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"The Nerve Cell and Its Processes"

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II. THE NERVE CELL AND ITS PROCESSES

A. The Soma

That part of a neuron which contains the nucleus and surrounding cytoplasm is the **soma.** It may be a gentle swelling along the course of an axon, as in bipolar neurons; or a quasi-detached appendage of the axon, as in unipolar cells with long stem-like processes; or terminal or subterminal, as in superficial sensory neurons; or at the junction of dendrites and axons, as in vertebrate multipolars. The position of the soma is not a fundamental feature, especially in distinguishing between axon and dendrite. We can think of the nucleus and the surrounding cytoplasm as a trophic apparatus forming a swelling that may lie within axonal membrane, within dendritic membrane, or where the two kinds of membrane meet. The soma may be large (>500 μm in diameter) with a watery nucleus, small (<2 μm) with a chromatin-rich nucleus and very little cytoplasm, or intermediate in size and nuclear composition. In some neurons the volume of the soma may be as little as 1/10,000th that of the axon; in others the volume may nearly equal or even exceed that of the axon.

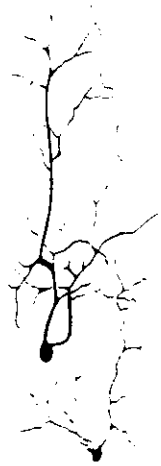
The contents of the soma and the diverse types of neurons are treated in Section II-H. First it will be helpful to discuss the two kinds of processes that project from nerve cells.

B. Axons

The **axon** is usually, but imprecisely, considered functionally to be a process specialized for conduction of excitation over considerable distances. The term is better defined on histological grounds. Microscopically an axon can be recognized as a long fiber that is relatively uniform in diameter, smooth surfaced, has branches at long intervals, is usually covered with a sheath of closely applied cells, has synaptic endings upon it at only a few spots, and generally lacks some cytoplasmic constituents of the soma (Fig. 2.9,B). Most neurons have one axon. Even with these distinguishing features, it is sometimes impossible to say whether a given process is an axon or whether a given cell has an axon. Nerve cells without demonstrable axons are called amacrine cells (Fig. 2.2). A general term for processes, noncommital as to their type, is **neurite.**

The main functional characteristic of the axon is its ability to conduct excitation nondecrementally over some distance—that is, to support the all-or-none nerve impulse (Chapter 4). But this ability is not strictly a defining criterion. Impulses sometimes arise a millimeter or more downstream from the beginning of the axon, or they may arise upstream in the dendrites. It is not certain whether

Figure 2.2
Amacrine cell or neurons without a definite axon.



From the optic lobe of Sepia, *a cuttlefish.* [*Cajal, 1917.*]

From the optic medulla of Calliphora, *a fly.* [*Cajal and Sanchez, 1915.*]

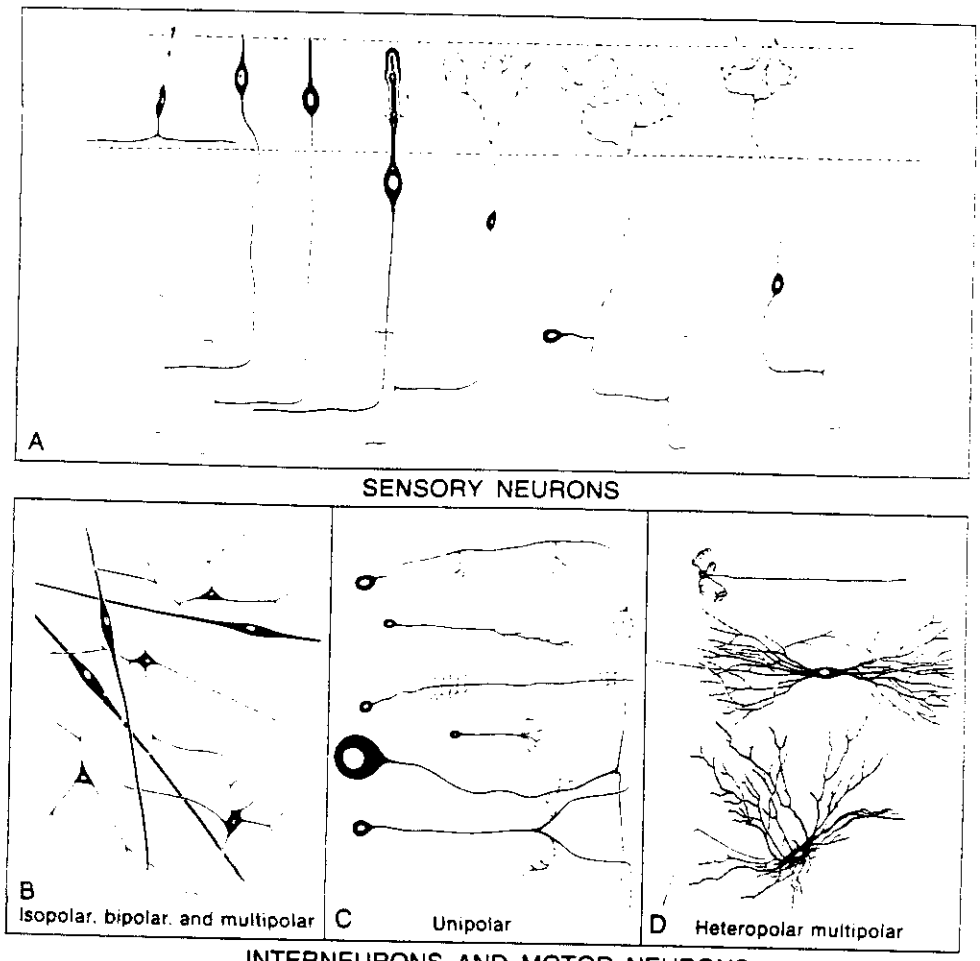


Figure 2.1
Types of neurons, distinguished on the basis of number and differentiation of processes. A. Sensory neurons. The most primitive (far left) send axons into a superficial plexus. In animals with a central nervous system, the commonest form is a similar bipolar cell in the epithelium with a short, simple or slightly elaborated (arthropod scolopale) distal process and an axon entering the central nervous system and generally bifurcating into ascending and descending branches. A presumably more derived form (third from right) is that with a deep-lying cell body and a long, branching distal process with free nerve endings. In vertebrates, such cells secondarily become unipolar and form groups in the dorsal root ganglia. Shown on the far right is a vertebrate vestibular or acoustic sensory neuron that has retained the primitive bipolar form but has adopted (presumably secondarily) a specialized nonnervous epithelial cell as the actual receptor element. B. Isopolar, bipolar, and multipolar neurons in the nerve net of medusa. These may be either interneurons or motor neurons or both; no differentiated dendrites can be recognized. C. Unipolar neurons representative of the dominant type in all higher invertebrates. Both interneurons and motor neurons have this form. The upper four are examples of interneurons and the lower two of motor neurons. Afferent branches may be elaborate but are not readily distinguished from branching axonal terminals. The number and exact disposition of these two forms of endings and of major branches and collaterals are highly variable. D. Heteropolar, multipolar neurons—the dominant type in the central nervous system of vertebrates. The upper two are interneurons; the lower one, a motor neuron. [Bullock and Horridge, 1965.]

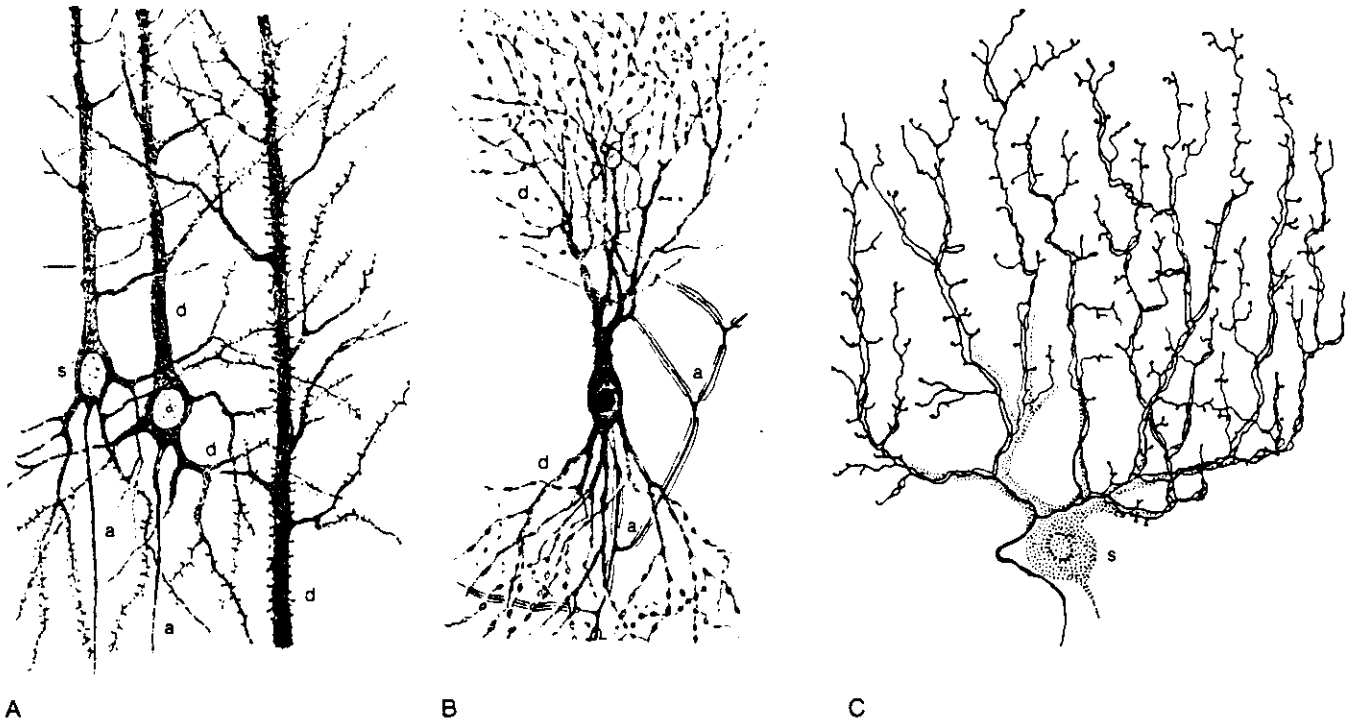
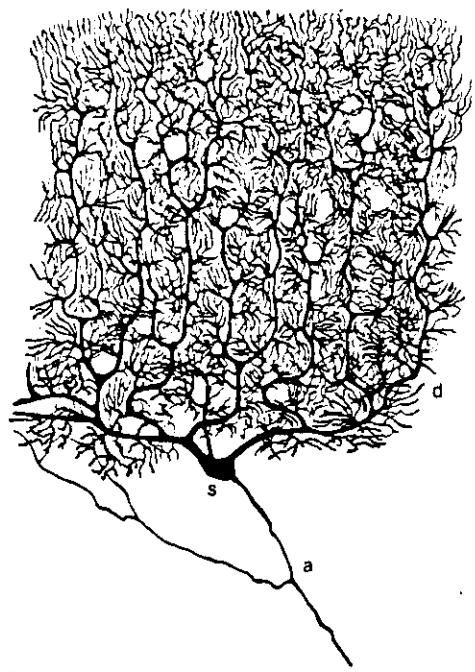


Figure 2.3
Axons and dendrites. Several types of neurons from the mammalian brain, impregnated by the Golgi method. The axons (*a*) are shown in color; dendrites (*d*) and somas (*s*) are in black. **A.** Pyramidal cells of the cerebral cortex, each with an axon extending from the lower pole of the soma, three or four basal dendrites extending sideways and downwards, and a thick apical dendrite extending upwards and out of the picture; at the right an apical dendrite whose soma is below and out of the picture. **B.** Pyramidal cell of the hippocampus with two sets of dendrites. **C.** Purkinje cell of the cerebellar cortex, faintly stained, with the axon of a distant soma, probably from the inferior olive of the medulla, entwining the dendrites; this axon is called a climbing fiber. **D.** Purkinje cell with its dendrites well stained; they form a flat fan. **E.** Basket cell of the cerebellar cortex with dendrites extending upwards and an axon forming terminal baskets around a row of faintly shown Purkinje cell somas. **F.** Cell from the cerebral cortex, with short axon, often called Golgi type II or intrinsic neuron because it does not project beyond the local region. Golgi impregnation. **G.** Motor neuron of the electric lobe of the medulla of the electric ray, *Torpedo*, teased out after dissociating the tissue, therefore with the processes broken off. Also shown are the bases of the dendrites and the axon (axon hillock) leading into the initial segment of myelinated fiber. [Cajal, 1909.]



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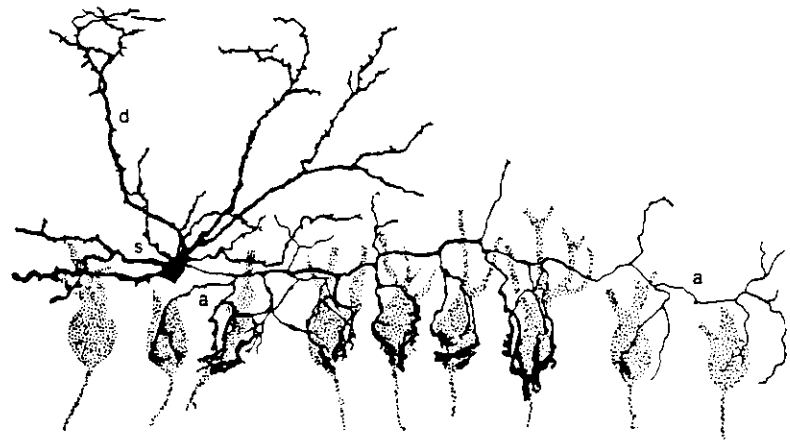

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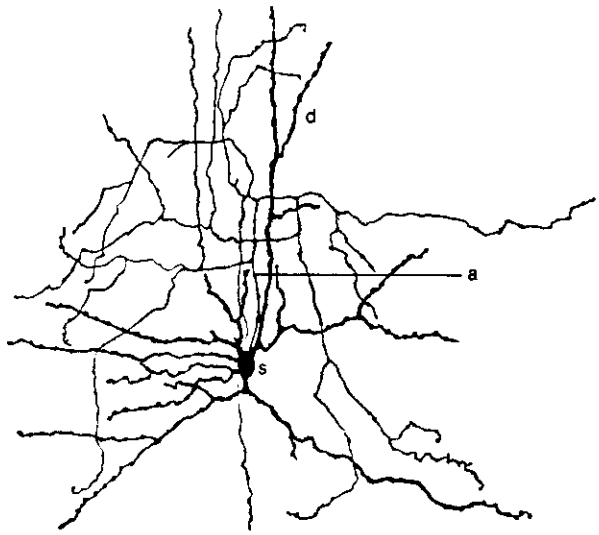

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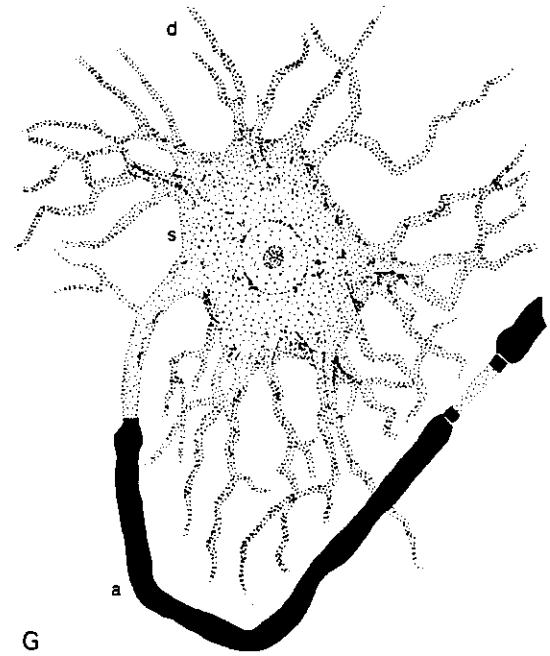

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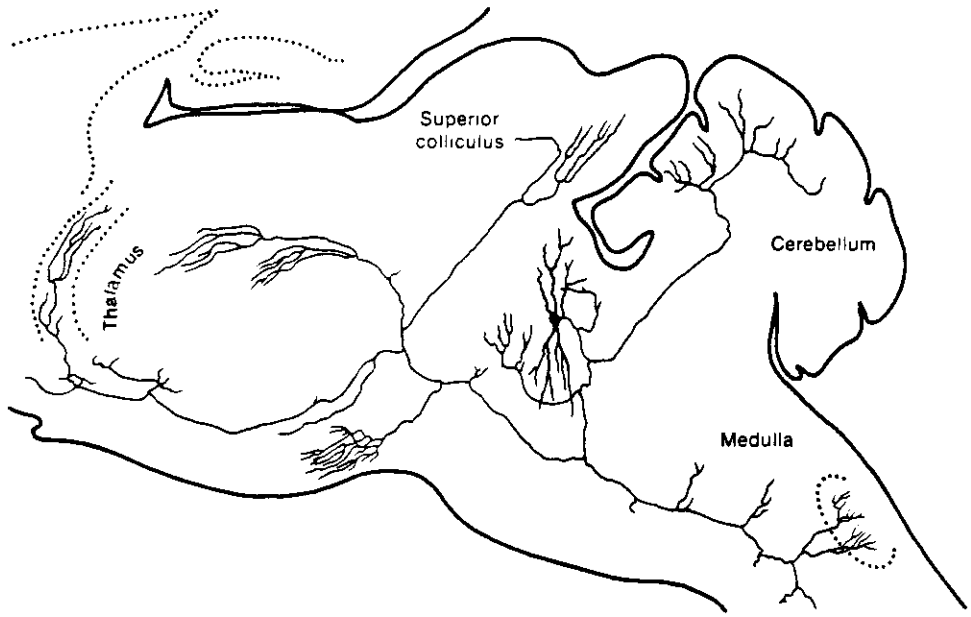


Figure 2.4
Neuron with extensive system of branching axons. A cell in the locus coeruleus, a nucleus in the floor of the fourth ventricle, in the pons; Golgi impregnation; mouse. Collaterals distribute very widely in many parts of the brain. [Courtesy of M. A. and A. B. Scheibel.]

impulses arise at all in neurons with very short neurites (see Glossary). Some axons—for example, many of those in the vertebrate retina—function normally without impulses. Terminals of axons in many parts of the body probably fail to conduct all-or-none impulses to the very end but revert to graded local potentials.

The term "axon" therefore continues to be based primarily on histological criteria (Fig. 2.3). Even these, however, are not always unambiguous; the diversity of neuron form is, after all, due partly to the variety among axons. Some are relatively short; others give off relatively numerous collaterals (Fig. 2.4). In certain places in the central nervous system, axons are found without any sheath cell investment. Some axons receive synaptic endings not only at the origin and near the terminals but at the node of Ranvier. Some neurons have more than one axon; for example, bipolar neurons, T-shaped unipolars, and some multipolars.

The distinction between axon and dendrite is usually clear in vertebrates, but in invertebrates the distinction can be difficult, suggesting that the two kinds of processes are less differentiated in lower forms.

C. Dendrites

Dendrites are often defined as processes specialized to act as the receptive regions for the neuron. They *are* the principal receptive apparatus, but these processes have recently been found to be transmissive (presynaptic) in some places as well; conversely, some axons are known to have receptive (postsynaptic) junctions. We are faced with a historic term and an evolving concept. The term "dendrite" was established for and should still be defined as a cytological category of processes that are relatively short, frequently branched, irregular in diameter, tapering, unsheathed, often beset with spines (see Fig. 2.3), containing cytoplasm resembling that in the soma, and receiving large numbers of synaptic endings over much of their surface. The distinction between axon and dendrite is more basic than that between either process and the soma (Fig. 2.5). The finer and more distal branches of dendrites are probably incapable of conducting all-or-none impulses, but instead are specialized to produce synaptic potentials in response to adequate presynaptic events. Reception is not the *only* role of the dendrites. They integrate converging input, generate spontaneous slow changes of state, both send and receive impulses at reciprocal synapses, and at some points initiate impulses (see Chapters 5 and 6).

The boundary between dendrite and soma is often indefinite. Dendrites branch in a wide array of patterns; these may be systematized in a simplified scheme for the vertebrates (Fig. 2.6).

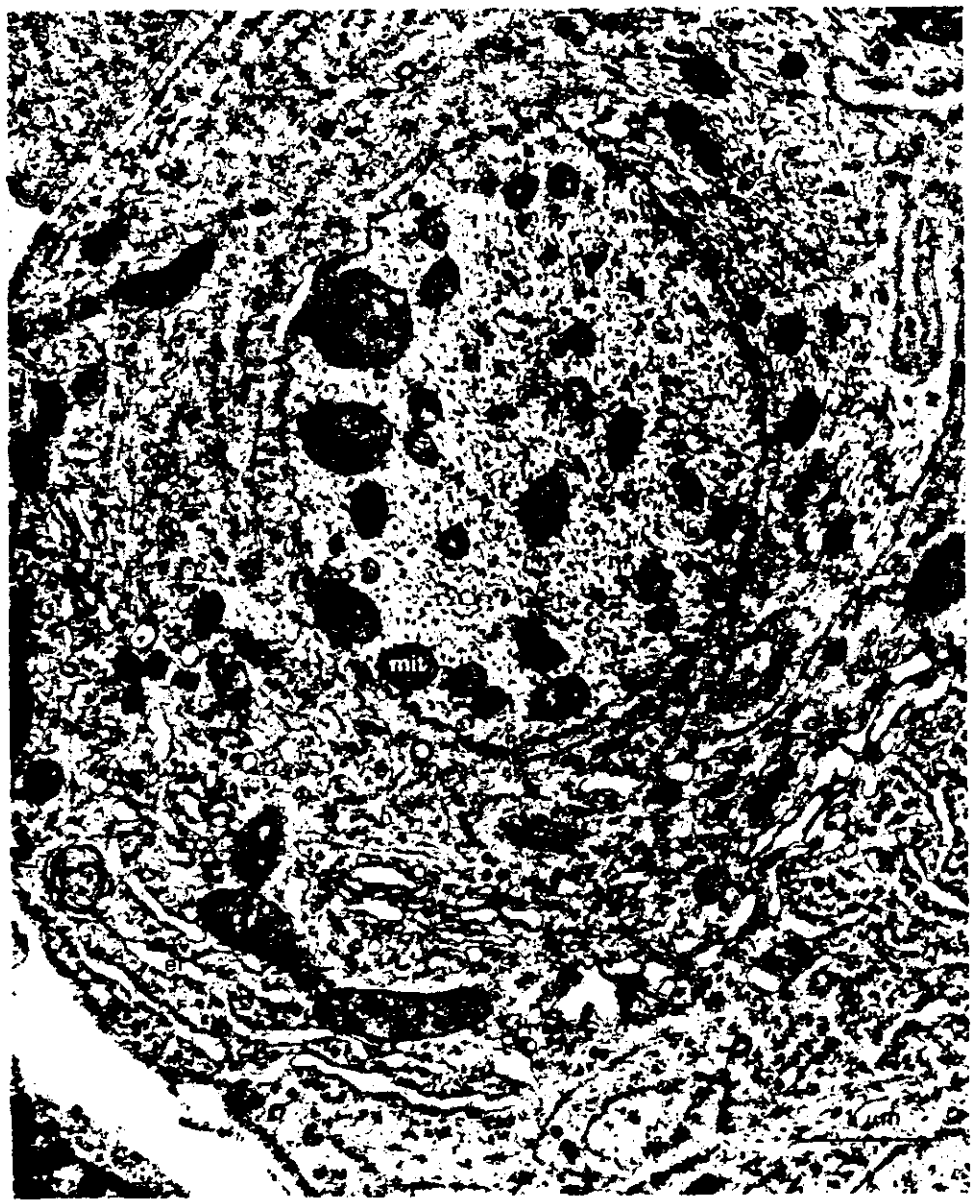
In invertebrates the term "dendrite" can rarely be applied properly on the basis of known optical and electron-microscopical features. Perhaps there is a real difference in the degree of differentiation of processes in invertebrates compared to vertebrates (see also p. 436). Whenever it is necessary to speak of the "receptive processes" or the "proximal branches" of invertebrate neurons, those terms should be used instead of the anatomical term "dendrite."

