

## OVERVIEW

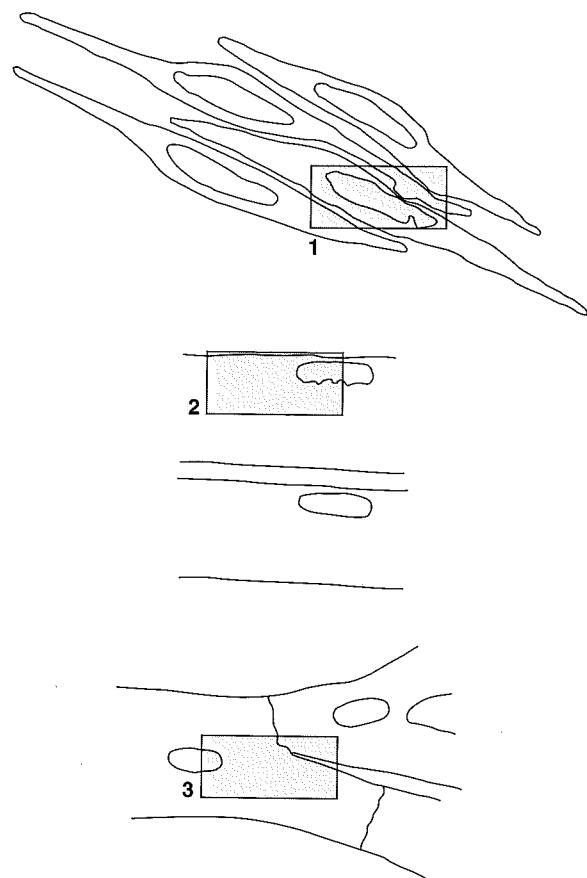
**Muscle fibers** are specialized contractile cells. By working together they are able to control the movement of hollow organs and vessels (smooth muscle), the skeletal system (skeletal muscle), and the heart (cardiac muscle). Each type of muscle cell has a different morphology that is suited to its location and type of contraction.

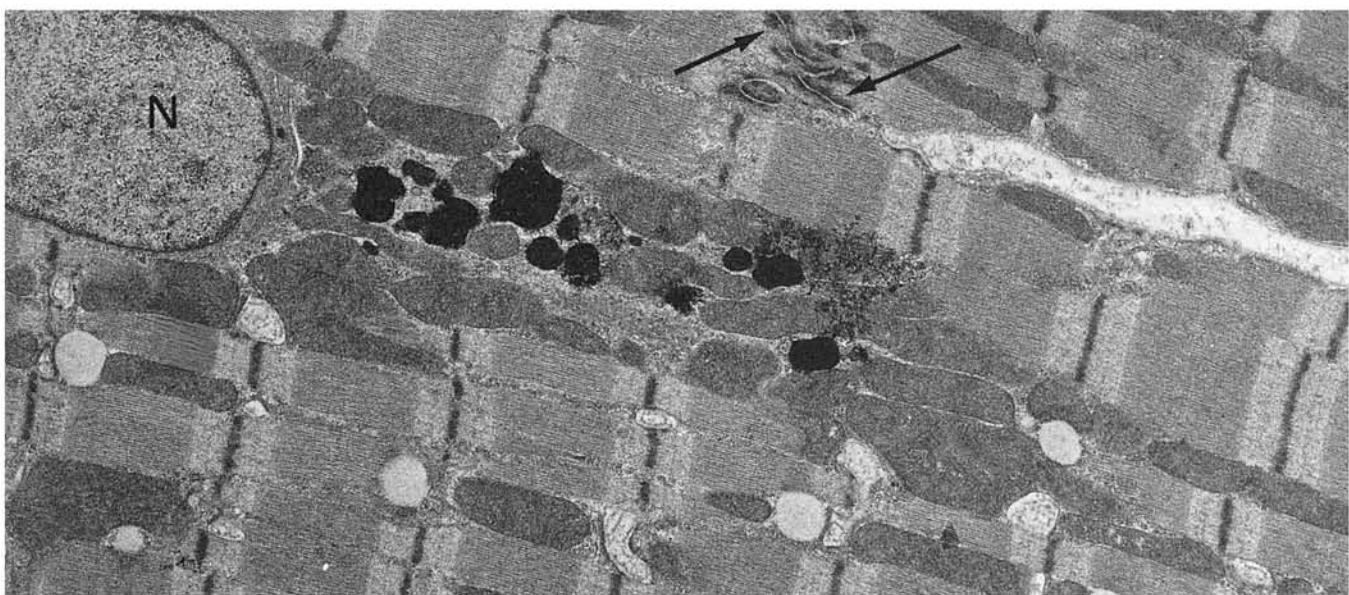
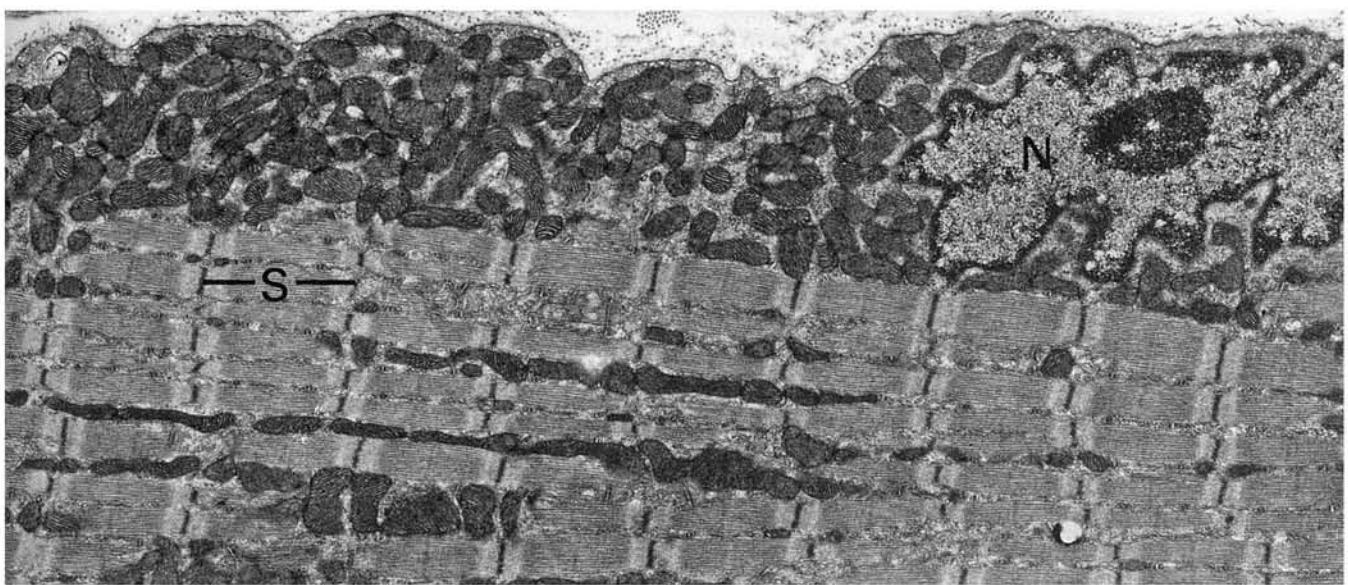
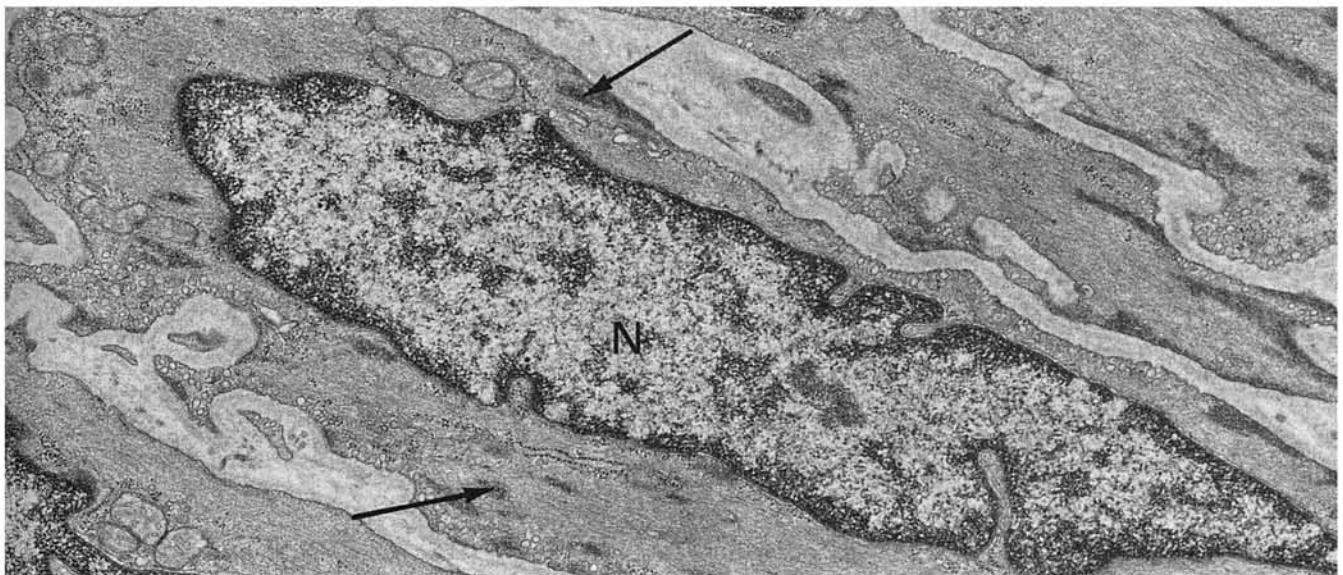
**Smooth muscle** fibers (micrograph 1) are small, with a central nucleus (N) and tapered ends. They group together in a staggered fashion in the walls of many organs. The fusiform shape facilitates the twisting that takes place during contraction. Even though well-defined contractile units are not obvious, a certain level of organization exists. Actin inserts into dense bodies (arrows) within the cytoplasm and at the cell margins.

**Skeletal muscle** fibers (micrograph 2) are large multinucleated syncytia that take a direct path from the point of origin to insertion. Contraction is linear and results from the shortening of discrete units, sarcomeres (S), arranged in series. Nuclei (N) sit in the peripheral cytoplasm, where they direct the synthesis of proteins important in contraction and synaptic activity.

**Cardiac muscle** fibers (micrograph 3) are intermediate in size between smooth and skeletal muscle fibers. Typically each fiber has several branches and one centrally placed nucleus (N). Individual fibers are bound together by intercalated discs (arrows), elaborate junctional complexes that occupy the entire ends of the cells where they contact each other. The tightly associated branching fibers form a network that acts as a functional syncytium, carrying contraction on an elaborate path through the atria and ventricles.

Whereas voluntary skeletal muscle fibers are individually innervated and only contract with neural input, involuntary smooth and cardiac muscle fibers can contract spontaneously. The autonomic innervation to involuntary muscle alters the speed and force of contraction, and the electrical signal is transmitted by gap junctions between cells. All three muscle types are surrounded by a network of reticular fibers that facilitates the coordination of contraction.

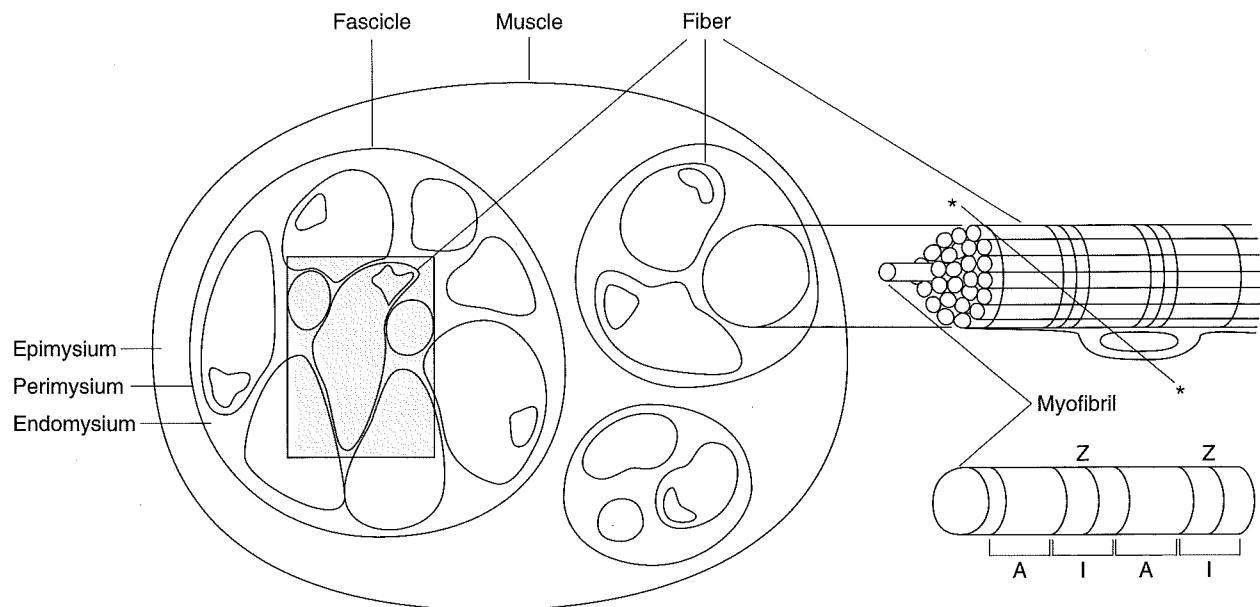




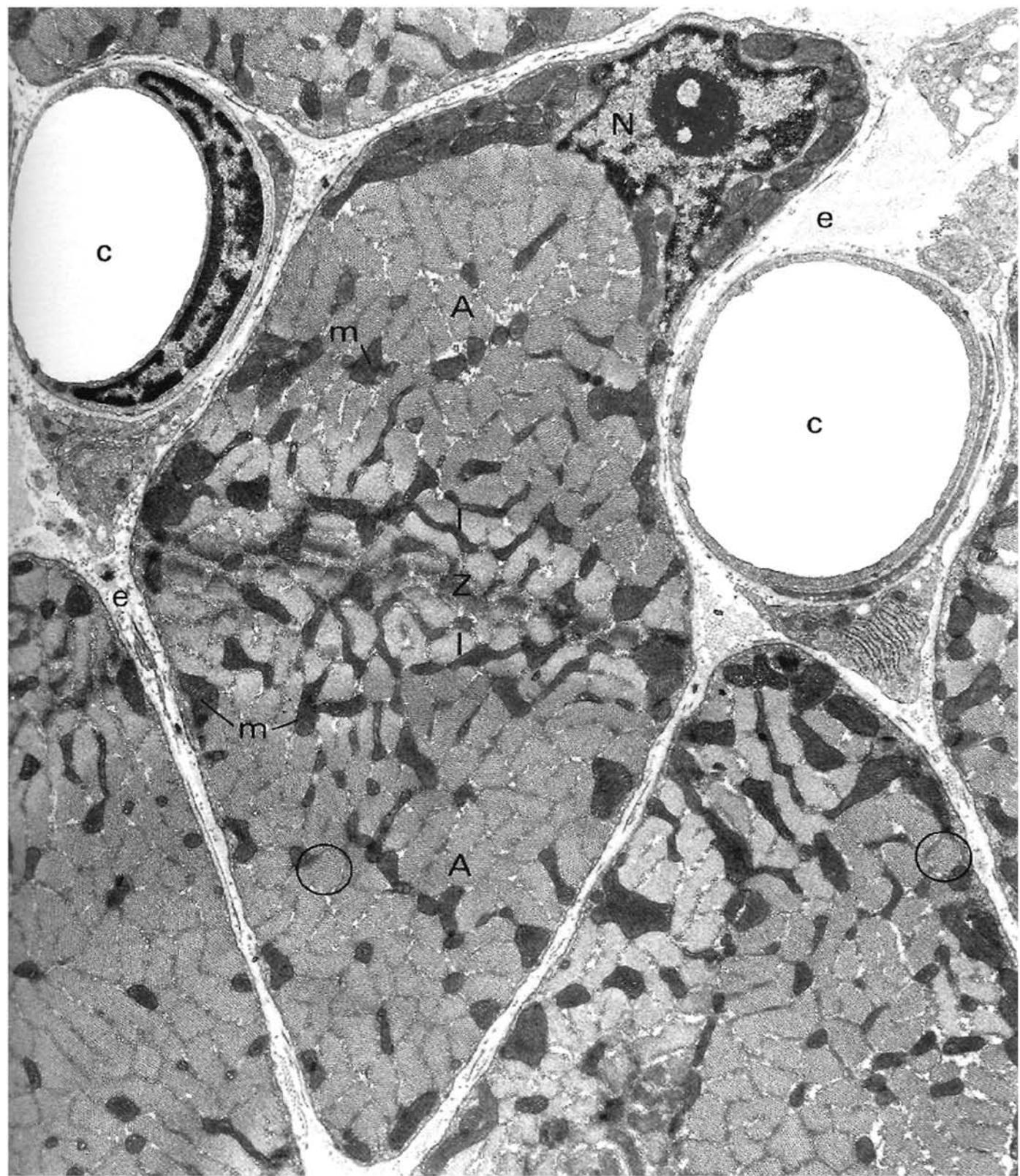
## SKELETAL MUSCLE: Fibers and Myofibrils

**Skeletal muscle fibers** are easily distinguished by their large size, peripheral nuclei (N, micrograph), and cytoplasm packed with well-defined units, **myofibrils** (circles, micrograph). Organelles such as mitochondria (m, micrograph) and smooth endoplasmic reticulum (sarcoplasmic reticulum) occupy the cytoplasm (sarcolemma) between myofibrils. The particular muscle in this micrograph undergoes a slow, continuous contraction with little fatigue. The extensive blood supply (note the two capillaries, c, on either side of the fiber) and many mitochondria reflect the high oxygen demand associated with its aerobic metabolism.

