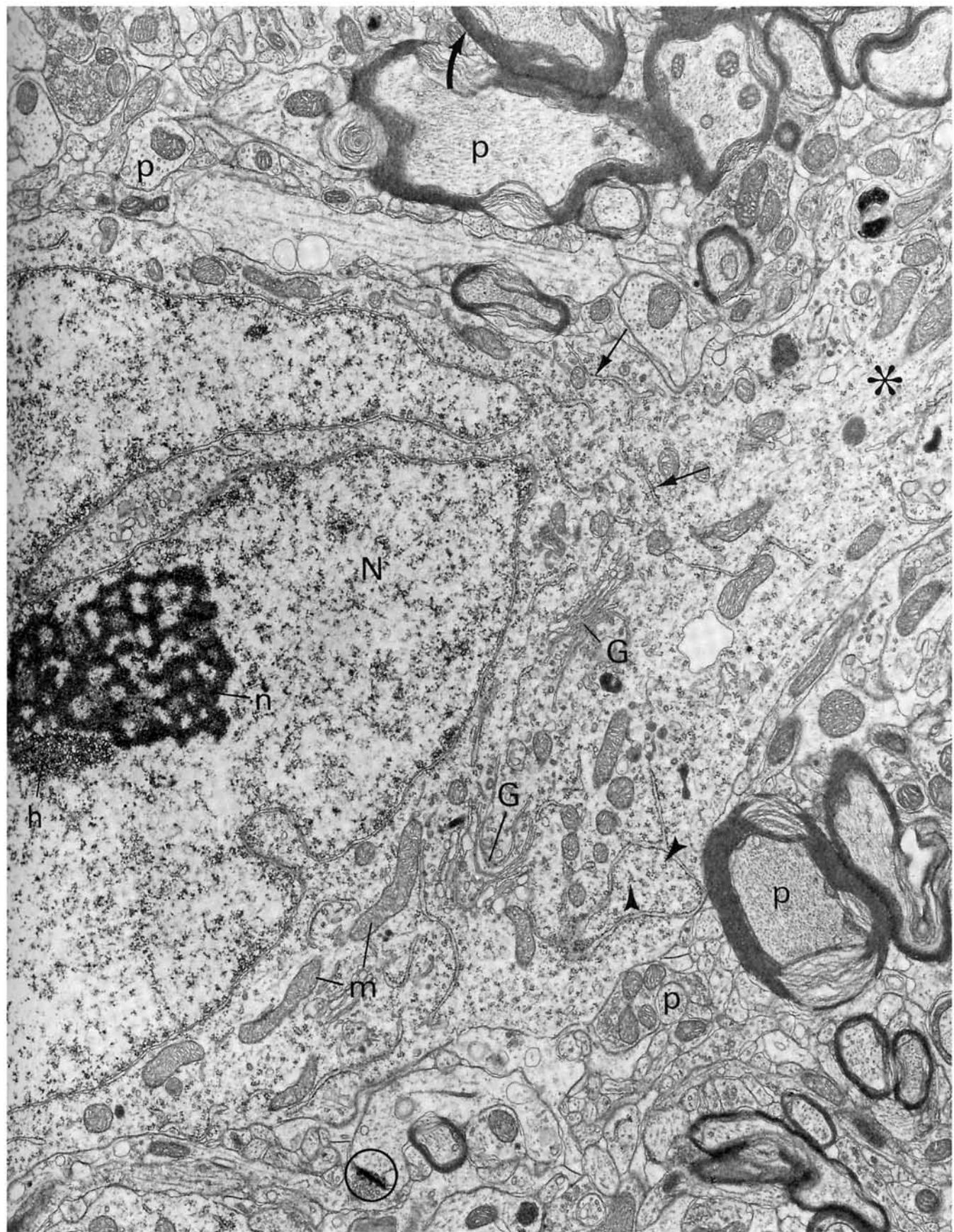
The cell body of a neuron from the central nervous system (CNS) occupies the center of the micrograph. A single large nucleolus (n) with its associated heterochromatin (h) lies in the indented nucleus (N). The cytoplasm surrounding the nucleus contains mitochondria (m), free (arrowheads) and attached (arrows) ribosomes, and several Golgi (G). In this micrograph only one process (*) can be observed extending from the cell body.

Most of the area outside the cell body consists of neuron processes (p, micrograph, in cross and oblique section) packed directly adjacent to one another. These processes represent over 90% of nerve cell volume; in humans one axon can have a volume 10,000 times that of a liver cell. Components within the processes are maintained in large part by synthetic activity within the cell body.

Neuron processes associate with one another at **synapses** (circle, micrograph) to form a cellular network that extends into every region of the body. Information is carried long distances along these cellular pathways as self-propagated electrical signals, **action potentials**. These signals are involved in coordinating most activities in the body and are essential for events ranging from the stimulation of acid secretion in the stomach to complex thought processes in the brain.

Glial cells, nonneuronal cells that perform critical functions unique to nervous tissue, outnumber neurons 10 to 1 and carry out many functions essential to neuron survival. Glial cells in the CNS include astrocytes, oligodendrocytes, microglia, and ependymal cells; in the peripheral nervous system (PNS) they include Schwann cells and satellite cells. Some axons are surrounded by a myelin sheath (curved arrow, micrograph), a dense lipid encasement synthesized by oligodendrocytes in the CNS, and by Schwann cells in the PNS.



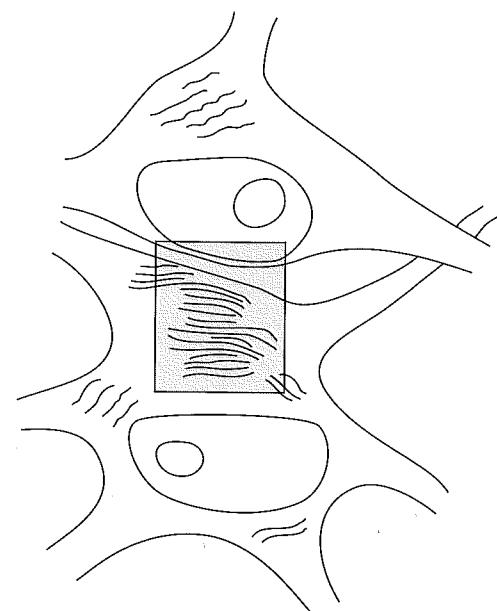


NEURON: Nissl Bodies

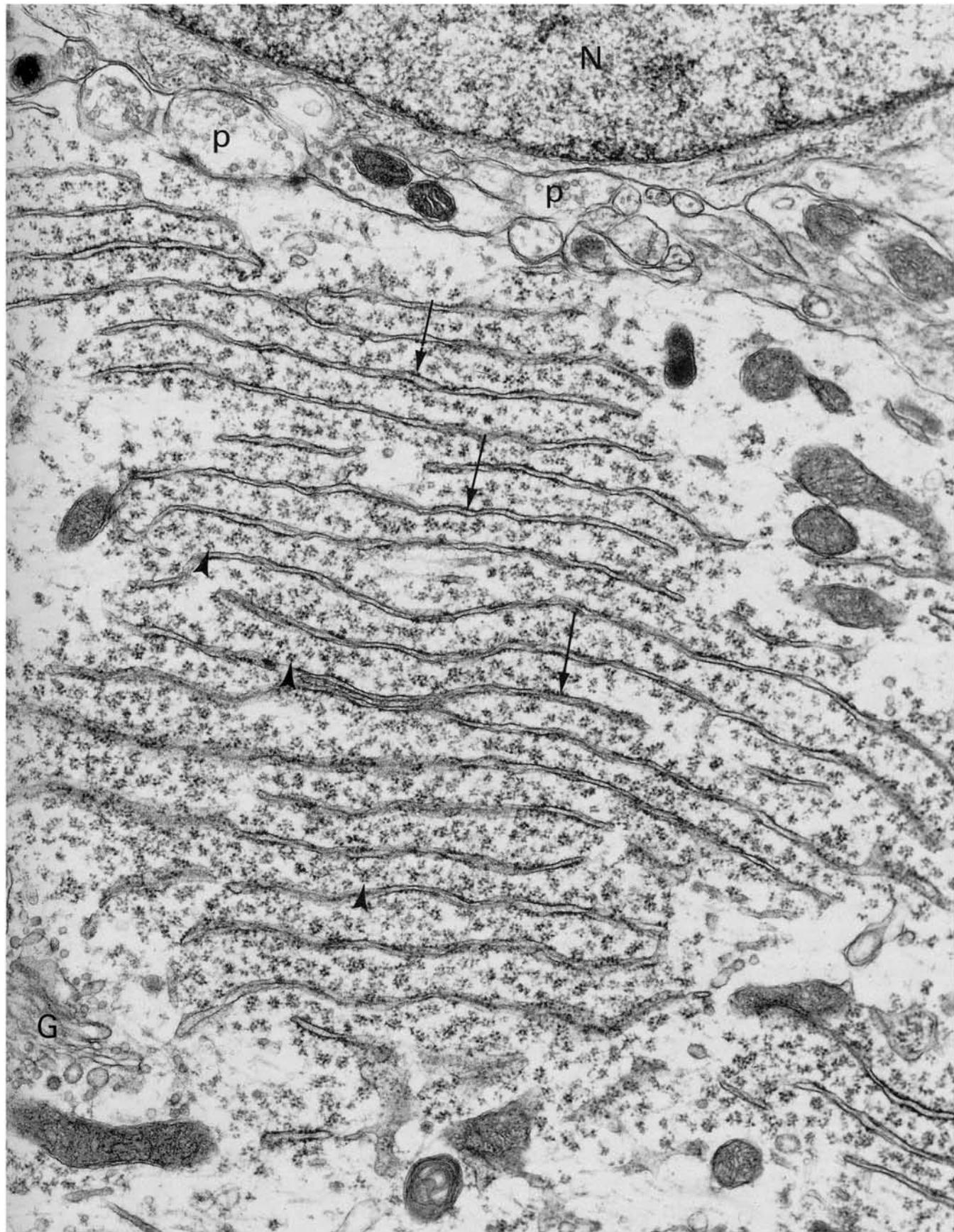
The **ribosomes** in many nerve cell bodies are arranged in a distinctive pattern. Flattened cisternae of rough ER (arrows, micrograph) alternate with groups of free polysomes (arrowheads, micrograph) to form **Nissl bodies**. The entire ribosome assembly in the micrograph represents a single Nissl body, seen in light microscope preparations as a blue dot when stained with a basic dye such as toluidine blue. Nerve cells express more of their DNA than any other cell type. The euchromatic nucleus (N, micrograph) and large number of polyribosomes within nerve cell bodies reflect active transcription and translation. In the micrograph, the Nissl body and the euchromatic nucleus are actually within two different neurons; nerve processes (p) can be seen between the two cell bodies.