D. Formed Elements in Nerve Cells

Neurons contain the structural components common to all cells, such as nuclei, nucleoli, mitochondria, and endoplasmic reticulum (Fig. 2.7). Some components are especially modified. We will deal here only with a few that are particularly important or unique to nerve cells (Fig. 2.8).

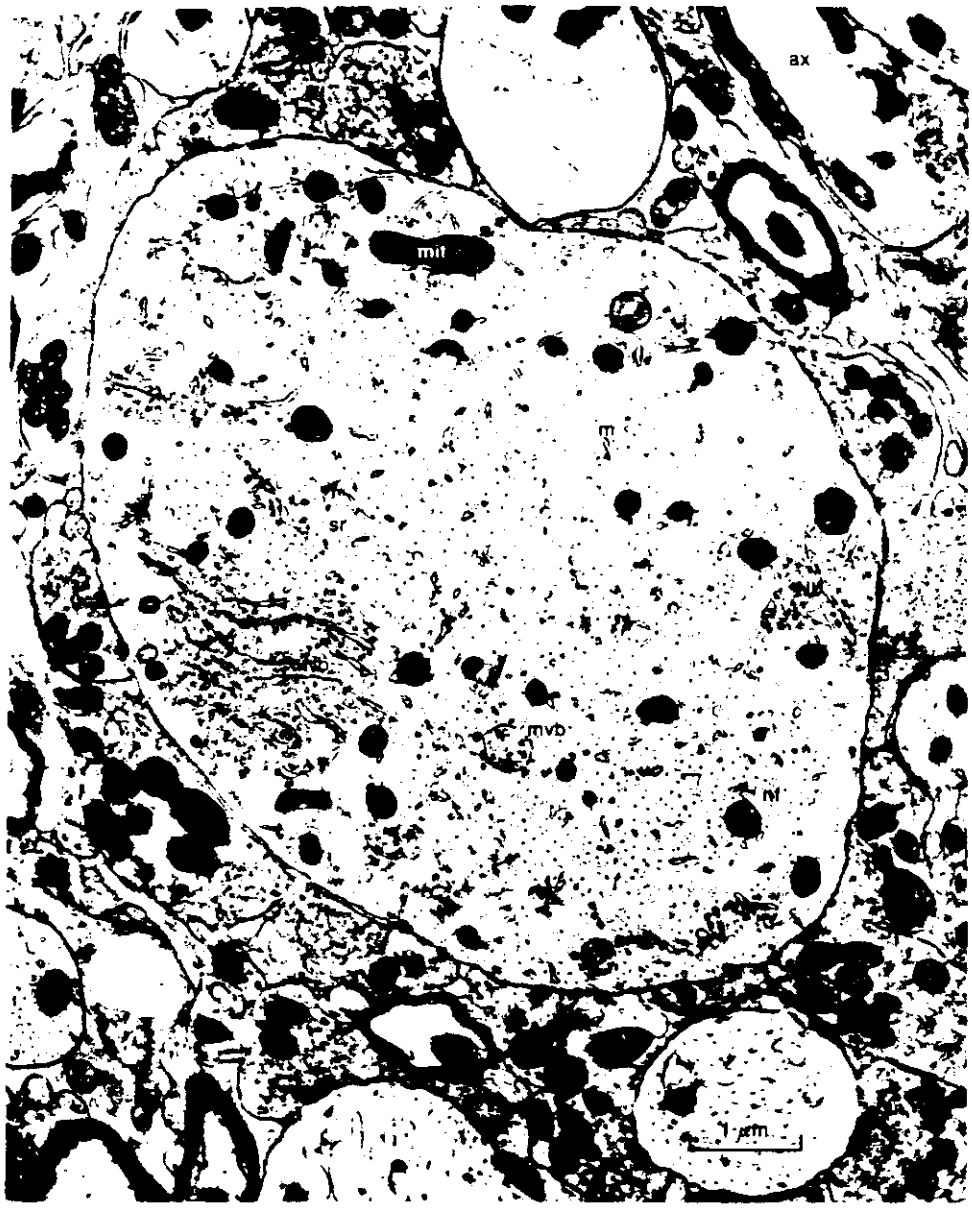
Synaptic vesicles and the junctional specializations associated with them are probably as diagnostic of neurons as any other component, although confined to limited parts of the cell surface and hence not always readily found. They are treated in Section II-G, below.

Fibrillar Structures. These are nearly ubiquitous in nerve cell cytoplasm—



A

Figure 2.5
Axon and dendrite as seen in electron micrographs. **A.** The initial segment of an axon of a dorsal root ganglion cell from a rat. **B.** A dendrite (probably of a motor neuron) in the ventral horn of the spinal cord of a rat. *al*, axonal surface membrane; *At*, axon terminal; *ax*, axon; *den*, dendrite; *er*, gran-



B

ular endoplasmic reticulum; G, Golgi apparatus; *m*, microtubules; *mit*, mitochondrion; *mvb*, multivesicular body; *nb*, Nissl body; *nf*, neurofilaments; *sr*, smooth endoplasmic reticulum. The arrows in part B show synapses. [Peters et al., 1970.]

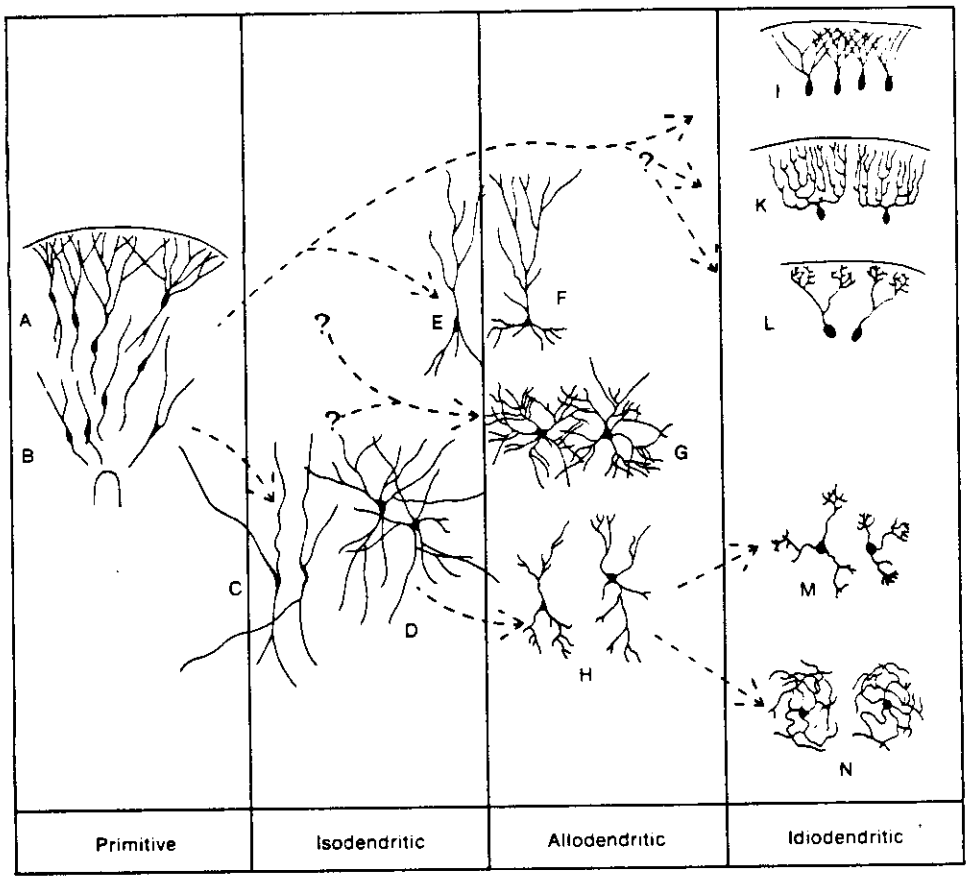


Figure 2.6
Diagram illustrating the probable phylogeny of vertebrate dendritic patterns. Two basic primitive types are found in lower vertebrates (left). Neurons with subpial tufts (*A*), are seen intermingled with periventricular leptodendritic neurons (*B*). The undifferentiated isodendritic pool is represented by the neurons labeled *C* and *D*, and probably by *E*. As a result of morphological differentiation, various specific dendritic patterns (allodendritic) begin to appear in *F* (pyramidal neurons with basilar dendrites), *G* (allodendritic neurons of the diencephalon), and *H* (allodendritic neurons of rhombencephalon). Eventually, certain highly differentiated forms (idiodendritic) appear; *I*, tufted granule cells of gyrus dentatus; *K*, Purkinje cells; *L*, mitral olfactory neurons; *M*, tufted neurons of various secondary sensory centers; *N*, wavy precerebellar neurons. [Ramón-Moliner, 1968.]

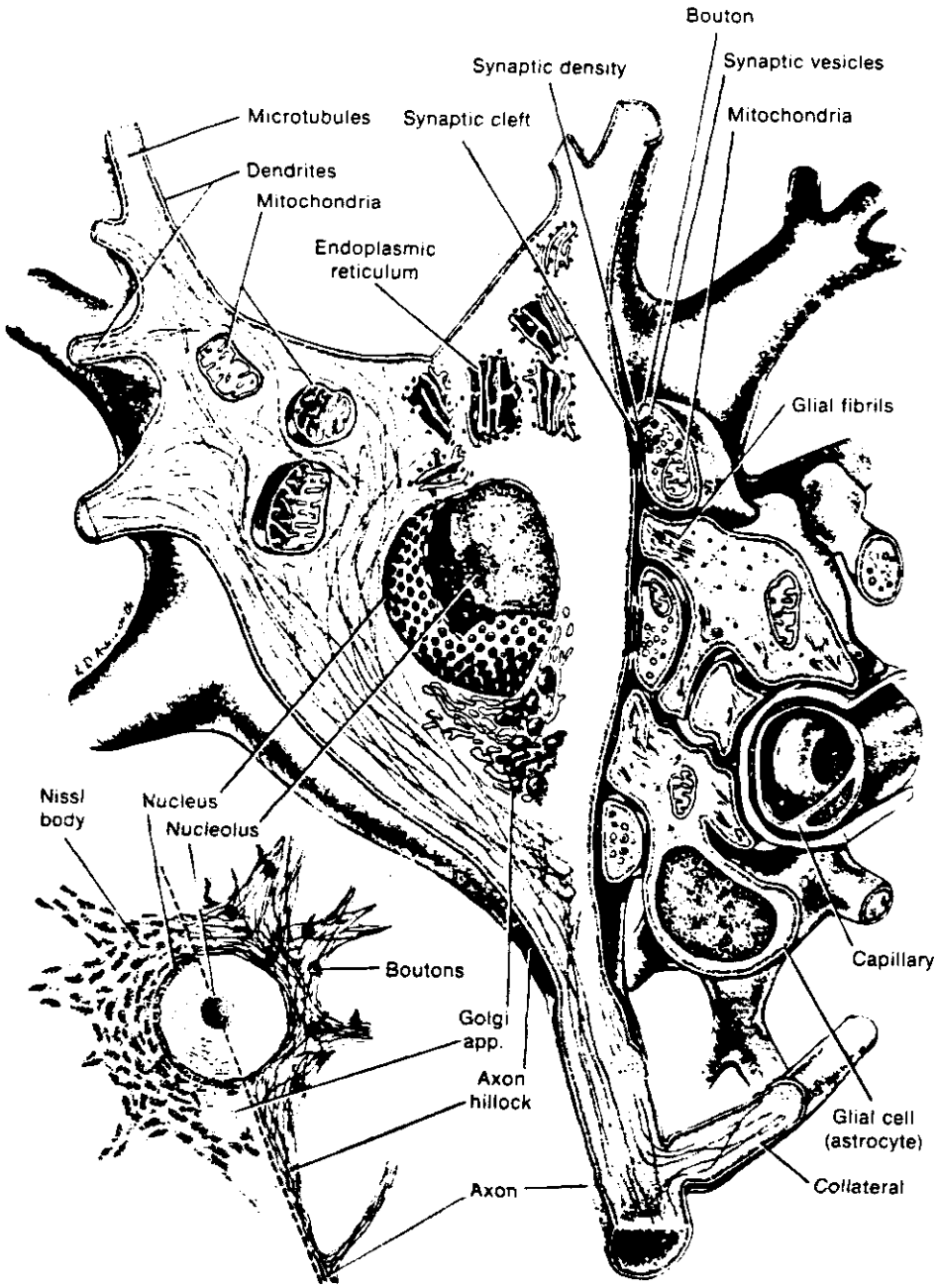


Figure 2.7
Nerve cell soma, showing organelles. The small view shows details seen at the light-microscope level. A stain selective for Nissl bodies was used on the left half; one selective for neurofibrils, on the right. The large diagram shows details seen at the electron-microscope level. [Willis and Grossman, 1973.]

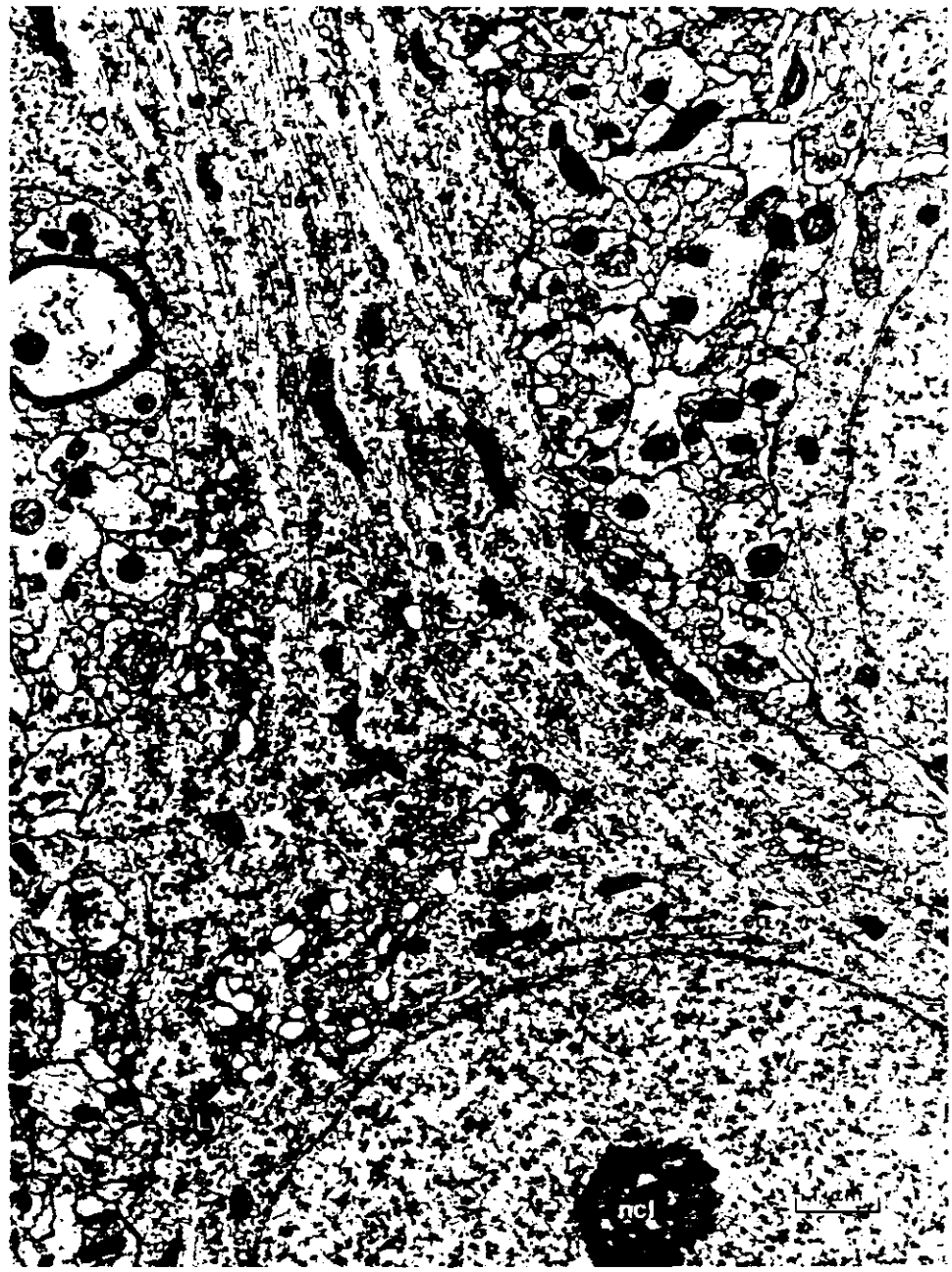


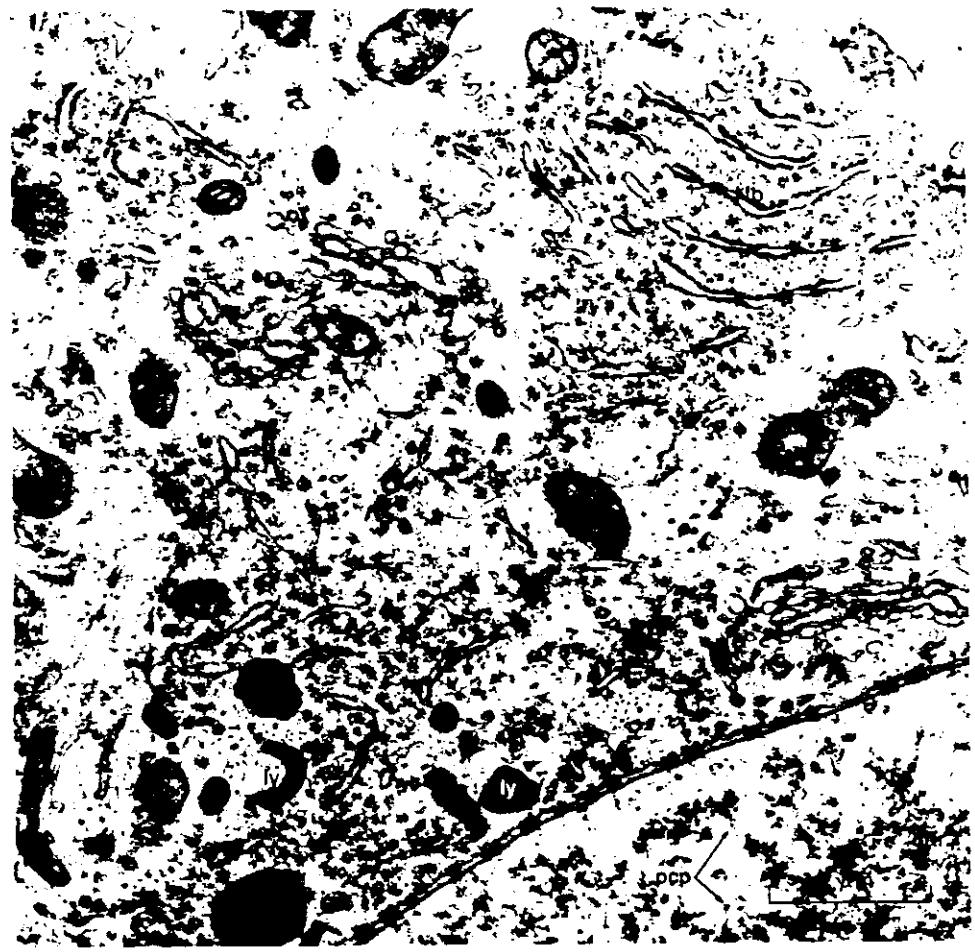
Figure 2.8
Formed elements in the neuron as seen in low-magnification electron microscopy; pyramidal cell soma in the cerebral cortex of a rat. *at*, axon terminals; *den*, dendrite; *er*, endoplasmic reticulum; *G*, Golgi apparatus; *ly*, lysosomes; *m*, microtubules; *mit*, mitochondria; *nf*, neurofilaments; *ncl*, nucleolus; *r*, clusters of free ribosomes; *sr*, smooth-surfaced endoplasmic reticulum. [Peters et al., 1970.]

axonal, dendritic, and somatic. There appear to be at least two basic types, neurofilaments and microtubules. **Neurofilaments** are fine threads 60–100 Å thick that are oriented roughly lengthwise in the processes and are commonly distributed uniformly throughout the cross section of a process. They are unbranched and of indefinite length. Some details of their ultrastructure (Fig. 2.8, 2.9,A) and composition are known, but their function is entirely unclear.

Microtubules, similarly, are longitudinal, unbranched organelles of indefinite length but with an outside diameter of 200–300 Å and a thick wall composed of spiral strings of bead-like globular proteins (Fig. 2.9,A). Their function is uncertain, but they may be involved in some form of transport of material along the axon. The distribution of both kinds of elements is not entirely uniform either among phyla or within the neurons of a given animal, and generalizations about their occurrence are not yet secure, let alone interpretable in terms of function.