Skeletal muscle fibers are grouped into **fascicles**, and groups of fascicles are bound together to form a muscle. Individual fibers are surrounded by an **endomysium** (e, micrograph) of loose connective tissue, fascicles are surrounded by **perimysium**, a thin cellular sheath, and groups of fascicles are bound together by an **epimysium** of dense connective tissue.



In longitudinal section, each myofibril exhibits a series of light **I-bands** and dark **A-bands**. Thin dark **Z-lines** bisect the I-bands. This arrangement reflects a precise organization of the contractile proteins actin and myosin within individual myofibrils (see Muscle, page 100, for details). The micrograph was taken from an oblique section (\*, diagram) that cut through the nucleus and different bands in a single cell. Consequently, sequential A, I, Z, I, A areas are evident in the micrograph.



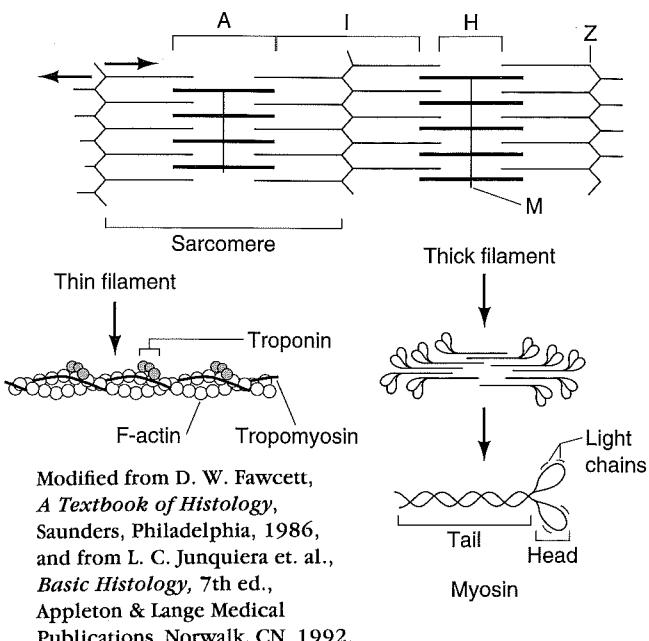
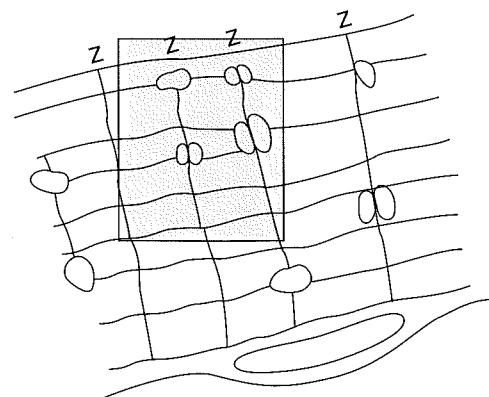
## SKELETAL MUSCLE: Sarcomere

The contractile unit of skeletal muscle, the **sarcomere**, consists of highly ordered arrays of thin and thick filaments. One sarcomere (S, micrograph) is defined at each end by a Z-line (Z, micrograph). **Thin filaments**, anchored in the  $\alpha$ -actinin-rich Z-line, project part way into the myosin-containing A-bands (A, bracket, micrograph) of adjacent sarcomeres. They are polarized in opposite directions on each side of the Z-line (arrows, diagram). **Thick filaments** are anchored in the center of the A-band at the denser M-line (M, micrograph). Crossbridges form between the thick and thin filaments in the region of overlap. The movement of the myosin heads within the thick filaments pulls the thin filaments toward the M-line, shortening the sarcomere length and thus the muscle fiber. With sarcomere shortening, both the I-band (I, bracket, micrograph), which contains only thin filaments, and the H-band (H, bracket, micrograph), which contains only thick filaments, become narrower.

Each thin filament is composed of **F-actin** and the associated proteins **tropomyosin** and **troponin**. The filamentous tropomyosin wraps around the F-actin while troponin, consisting of **C** (calcium-binding), **T** (tropomyosin-binding), and **I** (actin-binding) subunits, binds to the actin–tropomyosin complex at regular intervals.

Each thick filament is composed of many **myosin** molecules, each consisting of two heavy chains and associated light chains. The two heavy chains (200 kd each) are wound around each other to form an alpha helical coiled-coil tail with two globular heads. The tail region functions in the assembly of the thick filament while the heads contain the ATPase activity and the actin binding site. Two light chains (20 kd and 17 kd) associate with each heavy chain head. Myosin molecules are grouped in the thick filament in a staggered bipolar arrangement with a central region devoid of heads.

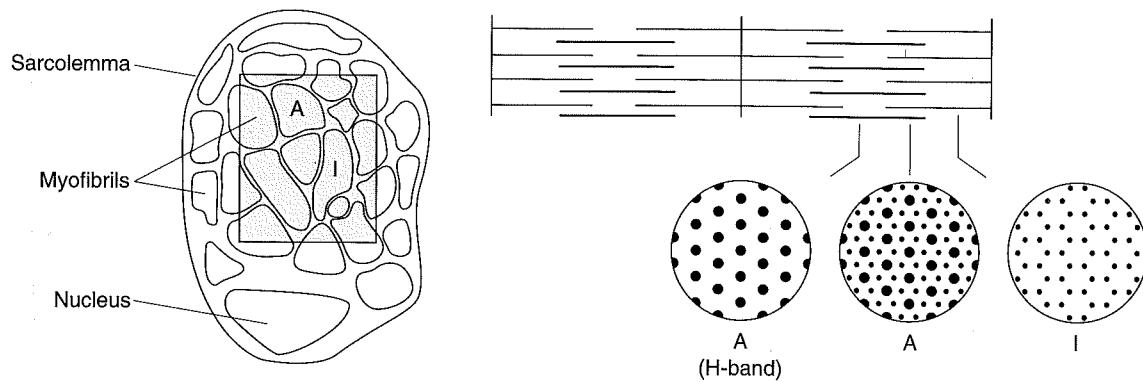
An action potential generated at the neuromuscular junction is propagated quickly to all regions of the cell via invaginations of the cell membrane (sarcolemma) called transverse tubules (**T-tubules**) (arrows, micrograph). In skeletal muscle, T-tubules occur at the A–I junctions. In response to the action potential, calcium is released from the sarcoplasmic reticulum and initiates contraction. Calcium binds to troponin C, altering the conformation of both troponin and tropomyosin, thus exposing the myosin binding site on the actin. Cross-bridges form and contraction initiates, powered, in this “fast” muscle, by ATP generated from glycogen (arrowheads, micrograph) breakdown.





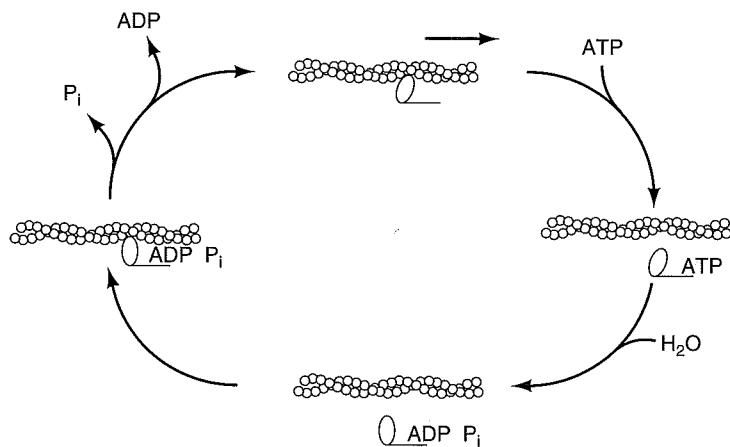
## SKELETAL MUSCLE: Myofilaments

In the cross section in the micrograph, **myofibrils** (My) are clearly defined by surrounding sarcoplasmic reticulum (arrows). This section cut through myofibrils within a region of the **A-band** (A, micrograph), where thick and thin **myofilaments** overlap, and through the **I-band** (I, micrograph), which contains thin, but not thick, filaments. In the A-band, thin filaments are arranged in a hexagonal pattern around the thick filaments, with each thin actin filament associated with three thick myosin filaments (circles, micrograph).

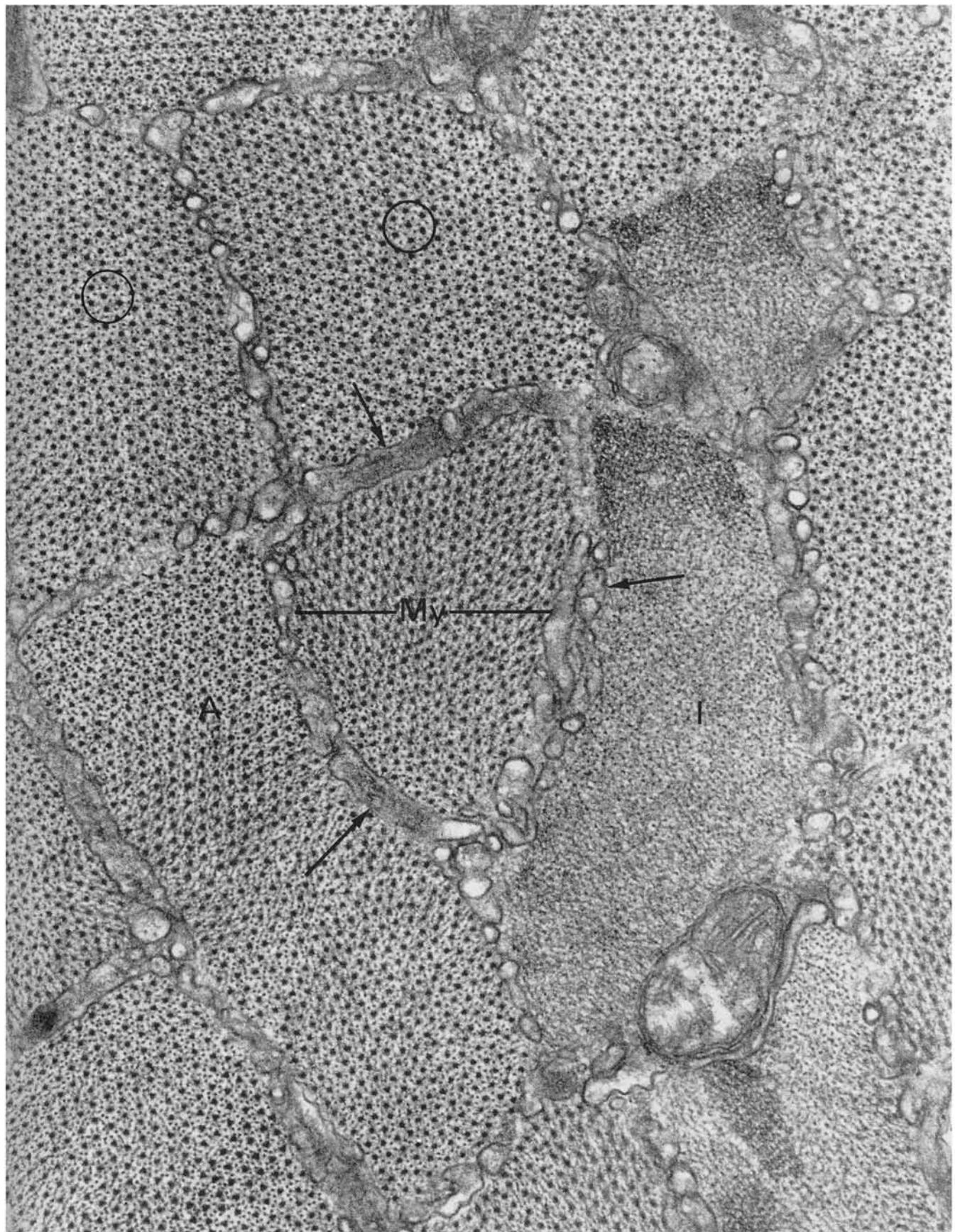


Modified from D. W. Fawcett, *A Textbook of Histology*, Saunders, Philadelphia, 1988.

A proposed sequence for **force generation** between thick and thin filaments in the A-band is shown below. As illustrated, when myosin binds to actin,  $P_i$  and then ADP are released, resulting in a change in the orientation of the myosin head, the power stroke that moves the thin filament. ATP binds, myosin is released from actin, and ATP is hydrolyzed to ADP and  $P_i$  as the myosin head is cocked for another cycle.

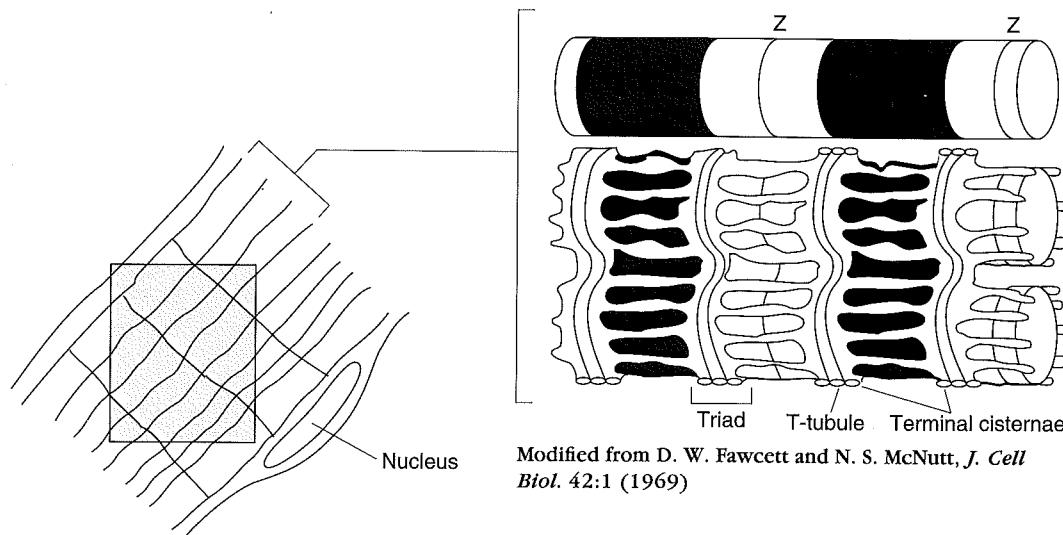


Courtesy of Dr. J. Spudich.



## SKELETAL MUSCLE: Triad

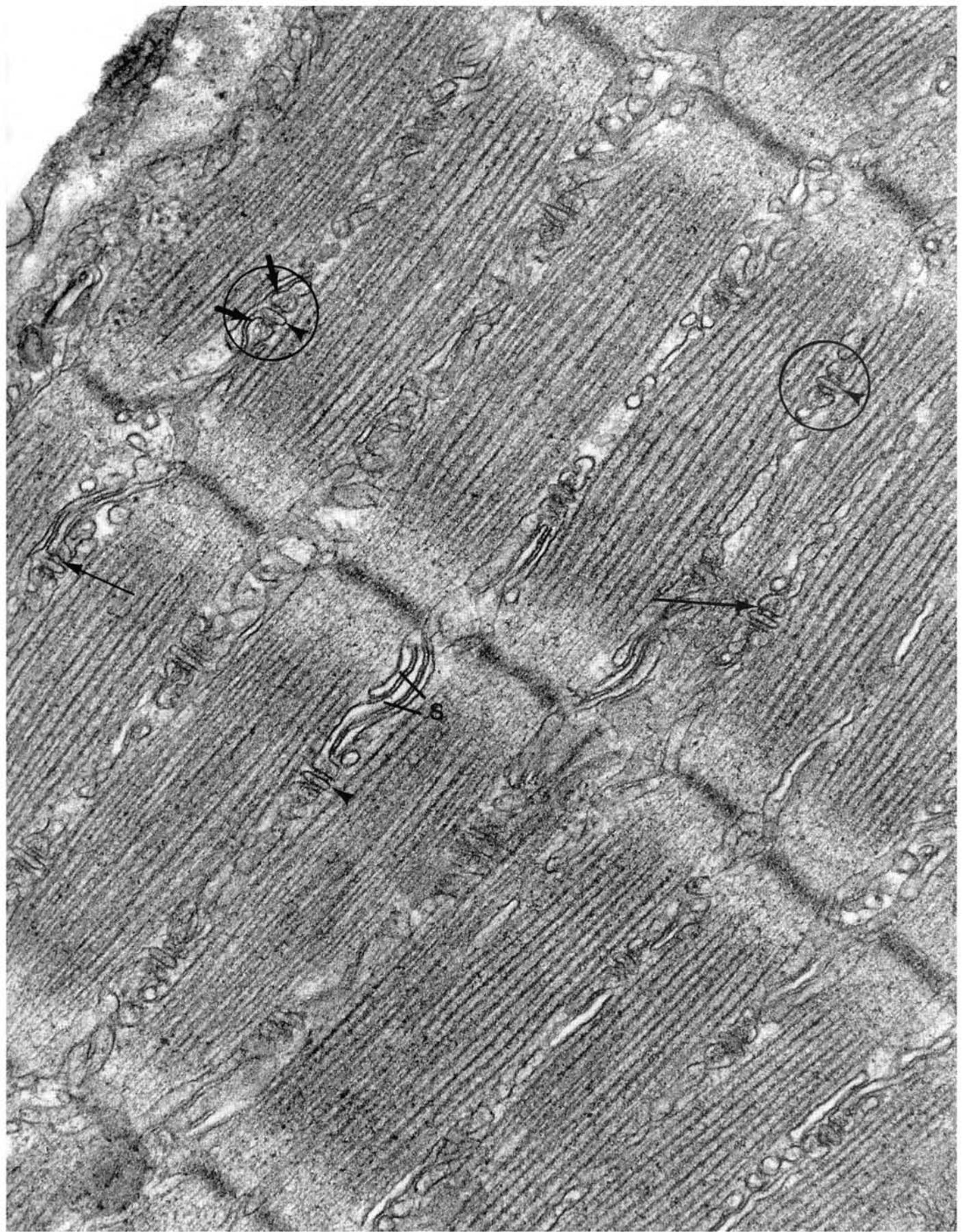
In skeletal muscle, the concentration of calcium within the sarcoplasm is regulated by the **sarcoplasmic reticulum** (s, micrograph). This organelle consists of membranous cisternae that encase each myofibril in a distinct arrangement. The sarcoplasmic reticulum comes into close contact with invaginations of the cell membrane, the **T-tubules**, at the **A-I junctions** and forms **triads** (circles, micrograph). Each triad consists of a central T-tubule (arrowheads, micrograph) flanked by two terminal cisternae (short arrows, micrograph) of the sarcoplasmic reticulum. Electron-dense “feet” (long arrows, micrograph) project from the sarcoplasmic reticulum across a 12-nm gap and attach at regular intervals to the T-tubule. Events in the triad area, where the terminal cisternae and T-tubules are intimately associated, are thought to couple the depolarization of the T-tubule to the release of calcium from the sarcoplasmic reticulum.