Proteins synthesized on the Nissl bodies are critical to a variety of essential neuron activities. Those produced on free polyribosomes include (1) enzymes used in the synthesis of neurotransmitters and (2) cytoskeletal elements needed for support and transport within nerve processes. Proteins synthesized on polyribosomes attached to ER include (1) membrane proteins that comprise ion channels and receptors and (2) synaptic vesicles and neuropeptide neurotransmitters. These components pass from the rough ER to the Golgi (G, micrograph), where they are sorted and directed to specific locations.

Ribosomes are found in the cell body and at the base of dendrites, but are not present in axons. Axonal proteins are synthesized on both free and attached ribosomes of the Nissl bodies and transported a considerable distance along the axon to their site of functioning. Certain neurotransmitters and synaptic vesicles are carried all the way to the end of the axon, in some cases a distance of 1 meter. The movement of these secretory vesicles to the site of exocytosis is an interesting example of cellular polarity.



Q



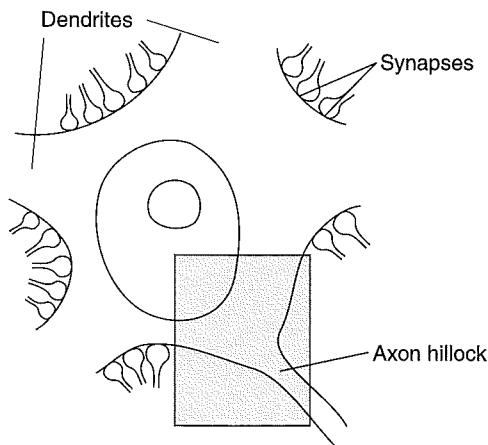
NEURON: Axon Hillock

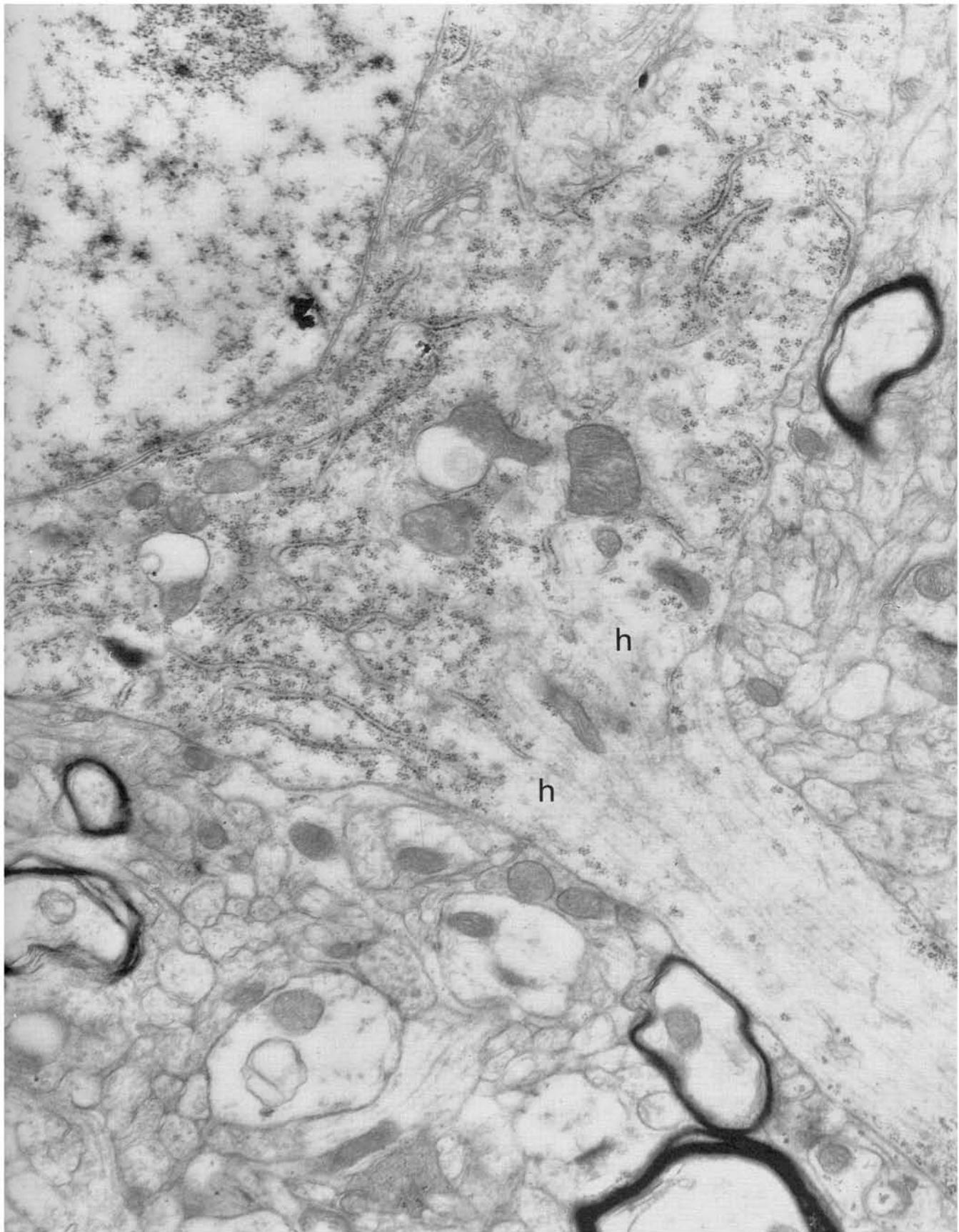
A single neuron receives input from up to a thousand other neurons and has synapses covering the cell body, dendritic processes, and axon hillock. The **axon hillock** (h, micrograph) is the initial segment of an axon, distinguished from the cell body by a well-organized cytoskeleton and the relative absence of ribosomes. This region, also called the **trigger zone**, is where the action potential originates.

The membrane of the neuron normally maintains a resting potential of -70 mV (inside negative); the resting potential is -30 mV in nonexcitable cells. During the transmission of nerve impulses across synapses, a neurotransmitter (ligand) released from one neuron binds to adjacent neuron receptors and causes ion channels to open or close. The alternating movement of ions (e.g., Na^+ , Cl^- , K^+) across these membrane channels results in either **depolarization** (stimulation) or **hyperpolarization** (inhibition).

The depolarizations and hyperpolarizations resulting from the opening or closing of ligand-gated channels travel to the trigger zone, where they are spatially and temporally summed. When the sum reaches a threshold (-55 mV), the voltage-gated Na^+ channels that are concentrated in the trigger zone open and the membrane depolarizes rapidly, initiating an **action potential**. The action potential is all or none and thus similar for all neurons; the unique information within each neuron is encoded in the frequency and duration.

The action potential is propagated undiminished down the axon by the continual movement of (1) Na^+ into the neuron through voltage-gated channels, depolarizing the membrane, and (2) K^+ leaving the neuron through voltage-gated channels, restoring the membrane potential to resting levels.