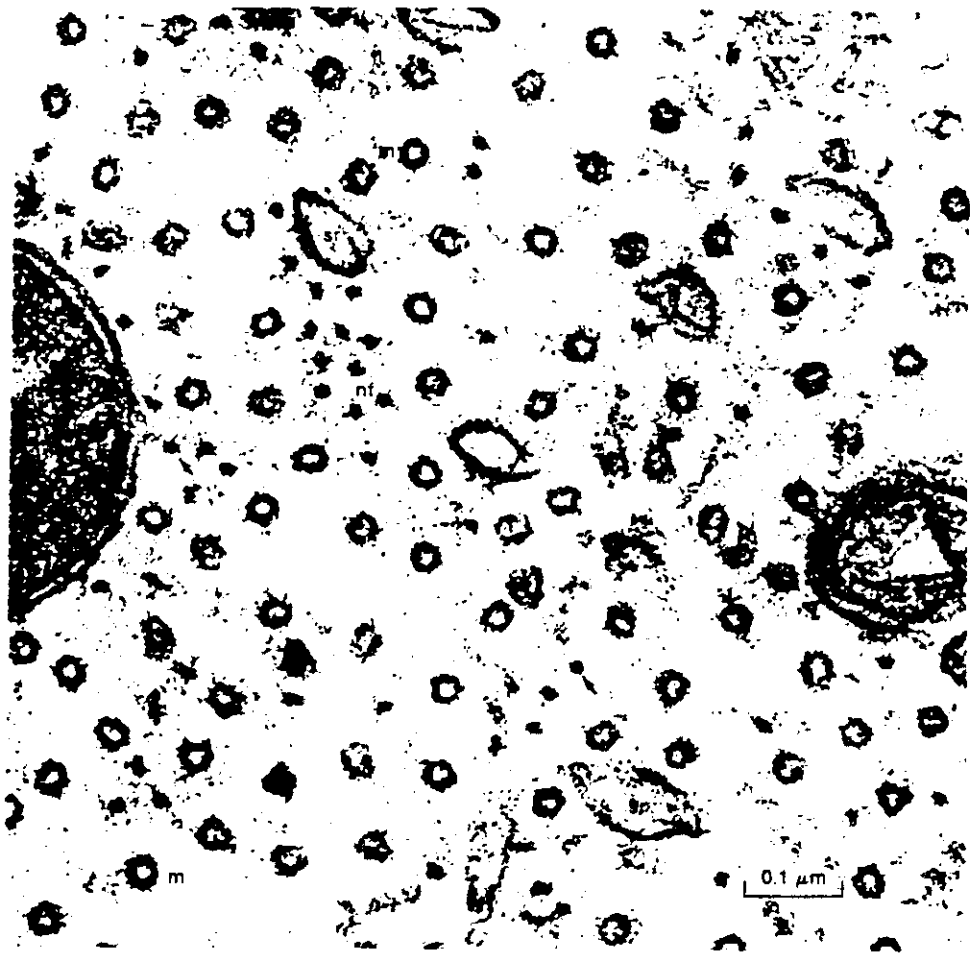
The classical neurofibril (Fig. 2.10) of light microscopy is at least an order of magnitude thicker than the neurofilaments and microtubules, which can be seen only in the electron microscope. Although this classical element is generally regarded as an artifactual clumping of filaments or tubules, it may represent a natural concentration, as in the center of the 75-μm earthworm giant axon. Neurofibrils are usually described on the basis of impregnation with silver, which certainly distorts the normal structures. Nevertheless, fibrils *are* visible in the living state in the axons and somas of earthworms, as well as in those of jellyfish, lobster, fish, chick, and other forms.

Nissl Bodies. Components of many nerve cells, these chromophilic bodies are rendered conspicuous under the light microscope by means of basic dyes, but they can also be seen in some unstained, living cells with the aid of phase-contrast microscopy or microspectrophotometry. Their ultraviolet absorption spectrum and their reaction to ribonuclease digestion show that one of the principal constituents of the Nissl bodies is ribonucleoprotein. The electron microscope shows that an individual Nissl body may consist of large or small stacks of rough-surfaced or granular endoplasmic reticulum (ER) (Fig. 2.9,B). Ribosomes are arrayed along the outer surface of the membranes and in clusters or rosettes between them. These bodies are believed to represent the sites of protein synthesis, a process that is particularly active in nerve cells. The shape, size, number, and distribution of Nissl bodies vary greatly, but are characteristic for each type of nerve cell. In many of the larger vertebrate neurons, Nissl bodies are large and have distinct shapes. They provide a sensitive index to the condition of the cell, since a host of pathologic causes (including damage to the axon, asphyxia, toxic substances and possibly extreme demands on the metabolic and synthetic capacities) can change their form and position. The most common reaction to damage is *chromatolysis,* in which the Nissl granules disappear (in the light microscope) or form poorly outlined masses near the surface of one side of the cell while the nucleus undergoes



A

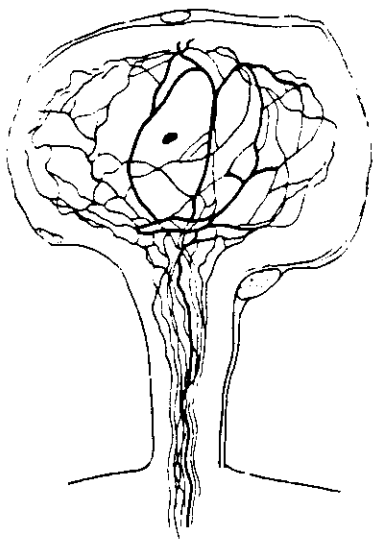
Figure 2.9
Formed elements in the neuron at high magnification; spinal cord of a rat. **A.** Nissl bodies (granular endoplasmic reticulum), nuclear envelope, Golgi apparatus (smooth cisternae near center and right edge.) **B.** Microtubules, neurofilaments. *ly.* lysosomes; *m.* microtubule; *Nb.* Nissl body; *nf.* neurofilament; *sr.* smooth endoplasmic reticulum; the arrows in part A indicate pores in the nuclear



B

membrane; the arrows in part B indicate spoke-like appearance due to the grouping of neurofilaments into fascicles in this type of dendrite. [Peters et al., 1970; micrograph B by Dr. Raymond B. Wuerker.]

Figure 2.10
Neurofibrils: organelles seen in the light microscope, usually after special metallic impregnation. [Cajal, 1909.]



Invertebrate neuron

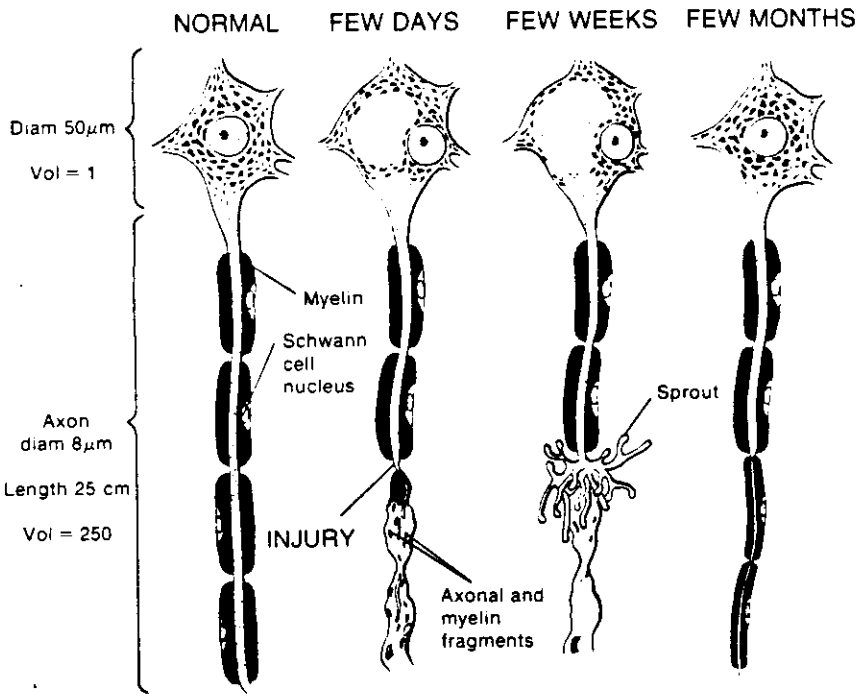
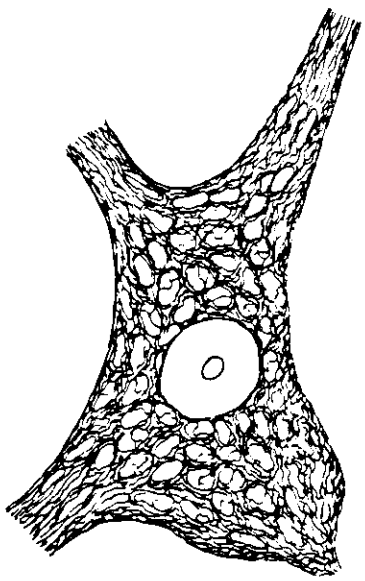


Figure 2.11
Regenerative stages of motor neuron after axon is severed. [Bodian, 1947.]



Vertebrate neuron

definite changes as well (Fig. 2.11). In some arthropod neurons, injury to the axon causes the ribonucleoprotein in the soma to concentrate in a ring around the nucleus. Changes of either kind may precede death of the cell or presage a gradual recovery. In many neurons, especialy among invertebrates, the corresponding rough-surfaced endoplasmic reticulum ("rough ER") is not collected into large bodies visible in the light microscope, but occurs in very small masses.

It is of great functional importance that rough ER is characteristically scarce or absent in axons but present in dendrites as well as in the soma. Granular endoplasmic reticulum is the chief protein-making machinery of the cell. How, then, does the axon, which may be a meter or more long and comprise the bulk of the neuron, get the proteins needed for normal function and replacement? The answer appears to be by movement of materials from the soma, a transport so formidable and important that we devote the next section to it. Even more characteristic of nerve cells than their Nissl bodies is their large endowment of cytoplasmic RNA, which is associated with a high rate of protein synthesis, particularly in the soma. This high rate

of protein synthesis is, in turn, associated with the voluminous transport of materials along the axon.

Other general cytological elements of nerve cells are standard and do not require special comment in this work; these include the Golgi apparatus (which consists of clumps of smooth-surfaced endoplasmic reticulum), the mitochondria, a centrosome, and lysosomes. In addition, various inclusions may be present in widely varying numbers; these include lipoidal globules of several kinds, pigment granules of several kinds, glycogen granules, iron-containing granules, spiral whirls of dense lamellae, and modified ciliary structures, especially in the dendrites of sensory neurons.

E. Axoplasmic Transport

Axoplasmic transport is a term for a complex of widely divergent phenomena that contribute toward the movement of materials from the nerve cell soma to and along the axon or in the reverse direction (Fig. 2.12). A wide array of substances and methods have been used to study these phenomena in various nerves of many animals. At least two rates of transport coexist, one at about 1–10 mm/day (Fig. 2.13) and another at about 100–1000 mm/day. Intermediate rates of about 50–70 mm/day have also been reported. Most observations have been on proximo-distal transport (away from the soma), but slow distal-proximal transport has been measured as well. The composite picture from the various studies is consistent with the time-lapse cinephotomicrographs of axons in tissue cultures and in vivo, showing concurrent slow and fast streams, often sporadic but nevertheless simultaneous, in the same and in opposite directions. The materials moved include insoluble proteins, soluble proteins, glutamate, catecholamine-containing granules, monoamine oxidase, and phospholipids. Several amino acids and inert sugars are said not to be transported. Apparently some substances and cytoplasmic inclusions are quite selectively transported, some at the slow and others at the fast rate. Certain of these are transported more rapidly if the axon carries many impulses during the test period. The selectivity of materials and inclusions transported is consistent with the long-known striking differences in texture, staining properties, and inclusions shown by the cytoplasm of the soma (somatoplasm) and that of the axon (axoplasm), commonly with a sharp boundary at the axon hillock (Fig. 2.14).

The mechanisms of these slow and fast translocations are not understood. There is evidently at one and the same time a slow proximo-distal bulk transport of the whole cylinder of axoplasm (Fig. 2.15) and a complex fluid transport of some axoplasmic components relative to others in both directions and at various rates within the axoplasm. The former is equivalent to continuous growth; the latter is a mechanodynamic puzzle. A hydrodynamic model that was once postulated, in which materials were propelled by the pressure of their own rapid synthesis in the soma, has been tested and discarded. Two other ideas are still favored by some authors. One is that periaxonal forces generate a peristaltic pressure wave that squeezes the axoplasm ahead of it. The other is that struc-

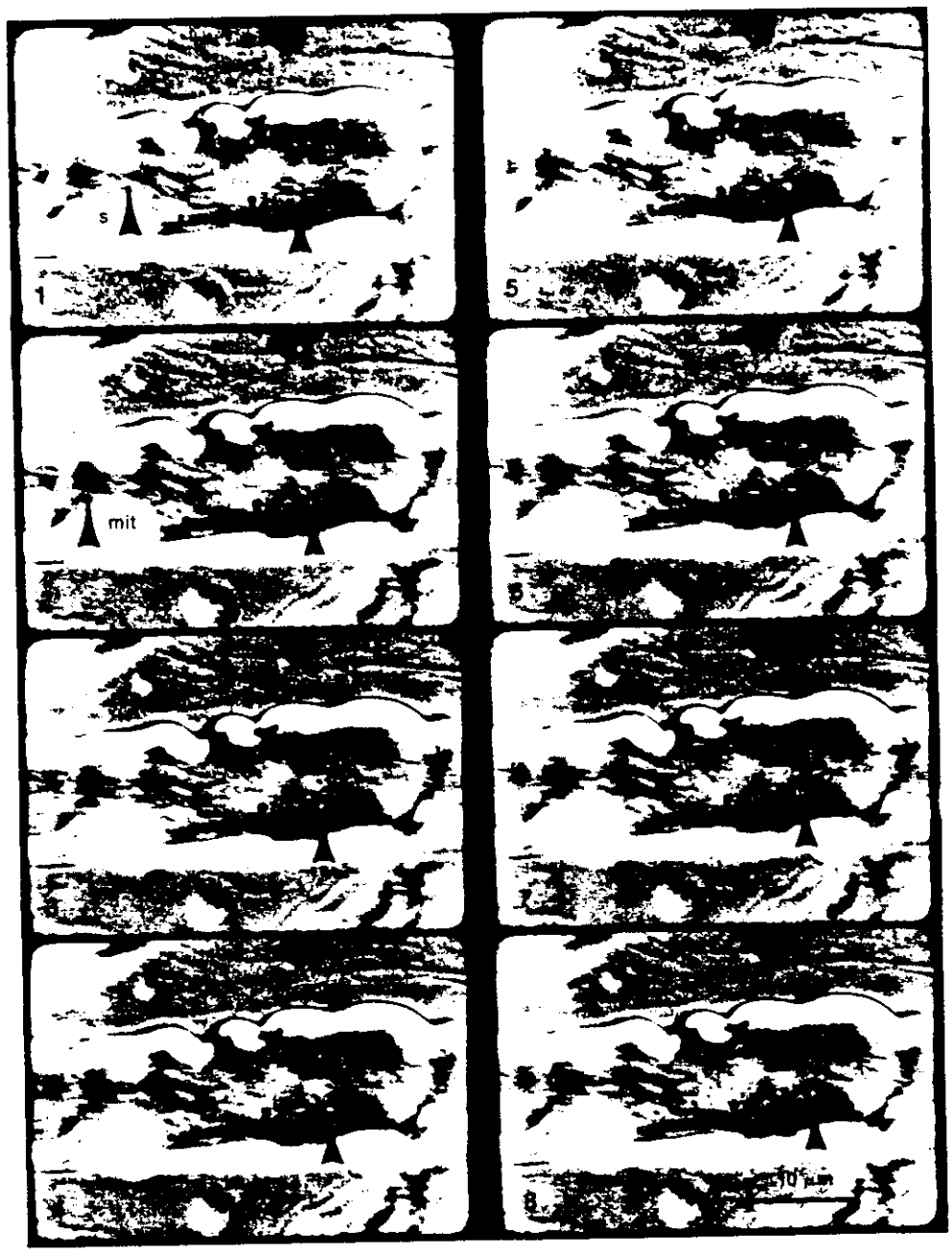


Figure 2.12
Movement of particles in the axoplasm. Frames from a cine film sequence of axoplasmic transport in peripheral axons isolated from adult chicken sciatic nerve; 120 frames min; Nomarski differential interference microscopy. This technique makes it possible to visualize fast, slow, and jerky movements, mainly distally but also centrally. Here the large myelinated axon contains mitochondria (*mit*) and spherical particles (*s*). The particle marked with an arrowhead moves about 5 µm in the 4-sec sequence shown here. [Kirkpatrick et al., 1972.]

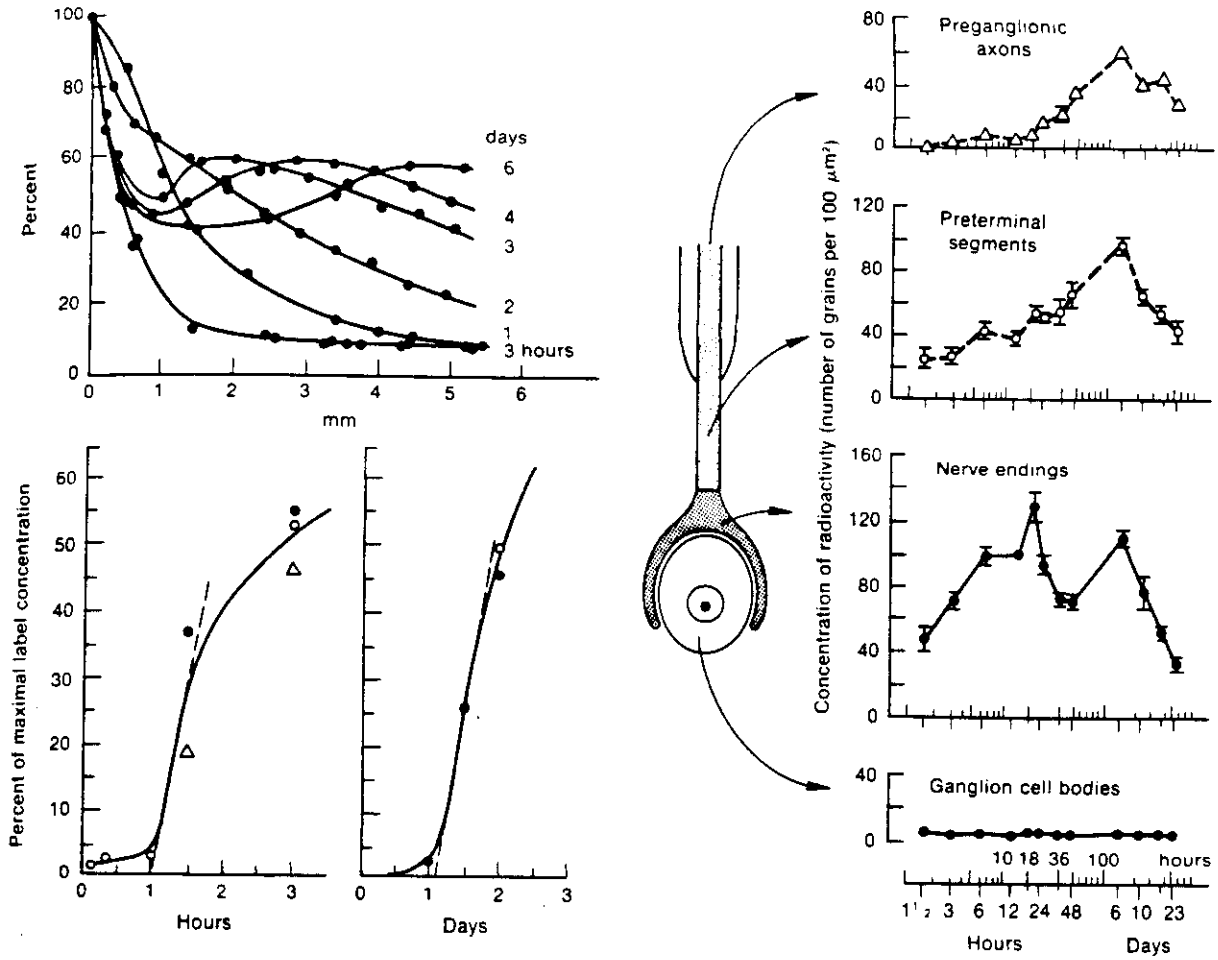
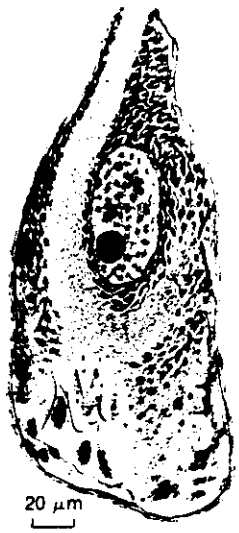


Figure 2.13
Axonal transport of materials. **Upper left.** Tritiated leucine was microinjected into the eyes of mice, where it became incorporated into retinal cells. On successive days the counts of silver grains in autoradiographs—normalized to 100% for each highest count (at "0 mm" = exit of optic nerve from bulb)—show an advancing crest traveling at about 1 mm/day. [Taylor and Weiss, 1965.] **Lower left.** Tritiated amino acid was injected into the chick brain stem; from there it moved out the parasympathetic preganglionic axons to the junctions (presynaptic calyces) with postganglionic cells in the ciliary ganglion. The graphs show the time of arrival of the first labeled molecules transported, respectively, by the fast and the slow flow. The ordinate is the percent of maximal label concentration recorded in presynaptic calyces by autoradiography (see Fig. 2.22) at various intervals. Open circles, [^{3}H] leucine; filled circles, [^{3}H] lysine; triangles, [^{3}H] fucose. The first labeled macromolecules arrive at the nerve ending by fast flow in about one hour; by the slow flow, after one day. **Right.** Data from the same experiment, plotted to show the increase in concentration of radioactivity at several places as a function of time. Note the sudden rise that begins in preganglionic axons after 24 hours; two peaks at 18 hours and 6 days are seen in nerve endings, but only the 6-day peak in preganglionic axons and preterminal segments. [Droz et al., 1973.]

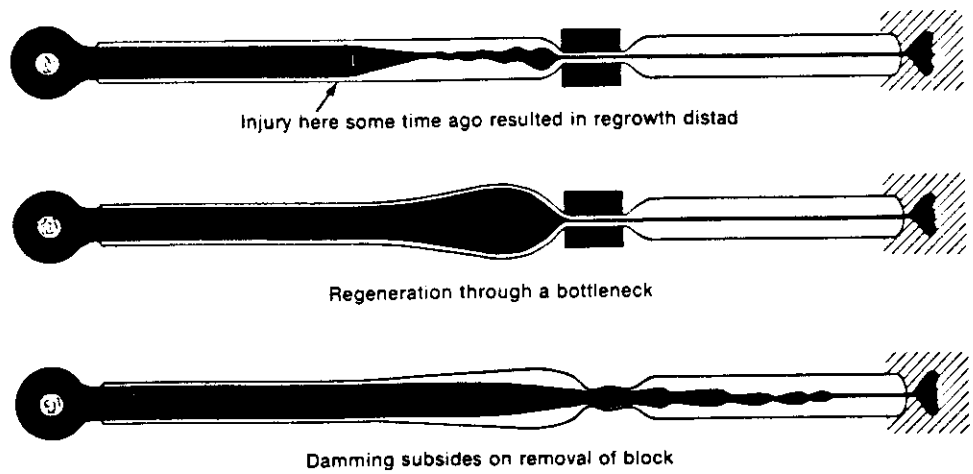
Figure 2.14
The contrast between axoplasm and somatoplasm.



Ganglion cell of Astacus, *a crayfish, showing intrasomatic origin of the axoplasm. Note also that strands of the sheath and its glial cell penetrate into the soma in some (= trophospongium) nerve cells.* [*Ross, 1922.*]

Ganglion cell of Helix, *a snail, with similar features, though the magnification is too low to look for trophospongium.* [*La Croix, 1935.*]

Figure 2.15
"Damming" of axoplasm in constricted nerve fibers. One of the first discoveries indicating axoplasmic flow. [*Weiss and Hiscoe, 1948.*]



tural changes in macromolecules in the axoplasm propel material selectively. Most interesting are new ideas that neurofilaments and/or microtubules contribute to axoplasmic transport by means of some kind of molecular cooperativity.