Modified from D. W. Fawcett and N. S. McNutt, *J. Cell Biol.* 42:1 (1969)

Most calcium is concentrated in the sarcoplasmic reticulum of the triads, bound to the acidic protein **calsequestrin** (note electron density in terminal cisternae). Evidence suggests that calcium is not only stored in the terminal cisternae, but is also preferentially released in this area. **Calcium-release channels** seem to be the same structures as the junctional feet seen on electron micrographs. Small alterations in the membrane charge of the T-tubules may lead to conformation changes in the junctional feet, thus opening the calcium-release channels.

During relaxation, calcium is pumped back into the sarcoplasmic reticulum throughout the nontriad regions by specific **calcium-ATPase complexes** that make up 90% of the membrane protein content of this region.



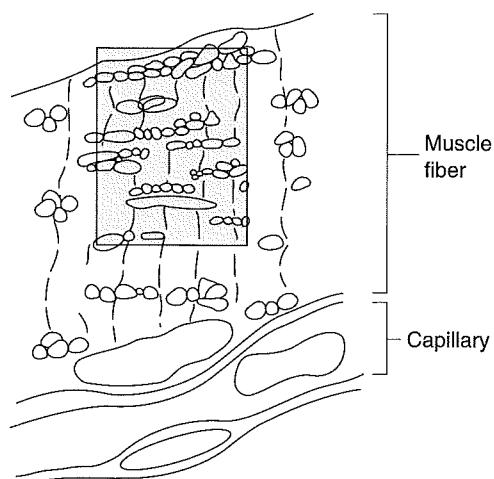
## SKELETAL MUSCLE: Fiber Type

Skeletal muscle fibers vary in their manner of contraction, biochemistry, and ultrastructure. Some undergo a **slow, continuous contraction** (e.g., postural muscles) and are fatigue resistant, while others undergo a **fast contraction for short periods** of time (e.g., extraocular muscles of the eye) and fatigue quickly. Slow muscle fibers (micrograph) have many mitochondria (m) but sparse sarcoplasmic reticulum (SR) separating relatively small myofibrils.

**Slow muscles** use aerobic metabolism almost exclusively for their energy demands. The numerous mitochondria are packed with cristae that contain high concentrations of enzymes involved in oxidative metabolism. Triacylglycerols stored as lipid droplets (L, micrograph) provide one source of energy. Oxygen is readily available from (1) myoglobin, an oxygen-binding heme protein concentrated in the cytoplasm, and (2) hemoglobin in the numerous capillaries associated with each fiber.

The slow contraction–relaxation cycle in these fibers is a result of unique characteristics of cellular components directly involved in the mechanism of contraction. In comparison to fast fibers, these slow fibers have (1) a lower density of calcium-pumping ATPase in the sarcoplasmic reticulum membrane, (2) different forms of myosin heavy and light chains, and (3) different forms of tropomyosin and troponin.

All the characteristics of a single muscle type, including myosin type, metabolic activity, fiber size, and density of capillaries, can be reversed by altering the **neural input**. When the innervation to fast and slow fibers is reversed, the muscle fibers change to the type corresponding to the new innervation. It is also known that exercise frequently results in a shift in muscle type. The relative plasticity of these phenotypes represents alterations in gene transcription and translation.





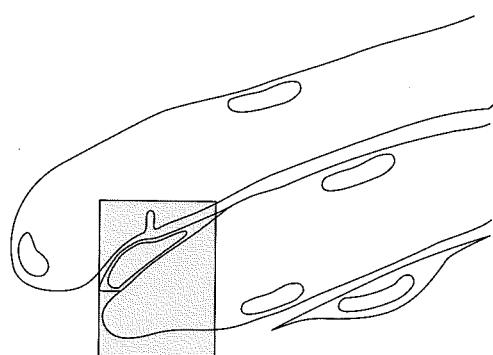
## SKELETAL MUSCLE: Satellite Cells

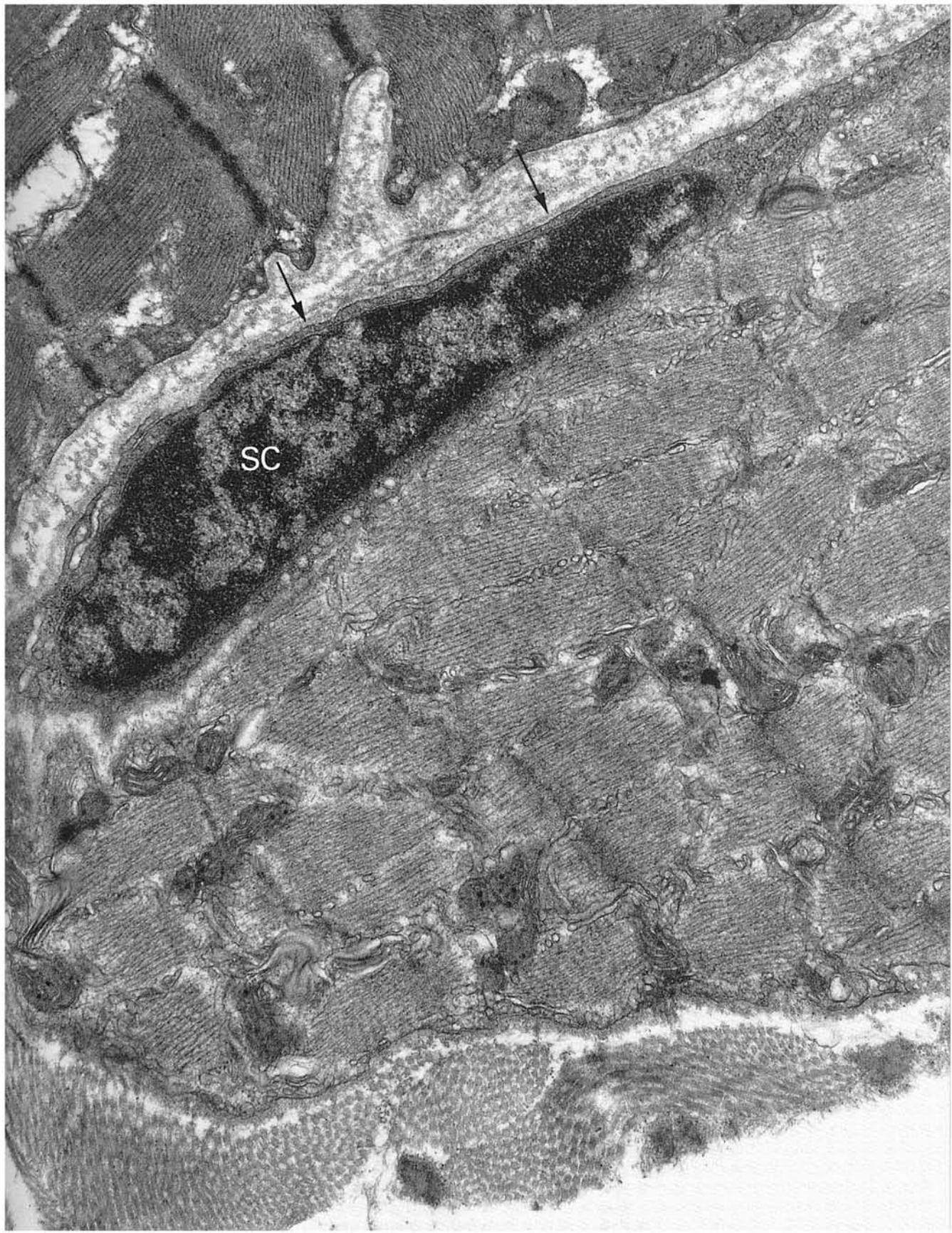
During development skeletal muscle fibers form by the fusion of myoblasts. At the completion of development, some myoblasts remain undifferentiated on the periphery of the multinucleated mature muscle fibers. These undifferentiated cells are the **satellite cells** (SC, micrograph) found within the basal lamina (arrows, micrograph) of the muscle fiber and tightly associated with the sarcolemma. There is approximately one satellite cell (with a single heterochromatic nucleus) for every 100 muscle fiber nuclei.

Satellite cells function in adult muscle during the hypertrophy related to exercise and during the regeneration and repair of injured, denervated, or disused fibers. During hypertrophy and the repair of individual fibers, satellite cells fuse with adjacent fibers and contribute to the synthesis of new myofibrils. During regeneration associated with injury, the satellite cells proliferate, differentiate, and fuse with each other to form new muscle cells.

Satellite cell proliferation is tightly regulated in normal adult muscle. In vitro studies suggest that activation that occurs following injury may be a response to (1) a factor released from crushed muscle cells themselves and (2) laminin, the major glycoprotein of the basal lamina. An intact basal lamina is essential for regeneration and provides more than just a physical scaffold.

The number of satellite cells decreases with age and is reduced in certain disease states. Duchenne muscular dystrophy (DMD), a fatal X-linked disorder affecting 1 in 3500 males, is associated with the wasting of skeletal muscle. The gene affected in DMD has been characterized, and its product, dystrophin, is absent in DMD muscle. In normal muscle cells, dystrophin, which shares structural homology with  $\alpha$ -actinin and spectrin, is found associated with the protoplasmic side of the cell membrane. A possible role for dystrophin as a link between the surface membrane and cytoskeleton has been suggested, and its absence in DMD muscle may compromise cellular integrity. The number of satellite cells in DMD is only 2% of normal, and the degenerating muscle cells are not replaced.



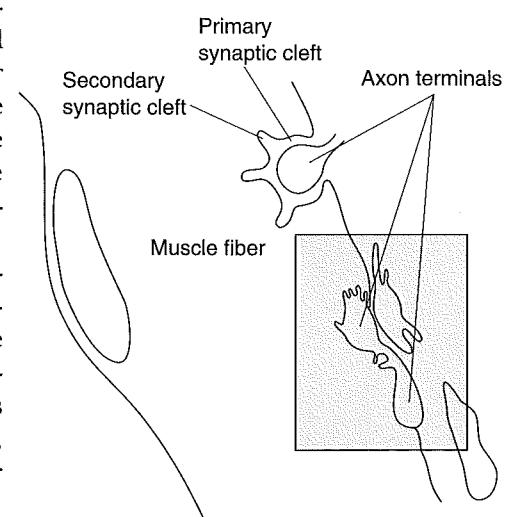
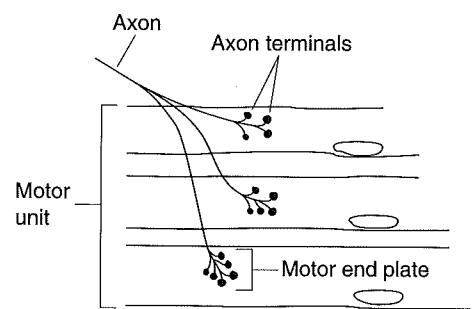


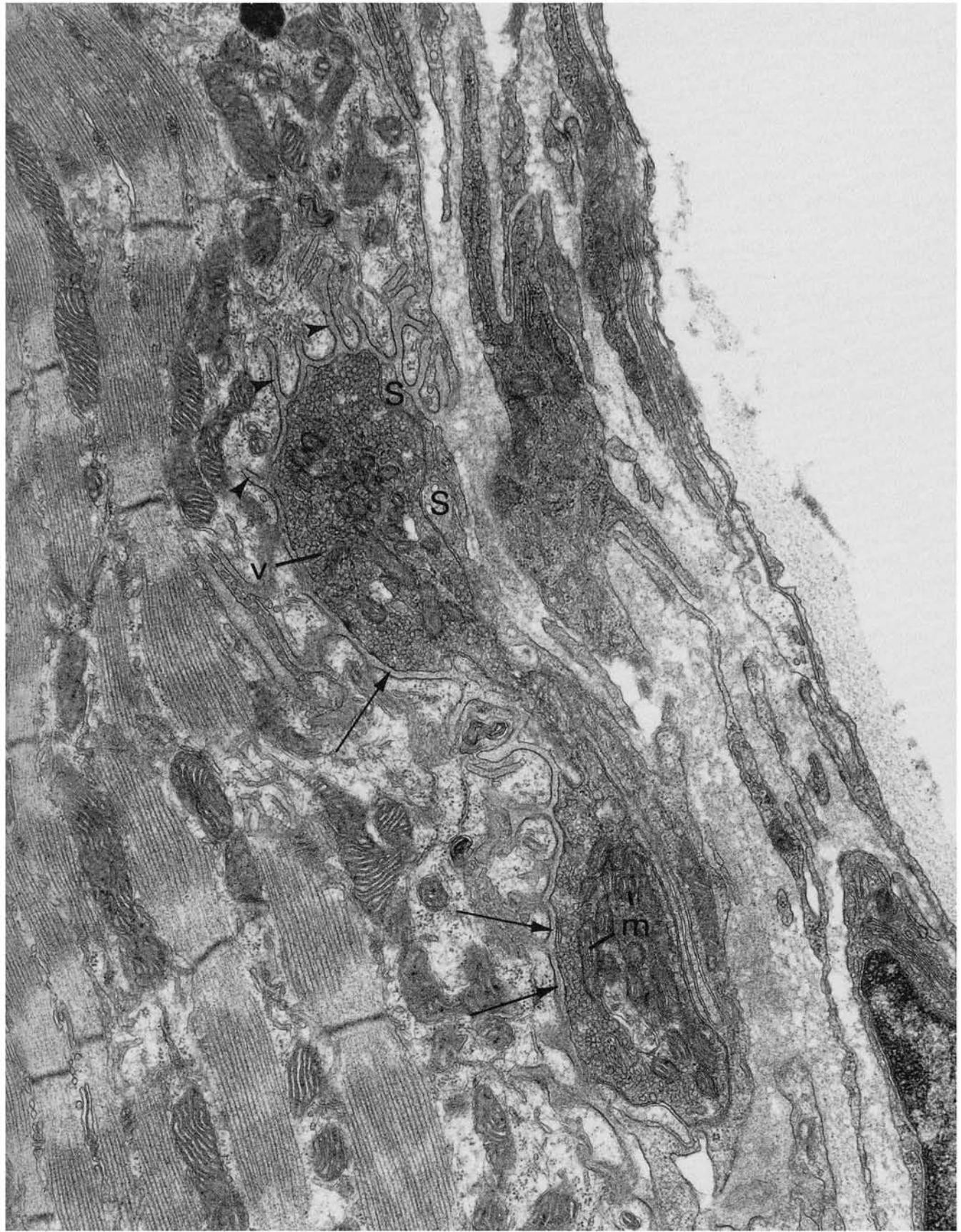
## SKELETAL MUSCLE: Motor End Plate

Muscle fibers are arranged in **motor units** composed of from 3 to over 150 fibers. All of the fibers in each motor unit are innervated by branches of a single axon and respond together and to the same degree to the axon impulse supplying the unit. While a single neuron may innervate many muscle fibers, each muscle fiber receives innervation from only one neuron. At the **neuromuscular junction**, the axon branches to form several **terminal swellings** that together constitute the **motor end plate**.

Two terminal swellings are present in the micrograph. Each swelling sits in a depression in the muscle fiber called a **primary synaptic cleft** (arrows, micrograph). The axon terminal contains many mitochondria (m, micrograph) and small synaptic vesicles (v, micrograph) holding the neurotransmitter acetylcholine. The region of the muscle cell adjacent to the nerve terminal forms deep surface junctional folds giving rise to **secondary synaptic clef**ts (arrowheads, micrograph). In the synaptic region the distance between nerve terminal and sarcolemma is 50 nm.

At the neuromuscular junction, the myelin sheath covering the axon is lost and Schwann cell cytoplasm (S, micrograph) comes into direct contact with the upper region of the nerve terminal. Schwann cells in this region exhibit ionic activity in response to synaptic events. In addition, if the axon is severed, the Schwann cell phagocytoses the axon terminals, clearing and remodeling the synapse region in preparation for reinnervation.