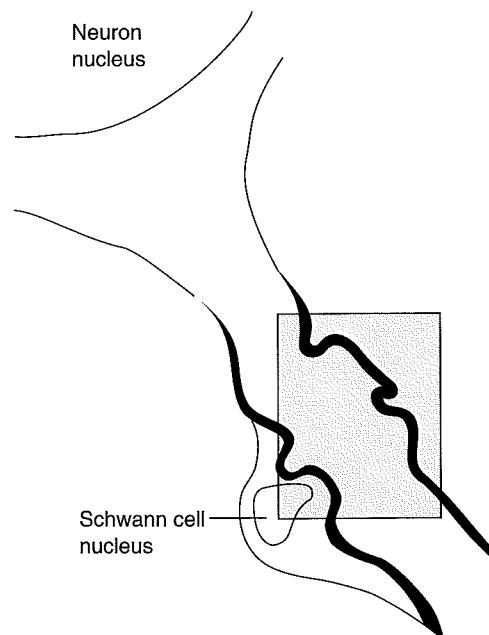
NEURON: Axonal Cytoskeleton

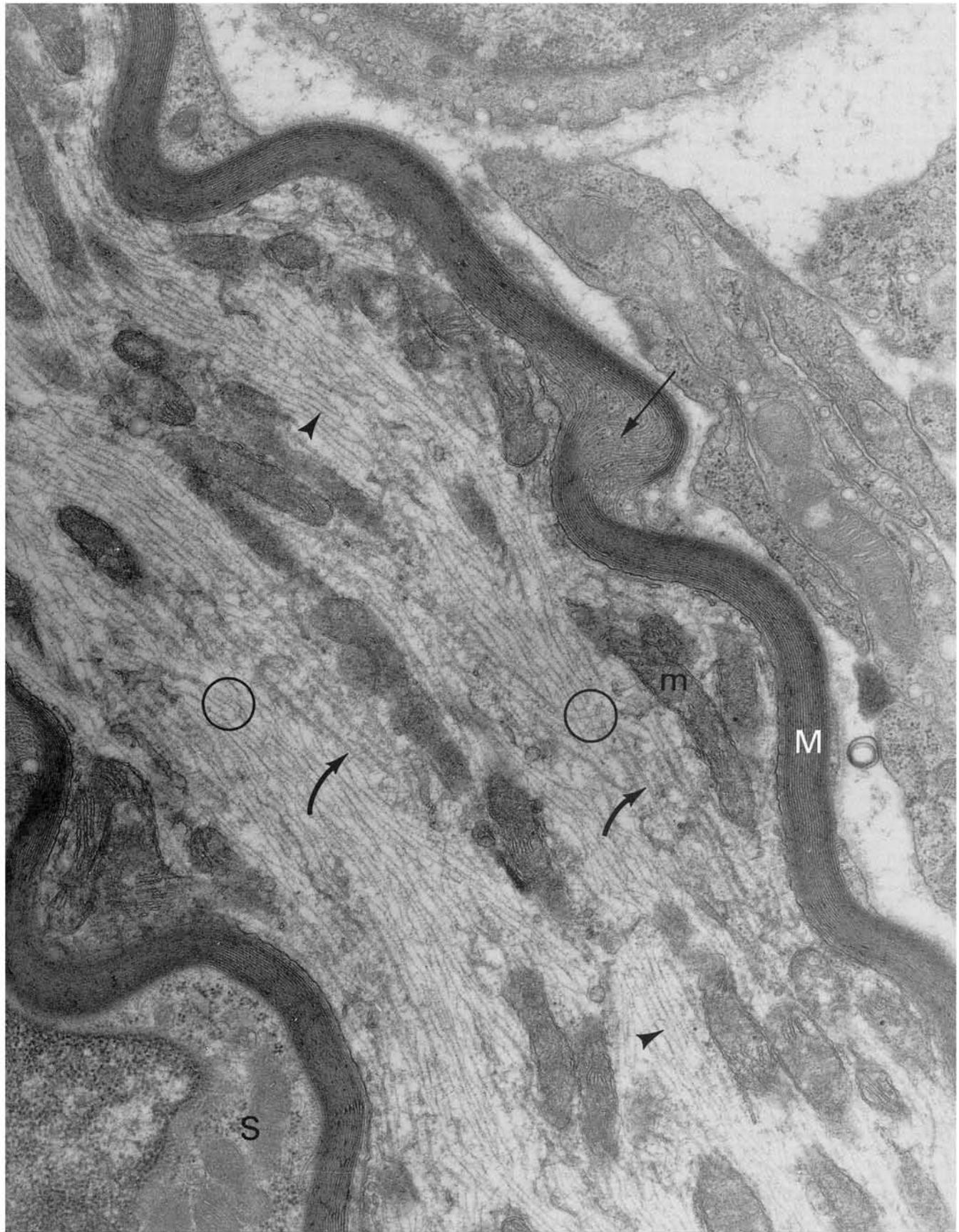
All axons have an abundance of **cytoskeletal elements** running parallel to their long axis. These filamentous proteins are the most prevalent proteins in axons. **Microtubules** (curved arrows) and **neurofilaments** (arrowheads) can be distinguished in the axoplasm of the myelinated axon in the micrograph. These structures, along with the third cytoskeletal element, **microfilaments** (not seen in the micrograph), are arranged within axons in a lattice that provides compartments and organization for the other cytoplasmic structures. The lattice is maintained by extensive crossbridges (circles, micrograph) both within and between cytoskeletal classes. This protein scaffolding is maintained by precursors that move down the axon via slow transport (0.1 to 3 mm per day). Slow transport is also used to carry soluble enzymes that are needed a considerable distance from the nerve cell body where they are synthesized.

Membranous organelles are carried by a fast transport system that is capable of rates of 100–400 mm per day. Organelles attach to microtubules and, in an energy-dependent fashion, are moved in both anterograde and retrograde directions (Cell, page 40). Vesicles carrying molecules specific to synaptic functioning, such as norepinephrine, move to the axon terminal via fast axon transport. Mitochondria (m, micrograph) supply the energy for this type of movement and are themselves moved on microtubules. Retrograde microtubule transport carries a varied assortment of organelles and molecules back to the cell body. Within the cell body, some (e.g., synaptic vesicles) are degraded in lysosomes, while others can have life-promoting (e.g., nerve growth factor) or life-threatening (e.g., viruses and toxins) effects.

The axon in this micrograph is myelinated. The myelin (M), synthesized by Schwann cells (S), is interrupted at regular intervals by **Schmidt–Lanterman clefts** (straight arrow). In these areas some Schwann cell cytoplasm remains between the tightly packed cell membranes that comprise the myelin. It has been suggested that the Schmidt–Lanterman clefts provide a route for the exchange of nutrients and metabolites between the axoplasm, Schwann cell cytoplasm, and interstitial fluid.

Axons induce the Schwann cell synthesis of important myelin proteins and are thus essential for myelination. In turn, myelination is essential to the normal conduction in these axons. If a myelinated axon is demyelinated either experimentally or during disease (e.g., multiple sclerosis), impulse conduction is slower and sporadic.





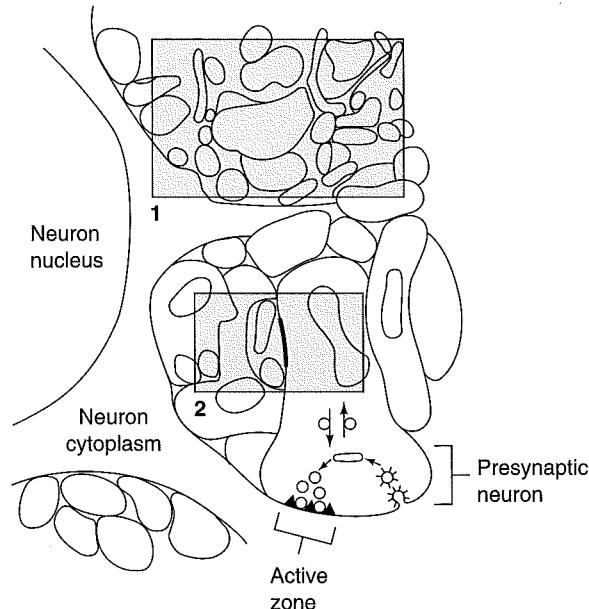
NEURON: Synapse, Neurotransmitters

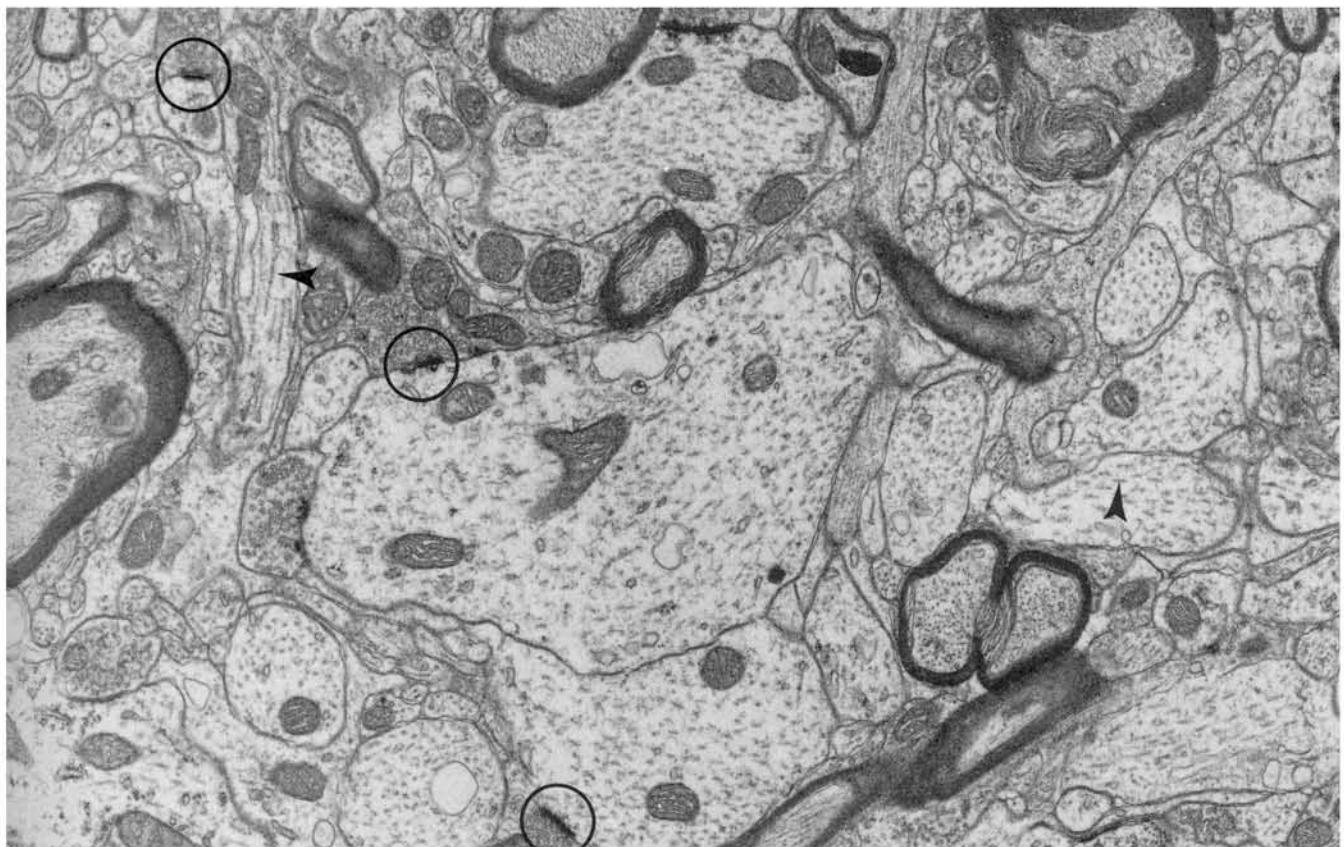
Information is transmitted from neurons to other cells in specialized regions known as **synapses**. Synapses occur either between neurons and the effector cells they innervate, such as muscles and glands, or between two neurons, as in the central nervous system (shown here) and peripheral autonomic ganglia.