The significance of axoplasmic transport is doubtless multiple. It is critical to the maintenance of the axon. The substances synthesized in the soma are needed not only by the axon but by certain of the peripheral cells that it innervates and perhaps by the Schwann cells that surround it. Axoplasm probably serves as a route for information about the end organ to which the axonal terminal is attached—information that must find its way to the soma in order to influence the plastic properties of the soma-dendrite complex. In case of injury to the axon, axoplasm may provide the route by which the soma feels the effect of distal damage and inaugurates the chromatolytic reaction. Synthesis is not confined to the soma; it also takes place to some degree in the axon and its terminals. The soma is not the only source of materials for axonal metabolism; it has been shown experimentally that the axon is capable of direct uptake of some molecules through extracellular space, Schwann cells, and the myelin sheath. The existence of rapid transport from soma to nerve endings and of local synthesis in nerve endings makes it possible to think of the presynaptic membrane as a site for some plastic changes, as in rapid learning. Before the new findings on rapid transport became available, the presynaptic site had seemed an unlikely one for such changes because of the remoteness of the soma (see also p. 363).

F. Physical Properties of Axons

Our knowledge of the physical properties of axonal materials, especially the changes in properties that accompany activity, is best treated here, although it is not entirely based on visible features of structure.

The viscosity of axoplasm varies widely among animals. In the giant axon of squids it is fluid enough to be expressed from a cut end by gentle squeezing, and this opportunity to obtain pure cytoplasm in quantity has been exploited in many studies. Viscosity is known to change measureably with electrical stimulation. Turgor has been measured in squid and cuttlefish axons, and tensile properties in crab nerve. A longitudinal orientation of more fluid channels is indicated by movements and shapes of droplets and vesicles. Stimulation of nerves has been found to alter staining character, volume, tension, and light-scattering in different preparations. Recent work has put some of these on a firm footing, especially changes with impulse conduction in light-scattering, in birefringence, and in phosphorescence after application of suitable dyes. It is still too early to know what these changes mean, but the hope is that they will give clues that may be interpreted in terms of alterations of molecular configuration during excitation or recovery.

On page 213 some evidence is cited of physical movements of nerve endings consequent to excitation.

G. Synapses

A **synapse** (Fig. 2.16) is the anatomical site of contact at which one nerve cell (the presynaptic one) can transmit a signal to another nerve cell (the postsynaptic one). This definition (a) implies that the neurons are separated by intact cell membranes, (b) distinguishes synaptic transmission from diffuse influence at some distance—for example, "field effects," or influence via neurosecretion, and (c) implies that each specialized site of contact is treated as *a* synapse. However, a single axon may synapse at several loci upon a single neuron and/or upon several different neurons. Likewise, a postsynaptic neuron often receives terminals from two or more presynaptic neurons within a small fraction of a micrometer—and in a characteristically organized manner, forming a triad or a compound synapse. Thus the definition also implies that there must be functional communication relevant to the information-processing role of neurons. There are many regions of so-called casual contact where, without exhibiting any visible specialization, neurons lacking the usual interposed glia are apparently incident. y juxtaposed; these regions are generally thought to have no functional influence, and are considered nonsynaptic. It may be only our ignorance, however, that permits the present ready dichotomy between synaptic regions and those nonsynaptic regions in which neuronal membranes may also lie

Figure 2.16
Some types of synapses distinguished on the basis of topographic relations. [*Bodian, 1972.*]

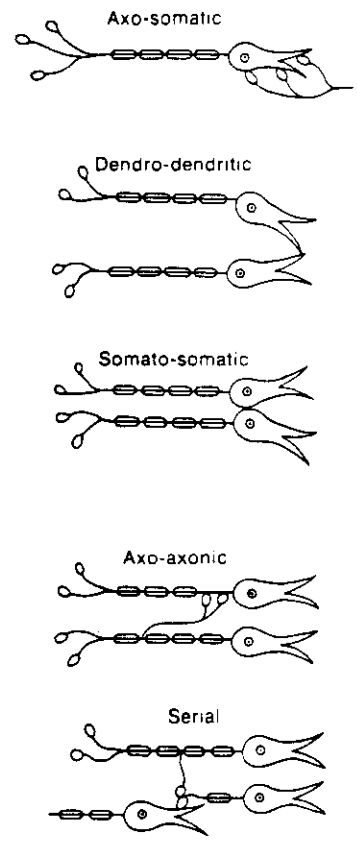
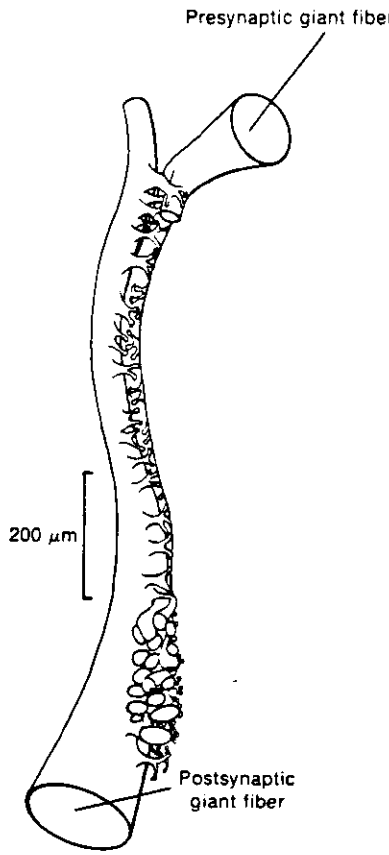
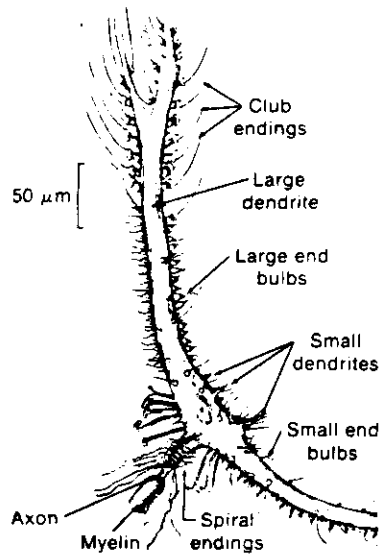


Figure 2.17
Diverse synapses upon giant neurons.



Giant synapse in squid. [Young, 1939.]



Mauthner's cell synapse in goldfish. [Bodian, 1952.]

separated by only a few hundred Ångstrom units of intercellular space. We cannot exclude the possibility that weak influences are mediated through such "nonsynaptic" regions.

The concept of the synapse and its function is discussed further in Chapter 5. In the same chapter it is explained that a common, though not necessary, property of synapses is polarized, or one-way, transmission. The idea that the neuron is usually polarized, normally receiving excitation at its dendritic side and conveying it to its axonal terminal, was originally inferred by Cajal from his histological studies. He enunciated it as the "doctrine of dynamic polarization" (see also p. 103). Like his neuron doctrine, it has received abundant confirmation from modern electron microscopy as well as neurophysiology, though with significant refinement and qualification. Polarization is not, however, a universal characteristic of synapses as a class. The class is basically heterogeneous, both functionally and morphologically (Fig. 2.17). As is discussed in Chapter 5, there are electrically and chemically transmitting synapses, excitatory and inhibitory synapses, and each of the four possible permutations as well as a great range of morphological varieties.

Rather than describe an arbitrary "typical" or "normal" synapse, we shall acknowledge the significance of variety by selecting for illustration a number of the better known configurations. Because of differences in the scale of observation and the techniques used for the light and electron microscopes, there is a natural division between description at low magnification, in which emphasis is on

topographic relations, and description at high magnification, in which emphasis is on ultrastructure and cell contacts.

Varieties of Contact at Low Magnification. The fabulous variety of characteristic forms of nerve fiber endings and synaptic contacts is one of the most impressive findings of anatomical science, as well as a distinguishing feature of the nervous system. It compels us to recognize a whole new field of study, the microarchitecture, or **architectonics,** of nervous tissue—a field that emphasizes spatial relations, geometry, and complex patterns. The first problem in attempting to deal with a welter of detail presented by nature is to discern **criteria for categorizing** that are not arbitrary or naive. Because our understanding of the functional significance of microarchitecture is still rudimentary, it is possible that the criteria used for classifying external form characteristics at low magnification, may not in fact include some of the most important features.

Synapses may be classified according to which parts of the presynaptic and postsynaptic neurons are involved: the contacts may be between presynaptic axonal terminal and postsynaptic soma, hence **axo-somatic,** or they may be **axo-dendritic** or, more rarely, **axo-axonal, dendro-dendritic,** or **soma-somatic.**

Another criterion is the general form of the whole array of axonal terminals that make contact with a given postsynaptic neuron (Fig. 2.18). We present here an incomplete list of examples modified from Cajal; more detail is given in Bullock and Horridge (1965).

1. Simple **contact-in-passing** between presynaptic axons and postsynaptic receptive processes (Figs. 2.18,A,C,D; 3.2,B; 3.3). This is possibly the dominant type of synapse in invertebrate neuropile (defined on p. 68 and in Glossary) (Figs. 2.54; 10.20,A; 10.25; 10.41; 10.51). Sometimes the simple contacts are single, whereas in other cases the two fibers touch, separate, and touch again several times before continuing on their courses.

2. Axo-dendritic connections by **climbing fibers** (Figs. 2.18,B; 2.19,B; 3.5,B; 3.16). This system resembles a vine entwining a tree. It offers extensive contact, serially ordered junctions, and private connection between two cells, contrasting in all these features with most of the other types. The best known example is the climbing fiber on the cerebellar Purkinje cell dendrite, which is also well established functionally as a powerful form of excitatory junction.

3. Axo-dendritic connection by **interdigitation.** In many places finger-like terminals of axons mesh, like gears, with corresponding dendritic projections. The most beautiful and diversified examples are found in the optic ganglia of insects (Figs. 10.41; 10.42; 10.43). Cajal, who himself analyzed this system in great detail, said "it seems that nature has attempted to show us in the insect nervous system . . . how in minimum space it is possible to organize a maximum of fine and subtle structures. . ." (1954, p. 81). Actually, for the sake of simplification, we are forcing into one rubric a multifarious array of endings in arthropods, cephalopods, vertebrates, and other groups (Figs. 2.29; 3.2; 3.3; 3.8; 10.31; 10.56). These exhibit the forms of brushes, tassels, tufts, taproots, shrubs, clubs, panicles, and other excrescences, each consistent and characteristic of its cell type. Moreover, specific localized terminal arborizations are known to arise at definite sites along the single stem process of unipolar cells, with a characteristic form of branching at each site.

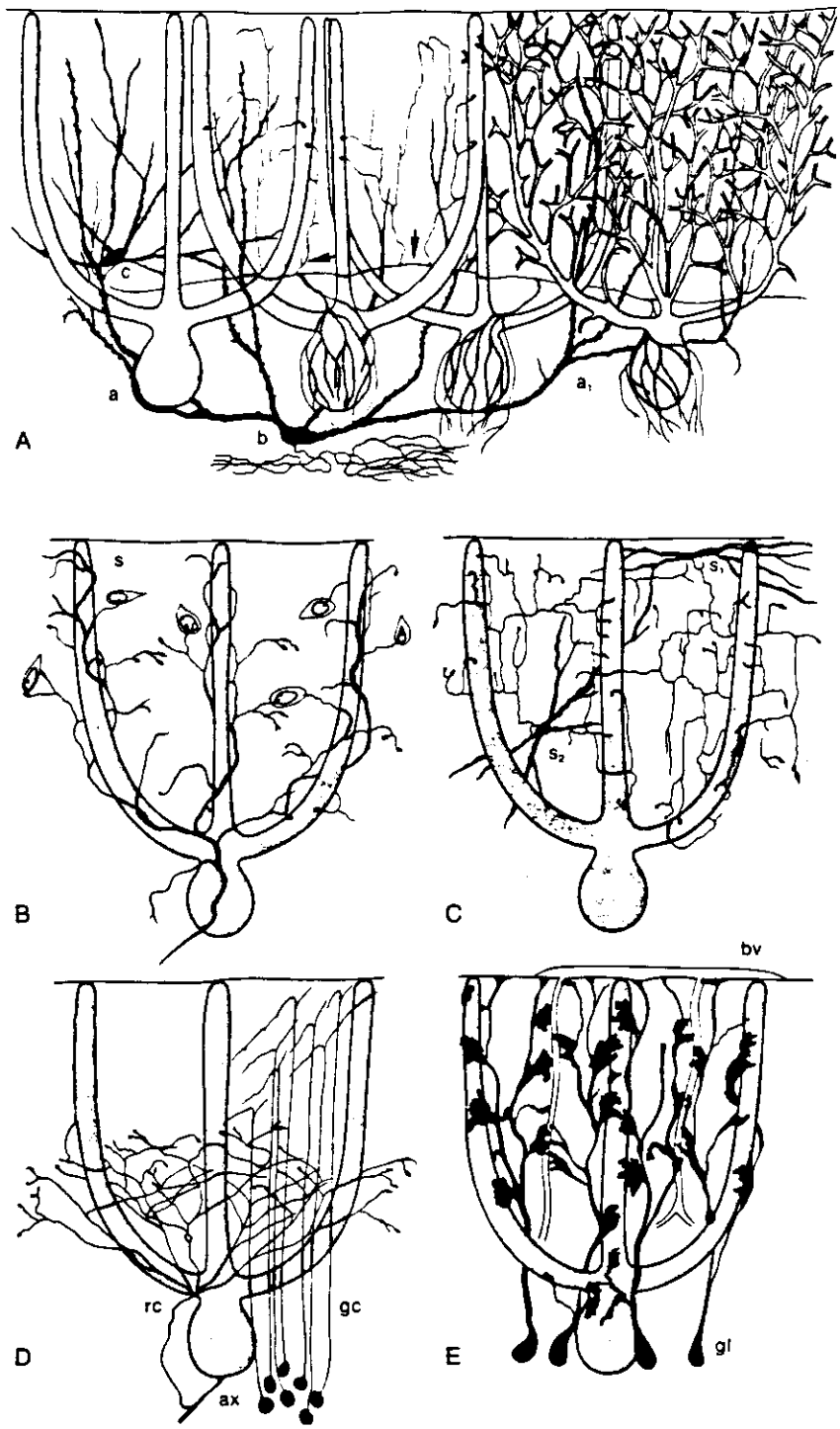


Figure 2.18
Variety of synapses on one neuron. Diagrams of the surroundings of Purkinje cell dendrites in the cerebellar cortex; the dendrites are shown greatly simplified, even in the upper right. **A.** basket cell axon (*c*) sends descending collaterals to make baskets (a_1) around Purkinje cell somas (*a*) and ascending collaterals (arrows) to make synapses in the molecular layer. Large Golgi type II ganglion cell (*b*) of the granular layer sends dendrites widely in the molecular layer. **B.** Climbing fiber is presynaptic not only to the Purkinje dendrites but to many adjacent elements, especially stellate cells (*s*). **C.** Axonal plexuses of stellate cells (s_1, s_2), which are short-axoned and therefore Golgi type II cells, lie within the dendrite arbor of one Purkinje cell. **D.** Recurrent collaterals (*rc*) from Purkinje axon (*ax*) form a plexus in the lower third of the molecular layer. Axons of granule cells (*gc*) ascend and bifurcate to run as parallel fibers at right angles to the plane of the flattened Purkinje dendrite arbor. **E.** Stalks of neuroglia cells (*gl*) make extensive contacts with the dendrites and with cortical blood vessels (*bv*). All elements are simultaneously present about each Purkinje dendrite system, and these systems extensively overlap. [Scheibel and Scheibel, 1958b.]

4. Axo-dendritic connections by **right-angled arrays**, with axons of great length (Fig. 2.19,A). This curious and provocative synapse is best known in the cerebellum, where smooth, free endings of granule cell axons run for about two millimeters as unbranched, unmyelinated, terminal filaments in the molecular layer parallel to the surface and to each other, while Purkinje cell dendrites richly ramify in a more-or-less perfectly flattened espalier (plane) at right-angles to them. Thus each granule cell axon makes minimal passing contact with about 45 Purkinje cells in an ordered sequence, and each of the latter is touched by about 90,000 parallel granule cell axons.

5. Axo-dendritic connections by **laminar plexuses.** Especially in the retina of vertebrates, cephalopods, and insects, terminal axon arbors are found in a narrow stratum, interlacing with similarly confined postsynaptic receptive processes (Figs. 2.37; 2.53; 2.56; 3.4; 3.20; 10.41; 10.42; 10.50; 10.51; 10.56). Laminar ramifications may be repeated at as many as eight levels and extend to defined and characteristic distances in each stratum.

6. **Multineuronal functional complexes** of different types. One axon may embrace a circumscribed cell cluster. In certain places the axon ends by exploding into a thicket of fine twigs that intertwine with a discrete population of postsynaptic cells. Even more elaborate knots of axons and dendrites of several neurons may form a defined unit called a glomerulus (Figs. 2.33; 2.34).

7. Axo-somatic connections by **thick nests.** This class is exemplified by the cerebellar basket, which is a form of axonal ending that fits neatly over a single Purkinje cell soma (Figs. 2.3,E; 2.18,A; 3.17). A single presynaptic neuron may send axonal baskets to many Purkinje cells (Fig. 3.19). These are one of the best established forms of inhibitory junctions.

8. Axo-somatic connections by **sparse nests.** In contrast to the preceding class, these resemble early entwinement by growing vines (Fig. 2.19,D,F).

9. Axo-somatic connections by **calyces** (a kind of cup) (Figs. 2.19,C,H; 2.29,A). In certain places the postsynaptic cells receive broad, flat, petal-like axon endings that virtually engulf the soma. Such synapses made a special contribution to the establishment of the neuron doctrine because of the direct evidence they offer of the discreteness and independence of neurons.

10. Axo-somatic connections by **thickened terminal tubercles** (Figs. 2.19,G; 3.2,A; 7.13). This term covers a heterogeneous assortment of specialized endings with large or small expansions that make contact with the soma and large dendrites. The axon may end in a warty tubercle or a swollen suction-cup-like body or a terminal button.

11. Axo-axonal connection by simple **end-to-end contact.** The giant fibers of earthworms (Fig. 10.19) and the lateral giants of crayfish (Fig. 10.27) are actually chains of segmental units, each bounded by a complete cell membrane. Contact is by a simple, symmetrical apposition of membranes. These synapses are nexuses and electrical.

12. Axo-axonal connections by **postsynaptic protuberances.** These are found in the giant synapse of the squid (Fig. 2.17), in the giant-to-motor synapse in crayfish (Fig. 10.27), and in many invertebrate neurons where small tufted projections from the postsynaptic axon act as specialized receptive appendages.

13. **Somato-dendritic connections.** This is a relatively uncommon synapse, but is known at least in sympathetic ganglia.

14. **Neuroeffector junctions by free branched endings.** Most neuromuscular junctions in invertebrates (Fig. 2.20), the junctions on smooth muscle in vertebrates, most neuroglandular junctions, and the junctions on ciliated cells, luminescent organs, and chromatophores appear to be simple terminals, or contacts-in-passing, of moderately to extensively branched axons.

15. Neuromuscular junctions with **postsynaptic folds.** The axon terminals on vertebrate skeletal muscle fibers of the common-

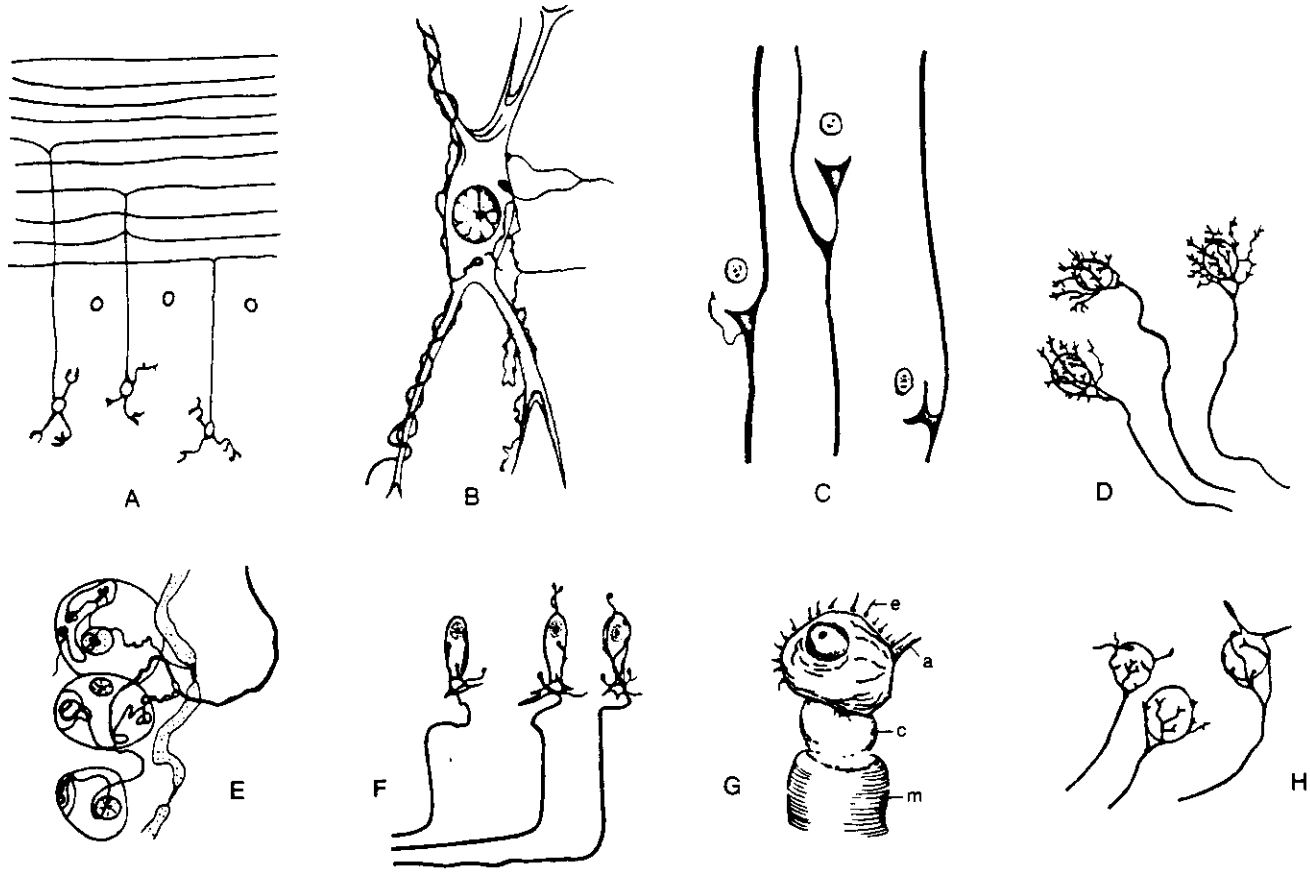


Figure 2.19
Types of synaptic endings observable with light microscopy and special stains; vertebrate central and peripheral nervous systems. **A.** Parallel fibers of cerebellar cortex making right-angle synapses with Purkinje cell dendrites, which lie in the plane vertical to the page. Golgi method. [Cajal, 1954.] **B.** Diagrammatic cell in Clarke's column of the spinal cord with its three types of synapses: (*i*) the "giant synapses" are seen on the large dendrites at the left, above and below, as entwining fibers from muscle spindle afferents; (*ii*) end feet on the right come from excitatory interneurons under the influence of skin afferents; (*iii*) the meshwork of extremely fine fibers on the soma comes from inhibitory interneurons in the pathway from antagonistic muscle afferents. [Szentágothai, 1961.] **C.** Cells of the tangential nucleus of a bird (young kite) receiving synapses from fibers of the vestibular nerve. Cajal method. [Cajal, 1954.] **D.** Terminal ramifications of afferent fibers in the lateral nucleus of the thalamus of a mouse. Golgi method. [Cajal, 1954.] **E.** Endings on intraparietal neurons of the auricle of the heart of a fish. Note the thick unmyelinated fiber terminating in special formations and the myelinated fiber giving off an unmyelinated collateral from the node of Ranvier. Method of Gros. [Laurent, 1957.] **F.** Nests formed by centrifugal fibers that reach the retina and surround cells, called associational amacrines. Methylene blue. [Cajal, 1954.] **G.** A cell in the reticular formation of the goldfish, which, besides small end bulbs (*e*), receives a large club ending (*c*) from a myelinated fiber (*m*); *a*, axon of postsynaptic neuron. [Bodian, 1942.] **H.** Calyces of Held in the nucleus of the trapezoid body of a kitten. Golgi method. [Cajal, 1954.]