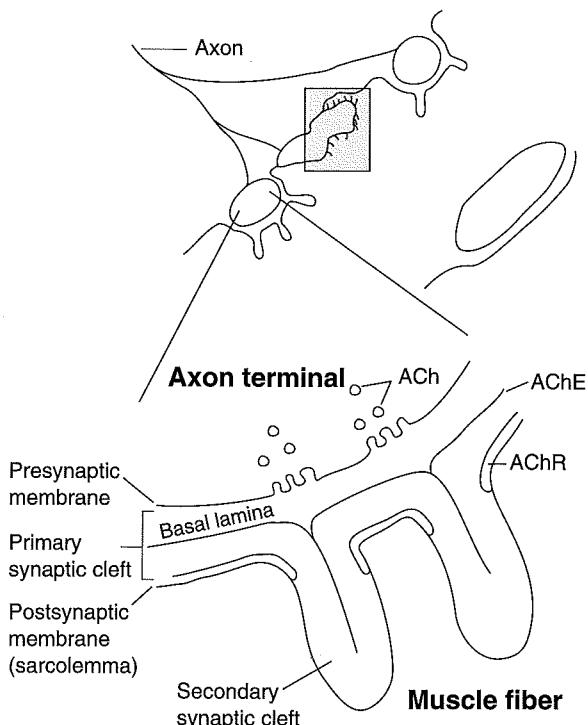


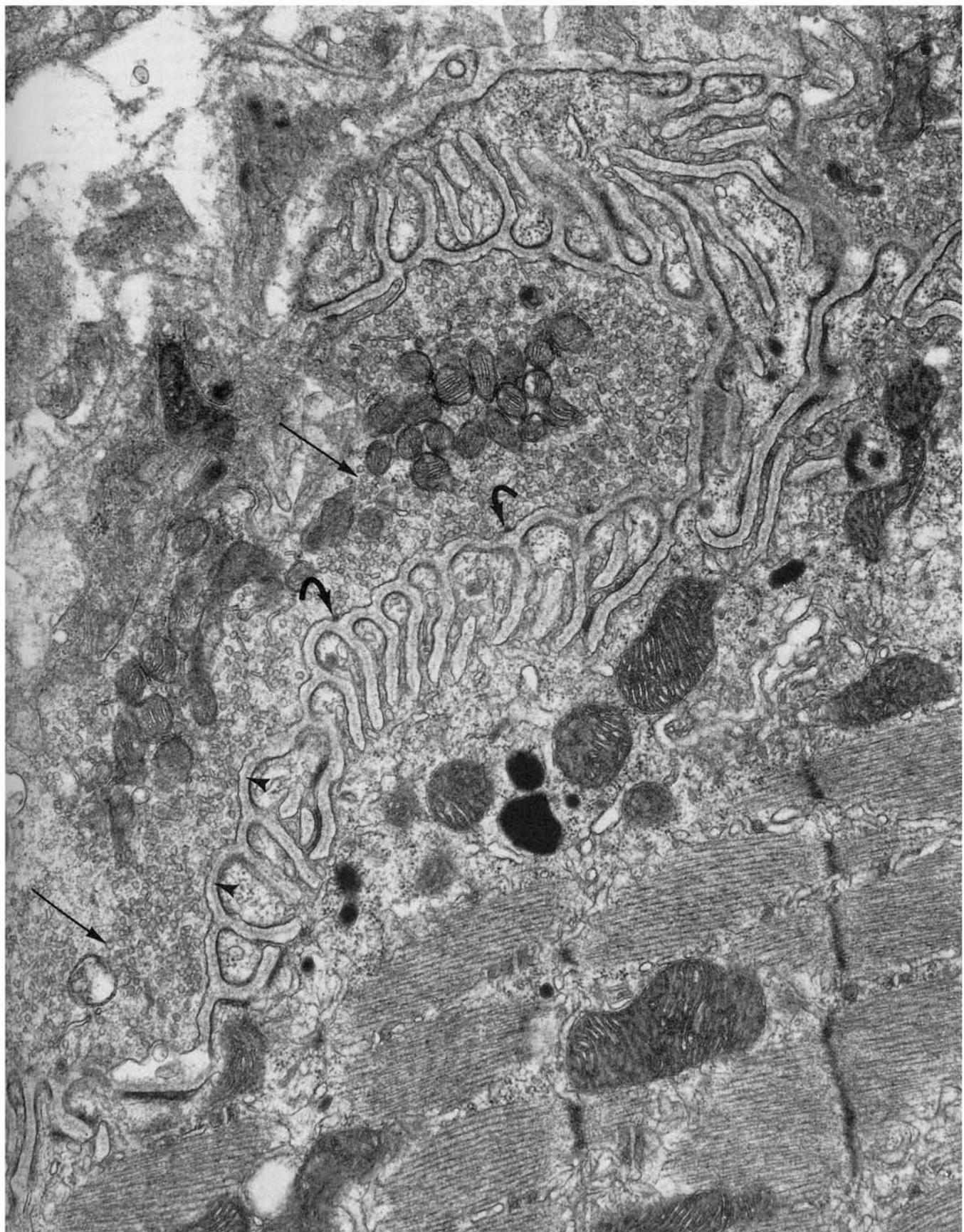
## SKELETAL MUSCLE: Synaptic Region

In skeletal muscle each nerve terminal contains tens of thousands of 50-nm **synaptic vesicles** (straight arrows, micrograph), each containing a defined amount ( $\sim 10,000$  molecules) of the neurotransmitter **acetylcholine** (ACh). When the nerve action potential reaches the terminal, calcium channels in the nerve presynaptic membrane open and calcium enters the cell. This triggers the fusion of a few hundred synaptic vesicles with the presynaptic membrane and the release of large quantities of ACh into the extracellular synaptic cleft. Synaptic vesicles fuse with the presynaptic membrane at **active zones** (curved arrows, micrograph), electron-dense areas directly across from the junctional folds.

Acetylcholine diffuses across the basal lamina (arrowheads, micrograph) and binds to **receptors** (AChR) in the sarcolemma. These receptors are concentrated on the crests and uppermost regions of the junctional folds. Each AChR is also an ion channel. When ACh binds to the receptor, the entry of sodium and other ions results in a depolarization of the muscle sarcolemma that is propagated as an action potential. ACh is rapidly hydrolyzed by **acetylcholinesterase** (AChE), which is bound to the **basal lamina** by a collagenlike tail. The rapid removal of ACh by AChE is necessary for the electrical recovery of the postsynaptic sarcolemma during normal muscle activity.

In addition to housing the AChE, the basal lamina in the synaptic region contains agrin, a protein that regulates the clustering of AChE and AChR. Components of the basal lamina are capable of inducing the differentiation of all postsynaptic specializations. When muscle fibers are destroyed, they regenerate within the basal lamina sheath of the original fibers and form junctional folds and concentrated receptors in the original synapse region of the sheaths, even in the absence of nerve terminals.





## SMOOTH MUSCLE: Overview

The **smooth muscle** fiber extending diagonally across micrograph 1 has an elongated, centrally placed nucleus (N), **dense bodies** (arrows), fibrillar material in the cytoplasm, and relatively few mitochondria (m). This fiber is in the wall of an arteriole (L: lumen; E: endothelial cell), where its contraction plays an important role in controlling peripheral resistance and thus blood pressure.

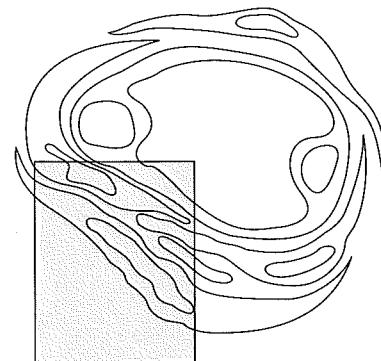
The fibrillar material of smooth muscle cells is shown in higher magnification in the inset. The largest structures are the **microtubules** (curved arrows), 25 nm in diameter, and the smallest are the **thin (actin) filaments** (arrowheads), 7 nm in diameter. Filaments between these two sizes represent primarily 10-nm **intermediate filaments**. **Myosin**, though present in smooth muscle and essential for its contraction, is not easily preserved in these cells. The assembly of smooth muscle myosin filaments is sensitive to the level of phosphorylation, and when these filaments do assemble, they do so in a wide range of sizes not easily distinguished from those of other smooth muscle filaments.

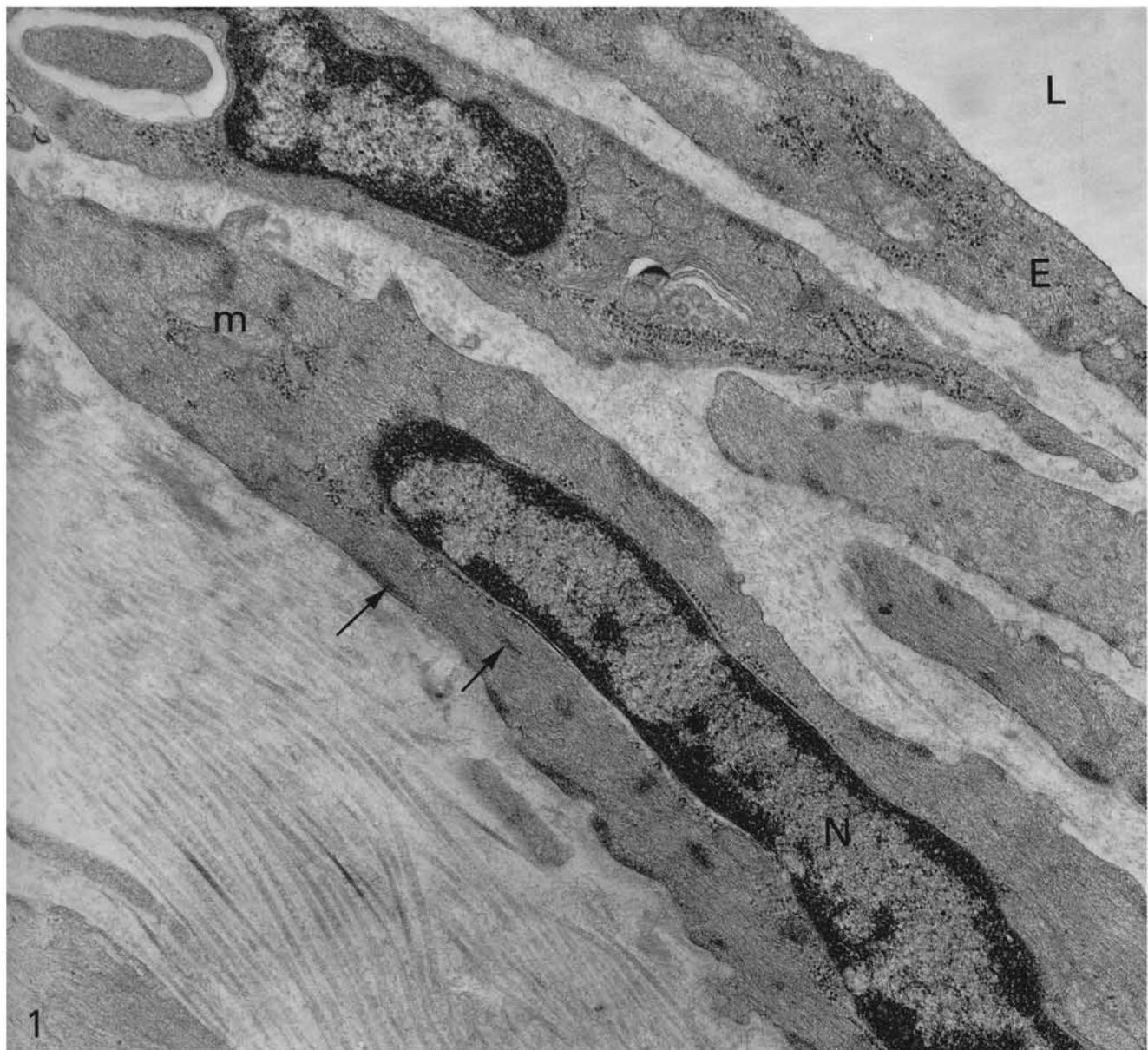
Contraction in smooth muscle depends upon actin–myosin crossbridges and ATP force generation as in other muscle types, but the mechanism differs and a highly organized arrangement of actin and myosin filaments is absent.

Even though smooth muscle does not have the regularly arranged sarcomeres of striated muscle, the following evidence suggests that a contractile unit exists.

1.  $\alpha$ -actinin is localized in dense bodies (as it is in the Z-line).
2. Actin inserts into dense bodies, with polarity directed away from the dense body (as true for actin insertion into the Z-line).
3. Myosin lines up with actin at a certain distance from dense bodies (suggesting some form of I- and A-banding arrangement).

Of the three muscle types, smooth muscle is unique in its ability to divide, to synthesize a wide variety of factors (e.g., prostacyclin, elastic fibers), and to respond to many different physiological mediators (e.g., hormones, mechanical stretch, and growth factors).





## SMOOTH MUSCLE: Contraction

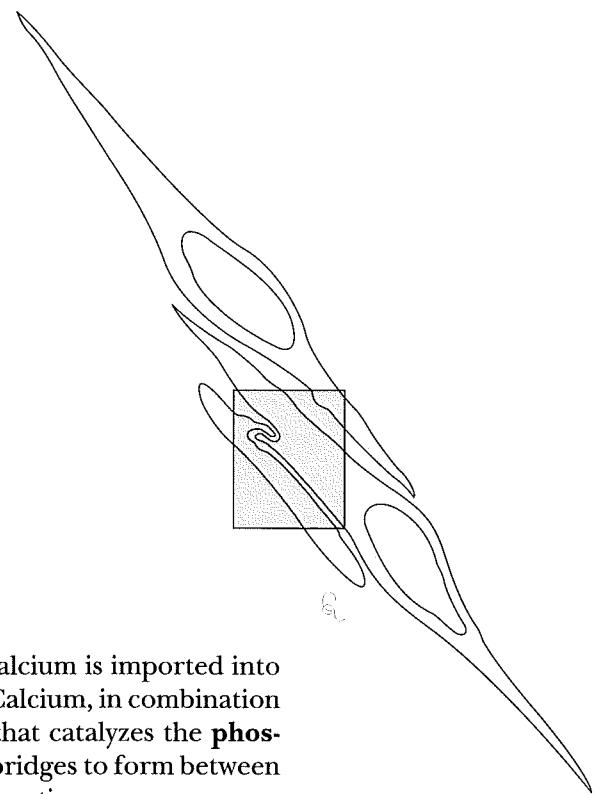
In this micrograph showing cross and longitudinal sections of smooth muscle cells, the **myosin filaments** (arrows) are well preserved and can be seen adjacent to **actin filaments** (arrowheads).

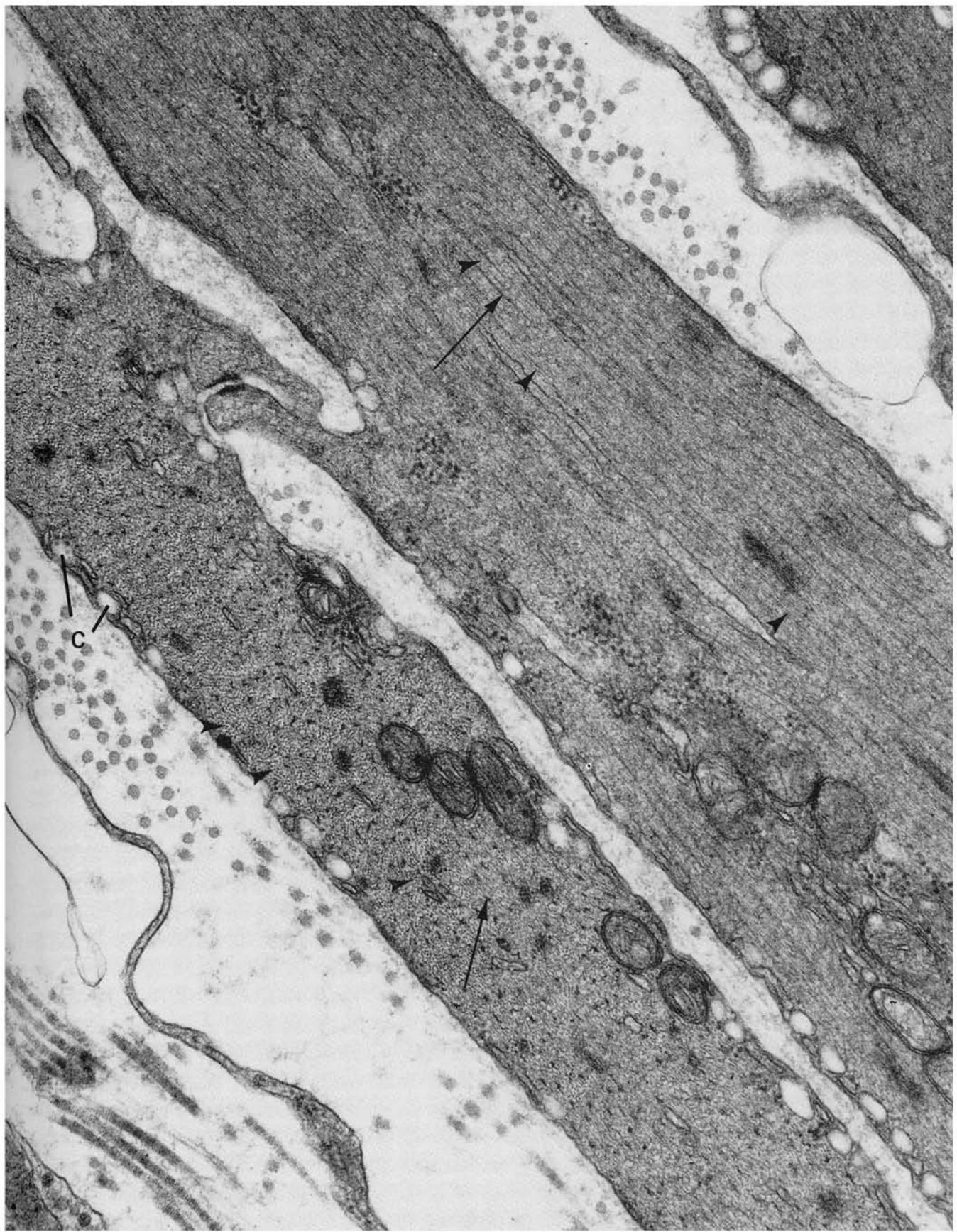
Smooth muscle thick and thin filaments differ from those in striated muscle in ratio (less myosin in smooth) and in structure. The thin filaments contain actin with a unique composition and associated tropomyosin, but not troponin. Thick filaments are variable in size and contain less organized, not necessarily bipolar, arrays of myosin.

The surface area of smooth muscle cells is increased by as much as 70% by flasklike invaginations, **caveolae** (c, micrograph), and it is often suggested that these structures are important in calcium regulation, perhaps by facilitating exchange with the extracellular fluid. As in all muscle, **calcium** regulates contraction, but the mechanism of regulation in smooth muscle involves myosin rather than the thin filament complex. Following receptor-mediated activation, extracellular calcium is imported into the cell and intracellular stores of calcium are released. Calcium, in combination with a soluble protein, **calmodulin**, activates a kinase that catalyzes the **phosphorylation of a myosin light chain**. This enables crossbridges to form between actin and myosin, with ATP hydrolysis resulting in contraction.