In micrograph 1, nerve-to-nerve synaptic regions are circled. At this relatively low magnification, the synaptic region is recognized by **electron densities** associated with the synaptic membranes and by the accumulation of small **synaptic vesicles** in the presynaptic terminal. When an action potential reaches the presynaptic nerve terminal, calcium channels in the cell membrane open and calcium rushes into the terminal. Synaptic vesicles then fuse with the cell membrane, releasing **neurotransmitter**. Neurotransmitter crosses the 20- to 30-nm synaptic cleft and binds to membrane receptors within the postsynaptic membrane, opening ion channels.

Synaptic vesicle exocytosis occurs between conical projections of electron-dense material (arrows, micrograph 2) in an “**active zone**” associated with the presynaptic membrane. Following exocytosis, excess membrane is recovered outside the active zone by pinocytosis in coated pits. Much of this membrane is locally recycled within the nerve terminal. However, some **vesicle turnover** occurs over considerable distance and involves retrograde transport of vesicles to the cell body, where they are digested by lysosomes. New vesicles are formed in the rough ER, packaged in the Golgi, and transported to the nerve terminal. Microtubules (arrowheads, micrographs 1 and 2), the predominant component of axons, carry vesicles to and from the cell body. The endocytosis and recycling of cell membrane during neurotransmitter release requires energy that is supplied by the mitochondria (m, micrograph 2), which are a typical component of pre-synaptic terminals.

Synapses in the brain can undergo long-lasting changes that increase their efficiency of operation (i.e., long-term potentiation). This process, a form of memory, involves, in part, information transfer from the postsynaptic neuron to the presynaptic neuron (a direction opposite to the classic synapse flow) and the release of increased amounts of neurotransmitter by the presynaptic neuron. Nitric oxide appears to be an important retrograde synaptic messenger needed for long-term potentiation.

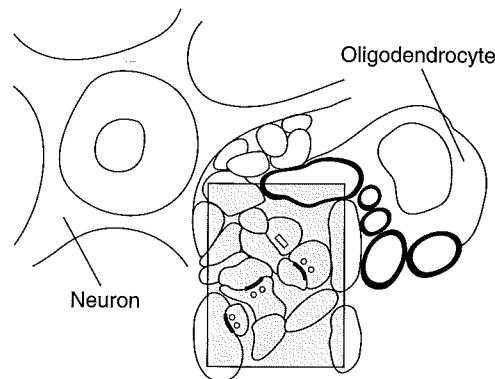




NEURON: Synapse, Classification

Chemical synapses between neurons are often classified into two groups based on observed differences in their ultrastructure. **Type I** has the appearance of synapse A (micrograph 1), with round synaptic vesicles and a prominent postsynaptic density. **Type II** has the appearance of synapse B (micrograph 1), with some flattened synaptic vesicles and symmetrical presynaptic and postsynaptic densities. Flattened synaptic vesicles have been associated with inhibitory action.

There are many types of **neurotransmitters**. Even though some neurotransmitters are associated with a specific neuronal response (e.g., GABA with inhibition), the action of other neurotransmitters, such as acetylcholine, can be inhibitory or stimulatory, depending upon postsynaptic neurotransmitter receptors. Neurotransmitters may have additional roles such as hormonal coordination of gastrointestinal activity (e.g., cholecystokinin) and building blocks of proteins (e.g., glycine).



Small-Molecule Neurotransmitters

- Acetylcholine
- Modified amino acids (catecholamines, dopamine, epinephrine, norepinephrine)
- Unaltered amino acids (γ -aminobutyric acid, or GABA, aspartic acid, glutamic acid, glycine)

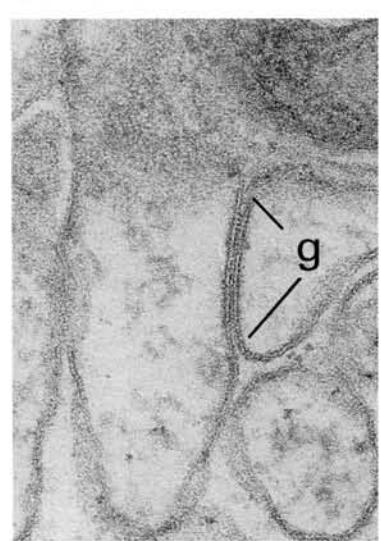
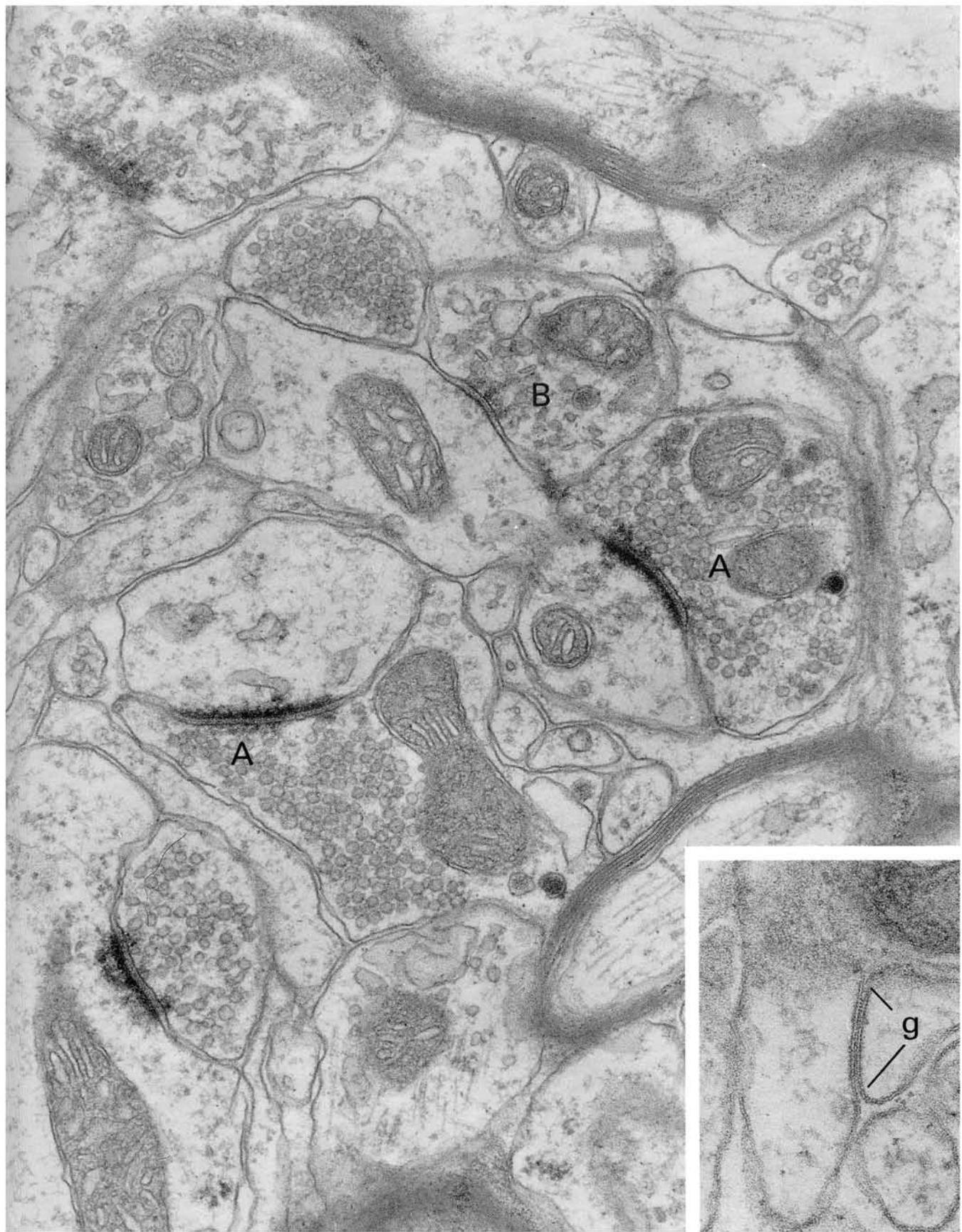
Large-Molecule Neurotransmitters

- Neuropeptides (cholecystokinin, β -endorphin, gastrin, secretin)

Synaptic efficiency depends upon the quick removal of neurotransmitter following its action on the postsynaptic cell. At the neuromuscular junction, acetylcholinesterase within the basal lamina carries out this function, however, at most nerve-to-nerve synapses excess neurotransmitter is taken up and degraded by the presynaptic neuron. Certain drugs (e.g., some antidepressants) act by inhibiting this reuptake and thus increasing the concentration of neurotransmitter remaining within the synaptic cleft.

Synapses are not fixed structures; they are continuously moving and reestablishing contacts. Changes in synaptic size, shape, and location occur in response to such diverse events as learning and exposure to anesthetics. Electron densities associated with postsynaptic cell membranes are composed of globular proteins resting in a filamentous cytoskeleton. One of the major globular proteins, a calcium-activated neutral protease, may regulate the turnover of the postsynaptic cytoskeleton and thus contribute to synaptic plasticity.