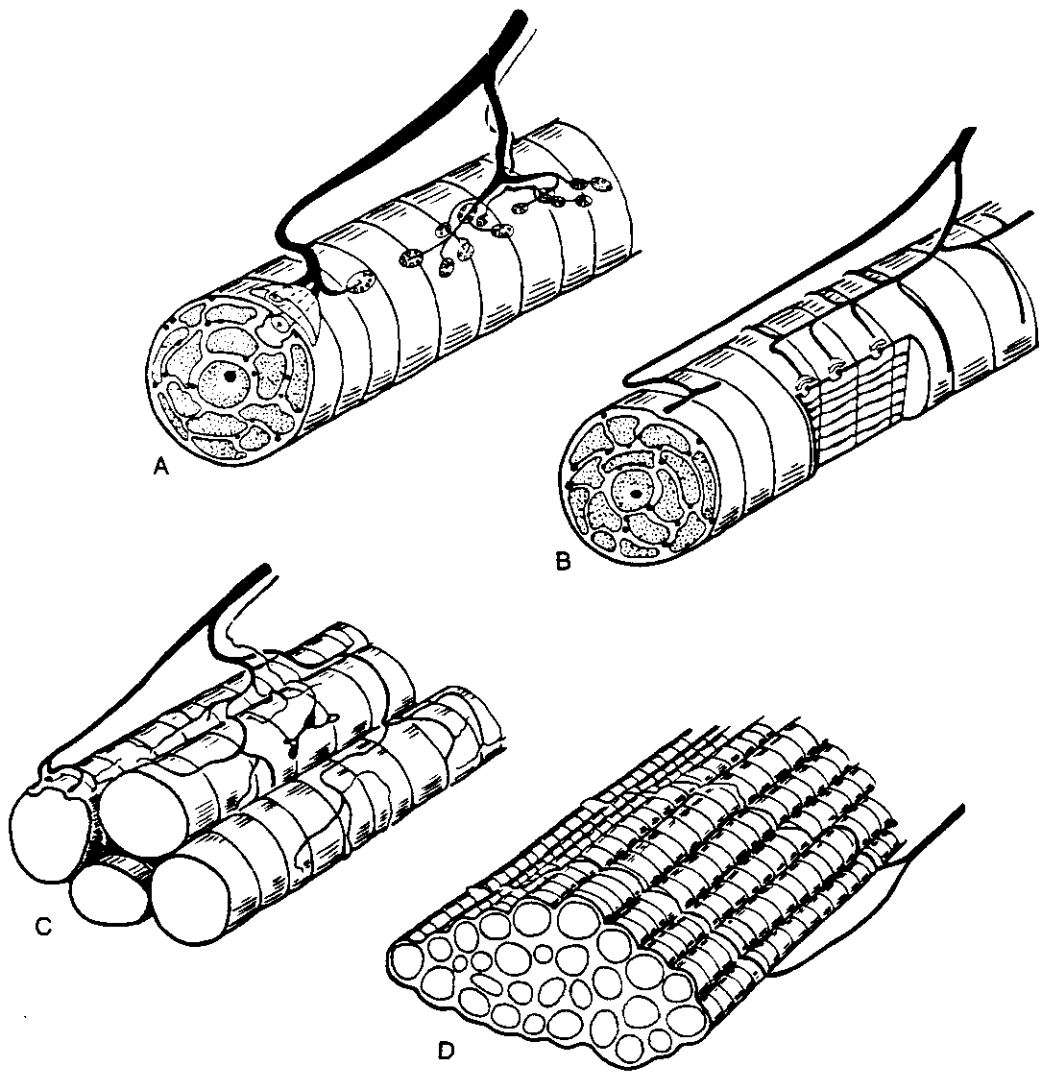


Figure 2.20
Insect neuromuscular endings. **A.** The end-plate type; general in leg muscles of coleopterans and hymenopterans (also in the proboscis of dipterans; note fibril columns, mitochondria, and glial cell covering nerve ending with vesicles. **B.** The metameric type with circular end branches approximately between every two Z-bands; found in *Dytiscus* (Coleoptera) leg muscle. **C.** The diffuse type; general in Orthoptera; note fast and slow nerve fibers. **D.** The simple transverse type, with rarely ramifying circularly disposed end branches; general in flight muscles of coleopterans and hymenopterans. Based on metallic impregnations and electron micrographs. [Courtesy J. Szentágothai and J. Hámori.]

est or twitch type are unique in the form of the expanded terminal apparatus (Fig. 2.21). The terminals spread more or less like a hand and involve a considerable area of the muscle surface; there is usually only one such ending, or end plate, on a given muscle fiber from a given axon, in contrast to the many in the next category. More remarkable is the specialization of the postsynaptic membrane; the muscle membrane is thrown into deep folds in which the presynaptic terminals do not follow, so that some space and intercellular material is left.

16. **Neuromuscular junctions with simple end plates.** In contrast to the previous class, end plates in muscle with multiterminal and polyneuronal innervation (see Glossary) are without subsynaptic folds (Figs. 7.2; 7.4; 7.5).

17. **Dendo-dendritic** contacts. Regarded as questionable until recently, these turn out to be common and are looming in importance (Fig. 2.58). They are often reciprocal (see p. 48 and Fig. 2.28).

18. **Soma-to-soma** connections are known and may have a similar interest.

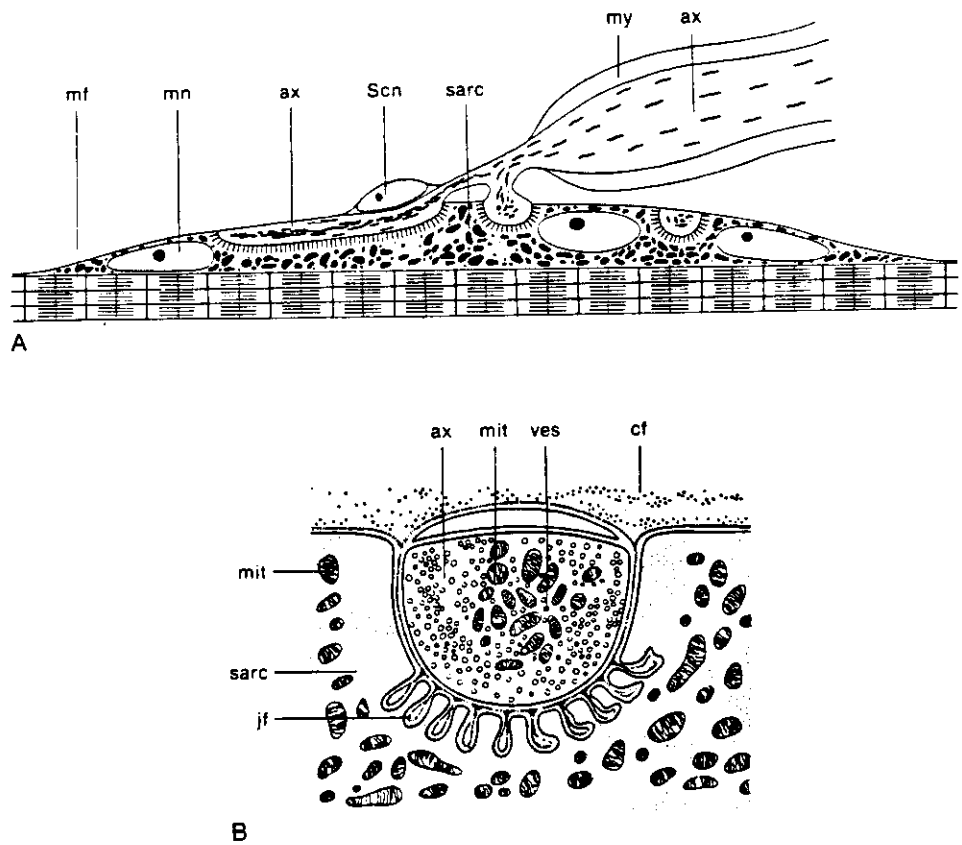


Figure 2.21
Vertebrate neuromuscular junction as revealed by the electron microscope. **A.** Schematic drawing of a motor end-plate at low magnification. **B.** Diagram of a cross section of one synaptic gutter and axon branch. *ax*, axoplasm; *cf*, collagen fibrils; *jf*, junctional fold; *mit*, mitochondria; *mf*, myofibrils; *mn*, muscle nuclei; *my*, myelin sheath; *sarc*, sarcoplasm; *Scn*, Schwann cell nucleus; *ves*, vesicles. [Couteaux, 1958, after Robertson.]

19. Contacts between **sensory terminals** and nonnervous receptor cells. These are found in the ear (Figs. 2.61; 2.65; 2.69), lateral line (Figs. 2.68; 2.72), taste buds (Fig. 2.71) and Merkel's and Iggo's skin receptors. They are properly called synapses, and show considerable variety. Doubtless their arrangement and form are functionally significant.

20. **Sensory endings that are themselves receptors.** Included strictly for comparison, this heterogeneous group includes sensory corpuscles, muscle spindles, olfactory neurons, free nerve endings in skin, and apparently all invertebrate receptors. Since these lack presynaptic elements, they are not synapses, but they are of interest here because of their form. The geometry of the endings is characteristic of each type and, we presume, related to function (see lower right margin). Section VI adds some details.

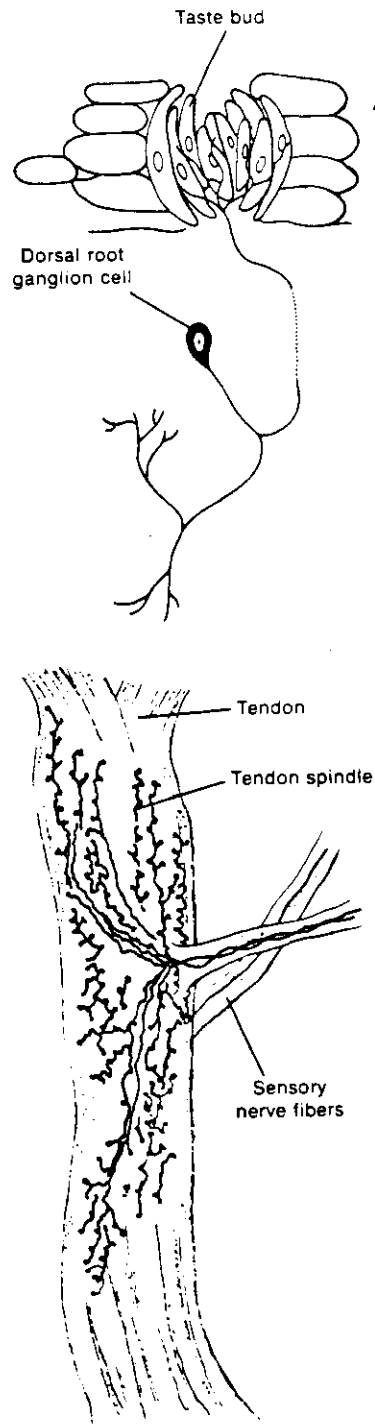
The list of synaptic forms by external configuration given above is not complete and includes several heterogeneous categories. In other words, there are a large number of presently distinguishable forms. Moreover, they do not occur at random but are consistent for given pre- and postsynaptic cells. Year by year, advancing anatomical information establishes in more detail and at additional sites the existence of consistent precision in the characteristics of the synaptic relations between specified neurons (see p. 99).

Varieties of Synapses at High Magnification. To the small handful of light-microscope methods available, the electron microscope (EM) adds a new and powerful method for revealing details of the processes of neurons and neuroglia. Previously they have been revealed only by very special metallic impregnations, by methylene blue staining, and recently by injected Procion yellow. In many animals no method yet attempted has made nerve fibers visible in the light microscope. Electron microscopy makes it possible to trace processes to the ends of their finest branches; with the light microscope, it was never certain whether we could see them to the very end. By means of the powerful but laborious method of reconstruction from serial sections, the forms, branches, destinations, and connections can be mapped completely in volumes of tissue a few score of micrometers on a side and as much as twenty or so micrometers in depth (Fig. 10.43). EM techniques have been combined with light-microscope observation and staining—for example, by Golgi impregnation or Procion injection, sometimes using alternately thick and thin sections to advantage. Techniques of filling the neuron and its processes have been extended to the electron opaque precipitate of a cobalt salt (Fig. 10.61).

Autoradiography combined with the EM can reveal how axoplasmic transport distributes proteins made from radioactive amino acids taken up by a neuron (Fig. 2.22). The problem of following branches and visualizing form in three dimensions has been reduced somewhat by applying the technique of scanning electron microscopy to surfaces created by tearing, cutting, or fracturing nervous tissue along cleavage planes at different stages of preparation. (See further, Section VII, p. 93.)

Of the utmost importance has been one of the simplest findings of electron microscopy—namely, that neurons and all their processes are bounded by continuous cell membranes, thus remaining distinct and separate from each other. This confirms elegantly the basic tenet of the neuron doctrine.

Criteria for recognizing synaptic junctions in the EM and for identifying the



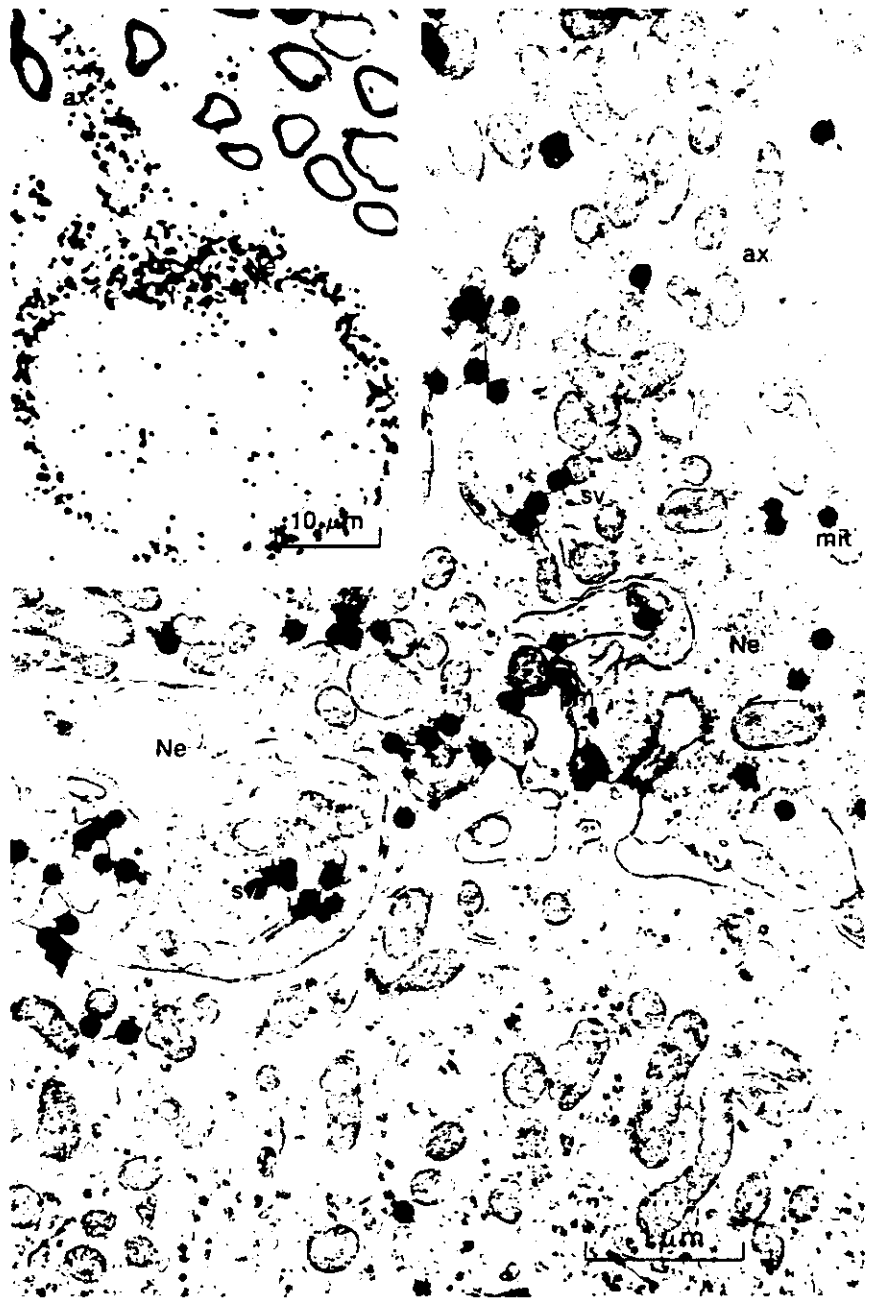


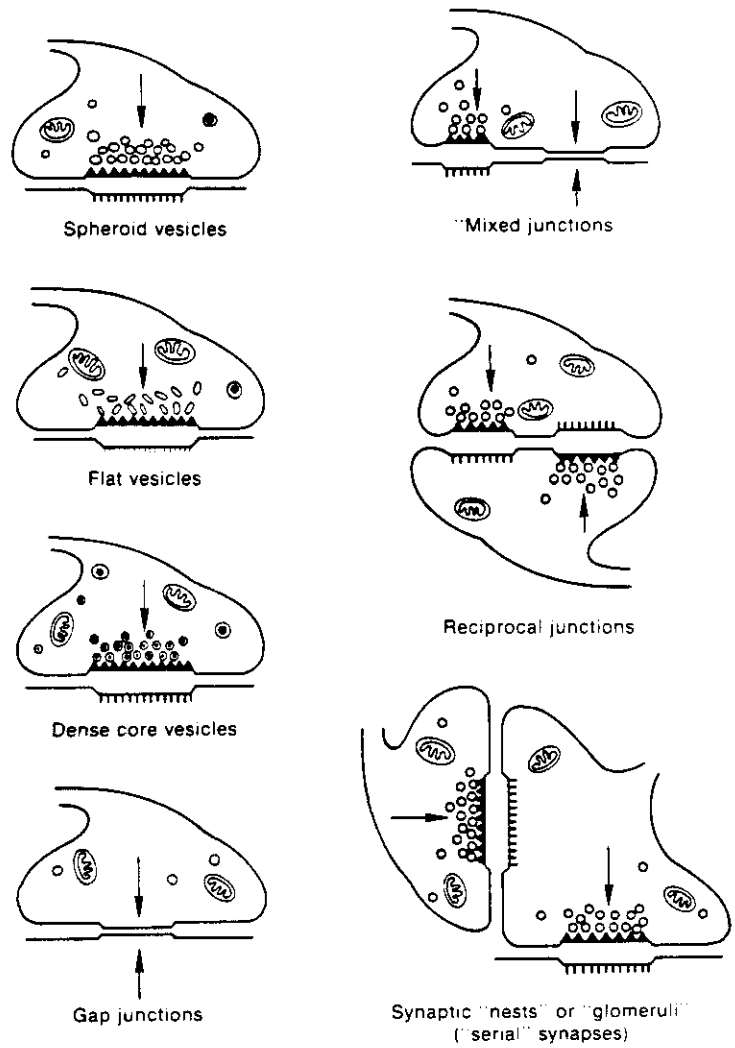
Figure 2.22
Autoradiographs visualizing axoplasmic transport of protein to synapses. ^{3}H-labeled amino acid was injected into the vicinity of the nerve cells in the brain and was taken up and synthesized by them into protein. After 18 hours the ciliary ganglion in the orbit was prepared and sectioned. Both pictures show the radioactivity of proteins transported in the axons of preganglionic parasympathetic neurons in the IIIrd nerve. The inset, taken by light microscope, shows the dense accumulation of silver grains over the terminal part of the axon (*ax*) and its expanded ending (*Ne*), which embraces the postsynaptic soma (called a calyx and referred to in Figure 2.8, B. The large view, taken by electron microscope, is from an area similar to part of the inset; most silver grains are seen to be concentrated over the areas also occupied by synaptic vesicles (*sv*) and presynaptic plasma membrane (*pm*). Only a few are seen over mitochondria (*mit*) or postsynaptic cytoplasm; these proteins are presumably concerned with renewal of membrane components of the synapse. [Courtesy of B. Droz.]

pre- and postsynaptic sides have been gradually established by a patient process starting with cases in which the identification of pre- and postsynaptic sides was already clear on other grounds. We cannot be certain that our criteria are infallible, especially whether they include all the regions of functional interaction between neurons. Unspecialized junctional regions may go unrecognized.

The principal feature that characterizes synapses in the EM is an apposition of the pre- and postsynaptic cell membranes. This means that the barrier of neuroglial processes that generally separate neurons has windows. Appositions without gaps ("tight junctions") function as high-resistance seals but probably not as synapses. Those with 20–50 Å spaces ("gap junctions") forming an array between points of direct contact are called nexuses; they function as low-resistance electrical synapses. More commonly there is a cleft of 200 Å or more, which is even wider than some common, supposedly normal intercellular spaces. The synaptic cleft is specialized by its uniform width and by an ordered arrangement of a macromolecular material, mucopolysaccharidal in character, that occupies the intercellular spaces of nervous tissue generally.