Cardiac and smooth muscle display an inherent electrical activity that is (1) modified by the action of the autonomic nervous system and (2) propagated to other cells via gap junctions.

Studies using digital video microscopy to track marker beads fixed to the outer surface of isolated smooth muscle cells show that twisting occurs along with contraction. These studies fit in nicely with the classical observation of corkscrew-shaped nuclei in light microscope preparations of smooth muscle. The arrangement of contractile units oblique to the long axis of the fiber and in parallel (versus in series as in striated muscle) permits large force generation and facilitates the unique capacity of smooth muscle to shorten to 20% of its length.





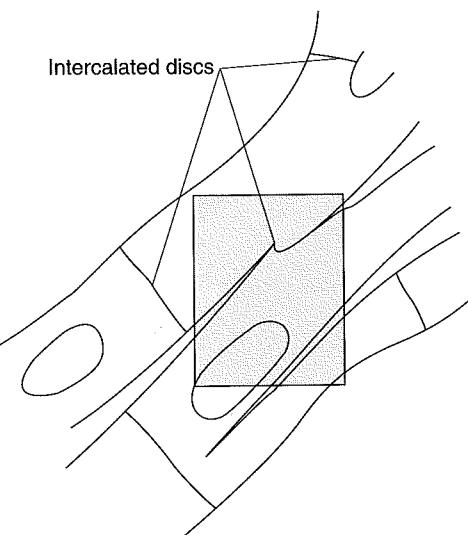
## CARDIAC MUSCLE: Overview

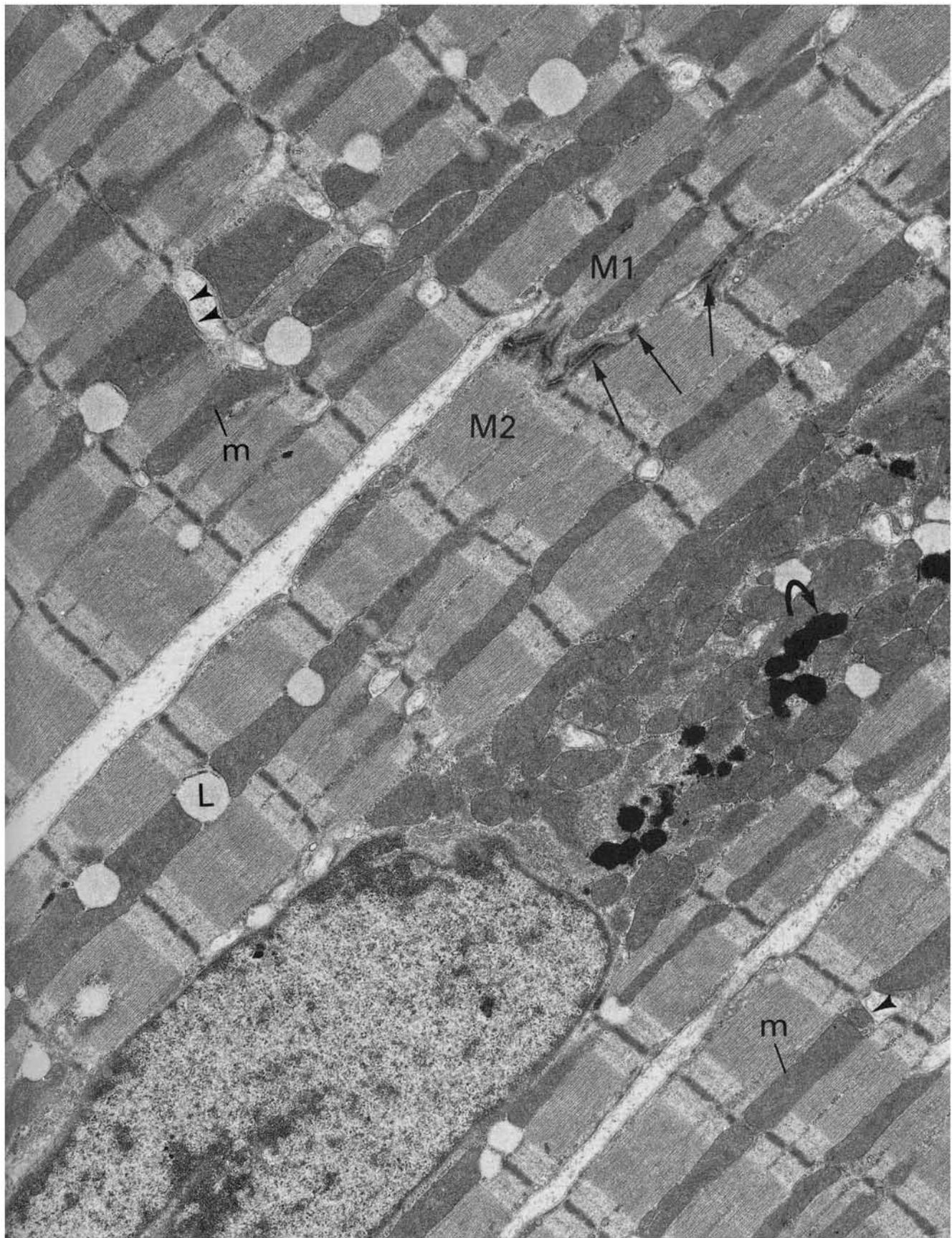
Cardiac muscle fibers form a branching network (M1 branches bind to M2 in the upper right of the micrograph) of cells tightly apposed at specific junctional regions called **intercalated discs** (straight arrows, micrograph). The nucleus lies in the center of the fibers, surrounded by sarcomeres.

The large number of mitochondria (m) and lipid droplets (L) in the cardiac fibers shown in this micrograph reflects the slow oxidative contraction pattern of these **ventricular cells**. Other regions of the heart contain fibers specialized for fast contraction, excitation conduction (e.g., Purkinje fibers), nerve input (e.g., nodes), and hormone production.

Excitation in cardiac muscle is spread along the cell surface and membrane invaginations (**T-tubules**) as in skeletal muscle. In cardiac muscle there is only one T-tubule per sarcomere that invaginates at the Z-line. T-tubules in section are identified by the presence of a basal lamina (arrowheads, micrograph), confirming that the space is extracellular. The action potential propagated along the cell surface and invaginations results in the flow of calcium into the cell from the extracellular fluid. This initial entry of calcium may cause a subsequent release of calcium from the sarcoplasmic reticulum. The sparsity of sarcoplasmic reticulum in the micrograph is characteristic of cardiac muscle in general, and the role of this organelle in the heart is not as well defined as it is in skeletal muscle. Calcium plays the same role in actin–myosin interaction and the resulting force generations in both cardiac and skeletal muscle.

Adult cardiac muscle cells do not normally divide and are not replaced. During their long life they accumulate **residual bodies** (curved arrow, micrograph) that contain aged cellular components removed in the process of routine turnover. The heart responds to increased demands for cardiac output resulting from disorders or normal increased activity (e.g., exercise) with an increase in mass; however, this reflects a hypertrophy of individual cells, not hyperplasia. With prolonged or extensive demands or injury, scar tissue replaces cardiac cells.



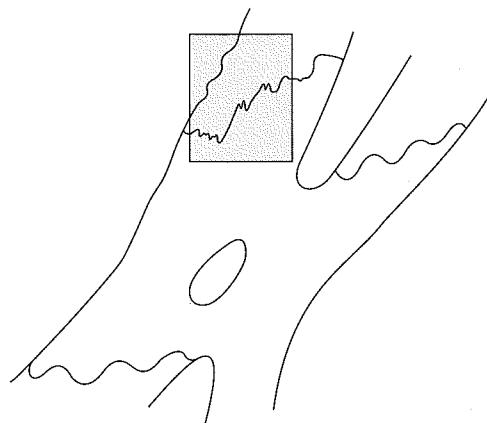


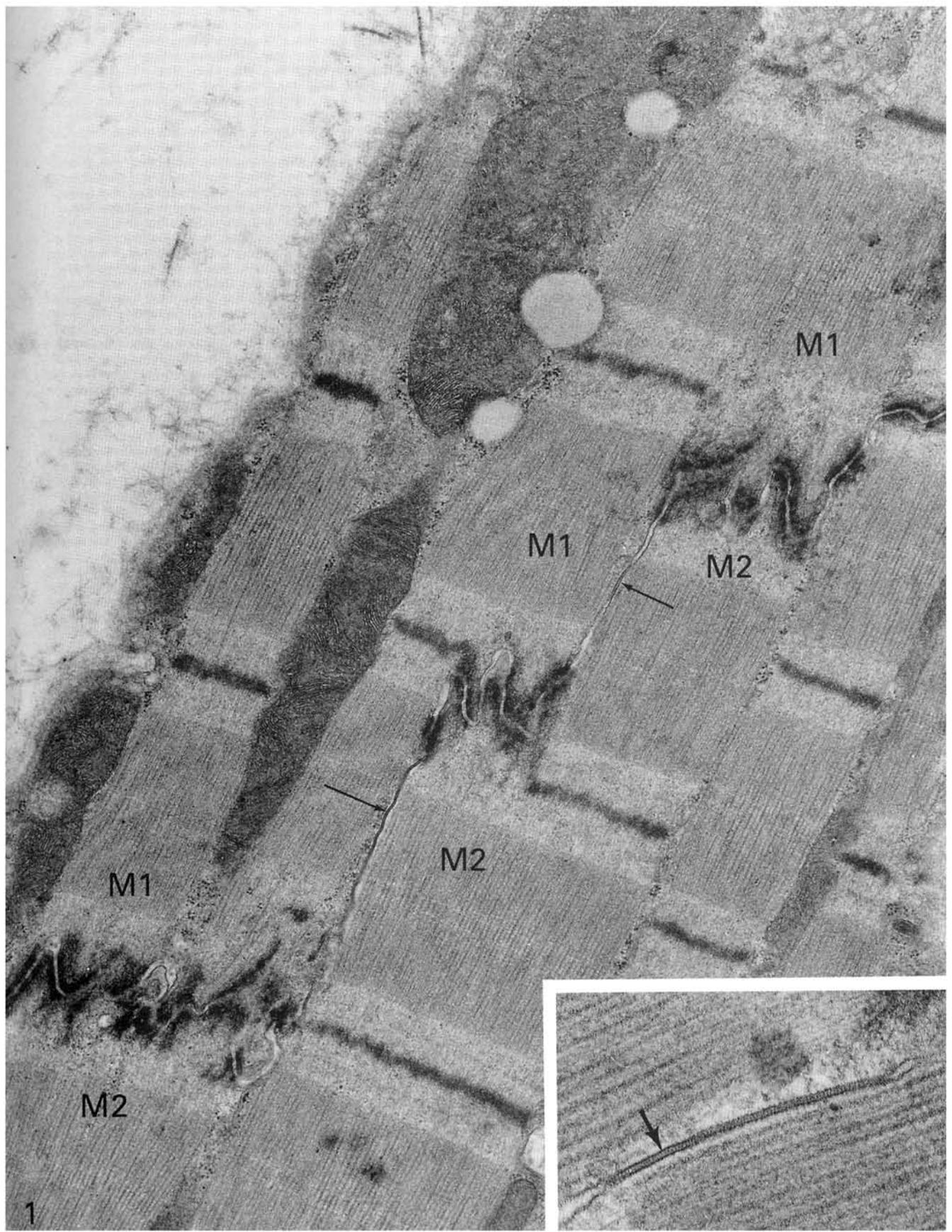
## CARDIAC MUSCLE: Intercalated Disc

The function of cardiac muscle depends upon a tight association and selective communication between individual cells. In micrograph 1 two cardiac muscle cells (M1 and M2) are seen attached end to end by an **intercalated disc**. Each disc consists of a stepwise arrangement of transverse and longitudinal components. The transverse part of the step, localized at the Z-line, contains primarily adherens junctions and is easily recognized by the cytoplasmic densities of associated proteins. Both **macula** (desmosome) and **fascia adherens** are found in this region but are not easily distinguished. The fascia adherens is the attachment site for actin filaments and contains both  $\alpha$ -actinin and vinculin, two proteins also characteristic of other regions of actin–membrane association. The desmosome is the attachment site for **desmin**, a type of intermediate filament. Desmin functions like other intermediate filaments associated with desmosomes, to distribute stress within individual cells.

Longitudinal parts of intercalated discs are composed primarily of **gap junctions** (arrows, micrograph 1 and inset). The cross striations bridging the intercellular space (inset) are connexons, the protein channels through which ions and small signal molecules move.

Gap junctions allow passage of the action potential through an extensive, intricate journey from its site of origin. The action potential is generated in the sinoatrial (S-A) node (the heart's most rapid pacemaker) by spontaneous depolarization of specialized cardiac muscle cells. It is transmitted in a defined sequence through the atria to a second specialized region, the atrioventricular (A-V) node, then to the bundle of His, Purkinje fibers, and ventricular fibers. Both the S-A and A-V nodes are innervated by sympathetic and parasympathetic neurons that control the speed of conduction and the rate and force of contraction.





# NERVE

## OVERVIEW

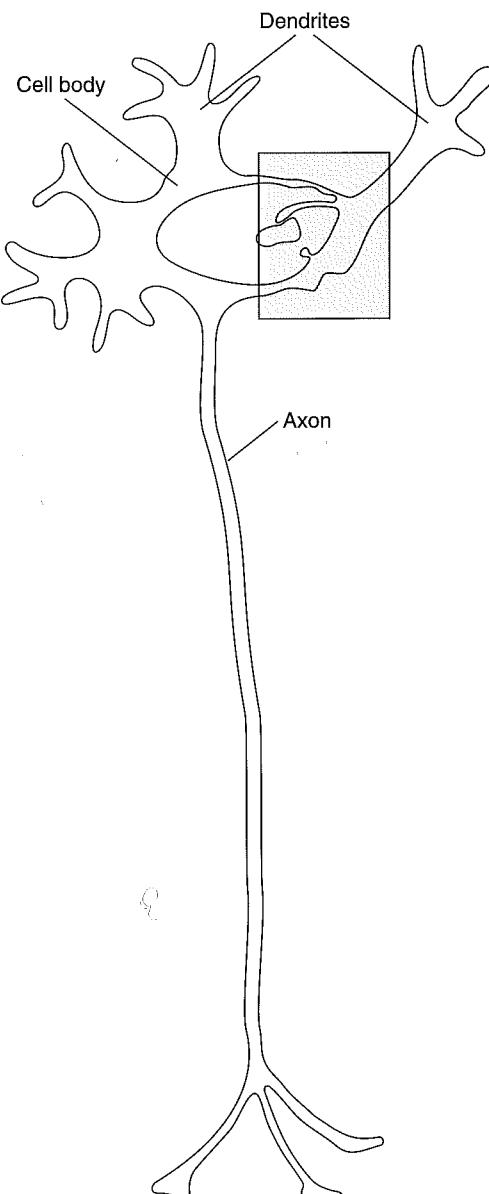
Most neurons consist of (1) a **cell body** with a large euchromatic nucleus and prominent nucleolus, (2) **dendrites**, thick, relatively short processes that carry signals to the cell body, and (3) the **axon**, a single long, thin process that carries signals away from the cell body. The size and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

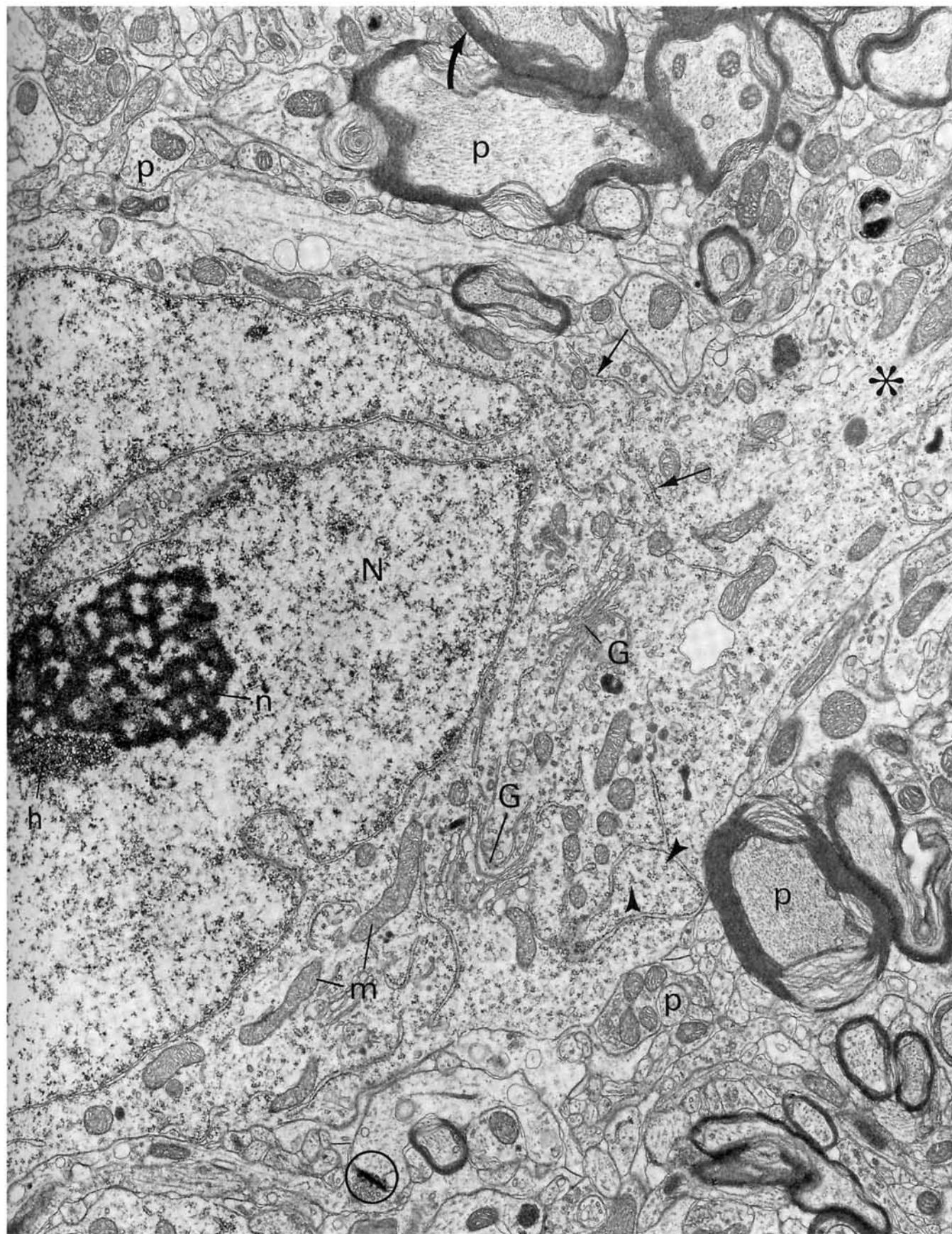
The cell body of a neuron from the central nervous system (CNS) occupies the center of the micrograph. A single large nucleolus (n) with its associated heterochromatin (h) lies in the indented nucleus (N). The cytoplasm surrounding the nucleus contains mitochondria (m), free (arrowheads) and attached (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.