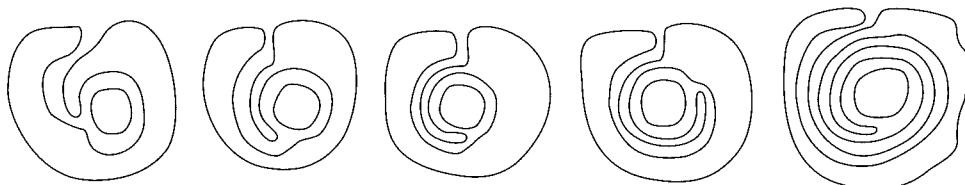
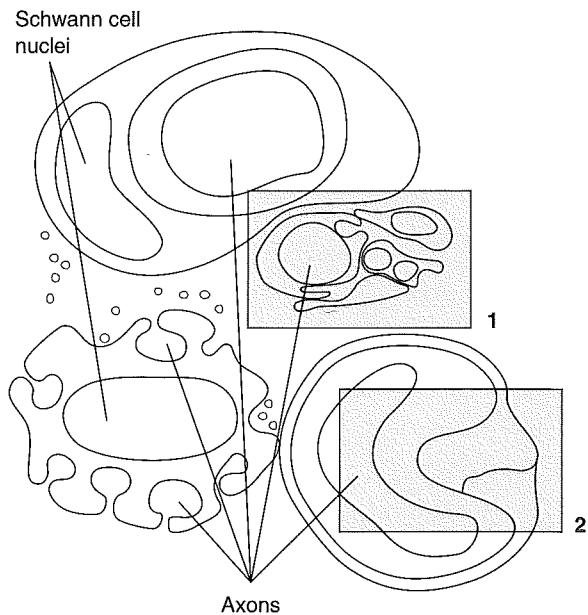
In addition to the coupling of neurons by neurotransmitters, some neurons are coupled electrically via gap junctions (g, inset). In this type of “synapse,” nerve processes, separated by an extremely small intercellular space (2-nm), are associated via connexons (see Epithelium, page 54) that carry current from one neuron to another. Gap junctions have been localized in regions of chemical synapse. Certain neurotransmitters (e.g., GABA) may control the opening and closing of gap junctions, and thus control the pattern of nerve firing.



GLIAL CELLS: Unmyelinated and Myelinated Axons

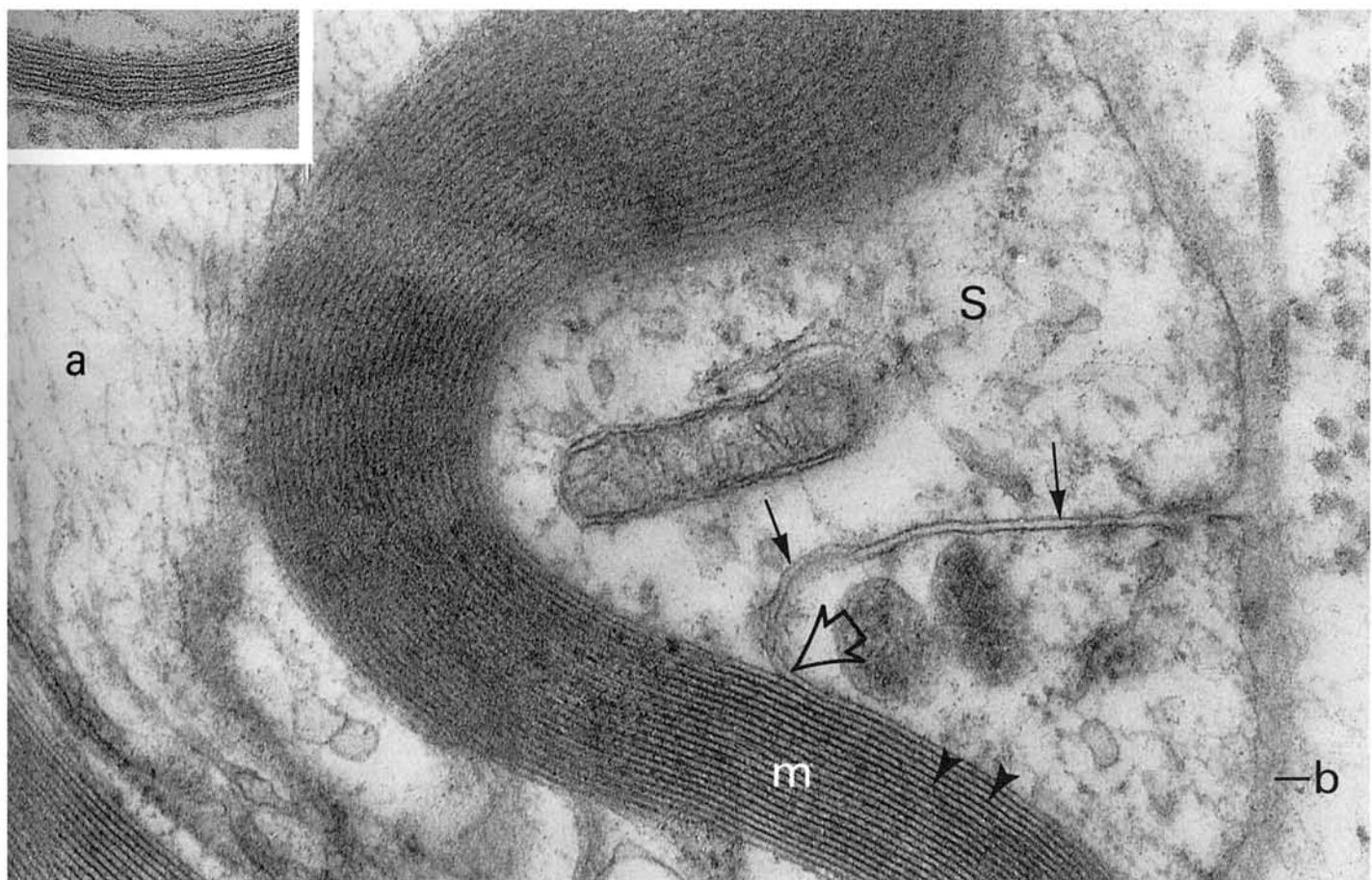
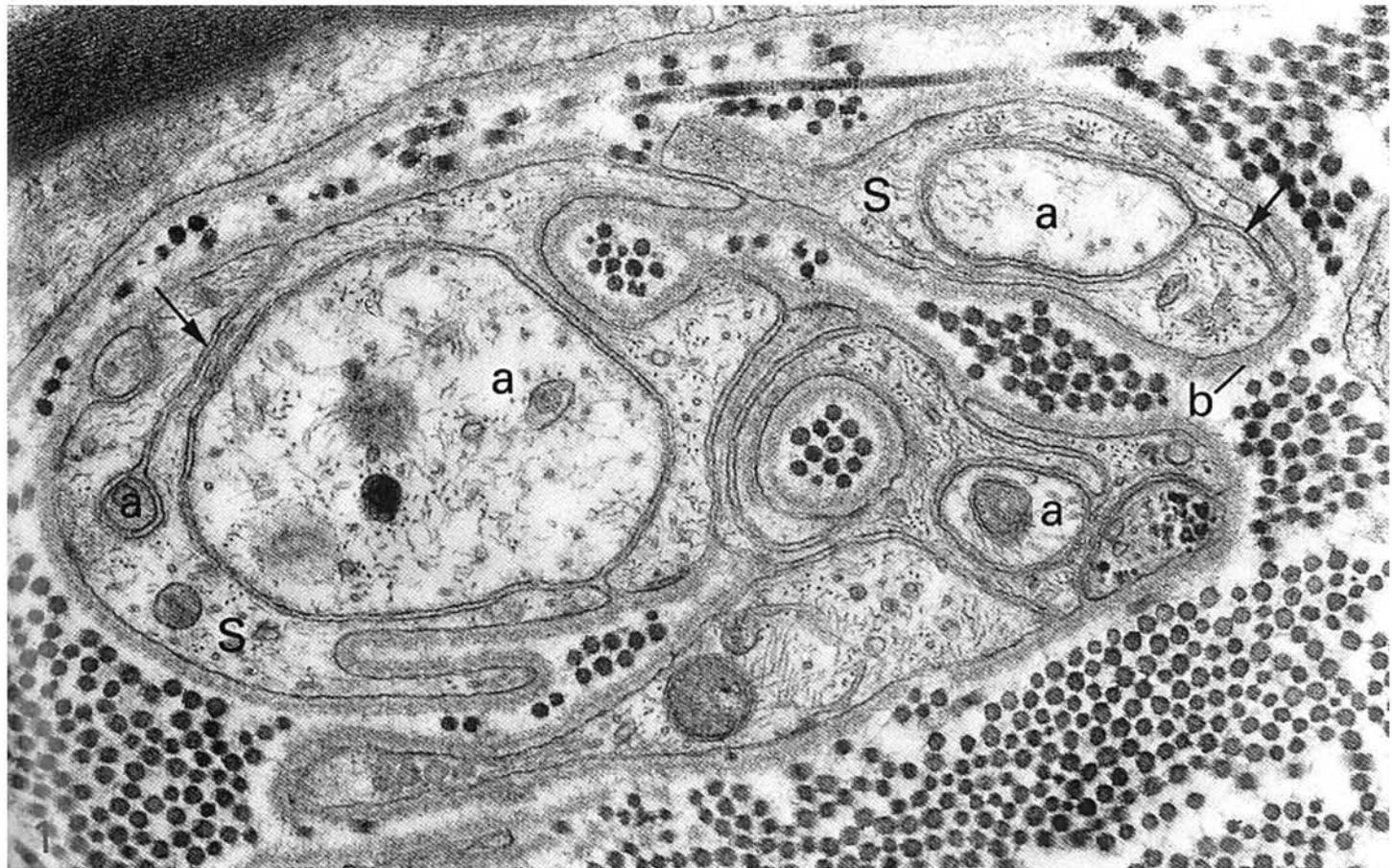
Schwann cells surround all axons in the peripheral nervous system (PNS). The association between Schwann cells and axons is intimate but it is different in complexity in **unmyelinated** and **myelinated** axons. Unmyelinated axons (a, micrograph 1) simply indent into the cytoplasm of a Schwann cell (S, micrograph 1). In this type of association, each Schwann cell can encase many axons. The connecting channel between each axon and the external surface of the surrounding Schwann cell is called the **mesaxon** (arrows, micrograph 1).