The regions regarded as synaptic on electron-microscopic grounds generally have several other characteristics as well (Fig. 2.23). The cell surfaces appear thickened due to a greater electron density and condensation of the cytoplasm subjacent on the postsynaptic side or on both sides. The most typical specializations are on the presynaptic side. There may be an array of local thickenings of the presynaptic membrane, forming a hexagonal pattern of dense inward projec-

Figure 2.23
Variations of synaptic structure and topography. Arrows indicate direction of transmission. [*Bodian, 1972.*]



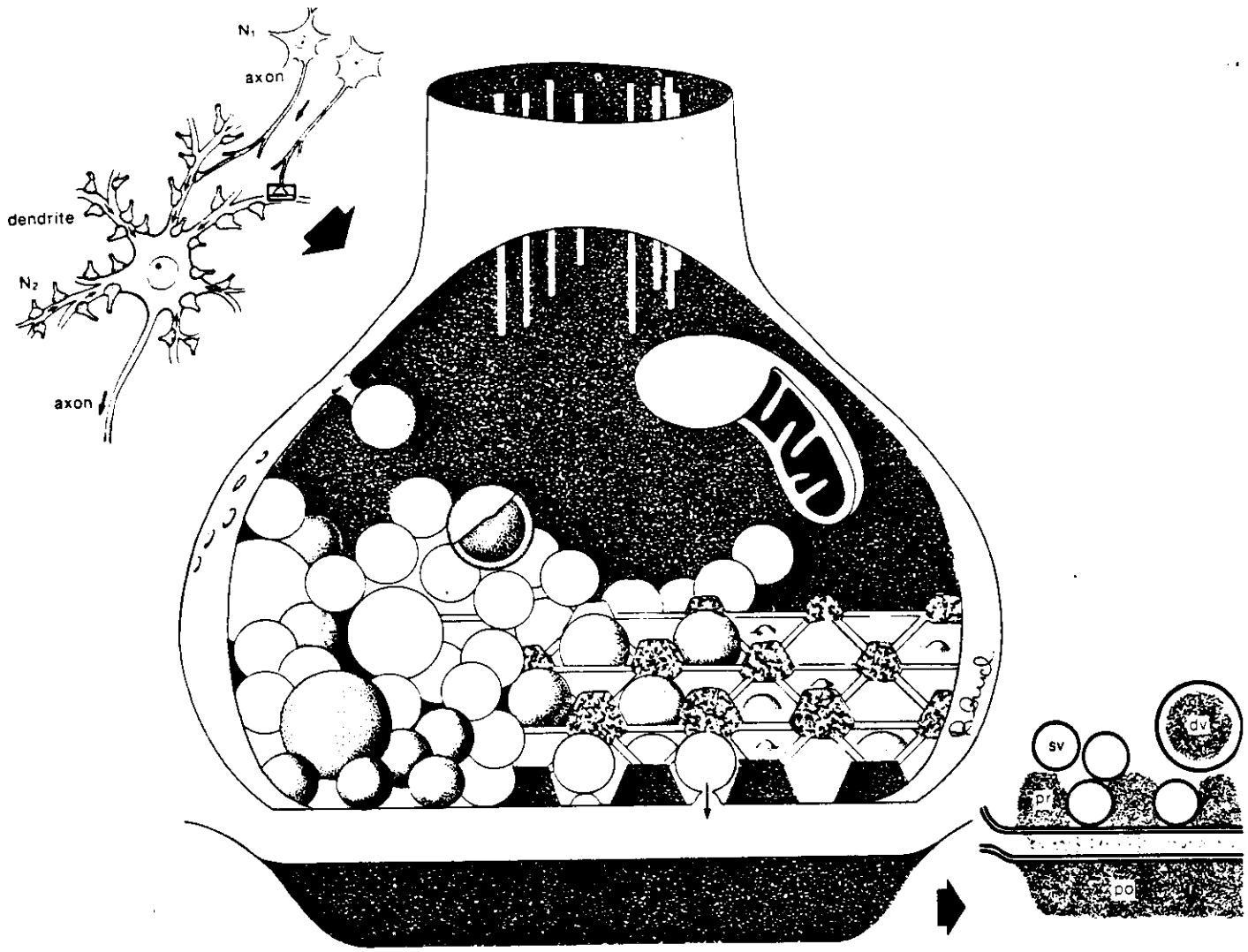


Figure 2.24
Left. Low-power diagram showing a presynaptic terminal within the rectangle. **Center.** An enlarged view of the same terminal, showing the vesicular grid, "synaptophores" and vesicles incorporated into the cell membrane, a single mitochondrion, neurofilaments, and the cleft, but no postsynaptic detail. **Right.** Diagram of terminal at lower magnification than the preceding, as seen with a different fixative: *dv*, dense core vesicle; *sv*, spherical vesicle; *pr*, presynaptic projection; *po*, postsynaptic cytoplasm. [Akert et al., 1972.]

tions, with a period of 800 Å, enclosing thin spots large enough for one synaptic vesicle (see below) and occupied in some proportion by such vesicles (Fig. 2.24). Neurofilaments are typically absent but in certain terminal buttons may form a whorl (Fig. 2.31). One or a few mitochondria are often present near the junction.

Most characteristic of the synaptic features seen in the EM is a clump of synaptic vesicles, near the membrane. These are generally confined to the presynaptic side, but sometimes vesicles are seen on both sides. There are at least four kinds of synaptic vesicles.

1. Light-core or clear spheroidal vesicles 200–500 Å in diameter. In certain junctions examined, these occur in excitatory synapses and contain acetylcholine, but they also occur in others that do not involve acetylcholine, including some probable inhibitory endings.
2. Light-core ovoidal or pleiomorphic vesicles (easily flattened by certain preparative procedures) of about the same diameter. These are typical of certain synapses known physiologically to be inhibitory. Generalization is not justified, however.
3. Granulated vesicles of about 500 Å. These may contain catecholamines.
4. Dense core vesicles of 800–1000 Å. These may also contain catecholamines.

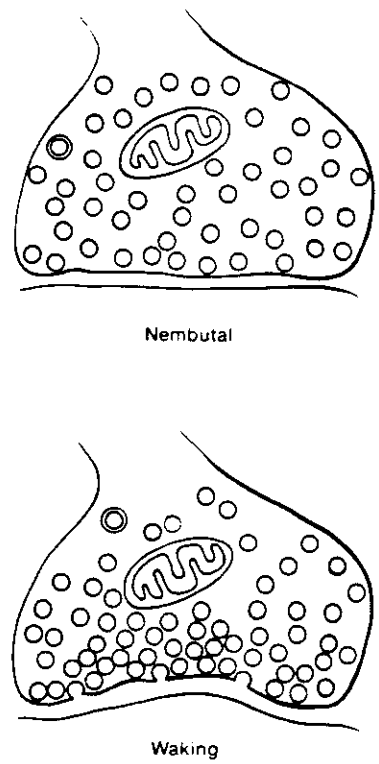
These classes and their physiological correlates are being modified with increasing knowledge, but it is clear that synaptic vesicles are not all alike, and that morphological and chemical-functional differentiation may go together. Therefore, it may be possible to use morphological criteria to infer the functional type or state of a synapse (Fig. 2.25). We must be prepared, however, to learn that the criteria are not universal.

One technical development of particular promise in this area is the discovery of means of breaking off the axonal terminals near their ends. The postsynaptic membrane also breaks away from its neuron and adheres to the presynaptic membrane, forming a composite little body, the synaptosome. These bodies can be concentrated by centrifugation, permitting chemical as well as EM characterization of synaptic structures collected from different parts of the brain and collected during different functional states. Further treatment can isolate synaptic vesicles and permit chemical analysis of accumulated samples.

New developments are making it possible to count all the synapses, defined by EM, in a given area of a section. Although it is premature to make general statements, there seems to be evidence of changes in the count with physiological state and with age. Counts can also be made of the dendritic spines, and these have been found in certain cases to increase with age and with stimulation by so-called enriched environments —those full of objects and variety (Fig. 2.26; see also Chapter 9).

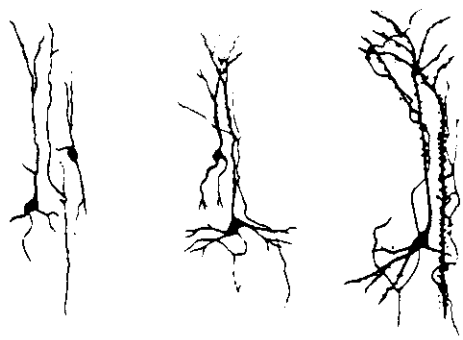
Other specialized synaptic structures occur commonly but not generally. We should not expect that the several types of junctions recognized above on the basis of light-microscopy would have a one-to-one correspondence with any classification of synapses based on EM evidence, since the scale of the former is much larger. Quite diverse configurations on that scale might have a common ultrastructural basis. Several types have, however, been distinguished on EM cri-

Figure 2.25
Change in synaptic morphology with change in state.

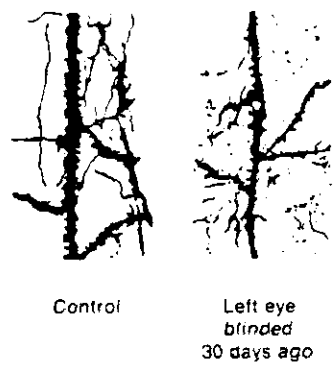


Synapses from anesthetized animals tend to be less arched, vesicles less aggregated and rarely opening to the cleft. [Akert and Livingston, 1973.]

Figure 2.26
Changes in synaptic substratum—that is, in dendrite morphology—with changes in age and experience.



Development of apical dendrites in neurons of kitten cortex. [Scheibel and Scheibel, 1963.]



Rabbit visual cortex apical dendrites in normal and unilaterally blinded adults. [Scheibel and Scheibel, 1968b.]

teria (Figs. 2.23; 2.27). Some examples are given in the following list.

1. **Symmetrical nexuses, or gap junctions.** Two apposed membranes with an overall thickness of 150 Å come within 20–40 Å of each other. This gap, as visualized by filling it with lanthanum, is actually a hexagonal array of 20 Å channels with a period of 100 Å; the channels communicate with the general intercellular space. Structures bridge the gap and put the two membranes into contact. Penetrating these bridges are channels perhaps 10 Å in diameter that allow ions and small molecules to pass between the cytoplasms of the two cells. The formation and dissolution of nexuses and low-resistance electrotonic coupling between cells are normal physiological and developmental processes. Nexuses correlate well with electrical transmission. Such junctions are distinguished from occluding, or tight, junctions, which have no gap or intercytoplasmic channels, and act as seals between cells to block the low-resistance pathway for current flowing along intercellular clefts. (Figs. 2.27 A,B,C; 2.28A).

2. **Axo-dendritic synapses** with narrow cleft. This category cannot be lumped with the preceding because, though transmission is electrical, it is polarized. The first example that was well studied both physiologically and ultrastructurally is the synapse between central giant and segmental motor axon, in the abdominal cord of the crayfish (category 12, p. 33; Fig. 10.27). The large postsynaptic axon, which supplies flexor muscles, sends short receptive processes, which may be regarded as microdendrites, into indenta: s of the presynaptic fiber (Fig. 2.27,F). The cleft is narrow, 15–20 Å. Vesicles may occur on either or both sides but are not numerous or in large clumps. Several examples are known in the vertebrates, including the excitatory electrical endings on the giant Mauthner cell of fishes. Not uncommonly, cells exhibit mixed electrical and chemical synapses, even in the same presynaptic fibers (Figs. 2.23; 2.29).

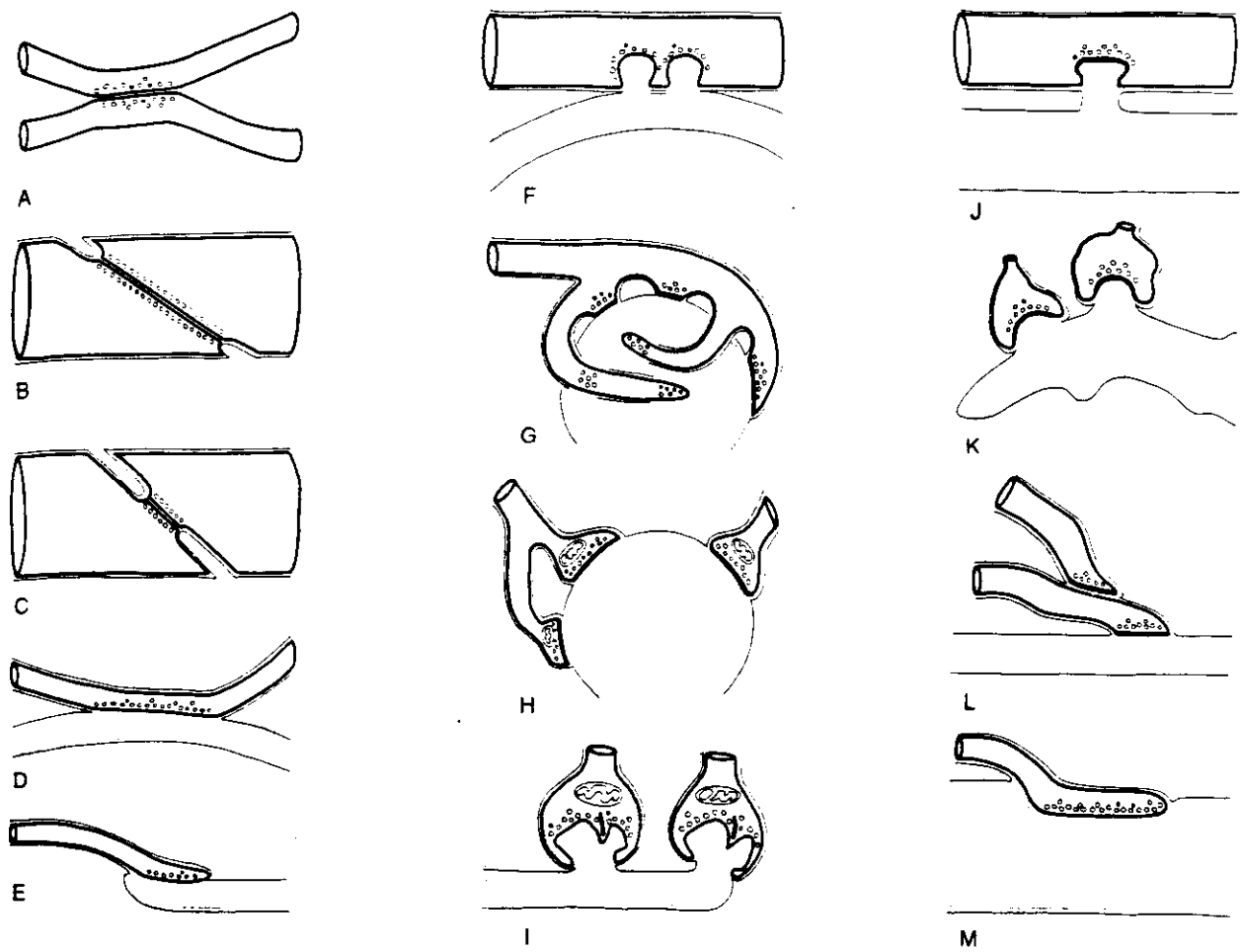


Figure 2.27
Types of synapses revealed by electron microscopy. Brown, presynaptic; gray, postsynaptic; black, the innermost extent of the sheath. **A.** Example of coelenterate axon-axon synapse in jellyfish ganglion, with vesicles on both sides and without adhering sheath cells. **B.** Earthworm septal synapse with close apposition of the membranes of the two cells and sparse vesicles on both sides. **C.** Crustacean septal synapse, as in B except that the synaptic area is restricted. Examples B and C have electrical transmission in either direction. **D.** Axon-axon synapse-in-passing typical of neuropile in many invertebrate ganglia, often with and often without sheaths. **E.** Axon terminal arborization ending on a fine dendrite in invertebrate *neuropile*. **F.** Crustacean giant-fiber-to-motor-neuron synapse, with postsynaptic motor fiber invaginated into the giant fiber. This example also has electrical transmission, but only in one direction. **G.** Axon arborization-to-soma synapse typical of vertebrate brain cells, but in invertebrates so far only clearly known as inhibitory endings on crustacean peripheral sensory cell of muscle receptor organ. **H.** Terminal buttons of axon arborizations typical of certain central neurons in vertebrates. **I.** Ribbon synapses between rod cell endings and dendrites of ganglion cells of vertebrate retina, with presynaptic specialization. **J.** Synapse between giant fibers of squid stellate ganglion, postsynaptic invaginated into presynaptic. **K.** Spine synapse (axon-dendrite) from cerebral cortical dendrite of vertebrates with postsynaptic specialization. **L.** Serial synapse, found so far in spinal cord, cerebral cortex, and plexiform layer of retina in vertebrates, but offering many potentialities for presynaptic inhibition and other complex interaction in neuropile. **M.** Specialized neuromuscular endings found in vertebrate skeletal muscle, with postsynaptic grooves. [Bullock and Horridge, 1965.]

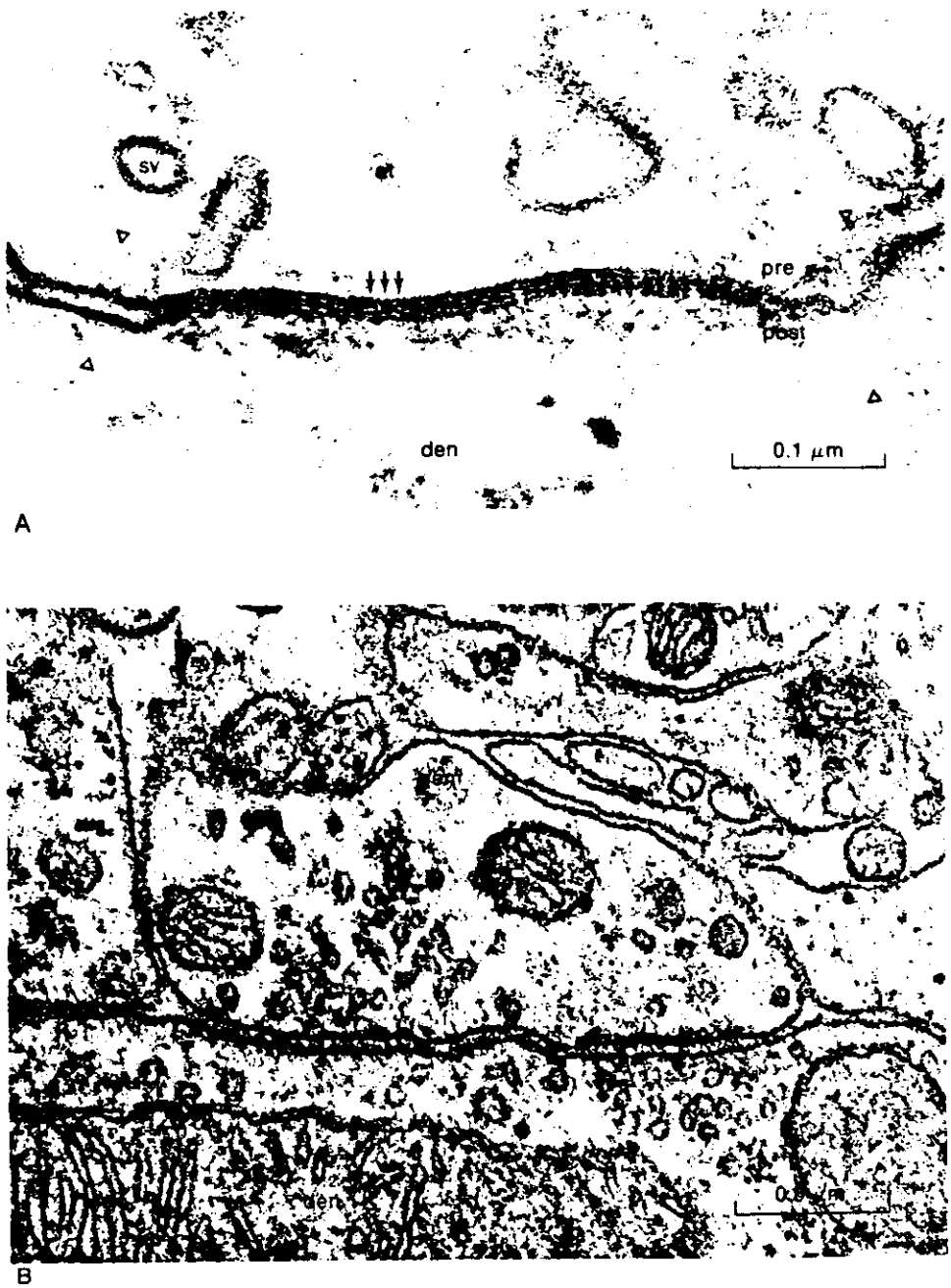
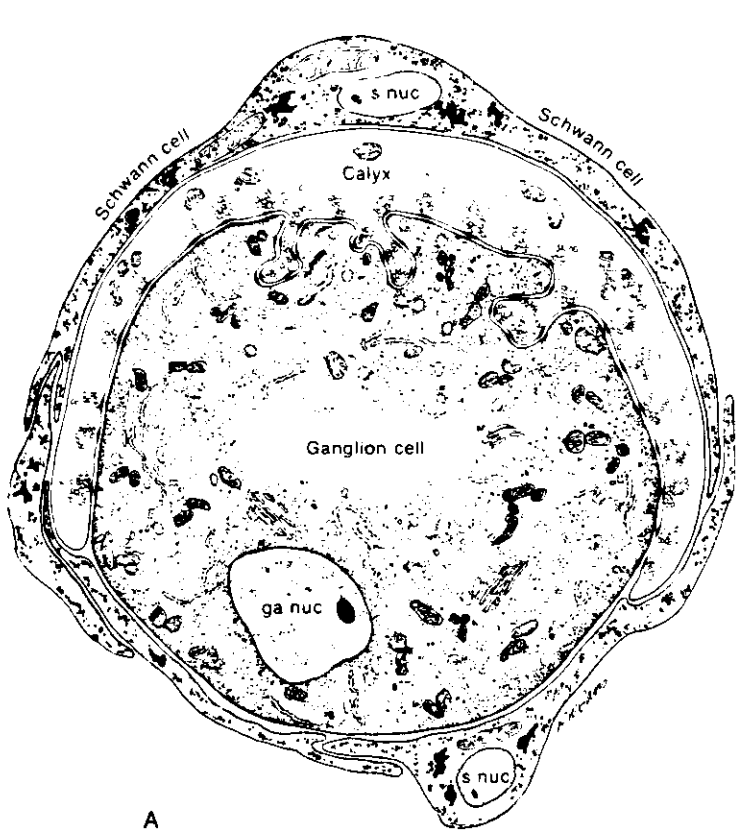


Figure 2.28
Electrical and dendro-dendritic synapses. **A.** Medulla oblongata of a goldfish. In the center of the field is a synapse between an axonal club ending (*at*) and the lateral dendrite of a Mauthner cell. At the synaptic junction, the pre- and postsynaptic membranes come into close apposition and are separated by a distance of only about 20 Å. Thus a seven-layered structure is formed. This is an electrical synapse. At the site of apposition, striations (arrows) occur in the gap, giving a ladder-like appearance to the junction. On each side of this "gap" junction, the pre- and postsynaptic membranes diverge from each other to form punctate adhesions (triangles). Within the axon terminal are synaptic vesicles (*sv*) bounded by triple-layered membranes. **B.** Olfactory bulb from a rat. In the lower half of the field is the secondary dendrite (*den*) of a mitral cell. This dendrite synapses with a gemmule (*gem*) protruding from a granule cell dendrite. At the synaptic junction between these two dendritic components are two synaptic complexes with opposite polarities, as indicated by arrows. Where the direction of transmission, as judged by the grouping of the synaptic vesicles, is from the mitral dendrite to the gemmule, a dense filamentous material (*f*) underlies the postsynaptic membrane. Where the direction is from the gemmule to the mitral cell dendrites, the polarity is not marked by a postsynaptic density. [Peters et al., 1970; micrographs by T. Reese, courtesy of M. W. Brightman.]