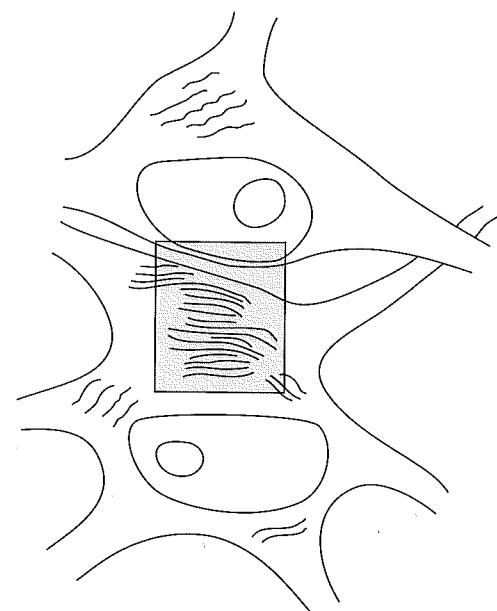


## NEURON: Nissl Bodies

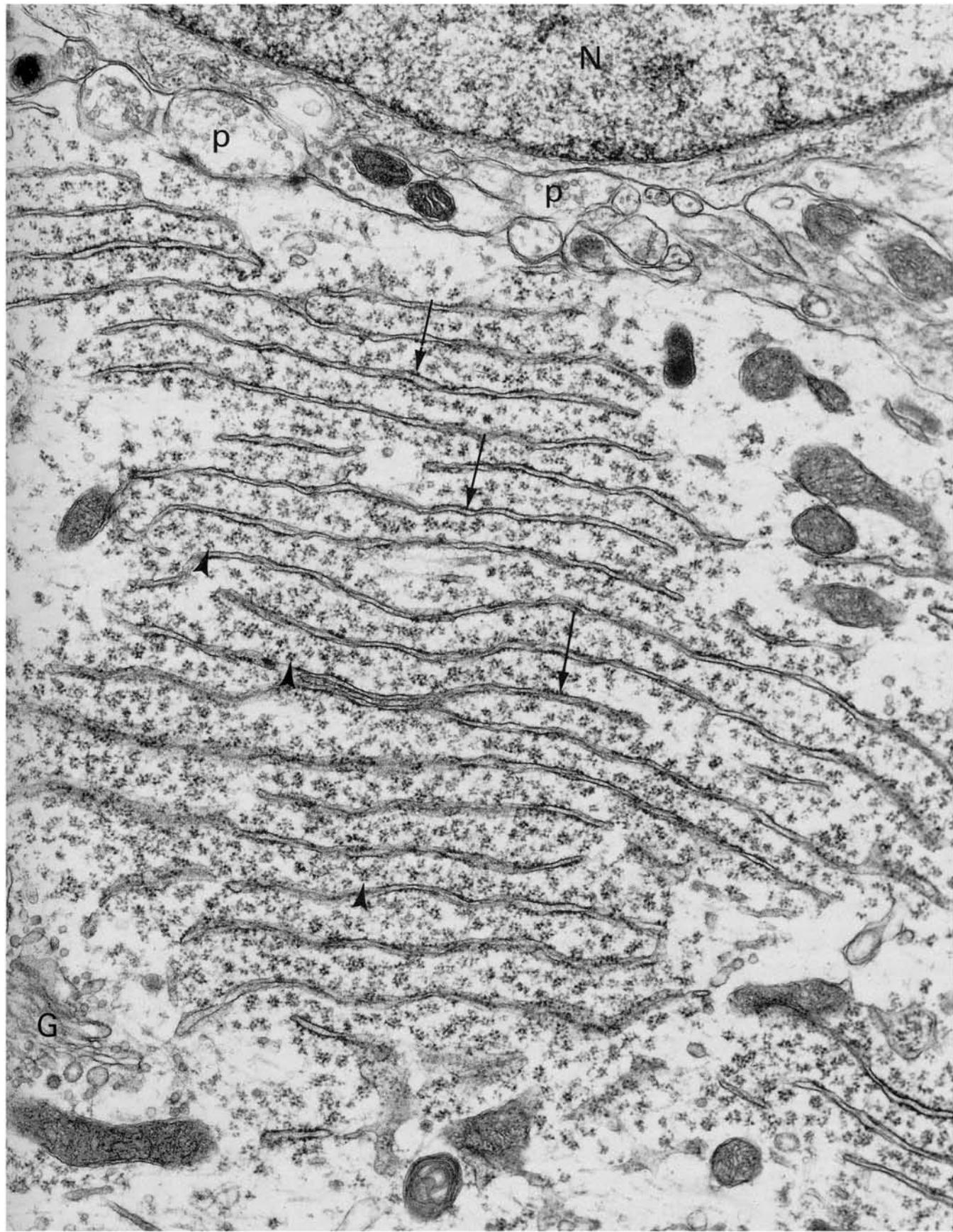
The **ribosomes** in many nerve cell bodies are arranged in a distinctive pattern. Flattened cisternae of rough ER (arrows, micrograph) alternate with groups of free polysomes (arrowheads, micrograph) to form **Nissl bodies**. The entire ribosome assembly in the micrograph represents a single Nissl body, 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



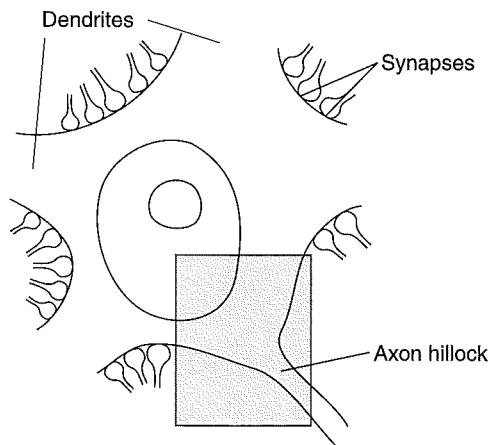
## NEURON: Axon Hillock

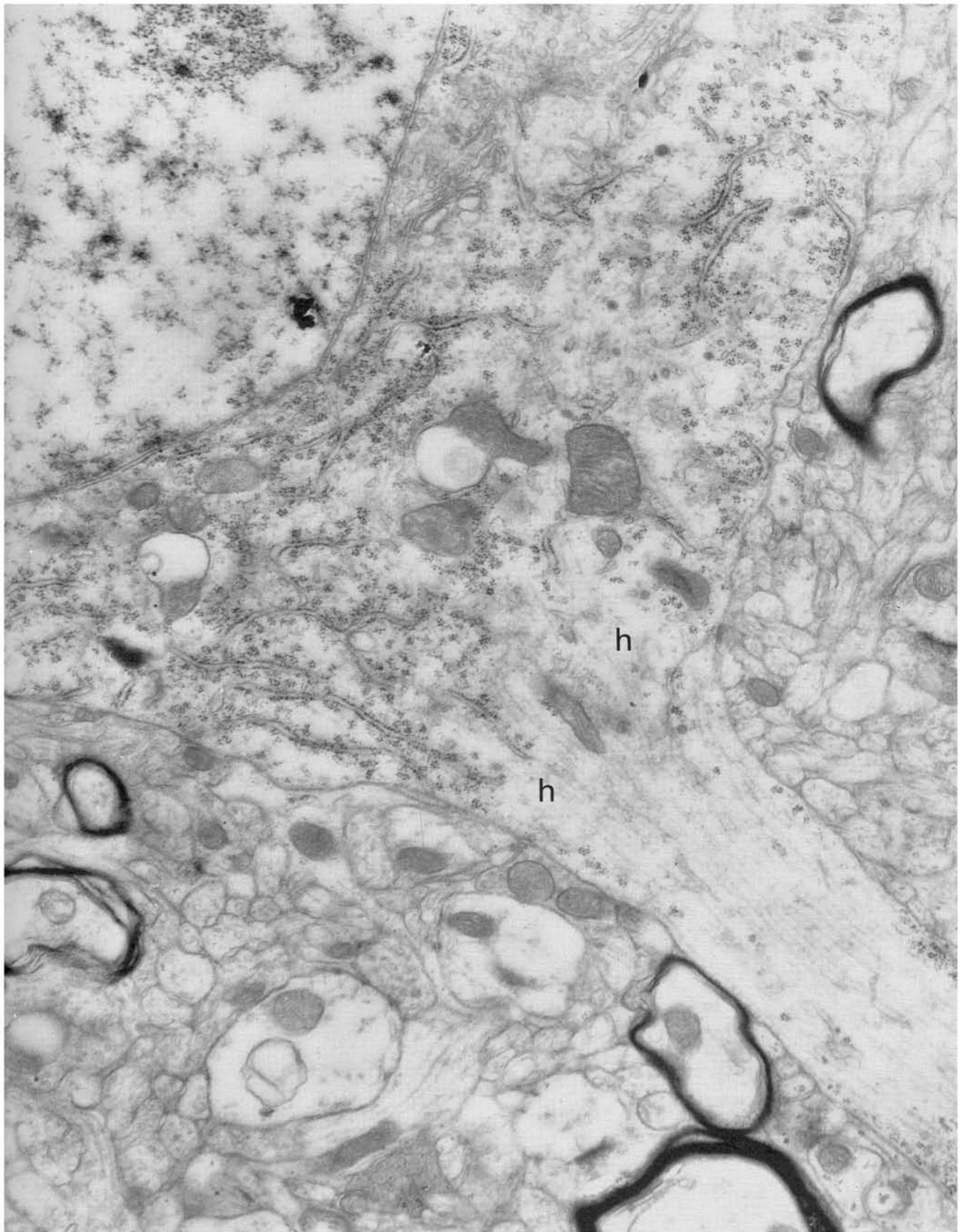
A single neuron receives input from up to a thousand other neurons and has synapses covering the cell body, dendritic processes, and axon hillock. The **axon hillock** (h, micrograph) is the initial segment of an axon, distinguished from the cell body by a well-organized cytoskeleton and the relative 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.,  $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{K}^+$ ) 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  $\text{Na}^+$  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)  $\text{Na}^+$  into the neuron through voltage-gated channels, depolarizing the membrane, and (2)  $\text{K}^+$  leaving the neuron through voltage-gated channels, restoring the membrane potential to resting levels.





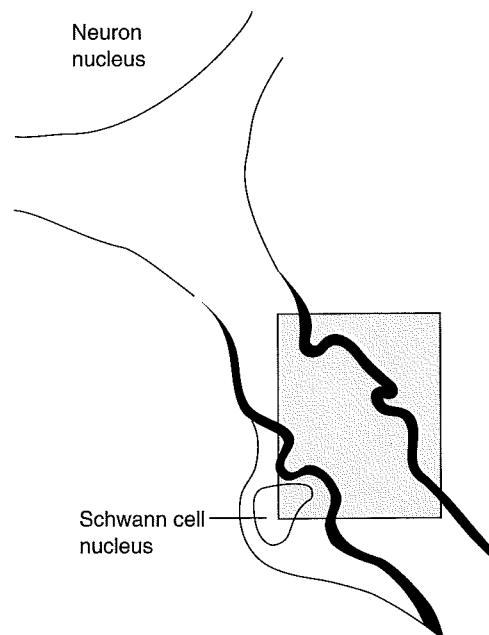
## NEURON: Axonal Cytoskeleton

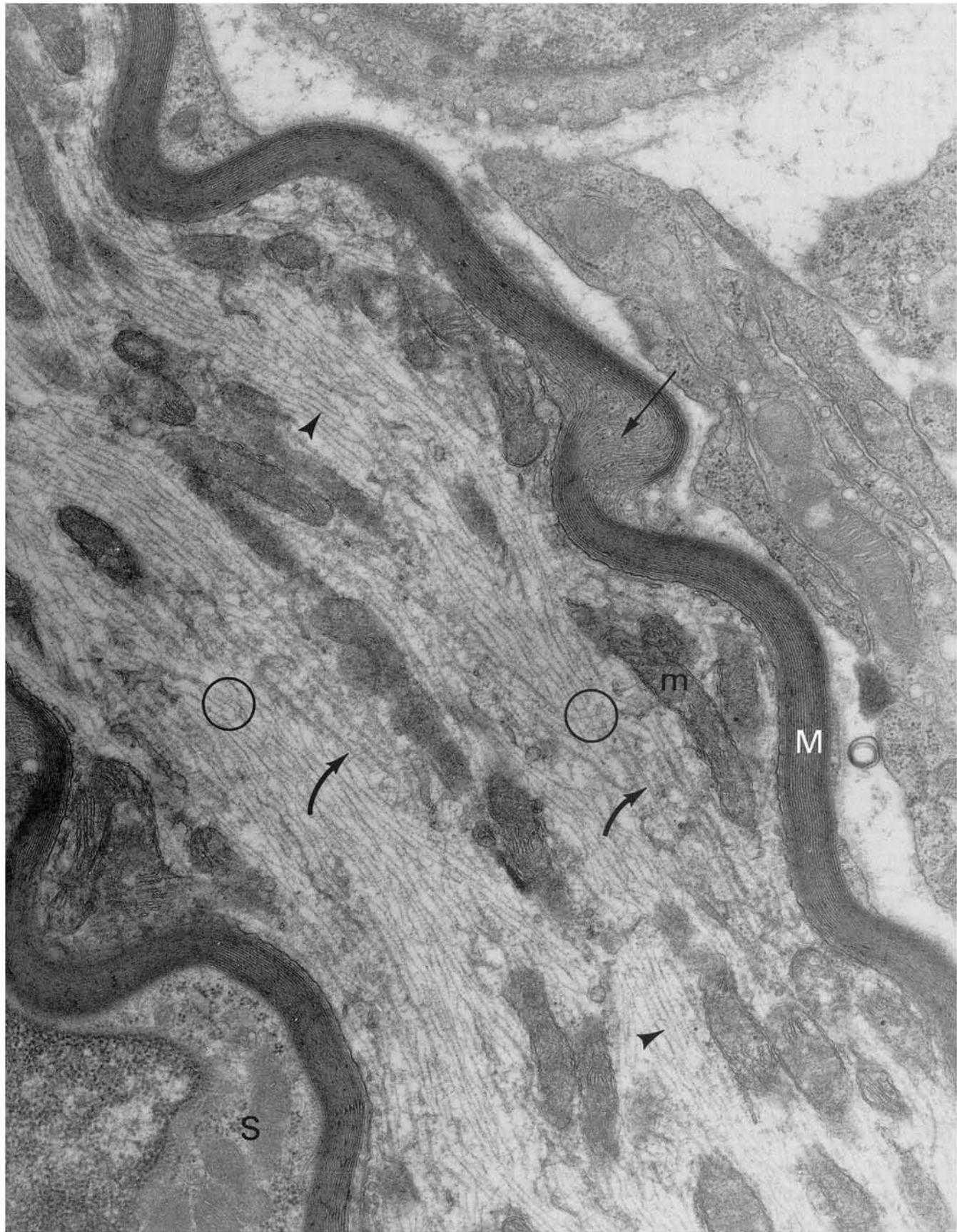
All axons have an abundance of **cytoskeletal elements** running parallel to their long axis. These filamentous proteins are the most prevalent proteins in axons. **Microtubules** (curved arrows) and **neurofilaments** (arrowheads) can be distinguished in the axoplasm of the myelinated axon in the micrograph. 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.





