Note: Large images and tables on this page may necessitate printing in landscape mode.

Bone: Introduction

As the main constituent of the adult skeleton, bone tissue supports fleshy structures, protects vital organs such as those in the cranial and thoracic cavities, and harbors the bone marrow, where blood cells are formed. Bone tissue is highly vascularized and metabolically very active. It serves as a reservoir of calcium, phosphate, and other ions that can be released or stored in a controlled fashion to maintain constant concentrations of these important ions in body fluids.

In addition, bones form a system of levers that multiplies the forces generated during skeletal muscle contraction and transforms them into bodily movements. This mineralized tissue confers mechanical and metabolic functions to the skeleton.

Bone is a specialized connective tissue composed of intercellular calcified material, the **bone matrix,** and three cell types: **osteocytes** (Gr. *osteon,* bone, + *kytos,* cell), which are found in cavities (**lacunae**) within the matrix (Figure 8â€“1); **osteoblasts** (*osteon* + Gr. *blastos,* germ), which synthesize the organic components of the matrix; and **osteoclasts** (*osteon* + Gr. *klastos,* broken), which are multinucleated giant cells involved in the resorption and remodeling of bone tissue.

Figure 8â€“1.

Section of bone tissue showing an osteocyte with its cytoplasmic processes surrounded by matrix. The ultrastructure of the cell nucleus and cytoplasm is compatible with a low level of protein synthesis.

Because metabolites are unable to diffuse through the calcified matrix of bone, the exchanges between osteocytes and blood capillaries depend on communication through the **canaliculi** (L. *canalis,* canal), which are thin, cylindrical spaces that perforate the matrix (Figure 8â€“2).

Figure 8â€“2.

Photomicrograph of dried bone ground very thin. The lacunae and canaliculi filled with air deflect the light and appear dark, showing the communication between these structures through which nutrients derived from blood vessels flow. Medium magnification.

All bones are lined on both internal and external surfaces by layers of tissue containing osteogenic cellsâ€”**endosteum** on the internal surface and **periosteum** on the external surface.

Because of its hardness, bone is difficult to section with the microtome, and special techniques must be used for its study. A common technique that permits the observation of the cells and organic matrix is based on the decalcification of bone preserved by standard fixatives. The mineral is removed by immersion in a solution containing a calcium-chelating substance (eg, ethylenediaminetetraacetic acid [EDTA]). The decalcified tissue is then embedded, sectioned, and stained.
Bone Cells

Osteoblasts

Osteoblasts are responsible for the synthesis of the organic components of bone matrix (type I collagen, proteoglycans, and glycoproteins). Deposition of the inorganic components of bone also depends on the presence of viable osteoblasts. Osteoblasts are exclusively located at the surfaces of bone tissue, side by side, in a way that resembles simple epithelium (Figure 8â€“3). When they are actively engaged in matrix synthesis, osteoblasts have a cuboidal to columnar shape and basophilic cytoplasm. When their synthesizing activity declines, they flatten, and cytoplasmic basophilia declines.

Figure 8â€“3.

Events that occur during intramembranous ossification. Osteoblasts are synthesizing collagen, which forms a strand of matrix that traps cells. As this occurs, the osteoblasts gradually differentiate to become osteocytes. The lower part of the drawing shows an osteoblast being trapped in newly formed bone matrix.

Some osteoblasts are gradually surrounded by newly formed matrix and become **osteocytes.** During this process a space called a **lacuna** is formed. Lacunae are occupied by osteocytes and their extensions, along with a small amount of extracellular noncalcified matrix.

During matrix synthesis, osteoblasts have the ultrastructure of cells actively synthesizing proteins for export. Osteoblasts are polarized cells. Matrix components are secreted at the cell surface, which is in contact with older bone matrix, producing a layer of new (but not yet calcified) matrix, called **osteoid,** between the osteoblast layer and the previously formed bone (Figure 8â€“3). This process, **bone apposition,** is completed by subsequent deposition of calcium salts into the newly formed matrix. Quiescent osteoblasts (not producing bone matrix) become flattened. However, they easily revert to the cuboidal shape typical of the active synthesizing state.