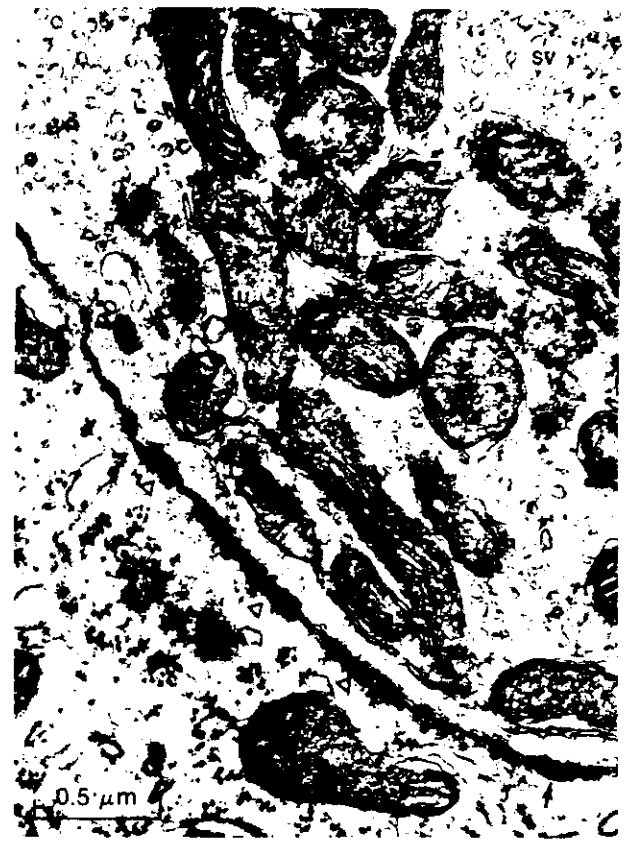


Figure 2.29
Mixed synapses. **A.** Calyciform synapse in the ciliary ganglion of the chick, as revealed by the electron microscope. Note the locally dense regions of the opposed synaptic membranes, the clusters of synaptic vesicles at these sites on the presynaptic side, and the uniform cleft width (300–400 Å). *ga nuc*, ganglion cell nucleus; *s nuc*, Schwann cell nucleus. [De Lorenzo, 1960b.] **B.** Lateral vestibular nucleus of a rat. Occupying the center of the field is a large axon terminal containing many synaptic vesicles (*sv*) and mitochondria (*mit*). This terminal forms a mixed synapse with the perikaryon of a Deiters neuron. At the synaptic junction, complexes of three types occur. (1) Complexes in which there is a close apposition between the pre- and postsynaptic membranes (asterisk). These are considered as probable electrical synapses. (2) Complexes in which there is a cleft between the pre- and postsynaptic membranes and a prominent postsynaptic accumulation of dense material (arrow). Such junctions usually have synaptic vesicles associated with them, so that they have the form of typical chemical synapses. (3) Complexes in which there is a space between the pre- and postsynaptic membranes and symmetrically disposed dense material (triangles). These are typical puncta adhaerentia—points at which cells adhere, but which are not considered to be synapses. [From Peters et al., 1970; micrograph B by C. Sotelo.]

Figure 2.30
Two subtypes of chemical synapses that differ in dimensions. [*Akert et al., 1972.*]

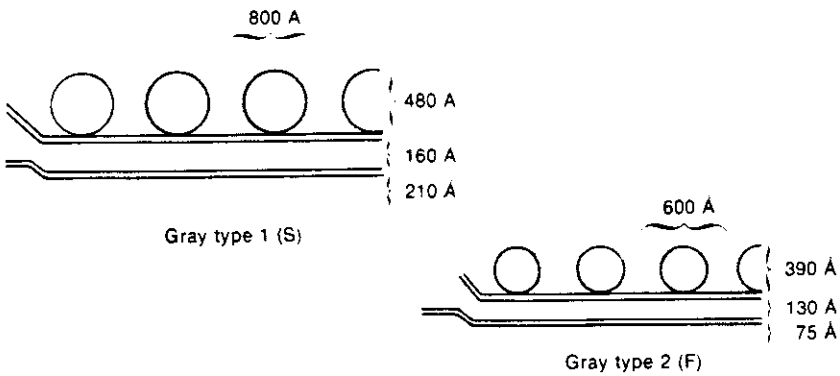
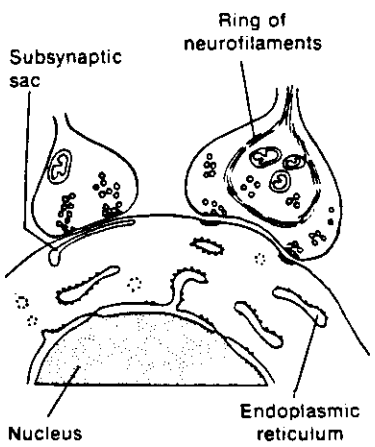
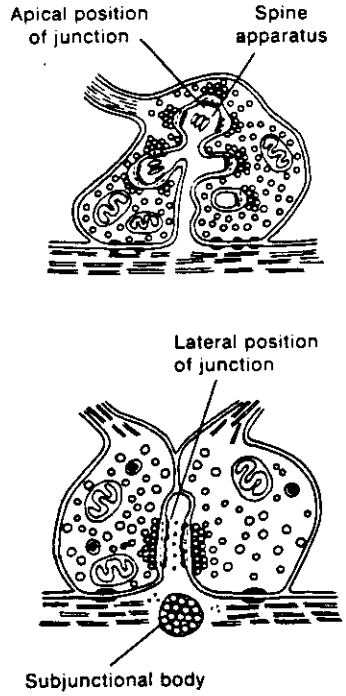


Figure 2.31
Varieties of axosomatic and axodendritic synapses.



Two subtypes of axosomatic synapse. [*Whitaker and Gray, 1962.*]



Two subtypes of axodendritic synapse. [*Hamlyn, 1962.*]

3. **Axo-axonal synapses with short receptive processes, clustered vesicles, and wide cleft.** Represented by the squid giant synapse (Figs. 2.17; 2.27; see also p. 434) this type is well known physiologically. Electrical transmission has been ruled out, and some evidence for glutamate as the transmitter is reported.

4. **Unspecialized axo-dendritic connections** between fine fibers in invertebrates. In earthworm, insect, and other fine-textured neuropiles, numerous localized areas are presumed to be synapses solely on the grounds that they make contact without intervening glia and that they have clusters of vesicles on one side, which is thought therefore to be presynaptic. These quite unspecialized synapses may occur as contacts of fibers crossing at right angles (and therefore of small area), as longitudinal contacts of large area, or as end-knob contacts (Fig. 2.27,D,E).

5. **Axo-somatic and axo-dendritic synapses.** These wide-cleft (200–300 Å) junctions have been subdivided into two categories (Figs. 2.30; 2.31). One is simple and small in diameter (ca. 0.25 μm); the other is large (0.5–1 μm) and has more postsynaptic densification. The first category includes terminal button synapses on spinal motor neurons, endings on postganglionic autonomic neurons, and inhibitory junctions on the crayfish stretch receptor cell—obviously a heterogeneous set. The second includes many junctions of the mammalian cortex. These synapses may also be subdivided by vesicle shape (see above) and on other grounds (Fig. 2.31).

6. **Axo-dendritic synapses on spines.** Dendritic spines are a late-developing specialization of certain cells in higher animals, and they exhibit some special features in fine structure (Figs. 2.27,K; 2.31; 2.32).

7. **Invaginated ribbon synapses.** In the vertebrate retina and elsewhere, there are junctions similar to those of category 5 that exhibit a special presynaptic ribbon of unknown function (Fig. 2.27,I).

8. **Serial synapses.** These are the supposed bases for presynaptic inhibition; axon *A* is presynaptic to axon *B*, which in turn is presynaptic to neuron *C*, the junctions being within a few micrometers (Figs. 2.23; 2.27,L).

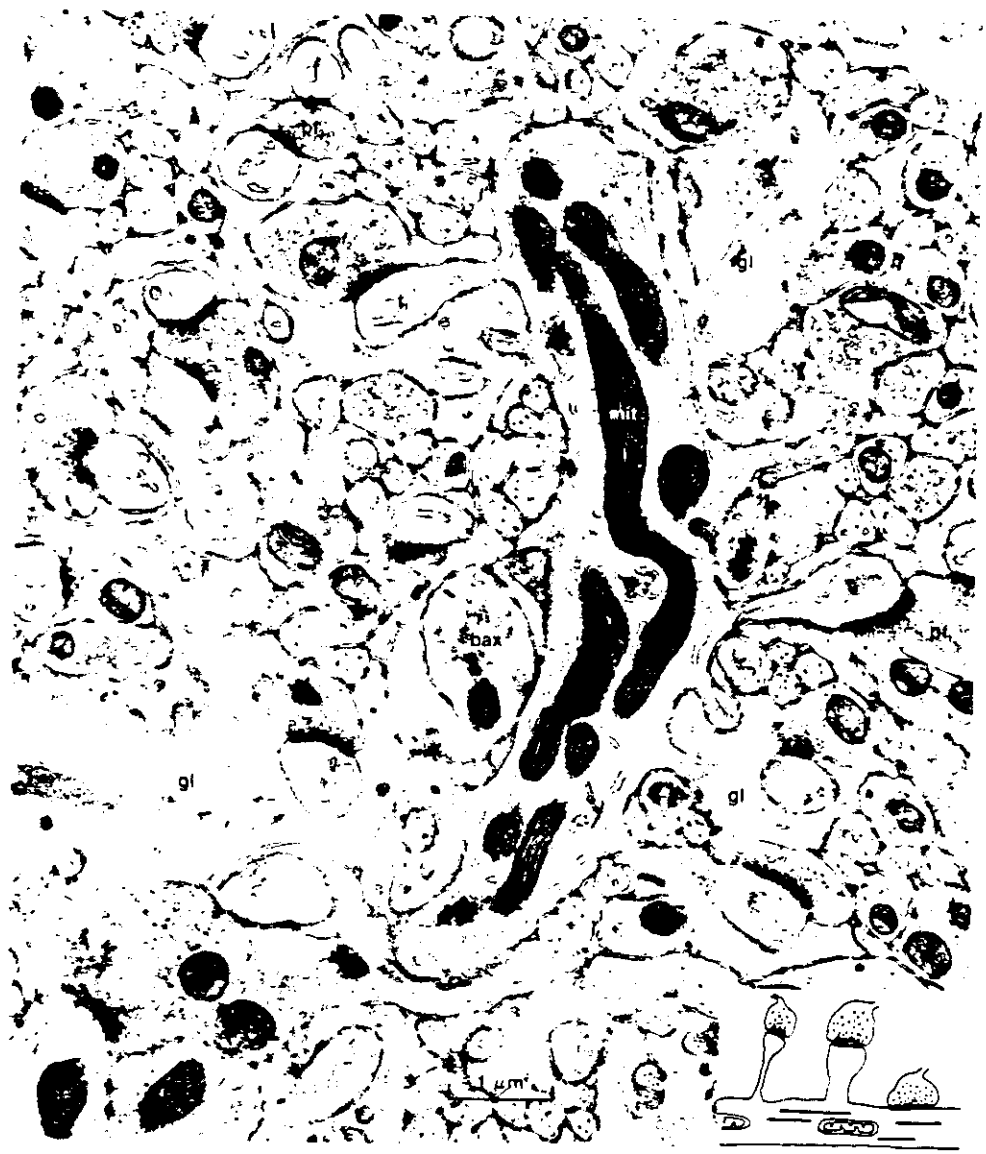
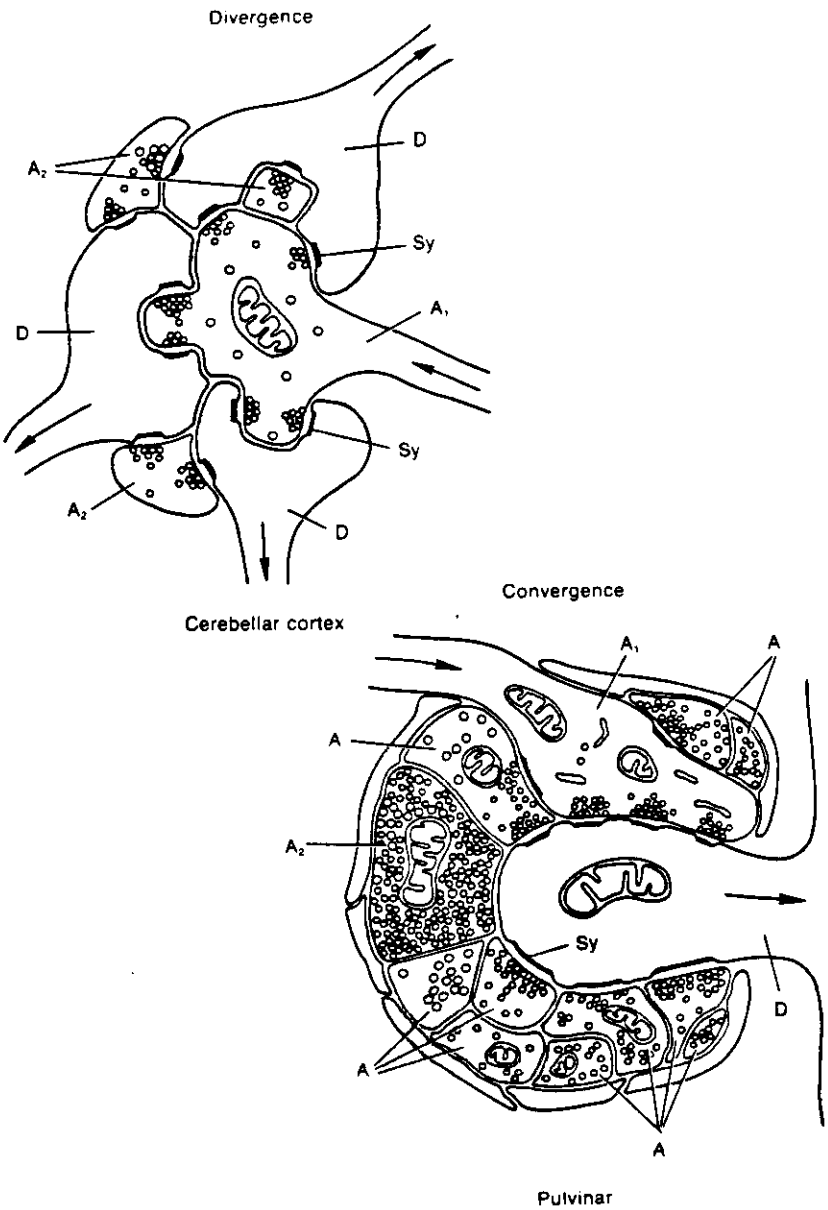


Figure 2.32
Synapses on spines of dendrites. In the center of the electron micrograph is the spiny branchlet of an adult rat cerebellar Purkinje cell; its covering is a layer of neuroglia (*gl*), and in its shaft are mitochondria (*mit*). A basket cell axon (*bax*) synapses directly onto the spiny branchlet. Two thorns (t_1, t_2) emerge from the shaft to synapse with parallel fiber axon varicosities (pf_1, pf_2); another parallel fiber varicosity (pf_3) is presynaptic to two Purkinje cell thorns (t). [Palay and Chan-Palay, 1974.] Inset at lower right is a low-magnification diagram of two synapses on spines contrasting with one on the dendritic shaft. [Scheibel and Scheibel, 1968b; courtesy of L. Westrum.]

Figure 2.33
Two types of synaptic glomeruli.



Complexes of synapses (Sy) *involving several neurons seem to have evolved independently many times. Some, as in the cerebellum, center on a single arriving axon terminal* (A); *others, as in the pulvinar of the thalamus, center on a single departing dendrite* (D). [*Steiger, 1967.*]

9. **Neuromuscular junctions with postsynaptic grooves** (Fig. 2.27,M). This class corresponds to the light-microscope category 17. Both postsynaptic membrane and cleft material give positive cytochemical tests for acetylcholinesterase.

10. Neuromuscular junctions without grooves. This corresponds to the light-microscope category 15.

11. **Reciprocal synapses.** Wide cleft junctions that resemble those in category 5, above, are sometimes not polarized exclusively in one direction, so that a certain dendrite is solely postsynaptic, but instead lie side by side, polarized in opposite directions, so that each neuron is both pre- and postsynaptic. They are usually dendrodendritic synapses (Fig. 2.28).

For the neurophysiologist it is important to note that one dendrite may bear morphologically diverse synapses; one presynaptic cell may produce morphologically different kinds of endings upon other fibers; one dendrite can be both pre- and postsynaptic.

Furthermore, one pre- or postsynaptic terminal specialization may make contact with several other neurons. That is, synapses are not always sites of intimate contact between one pre- and one postsynaptic unit, as we have already noted (p. 29). **Synaptic complexes** involving one or two enlarged central endings—in some examples, dendritic, in other examples, axonal—may be surrounded by an array of small terminals (Fig. 2.33). These end on each other as well as on the central element, and include both axon and dendrite terminals traceable to a number of cells, near and distant. The whole complex may be delimited by glia to form a characteristic knot, or **synaptic glomerulus** (Fig. 2.34). No doubt this is the site of rather complex, functional integrative transactions.

The extent and the specialization of dendritic surface available for synaptic

contacts are vastly increased by the development of **spines and crests,** especially in some neurons. These vary widely in the profusion in which they are developed in different parts of the brain and in different animal groups. Of special significance is the recent finding that they can be more or less developed according to environmental factors or experience (Chapter 9).

The number of synaptic endings on a neuron varies widely among neurons, and not just because neurons differ greatly in extent of dendritic surface. It is estimated that a Purkinje cell of the cerebellar cortex receives some 90,000 synaptic endings. Counts of synaptic junctions in electron micrographs of the outer layer of the rat cerebral cortex indicate more than $10^9/mm^3$. Such figures should certainly be added to the commonly cited estimate of 10^{10}-10^{11} neurons in the nervous system of man (which later workers regard as low by perhaps a factor of ten). It must also be appreciated that the dogma that functional contacts are all visibly recognizable rests on limited evidence.

H. Diversity of Nerve Cells

Nerve cells can be **unipolar, bipolar,** or **multipolar** according to the number of processes emerging from the soma. In some primitive neurons the processes are indistinguishable; those neurons are called **isopolar** (Figs. 2.3; 10.2). Neurons in which axon and dendrite can be distinguished are called **heteropolar** (Figs. 1.3; 2.1; 2.3). The dominant type of neuron in vertebrates is a multipolar, heteropolar neuron (Fig. 2.53); the dominant type in invertebrate central nervous systems is unipolar with a branching stem process (Fig. 2.37; 2.53).

Another classification is functional, though usually demonstrated anatomically: nerve cells are **sensory, internuncial** (interneurons), or **motor.** Interneurons are often classified according to their connections: **projection** neurons send an axon a considerable distance rostrally or caudally in the central nervous system; **commissural** neurons send an axon to corresponding structures on

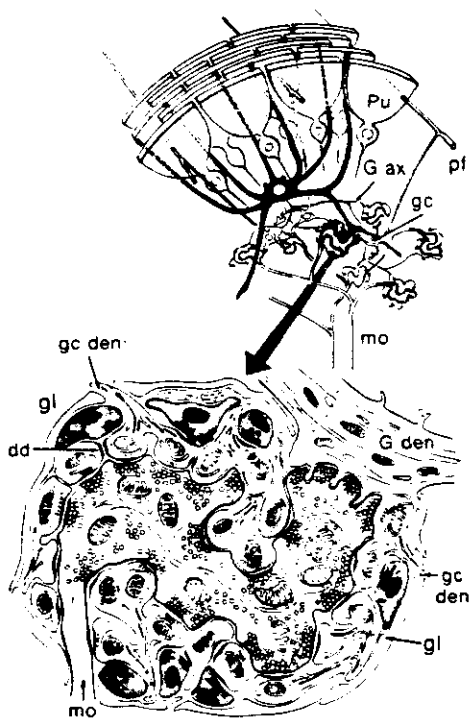


Figure 2.34
Synaptic glomeruli in the cerebellum. **Above.** A diagram at light-microscope magnification showing seven glomeruli in the layer of granule cells (*gc*). **Below.** One glomerulus shown at EM magnification. *mo,* mossy fiber afferents to the cortex; *G ax* (and shaded fibers below), axon from Golgi cell (dark shading signifies an inhibitory influence, in this case upon the dendrites in the glomeruli); *G den.* Golgi cell dendrite; *gc den,* granule cell dendrite; *gl,* glial capsule; *pf,* parallel fiber granule cell axon; *Pu.* Purkinje cell; *dd,* desmosomoid dendrodendritic contacts. [Szentágothai, 1970.]

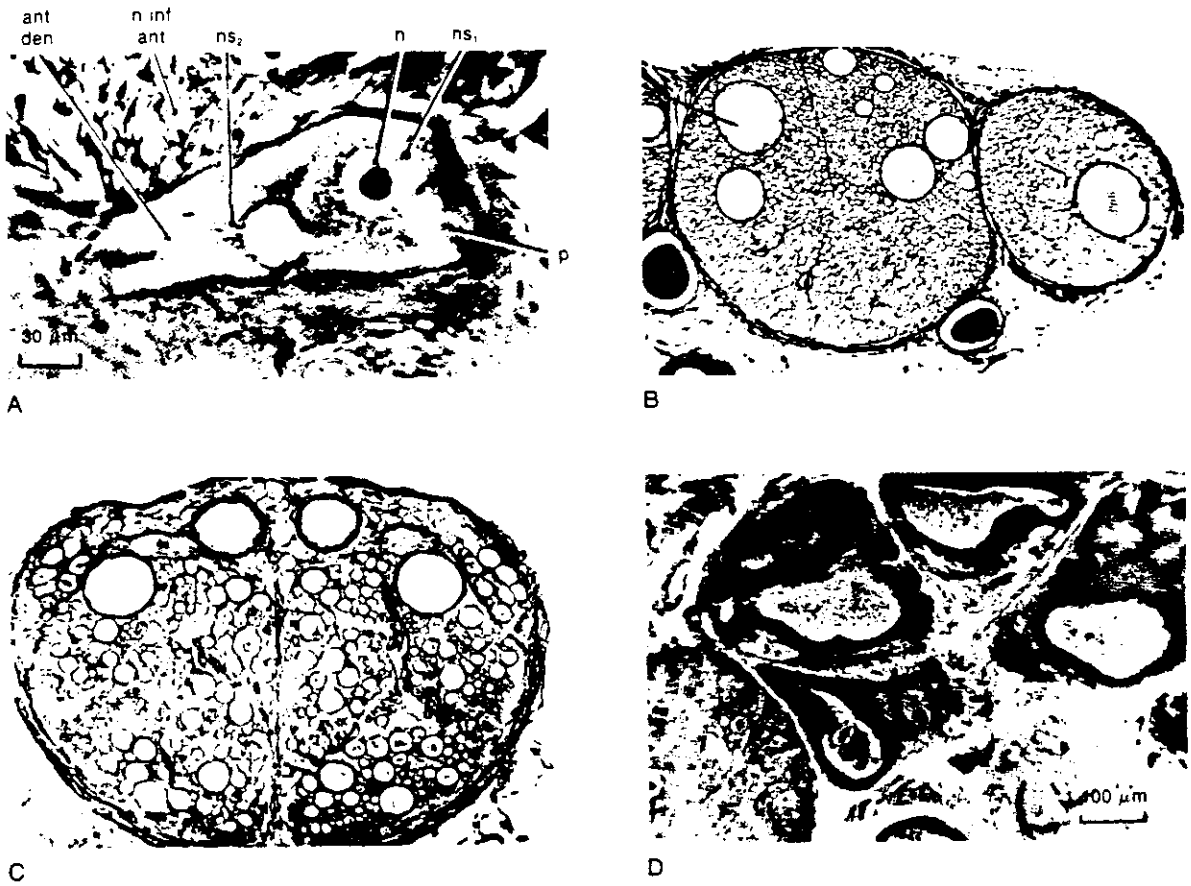


Figure 2.35
Giant cells and fibers. **A.** First-order giant cell in the brain of *Loligo*. Picroformol, hematoxylin, and eosin. [Young, 1939.] *ant den*, anterior dendrite; *n*, *nucleus*; *n inf ant*, anterior infundibular nerve; ns_1, central irregular granules of Nissl substance; ns_2, longitudinally arranged peripheral granules of Nissl substance; *p*, *pathway from axon to dendrites*. **B.** Transverse section of nerves of the *cuttlefish Sepia*, showing giant and small fibers. [Courtesy J. Z. Young.] **C.** Transverse section of the ventral cord of a crayfish fixed by the method of vom *Rath*. The four giant fibers are seen dorsally, and a motor axon is en route out of the cord, on each side, just about to pass dorsal to the lateral giants and to make synaptic contacts with them. [Robertson, 1961.] **D.** The somas of four large cells of the visceral ganglion of the gastropod *Aplysia*. The neuropile is below, right: a connective, which looks like a nerve, is forming on the left. Note the pigment in the large cell cytoplasm and especially the islands and trabeculae of glial tissue penetrating the cytoplasm (trophospongium). [Bullock, 1961.]

the opposite side; **intrinsic** neurons confine their axons to one side and level. Projection fibers, as well as entering sensory axons and exiting motor axons, may **decussate** (cross the midline) to other levels of the contralateral side or may remain ipsilateral with respect to their cell bodies.