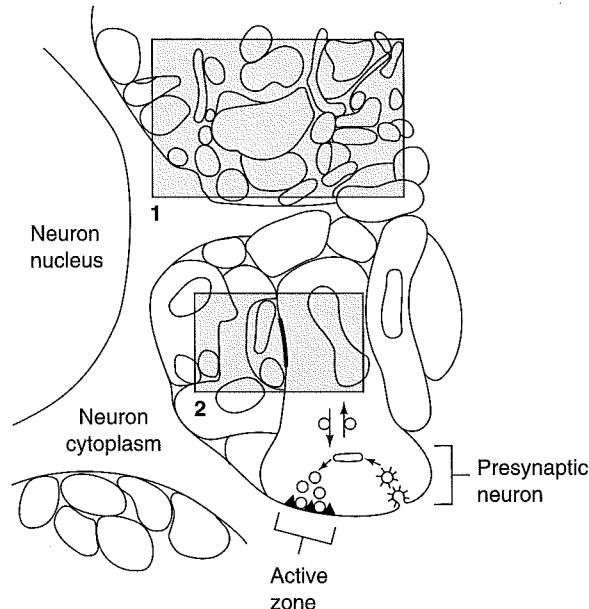
## NEURON: Synapse, Neurotransmitters

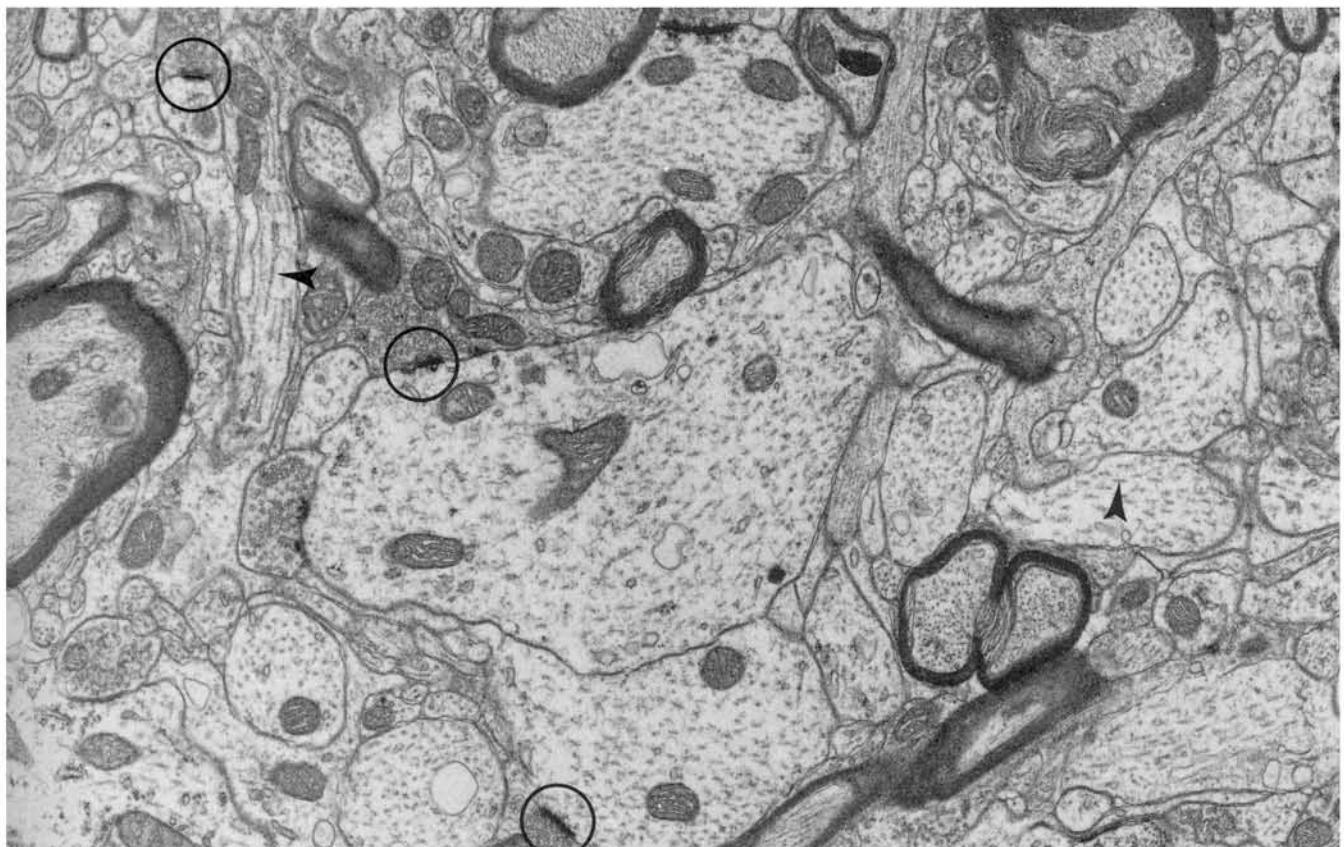
Information is transmitted from neurons to other cells in specialized regions known as **synapses**. Synapses occur either between neurons and the effector cells they innervate, such as muscles and glands, or between two neurons, as in the central nervous system (shown here) and peripheral autonomic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

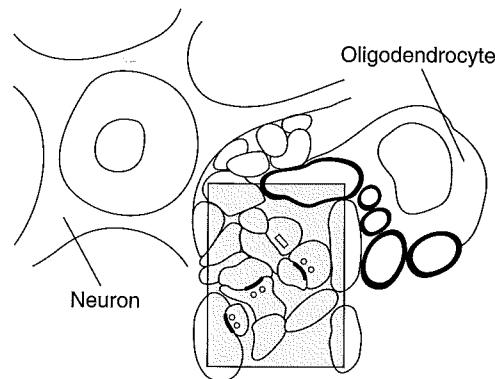




## NEURON: Synapse, Classification

**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 ( $\gamma$ -aminobutyric acid, or GABA, aspartic acid, glutamic acid, glycine)

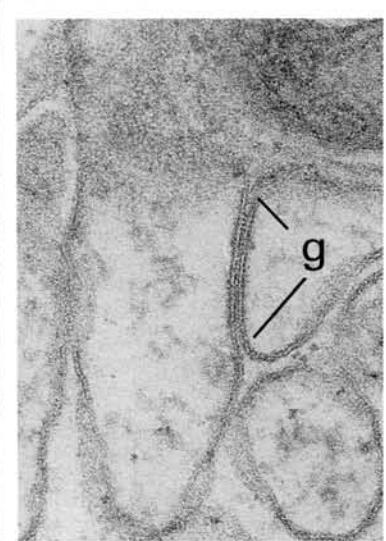
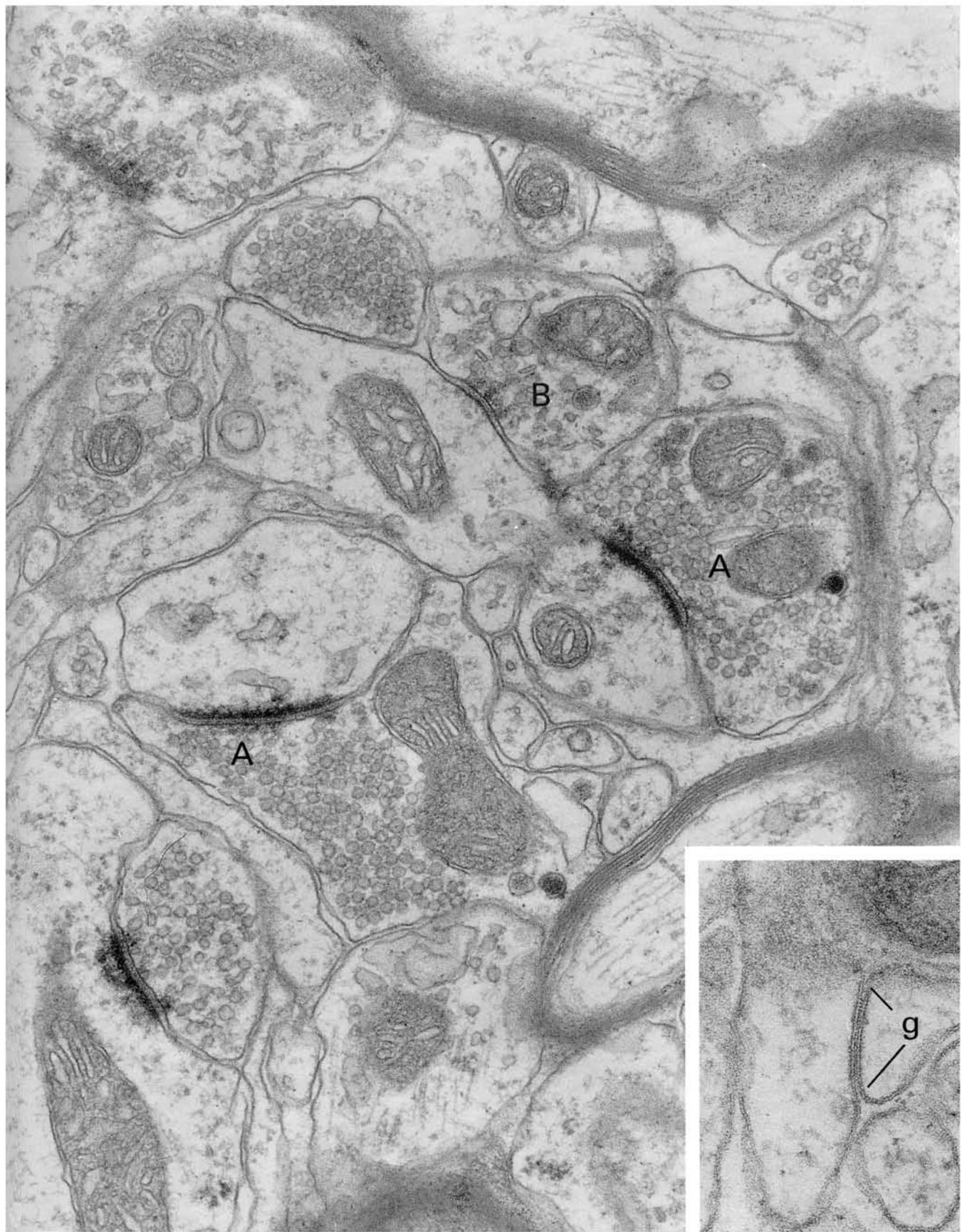
### Large-Molecule Neurotransmitters

- Neuropeptides (cholecystokinin,  $\beta$ -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.

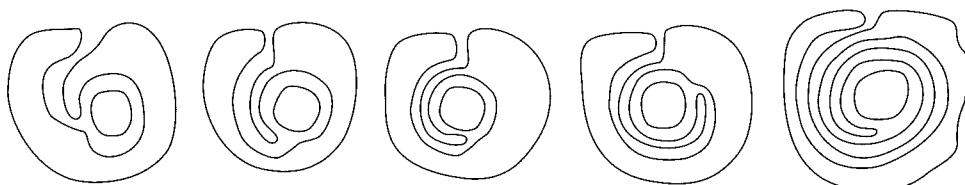
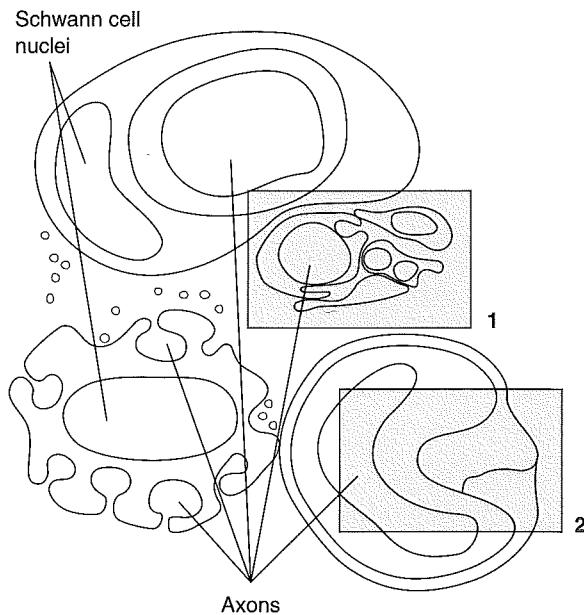
In addition to the coupling of neurons by neurotransmitters, some neurons are coupled electrically via gap junctions (g, inset). In this type of “synapse,” nerve processes, separated by an extremely small intercellular space (2-nm), are associated via connexons (see Epithelium, page 54) that carry current 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

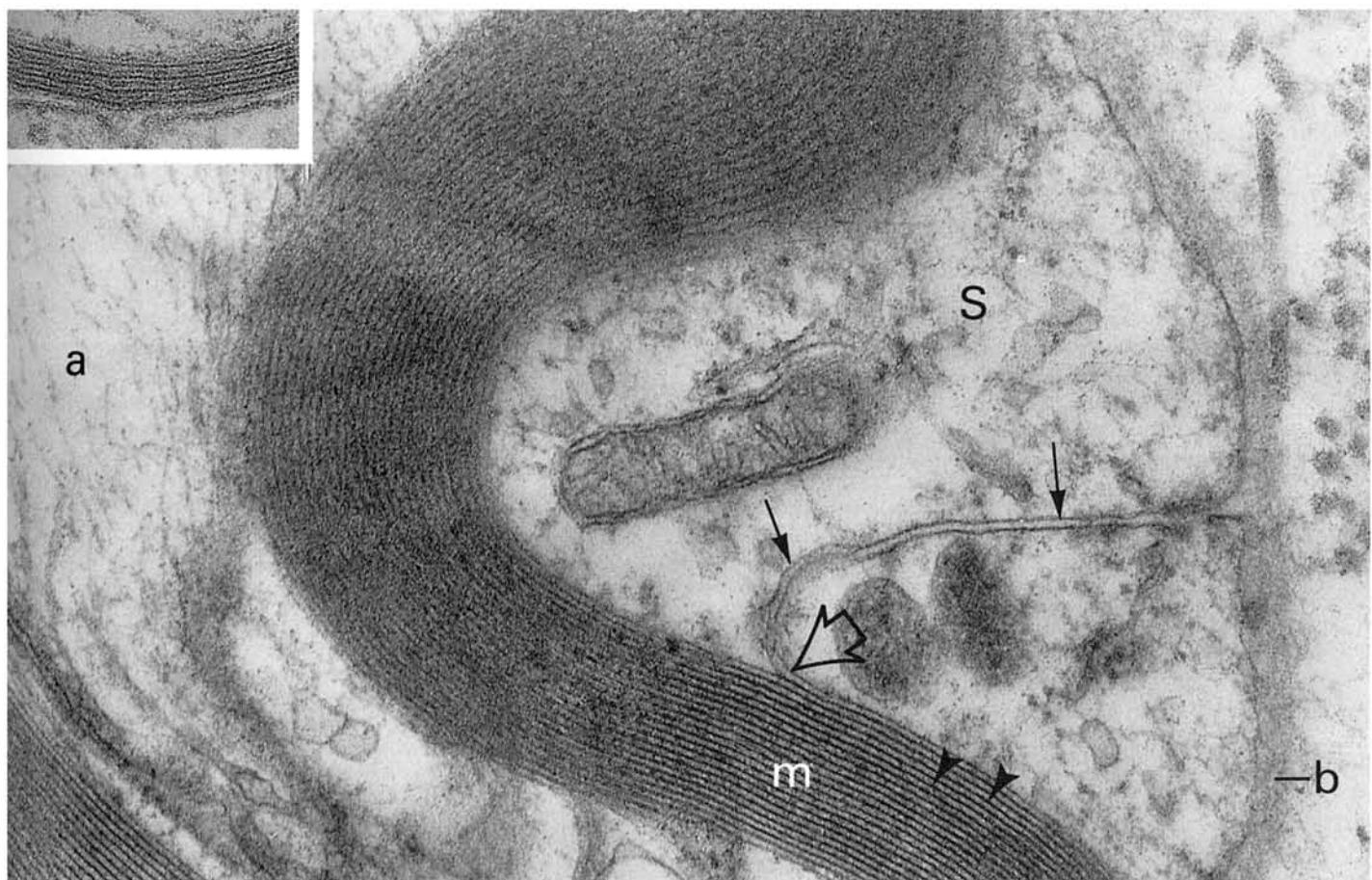
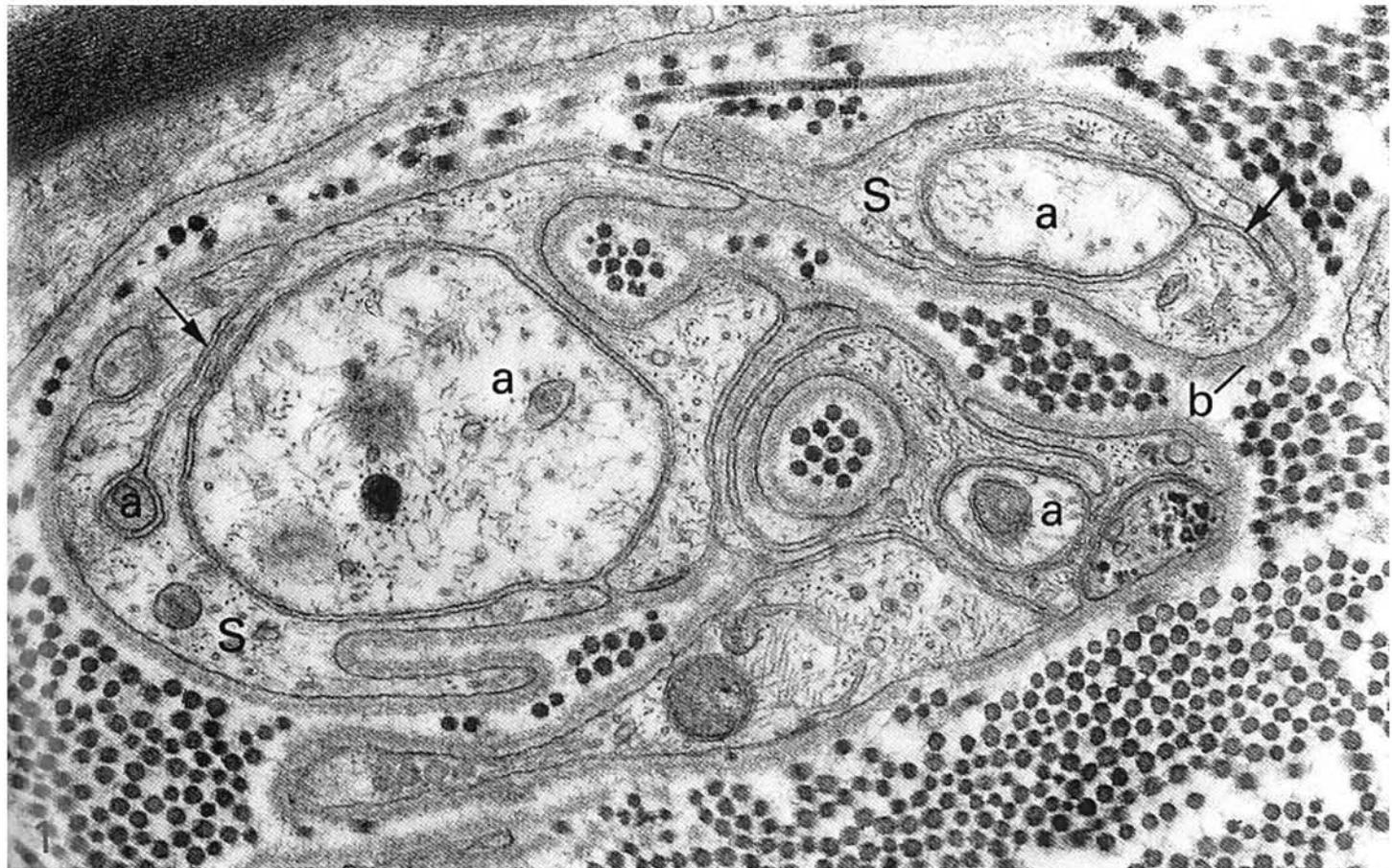
Schwann cells surround all axons in the peripheral nervous system (PNS). The association between Schwann cells and axons is intimate but it is different in complexity in **unmyelinated** and **myelinated** axons. Unmyelinated axons (a, micrograph 1) simply indent into the cytoplasm of a Schwann cell (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.