In the PNS, myelinated axons (a, micrograph 2) are each wrapped with many layers of Schwann cell membrane, which form a **myelin sheath** (m, micrograph 2). Myelin is formed by the growth, elongation, and spiral wrapping of the mesaxon (solid arrows, micrograph 2) and associated Schwann cell cytoplasm (S, micrograph 2) around the axon. A basal lamina (b, micrographs 1 and 2) defines the outer boundary of each Schwann cell.



In the process of myelination, Schwann cell cytoplasm is squeezed out so that the inner leaflets of the cell membrane pack together to form the **major dense line** (arrowheads, micrograph 2). As each successive wrapping overlaps the previous one, a periodicity of 12 nm is established between the major dense lines. This light-staining 12-nm area includes the outer membrane leaflets as well as the intercellular space between the outer membrane leaflets. The diameter of this intercellular space is determined by the size of the membrane components extending from the cell surface. At the point where the myelin wrapping begins (open arrow, micrograph 2), new myelin proteins with smaller extracellular domains are inserted into the outer surface of the membrane, which results in a reduced intercellular space. In the higher magnification inset, an interperiod line that represents these extracellular domains can be resolved between the major dense lines.

The composition of myelin is different from the composition of most cell membranes in several ways: myelin (1) has a high proportion of lipid to protein, (2) is deficient in several standard membrane proteins such as ion channels, and (3) contains unique proteins, such as myelin basic protein, that seem to be involved in the tight compaction of adjacent membranes.



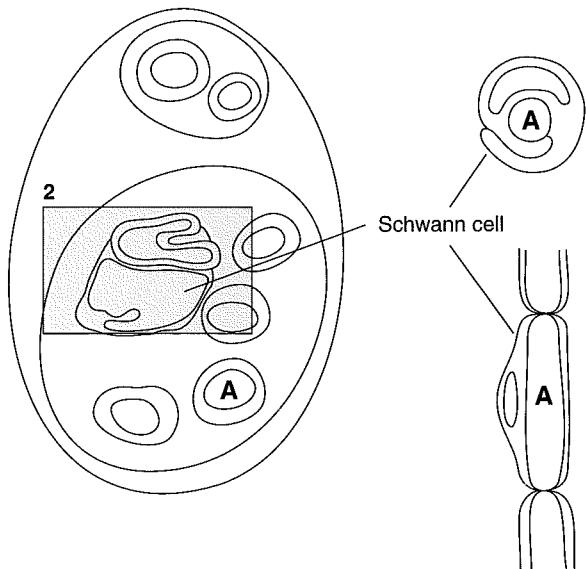
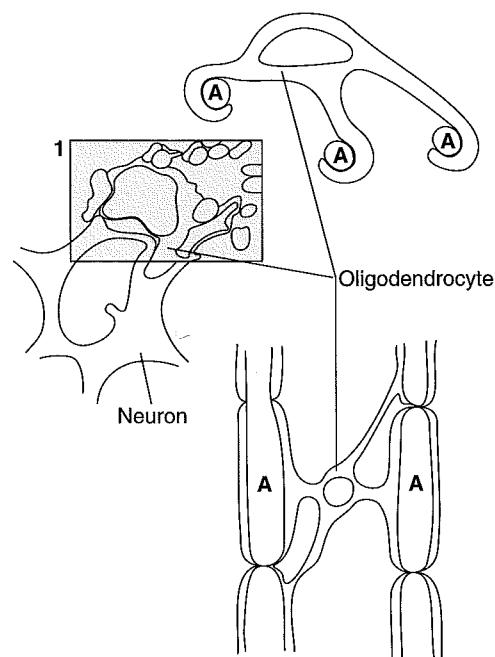
GLIAL CELLS: Oligodendrocytes and Schwann Cells

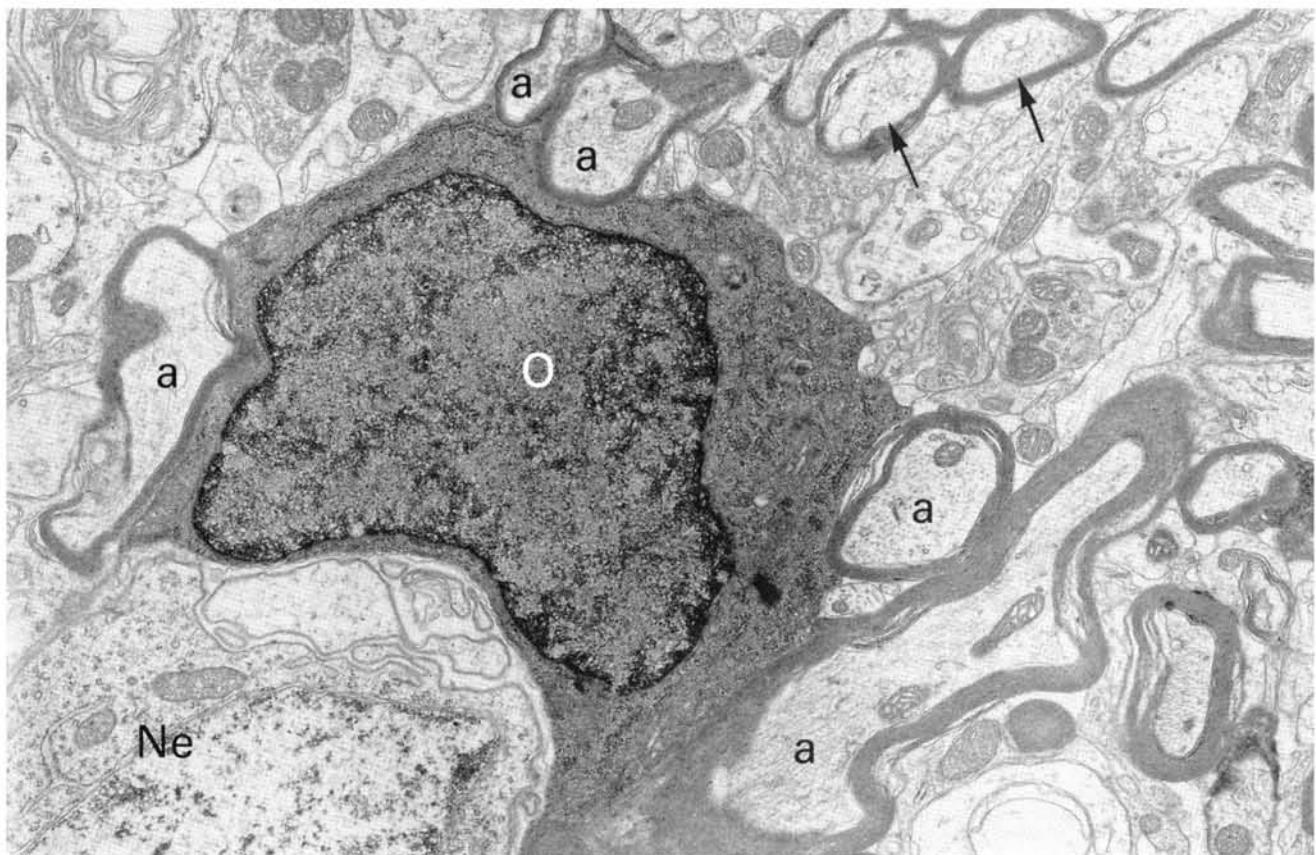
In the central nervous system, myelination is carried out by **oligodendrocytes** (O, micrograph 1). A single oligodendrocyte extends several processes that each myelinate a section (internode) of a different axon or of the same axon. The oligodendrocyte in micrograph 1 is seen in association with five axons (a) that it is myelinating. Some of the myelinated axons that appear to be separate (arrows) from the oligodendrocyte cell body may be connected by thin cytoplasmic processes that are not seen in this section.

One oligodendrocyte can myelinate up to 50 internodes, which involves the formation of myelin membrane 600 times the amount of membrane covering its cell body. The synthetic demands on this cell are reflected in its ultrastructure. The polysomes packed in the cytoplasm direct the synthesis of (1) enzymes needed to form the vast amounts of cell membrane that comprise myelin and (2) structural proteins within myelin itself. A comparison between the ultrastructure of the neuron cell body (Ne) and the oligodendrocyte (O) in micrograph 1 highlights the characteristic electron density of this glial cell.

The amount of protein synthesized by an oligodendrocyte that is myelinating several internodes is considerably greater than that of a **Schwann cell**, which myelinates only one internode of one axon in the PNS. In micrograph 2 the section passes through the nucleus (N), cytoplasm (C), and myelin (m) of a Schwann cell encased around a single axon (a).

In contrast to the CNS, myelinated axons in the PNS are typically separated from one another by collagen (c, micrograph 2). Like muscle, peripheral nerves are packaged by a hierarchy of connective tissue sheaths. Individual neurons bound together by an endoneurium are grouped into fascicles surrounded by a cellular sheath, the perineurium (p, micrograph 2). Fascicles, in turn, are surrounded by the epineurium, a dense connective tissue sheath that defines the nerve.





GLIAL CELLS: Node of Ranvier

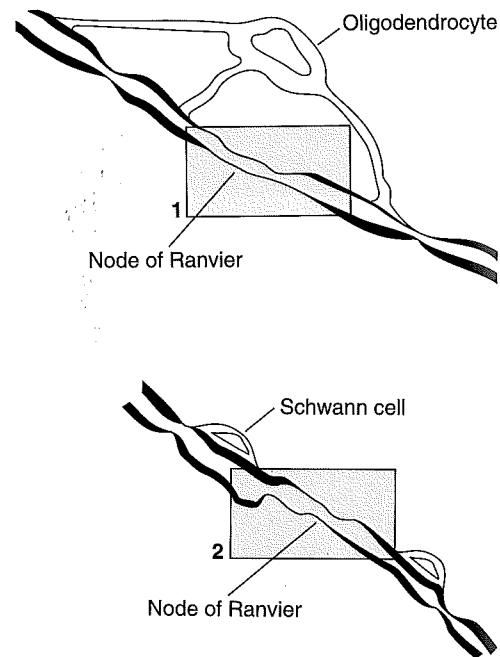
Action potentials initiated at the axon hillock are propagated down axons at different velocities, ranging from 1 to 100 meters/second (220 miles/hour). The **speed of impulse conduction** is related to axon diameter and the extent of myelination. As the diameter of an axon increases, internal resistance to ion flow is reduced and, consequently, impulse velocity is greater. Variation in axon (a) diameter is evident in micrograph 1 (courtesy of Dr. Larry Mathers), where many nerve processes are seen in cross section.