Osteocytes

Osteocytes, which derive from osteoblasts, lie in the lacunae (Figure 8â€“3) situated between lamellae (L. diminutive of *lamina,* leaf) of matrix. Only one osteocyte is found in each lacuna. The thin, cylindrical matrix canaliculi house cytoplasmic processes of osteocytes. Processes of adjacent cells make contact via gap junctions, and molecules are passed via these structures from cell to cell. Some molecular exchange between osteocytes and blood vessels also takes place through the small amount of extracellular substance located between osteocytes (and their processes) and the bone matrix. This exchange can provide nourishment for a chain of about 15 cells.

When compared with osteoblasts, the flat, almond-shaped osteocytes exhibit a significantly reduced rough endoplasmic reticulum (Figure 8â€“1) and Golgi complex and more condensed nuclear chromatin. These cells are actively involved in the maintenance of the bony matrix, and their death is followed by resorption of this matrix. Osteocytes are long-living cells.

MEDICAL APPLICATION

The fluorescent antibiotic tetracycline interacts with great affinity with recently deposited mineralized bone matrix. Based on this interaction, a method was developed to measure the rate of bone appositionâ€”an important parameter in the study of bone growth and the diagnosis of bone growth diseases. Tetracycline is administered twice to patients, with an interval of 5 days between injections. A bone biopsy is then performed, and the sections are studied by means of fluorescence microscopy. The distance between the two fluorescent layers is proportional to the rate of bone apposition. This procedure is of diagnostic importance in diseases such as **osteomalacia,** in which mineralization is impaired, and **osteitis fibrosa cystica,** in which increased osteoclast activity results in removal of bone matrix and fibrous degeneration.

Osteoclasts

Osteoclasts are very large, branched motile cells. Dilated portions of the cell body (Figure 8â€“4) contain from 5 to 50 (or more) nuclei. In areas of bone undergoing resorption, osteoclasts lie within enzymatically etched depressions in the matrix known as **Howship's lacunae.** Osteoclasts are derived from the fusion of bone marrow-derived mononucleated cells.

Figure 8â€“4.

Section showing three osteoclasts (arrows) digesting bone tissue. The osteoclast is a large cell with several nuclei and a ruffled border close to the bone matrix. Note the clear compartment where the process of bone erosion occurs. This compartment is acidified by a proton pump localized in the osteoclast membrane. It is the place of decalcification and matrix digestion and can be compared to a giant extracellular lysosome. Chondroclasts found in eroded regions of epiphyseal calcified cartilage are similar in shape to osteoclasts.

In active osteoclasts, the surface-facing bone matrix is folded into irregular, often subdivided projections, forming a **ruffled border.** Surrounding the ruffled border is a cytoplasmic zoneâ€”the **clear zone**â€”that is devoid of organelles, yet rich in actin filaments. This zone is a site of adhesion of the osteoclast to the bone matrix and creates a microenvironment between the cell and the matrix in which bone resorption occurs (Figure 8â€“5).

Figure 8â€“5.

Bone resorption. Lysosomal enzymes packaged in the Golgi complex and hydrogen ions produced are released into the confined microenvironment created by the attachment between bone matrix and the osteoclast's peripheral clear zone. The acidification of this confined space facilitates the dissolution of calcium phosphate from bone and is the optimal pH for the activity of lysosomal hydrolases. Bone matrix is thus removed and the products of bone resorption are taken up by the osteoclast's cytoplasm, probably digested further, and transferred to blood capillaries.

The osteoclast secretes collagenase and other enzymes and pumps protons into a subcellular pocket (the microenvironment referred to above), promoting the localized digestion of collagen and dissolving calcium salt crystals. Osteoclast activity is controlled by cytokines (small signaling proteins that act as local mediators) and hormones. Osteoclasts have receptors for calcitonin, a thyroid hormone, but not for parathyroid hormone. However, osteoblasts have receptors for parathyroid hormone and, when activated by this hormone, produce a cytokine called osteoclast stimulating factor.

Ruffled borders are related to the activity of osteoclasts.
Bone Matrix

Inorganic matter represents about 50% of the dry weight of bone matrix. Calcium and phosphorus are especially abundant, but bicarbonate, citrate, magnesium, potassium, and sodium are also found. X-ray diffraction studies have shown that calcium and phosphorus form hydroxyapatite crystals with the composition $Ca_{10}(PO_4)_6(OH)_2$. However, these crystals show imperfections and are not identical to the hydroxyapatite found in the rock minerals. Significant quantities of amorphous (noncrystalline) calcium phosphate are also present. In electron micrographs, hydroxyapatite crystals of bone appear as plates that lie alongside the collagen fibrils but are surrounded by ground substance. The surface ions of hydroxyapatite are hydrated, and a layer of water and ions forms around the crystal. This layer, the **hydration shell,** facilitates the exchange of ions between the crystal and the body fluids.