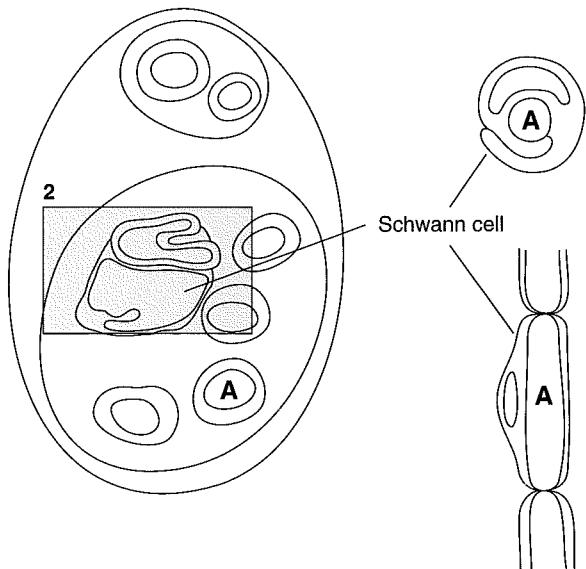
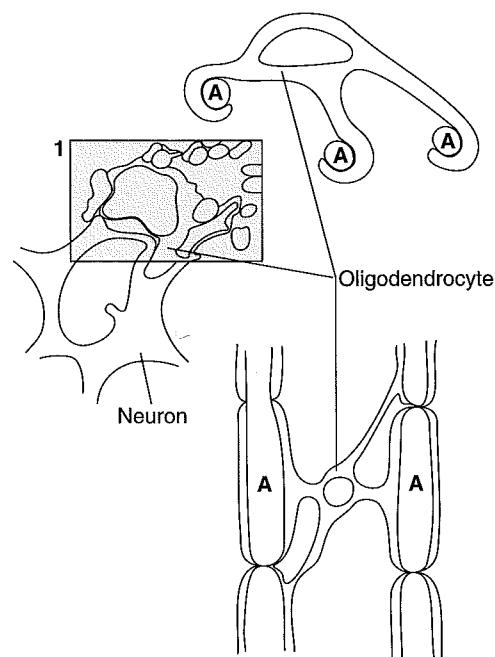
## GLIAL CELLS: Oligodendrocytes and Schwann Cells

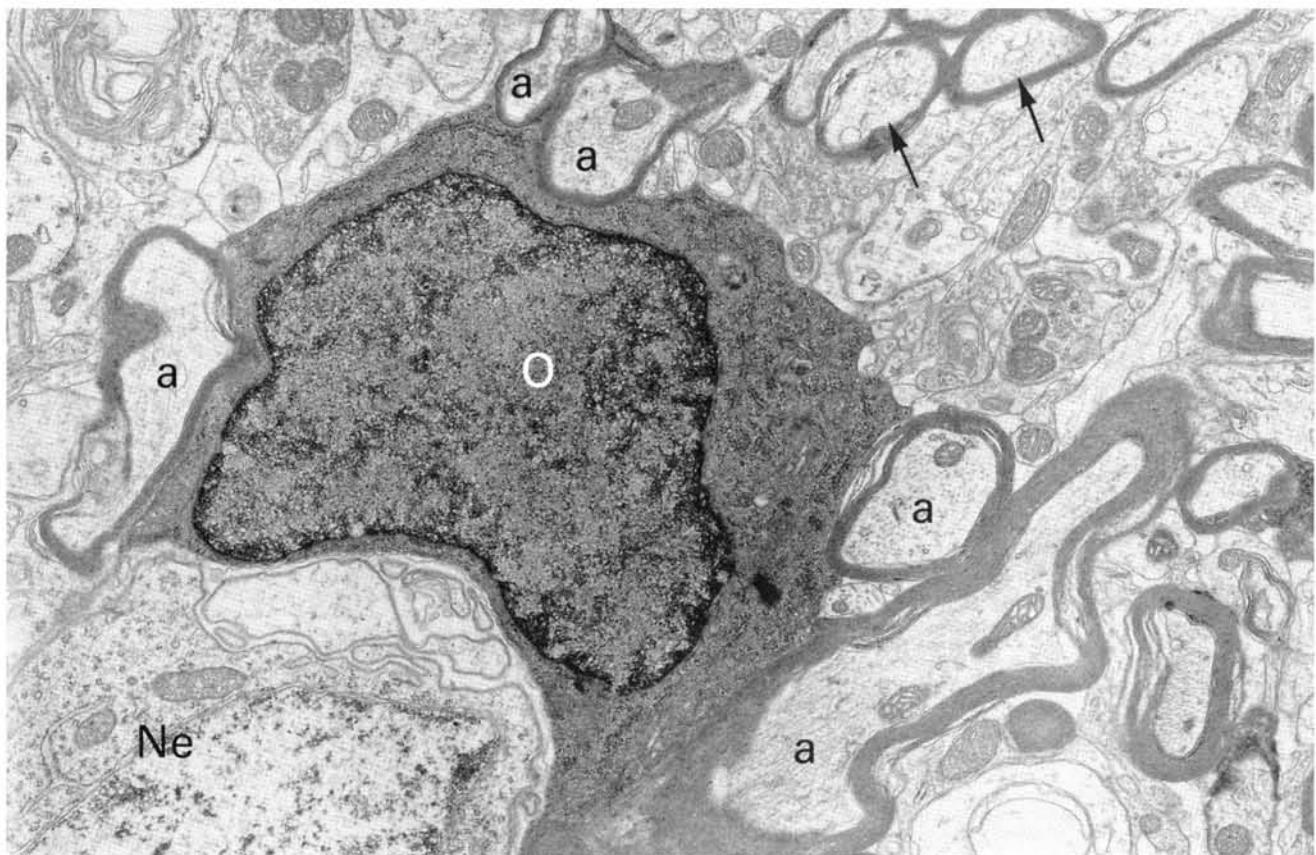
In the central nervous system, myelination is carried out by **oligodendrocytes** (O, micrograph 1). A single oligodendrocyte extends several processes that each myelinate a section (internode) of a different axon or of the same axon. The oligodendrocyte in micrograph 1 is seen in association with five 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

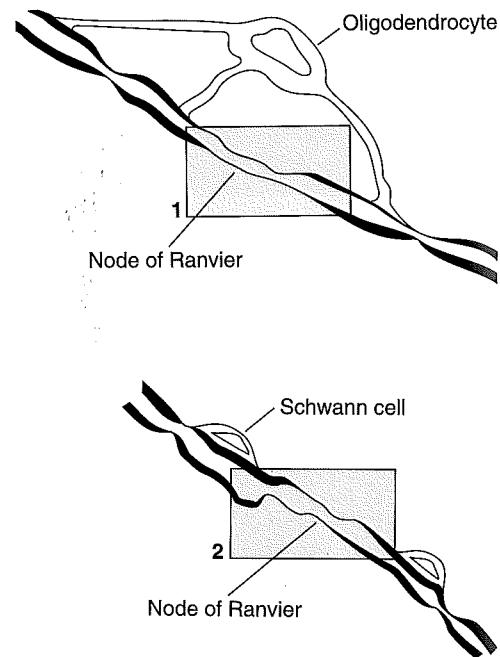
Action potentials initiated at the axon hillock are propagated down axons at different velocities, ranging from 1 to 100 meters/second (220 miles/hour). The **speed of impulse conduction** is related to axon diameter and the extent of myelination. As the diameter of an axon increases, internal resistance 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.

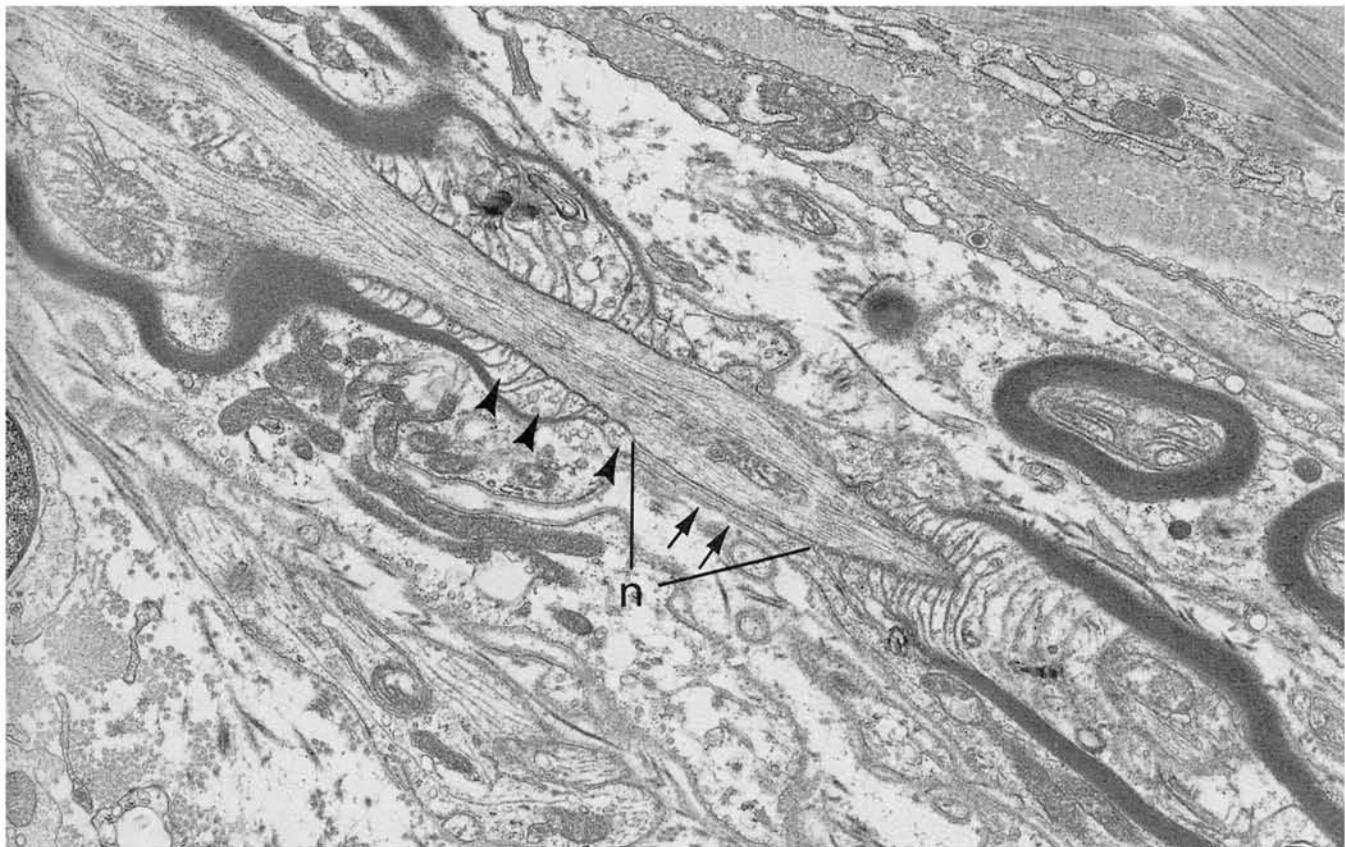
Most axons with a diameter of one micron and greater undergo myelination. The myelin coat increases the velocity of impulse conduction by increasing the membrane resistance and thus insulation, reducing membrane capacitance and ion loss during current flow. Ideally, the myelin insulation would be continuous 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  $\text{Na}^+$  channels. When these voltage-gated channels open,  $\text{Na}^+$  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

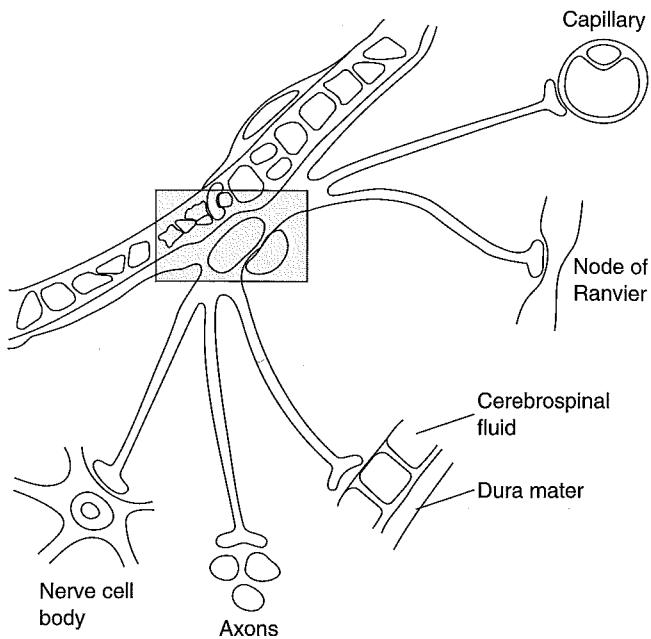
**Astrocytes** (A, micrographs 1 and 2, micrograph 2 courtesy of Dr. Larry Mathers), the most common glial cell in the central nervous system, are shaped like neurons, with many long processes extending from a central cell body. Each elongated process terminates in an “**end-foot**” that rests on nerve 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.

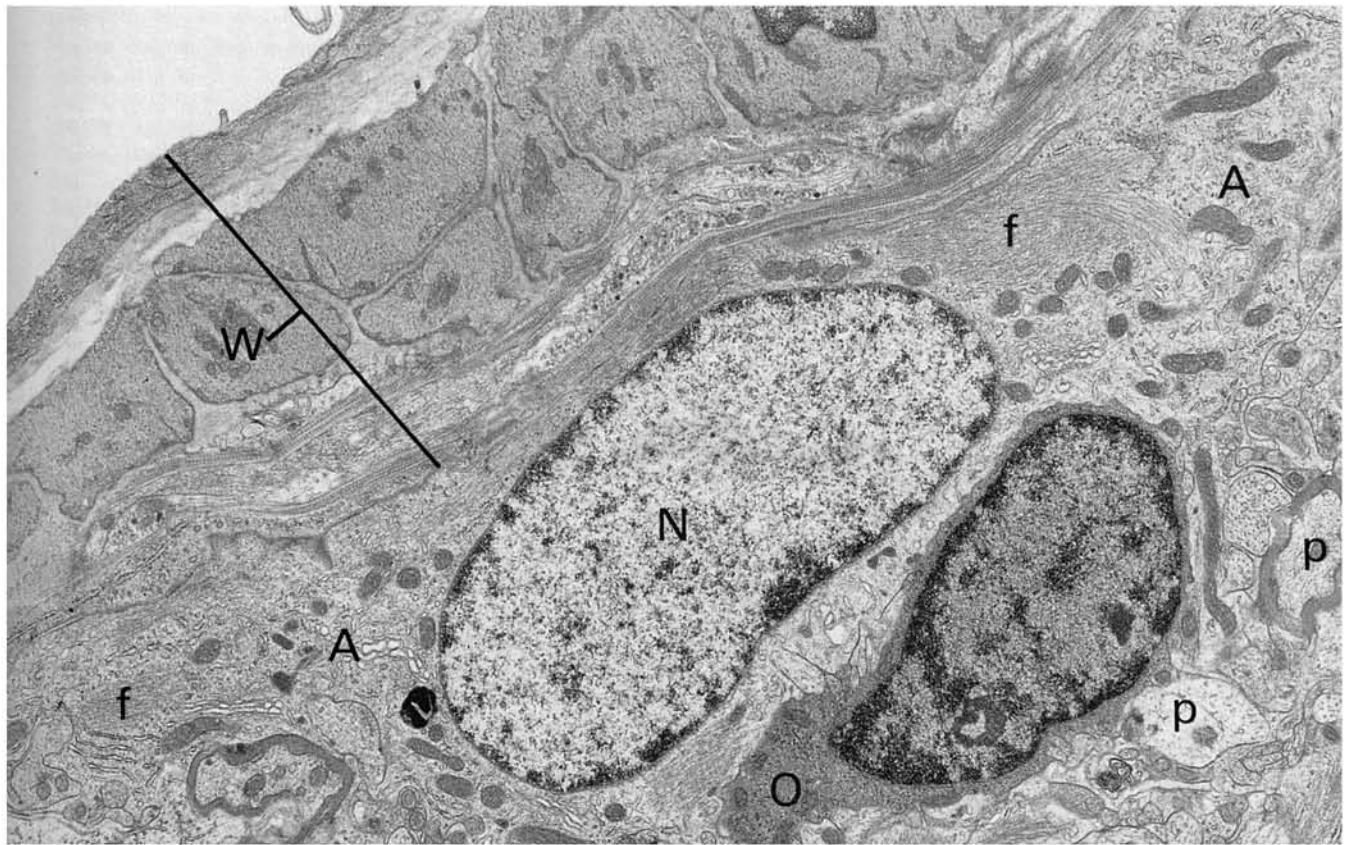
The euchromatic nucleus (N, micrographs 1 and 2) of astrocytes reflects, in part, the synthesis of the cytoskeleton. However, most of the nuclear activity is needed to maintain the extensive volume of cytoplasmic processes. Oligodendrocytes (O, micrographs 1 and 2), even though smaller cells, are also 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.