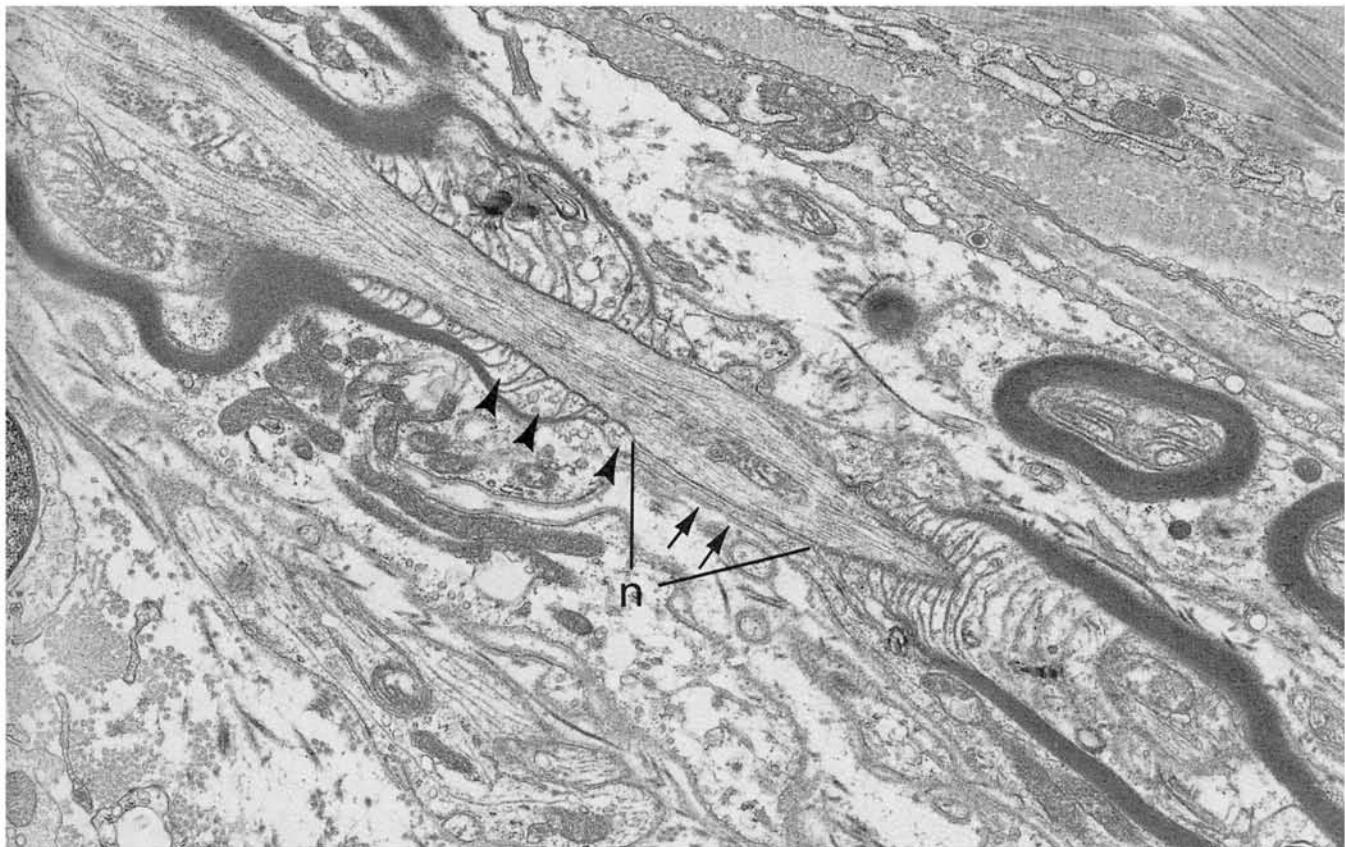
Most axons with a diameter of one micron and greater undergo myelination. The myelin coat increases the velocity of impulse conduction by increasing the membrane resistance and thus insulation, reducing membrane capacitance and ion loss during current flow. Ideally, the myelin insulation would be continuous from the axon hillock to the terminal bouton, much like the continuous insulation around a wire. In neurons, however, the self-propagated action potential has a tendency to fade and thus needs to be reinforced at regular intervals. Reinforcement of the action potential occurs in regions devoid of the myelin sheath, known as **nodes of Ranvier** (n, micrographs 1 and 2).

In the node regions, current passing longitudinally within the axon activates Na^+ channels. When these voltage-gated channels open, Na^+ rushes in, bringing positive charges to the inside of the axon to renew the action potential. This potential change is propagated rapidly to the next node. The distance between each node (1–2 mm) represents the maximum separation that still allows for undiminished axon current.

At the node of Ranvier in both CNS (micrograph 1) and PNS (micrograph 2), oligodendrocytes and Schwann cells terminate in a characteristic manner; several “fingers” of glial cytoplasm (arrowheads, micrographs 1 and 2) make intimate contact with the axon. These specializations are formed as the glial cell cytoplasm wraps around the axon. Junctions that form between glial cell and axon at the borders of the node maintain the different ion channel composition characteristic of node and internode regions. Sodium channels are concentrated in the node, where the axon is exposed to the extracellular fluid and most ion exchange occurs, and are sparse in the myelinated internode regions where very little ion exchange occurs.

Nodes in the PNS are surrounded by a basal lamina (arrows, micrograph 2) that is continuous with that of the Schwann cells. The basal lamina covering is important to the regeneration of PNS fibers. When axons are severed and the distal portion resorbed, regeneration will occur if the basal lamina and associated collagen remain to form an “endoneurial” tube. The absence of a defined basal lamina and the inhibitory effects of oligodendrocyte myelin are two factors that may prevent axon regeneration in the CNS.





GLIAL CELLS: Astrocytes

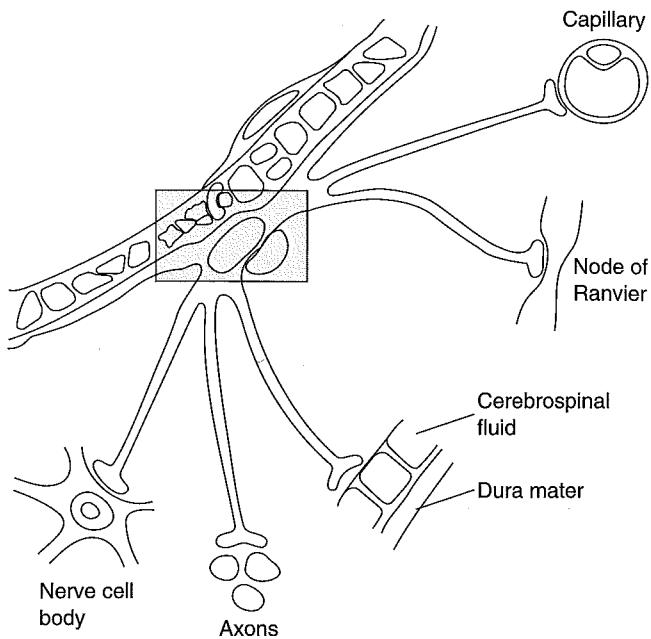
Astrocytes (A, micrographs 1 and 2, micrograph 2 courtesy of Dr. Larry Mathers), the most common glial cell in the central nervous system, are shaped like neurons, with many long processes extending from a central cell body. Each elongated process terminates in an “**end-foot**” that rests on nerve cells bodies, nerve processes, blood vessels, other astrocytes, or the inner surface of the meninges covering the brain. Astrocyte cytoplasm contains a characteristic **intermediate-sized filament** composed of glial fibrillary acidic protein. These filaments (f, micrographs 1 and 2) are obvious in routine electron micrographs, both next to the nucleus and within the processes that pass between axons and dendrites.