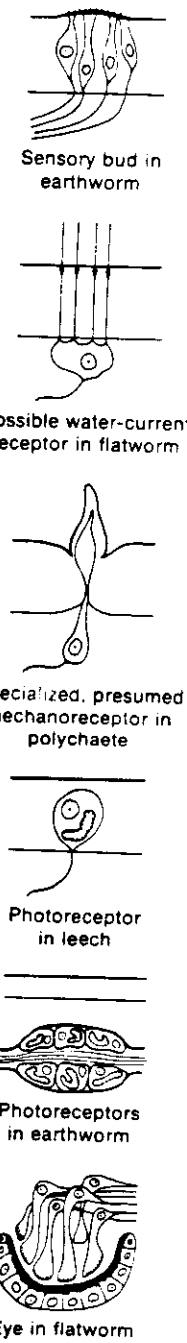
Nerve cells are diverse in size and nuclear-cytoplasmic ratio. **Globuli** (Figs. 10.14; 10.20,B; 10.30; 10.31) and **granule cells** (Figs. 3.15; 10.75) in invertebrates and vertebrates, respectively, are the smallest nerve cells (e.g., soma less than 3 μm in insects; 10 μm in mammals) and typically have sparse cytoplasm and relatively large nuclei (ratio of diameters, nucleus : soma $\simeq$ 1) with dense chromatin. Large cells may range from 10 μm in soma diameter in small worms and insects to about 50 μm in whales. In some animals, **giant cell** somas and axons are found that reach maximum diameters of about 800 μm and 2000 μm, respectively (Fig. 2.35). Giant axons are generally larger than their cell bodies and are usually discontinuously larger than the next largest fibers, rather than being merely the end of a continuous spectrum. But *Aplysia* cell somas 800 μm in diameter have axons only about 50 μm in diameter. Conversely, giant axons may not have giant cells: squid axons 800 μm in diameter come from many cells about 40 μm in diameter by fusion of their processes (Fig. 10.52). The ratio of axoplasm to somatoplasm volume is therefore widely divergent, from less than one in small, short-axon globuli cells to more than 10,000 in serpulid polychaete giants; the figure 250 has been given for a spinal ventral horn motor neuron in a monkey. There is no modern theory for this great range or for the meaning of giant cell bodies. Giant axons are thought to be of value in two ways. One is their high conduction velocity, though we should note that this is expensive in terms of volume, synthesis, and metabolism. The other is the large extracellular current and hence spike voltage, as felt by neighboring units; this may be of significance in influencing their excitatory state.

The **evolution of nerve cell types** can be inferred, to a degree, from their distribution among the phyla (Fig. 2.1). Cells with only one type of process (isopolar) are common in coelenterate nerve nets, where these processes may be quite long and axonal. Differentiated integrative processes and dendrites appear to be a later achievement than axons.

Sensory cells are generally bipolar, and the soma is situated primitively in the epithelium (Figs. 2.36; 2.61; 2.63), with a long axon extending into the nerve net, or, in most places in animals from flatworms to higher groups, into the central ganglia. This bipolar type persists as the common sensory neuron of invertebrates and is represented in vertebrates by the olfactory receptors and perhaps the rods and cones of the retina. But a trend begins in lower invertebrates toward deeper-lying bipolar cells, longer distal processes, more branching of those processes, and, eventually, clustering of the cells into ganglia. The extreme is the vertebrate dorsal root ganglion whose cells, originally bipolar, have become unipolar, with a T-shaped stem process that sends long axons both centrally and peripherally. Cell bodies of sensory neurons are nearly all outside the central nervous system.

Interneurons and motor neurons are not clearly distinguished in the most primitive systems, but distinct interneurons can already be seen in the earliest forerunners of ganglia—the nerve rings and marginal ganglia of medusae

Figure 2.36
Primary sensory neurons in lower animals.



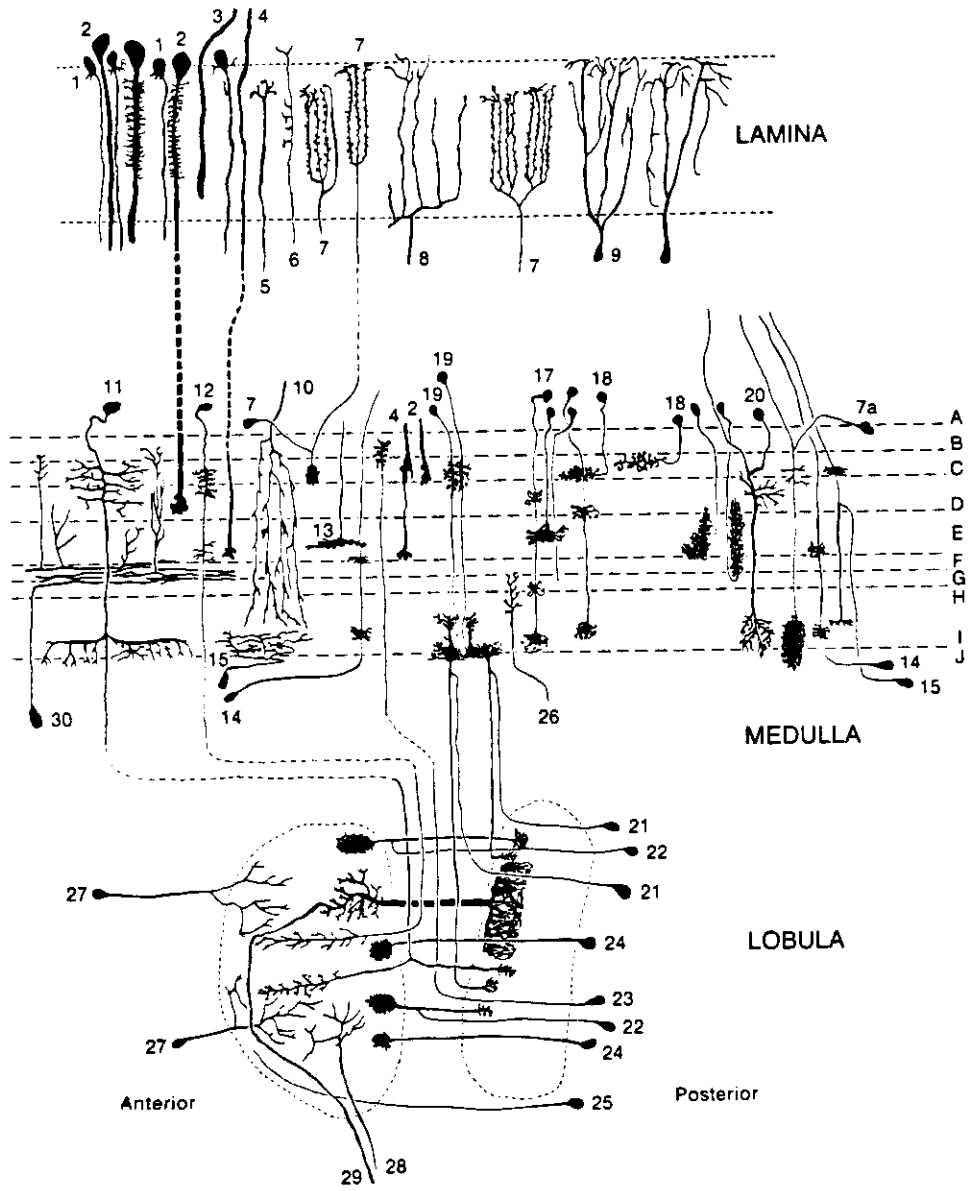


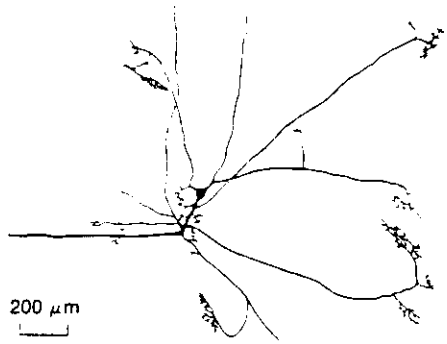
Figure 2.37
A variety of unipolar neurons, from the optic ganglia of a fly. The lamina, medulla, and lobula are successively more centrally situated neuropile masses in the optic ganglia. The numbers distinguish recognized types of neurons and represent only some of the known types (see also Figs. 10.41 to 10.43). [Cajal and Sanchez, 1915.]

(Figs. 10.2; 10.6). In the Platyhelminthes —the lowest group with a central nervous system—there is an abrupt change to an abundance of relatively advanced, central unipolar cells, but there are still many of the primitive cell types (Fig. 10.13).

In all the higher invertebrates an overwhelming majority of the interneurons and motor neurons are unipolars (Fig. 2.37); this cell type is far and away the most widespread form of central neuron in the animal kingdom. Literally scores of types of unipolar interneurons can be distinguished on the basis of significant differences in the character, extent, layering, and destination of their processes, reaching a peak in the optic ganglion of higher arthropods and cephalopods. The afferent and integrative branches are not always easy to recognize microscopically; they generally come off the axon, and may do so at many widely separate points along an axon, as may the efferent terminals. Therefore, in such neurons impulses may arise at different sites nearer or farther from the soma and conduct both ways, even meeting and cancelling. Unipolars are rarely found outside the central nervous system in invertebrates or inside the central nervous system in vertebrates. Somas of interneurons and motor neurons are nearly all inside the central nervous system in higher animals, except for the nerve supply to viscera.

Multipolar heteropolar cells are nearly universal among vertebrate interneurons and motor neurons, but are found in invertebrates only in a few special places (Fig. 2.38). In vertebrates there are multipolar isopolar cells in several special places, including some that appear to lack an axon; these are called **amacrine cells** (Figs. 2.2; 3.20). Differentiation of

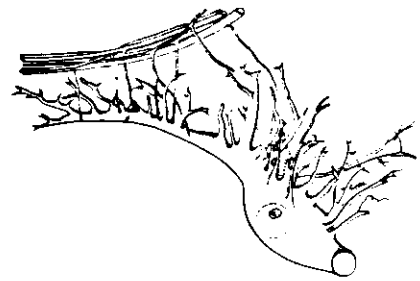
Figure 2.38
Multipolar neurons in invertebrates.
[Bullock and Horridge, 19c5; after various authors.]



Pacemaker cell, cardiac ganglion (crab)

Follower cell, cardiac ganglion (crab)

Ventral ganglion cell (crayfish)



First-order giant cell (squid)

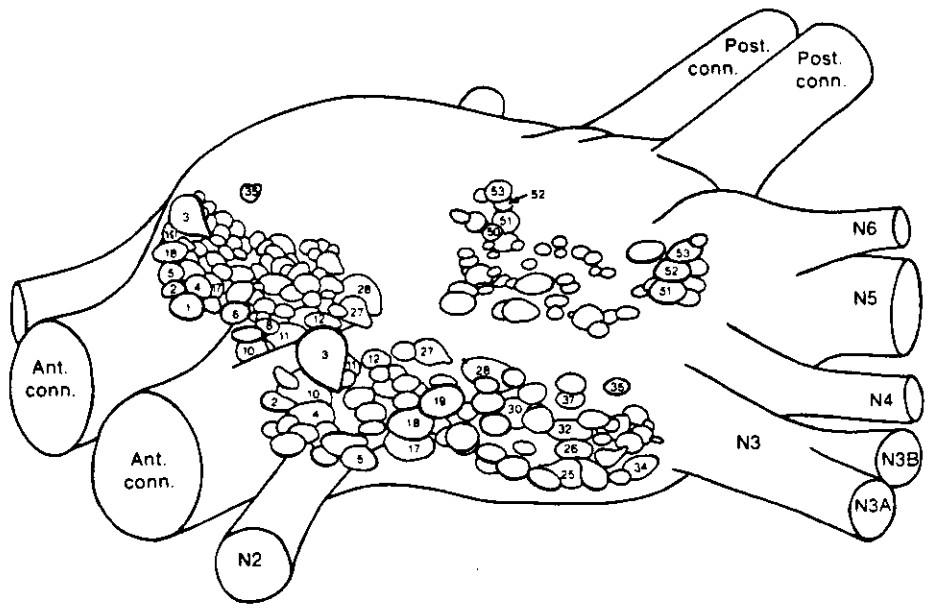


Figure 2.39
Identified cells. Motor neurons in the metathoracic ganglion of a cockroach. The numbered somas are some of the known and consistent cells identifiable in every individual. *Ant. conn.*, connectives to next anterior ganglion; *Post. conn.*, posterior connectives; *N2* to *N6*, peripheral nerve trunks. [Cohen, 1970.]

vertebrate multipolars is much advanced; a large number of special forms can be distinguished. Indeed, even if we knew nothing about physiological, chemical, pharmacological, immunological, developmental, and pathological specificities, we would still be forced to recognize here the most elaborated specificity of cell types from the arrangement, distribution, orientation, and connections of the processes. The development of dendrites in extensive and characteristic arbors (branching patterns), resembling distinctive species of trees and shrubs, reaches a peak in vertebrates.

Identifiable neurons are a prominent feature of hirudineans, crustaceans, insects, and gastropods (Fig. 2.39). These are neurons so consistent as to be recognizable in each individual animal, characterized by input and output connections, coupling functions, principal branches, cytologic texture, pharmacology, and often the position of the soma. Such unique cells are most common among motor neurons; many interneurons, but fewer sensory neurons, are also identifiable. Examples are referred to in Chapters 3, 5, 6, 7, 9, and 10. This phenomenon is an indicator of the high degree of specification in many nerve cells and animal groups. It does not yet tell us how far specificity goes into the finest branches and endings, nor does it quantify consistency of transfer functions. The recent history of the subject has shown rather dramatically that this once-rare kind of consistency among neurons actually extends to many types and groups. We do not yet know how far it

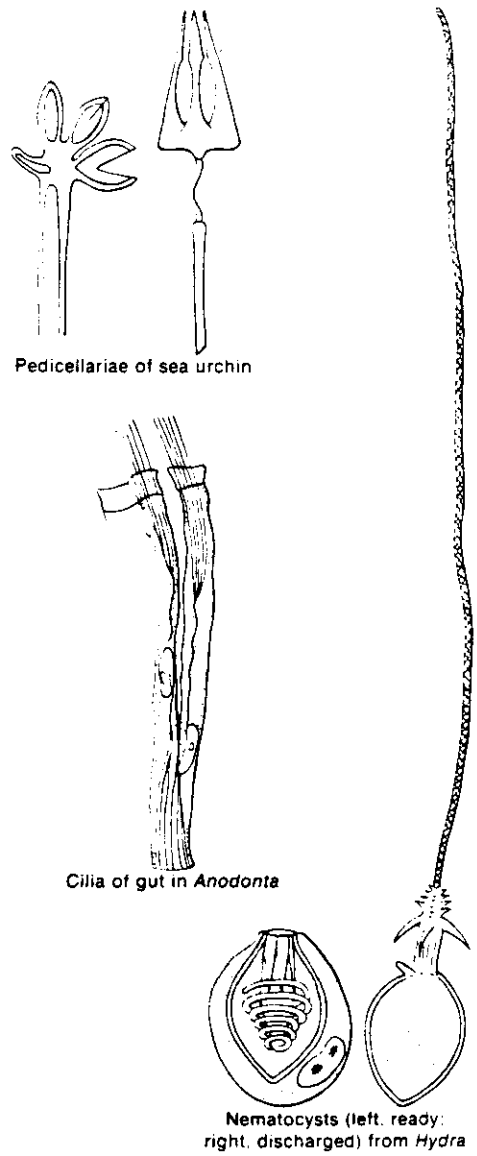
Box 2.1 Origin of Neurons

In what structures did nervous functions arise? Many nonnervous cells, undifferentiated with respect to nervous functions, nevertheless carry out these functions, both in lower animals and in parts of higher animals. That is, many unspecialized cells have a limited capacity to be excited, to select adequate stimuli, to propagate changes, to correlate with the existing state or with other stimuli, and to respond adaptively. For example, Protozoa and Porifera seem to have no visible structures (apart from certain effectors) that are differentiated for such functions; nevertheless, those activities are carried out (see Bullock and Horridge, 1965, Chapter 7). Even the spread of excitation from cell to cell can occur to an important degree in some epithelia (e.g., *Hydra* and amphibian larvae) and in some smooth muscles. Some special cell-to-cell contacts and channels, possibly mediating such conduction, have been shown in the EM.

Preceding the development of specialized receptor cells and neurons were intracellular effector organelles and **independent effector cells.** Cilia, gland cells, and smooth muscle cells, as well as effectors of more limited distribution, can function without a nerve supply. Secondarily, they often receive innervation superimposing control on their intrinsic spontaneity.

It is generally believed that the first nerve cells were sensorimotor, derived from an epithelium and connected to effector cells. This hypothesis is attractive, mainly for lack of alternatives, but it has not been substantiated by a clear demonstration of the existence of such cells. The coelenterates possess the most primitive, unequivocal nervous system, but they are apparently already too far along in evolution. Even these simple forms have a diversity of neurons, including what may represent the second stage. Presumably, from primitive sensorimotor nerve cells there first differentiated a combined internuncial-motor nerve cell, from which pure interneurons and pure motor neurons later evolved.

Effectors believed to be independent of the nervous system.



Pedicellariae of sea urchin

Cilia of gut in *Anodonta*

Nematocysts (left, ready; right, discharged) from *Hydra*

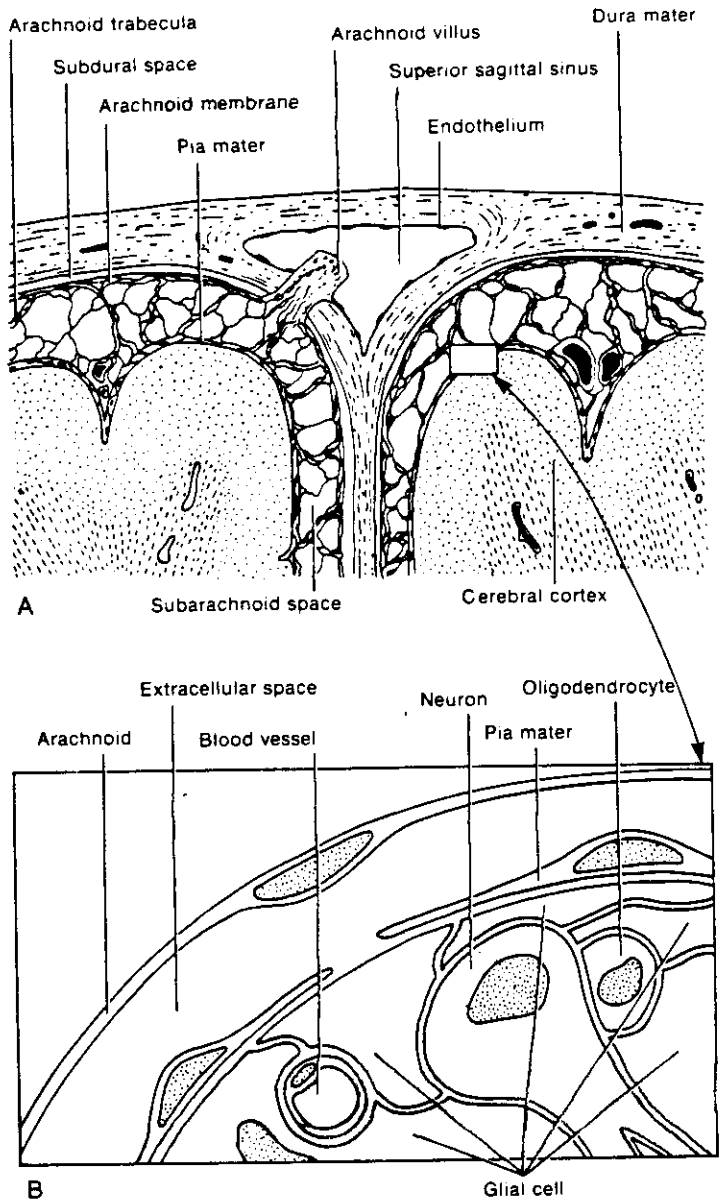


Figure 2.40
The surface of the brain and its coverings. **A.** Low-magnification diagram of the meninges in man. The small streaks in the brain tissue are sections of blood vessels. [Weed, 1923.] **B.** High-magnification diagram of a portion of the same, showing relatively open space between neurons and glial cells. This intercellular space is continuous with both ventricular and extraventricular cerebrospinal fluid space. The barrier to the passage of protein out of or into the blood is known to be at the endothelium lining the blood vessels. [Bunge, 1970.]

will extend or where to set the upper limit upon the fineness of the specificity, upon the animal groups or central levels that possess unique or nearly unique neurons or upon the hierarchial position of such units in recognition and command. But it seems inevitable that advance in anatomical and related physiological and chemical knowledge will increase the known degrees of specificity in the vertebrates as well as in the invertebrates.

III. NEUROGLIA AND SHEATHS

Nonnervous cells having some special relationship to nerve cells or fibers are called **neuroglia,** or simply glia, except that the term is not applied to the cells of blood vessels, trachea, muscle fibers, glands, epithelia, and connective tissue, though these are all associated in certain places with nervous tissue. Where the coverings of ganglia and nerves are attributable to ordinary connective-tissue elements, the term should not be used, but it is often difficult to decide, especially in invertebrates. The cells that form intimate sheaths around individual axons are glial. Most types of neuroglia share a common ectodermal origin with nerve cells (see Chapter 9).

The **coverings of ganglia** and central nervous tissue evolve from simple to complex in the animal series. Lower forms have nothing more than a basement membrane of secreted extracellular lamella. Higher invertebrates and lower vertebrates have simple cellular coverings. Mammals have complex meninges of several layers (Fig. 2.40). A tough outer membrane, the **dura mater,** contains inelastic connective tissue fibers in a dense, strong sheet. Under this is a delicate, complex investment made up of the leptomeninges—the **arachnoid,** next