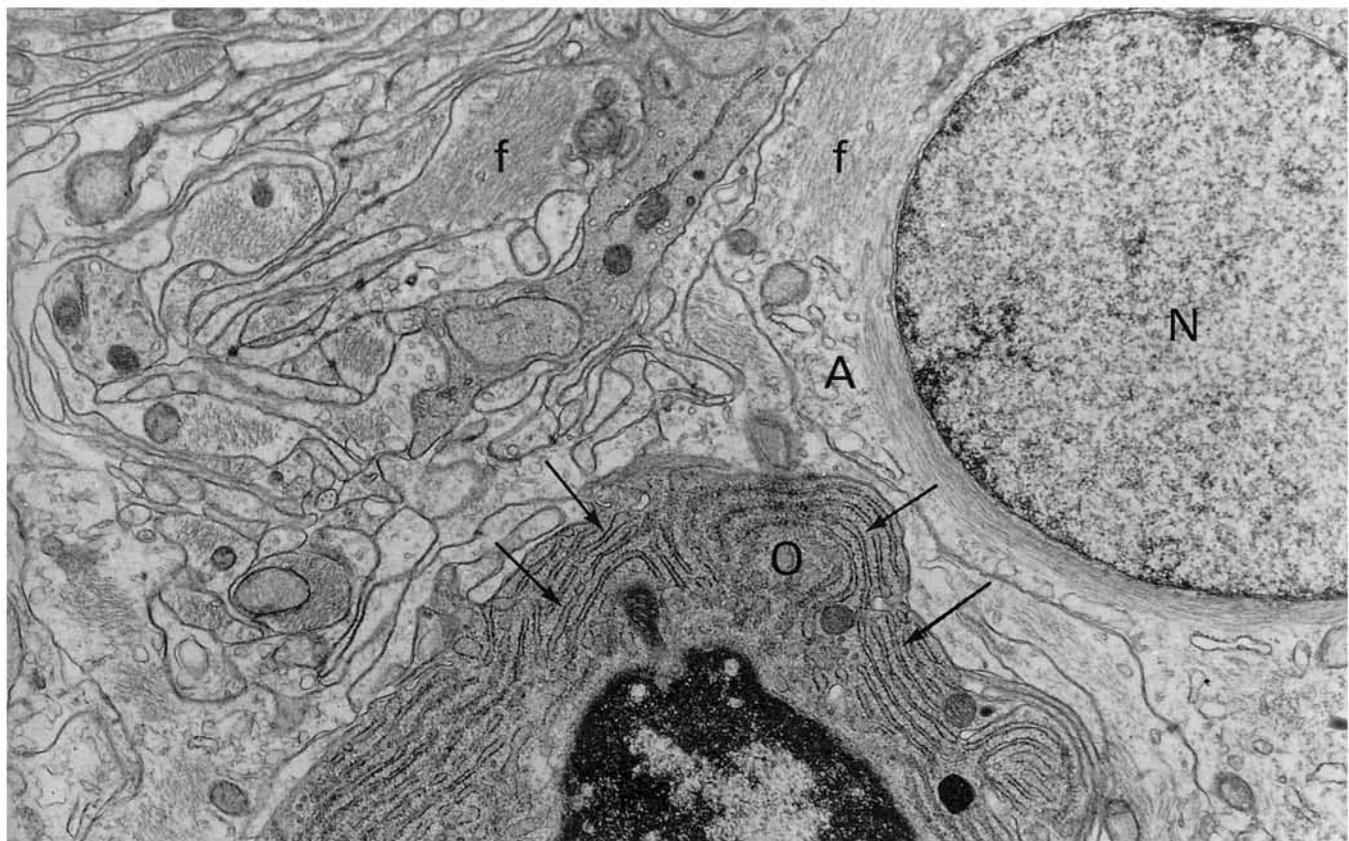
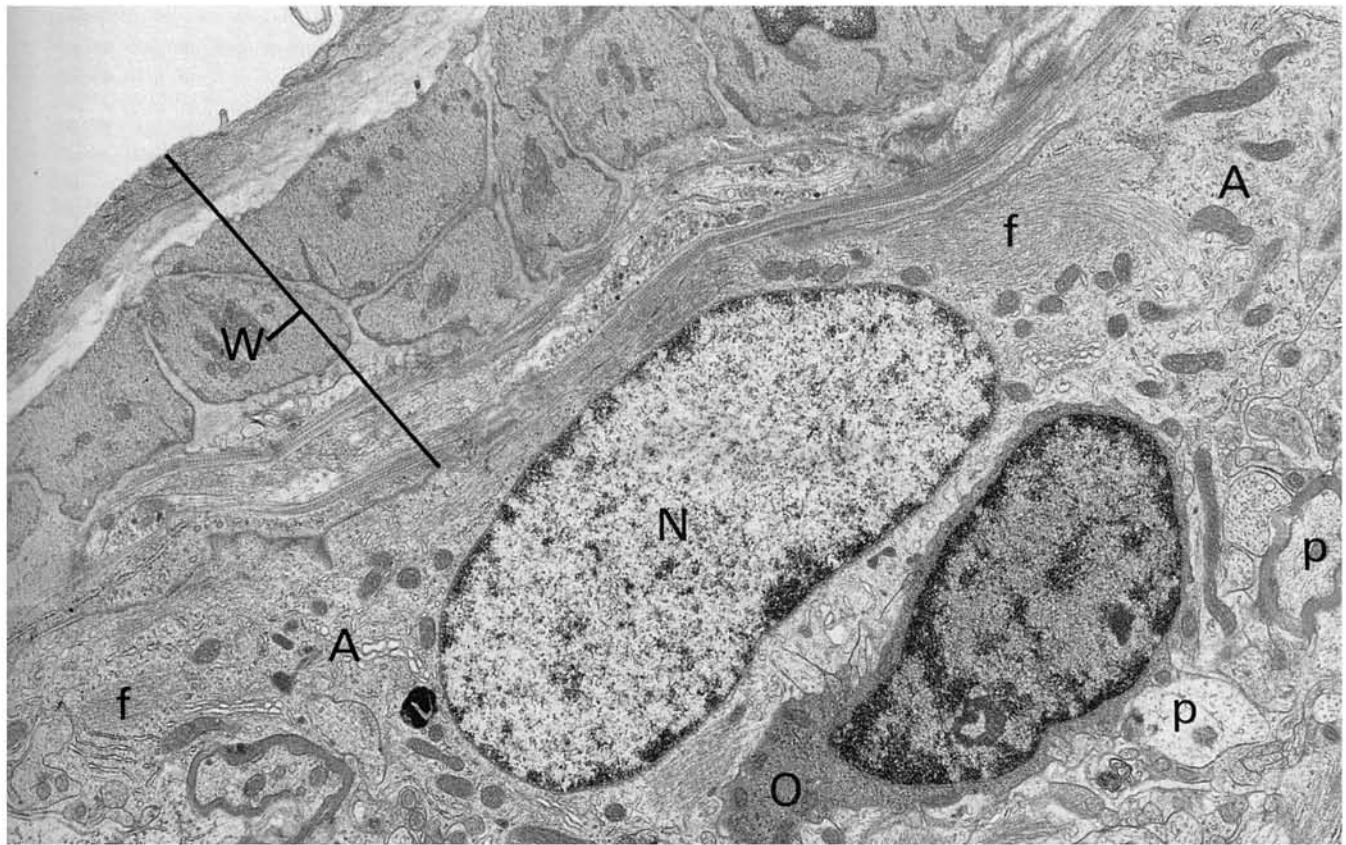
The euchromatic nucleus (N, micrographs 1 and 2) of astrocytes reflects, in part, the synthesis of the cytoskeleton. However, most of the nuclear activity is needed to maintain the extensive volume of cytoplasmic processes. Oligodendrocytes (O, micrographs 1 and 2), even though smaller cells, are also extremely active. Their activity, however, is more specific and directed toward the synthesis of myelin. Rough ER (arrows, micrograph 2), where myelin protein synthesis occurs, dominates their cytoplasm.

Astrocytes have unique functions relating to their intimate association with blood vessels and neurons. In capillaries, they induce and maintain the blood-brain barrier (see Blood Vessels, page 150). Even in larger vessels, such as the arteriole in micrograph 1, astrocytes form a layer between the vessel wall (W) and neuron processes (p).

A network of astrocytes may form a significant nonneuronal communication system. Potassium, which has a pronounced effect on neuron functioning, accumulates in astrocyte end-feet associated with nerve processes. This ion may be moved from the microenvironment surrounding neurons, through an astrocyte network, to the blood or cerebrospinal fluid. Gap junctions between astrocytes could account for the transportation of potassium for considerable distances. A separate indication of sophisticated ion transport in astrocytes is their ability to respond to the neurotransmitter glutamate with a calcium wave that is transmitted from cell to cell. These waves travel over long distances without diminishing, like the neuron axon potential.

Following nerve degeneration, astrocytes proliferate and accumulate in areas of injury. This repair activity may interfere with neuron regeneration in the CNS.





GANGLIA

In the peripheral nervous system, neuron cell bodies are localized within **ganglia**. In both **dorsal root (sensory)** and **autonomic** (sympathetic and parasympathetic) ganglia, the cell bodies are covered with specialized glial cells called **satellite cells**. In the dorsal root ganglia (micrograph 1) the nuclei of three satellite cells (S) can be observed tightly apposed to the nerve cell body. In the autonomic ganglia (micrograph 2), even though nuclei of satellite cells are not seen in the section, a thin rim of satellite cytoplasm (cy) wraps the nerve cell body. In both types of ganglia, collagen (c, micrographs 1 and 2) provides the supportive framework.

Sensory neurons of the dorsal root ganglia are **pseudounipolar**, with only one process extending from the cell body. A short distance from the cell body the nerve process divides, with one branch leading to the periphery and one to the CNS. Information from the region of sensory input (e.g., pain receptors in skin) is carried directly to the CNS, bypassing the cell body. No signal information is processed in the cell body, which is solely “nutritive”; i.e., it maintains the turnover of cellular components. This, in itself, requires extensive synthetic activity as evidenced by the large cell body, euchromatic nucleus (N, micrograph 1), and prominent nucleolus (n, micrograph 1).

Unlike sensory neurons, autonomic neurons have a typical **multipolar** arrangement. In autonomic ganglia, postsynaptic dendrites and cell bodies receive and process information from synaptic contact with presynaptic neurons. The numerous nerve fibers (p, micrograph 2) that surround and separate each cell body in autonomic ganglia reflect the role of these ganglia in processing and communication. In contrast, in dorsal root ganglia, which are not regions of synaptic information transfer, neuron cell bodies are tightly grouped together, with few intervening nerve processes. In micrograph 1, note the presence of three other neuron cell bodies (arrows) directly adjacent to the central one.

All of the nerve processes observed in micrograph 2 are unmyelinated and grouped together by the Schwann cell cytoplasm that encases them. In one group of nerve fibers, the section cuts through the nucleus of a Schwann cell (Sc, micrograph 2).

Synapses continually rearrange on the surface of the autonomic ganglia nerve cell bodies. As synapses move, so do satellite cells. The neuron cell bodies and surrounding satellite cells are connected by gap junctions and may communicate in ways important in this synaptic adjustment.