MEDICAL APPLICATION

In the genetic disease **osteopetrosis,** which is characterized by dense, heavy bones ("marble bones"), the osteoclasts lack ruffled borders, and bone resorption is defective.

The organic matter in bone matrix is type I collagen and ground substance, which contains proteoglycan aggregates and several specific structural glycoproteins. Bone glycoproteins may be responsible for promoting calcification of bone matrix. Other tissues containing type I collagen are not normally calcified and do not contain these glycoproteins. Because of its high collagen content, decalcified bone matrix intensely binds stains for collagen fibers.

The association of minerals with collagen fibers is responsible for the hardness and resistance of bone tissue. After a bone is decalcified, its shape is preserved, but it becomes as flexible as a tendon. Removal of the organic part of the matrixâ€”which is mainly collagenousâ€”also leaves the bone with its original shape; however, it becomes fragile, breaking and crumbling easily when handled.
Periosteum & Endosteum

External and internal surfaces of bone are covered by layers of bone-forming cells and connective tissue called periosteum and endosteum.

The **periosteum** consists of an outer layer of collagen fibers and fibroblasts (Figure 8â€“6). Bundles of periosteal collagen fibers, called **Sharpey's fibers,** penetrate the bone matrix, binding the periosteum to bone. The inner, more cellular layer of the periosteum is composed of fibroblastlike cells called **osteoprogenitor cells,** with the potential to divide by mitosis and differentiate into osteoblasts. Autoradiographic studies demonstrate that these cells take up [^{3}H]thymidine, which is subsequently encountered in osteoblasts. Osteoprogenitor cells play a prominent role in bone growth and repair.

Figure 8â€“6.

Schematic drawing of the wall of a long-bone diaphysis showing three types of lamellar bone: haversian system and outer and inner circumferential lamellae. (For interstitial lamellae, see Figure 8â€“10.) The protruding haversian system on the left shows the orientation of collagen fibers in each lamella. At the right is a haversian system showing lamellae, a central blood capillary (there are also small nerves, not shown), and many osteocytes with their processes.

Figure 8â€“10.

Schematic drawing of diaphyseal bone remodeling showing three generations of haversian systems and their successive contributions to the formation of intermediate, or interstitial, lamellae. Remodeling is a continuous process responsible for bone adaptations, especially during growth.

The **endosteum** (Figure 8â€“6) lines all internal cavities within the bone and is composed of a single layer of flattened osteoprogenitor cells and a very small amount of connective tissue. The endosteum is therefore considerably thinner than the periosteum.

The principal functions of periosteum and endosteum are nutrition of osseous tissue and provision of a continuous supply of new osteoblasts for repair or growth of bone.
Types of Bone

Gross observation of bone in cross section shows dense areas without cavitiesâ€”corresponding to **compact bone**â€”and areas with numerous interconnecting cavitiesâ€”corresponding to **cancellous** (**spongy**) **bone** (Figure 8â€“7). Under the microscope, however, both compact bone and the trabeculae separating the cavities of cancellous bone have the same basic histological structure.

Figure 8â€“7.

A: Thick section of bone illustrating the cortical compact bone and the lattice of trabeculae of cancellous bone. (Courtesy of DW Fawcett.) **B:** Section of cancellous (spongy) bone with its characteristic random disposition of collagen fibers. Picrosirius-polarized light (PSP) stain. Low magnification.

In long bones, the bulbous endsâ€”called **epiphyses** (Gr. *epiphysis,* an excrescence)â€”are composed of spongy bone covered by a thin layer of compact bone. The cylindrical partâ€”**diaphysis** (Gr. *diaphysis,* a growing between)â€”is almost totally composed of compact bone, with a small component of spongy bone on its inner surface around the bone marrow cavity. Short bones usually have a core of spongy bone completely surrounded by compact bone. The flat bones that form the calvaria have two layers of compact bone called **plates** (tables), separated by a layer of spongy bone called the **diploÃ«.**

Microscopic examination of bone shows two varieties: **primary, immature,** or **woven bone** and **secondary, mature,** or **lamellar bone.** Primary bone is the first bone tissue to appear in embryonic development and in fracture repair and other repair processes. It is characterized by random disposition of fine collagen fibers, in contrast to the organized lamellar disposition of collagen in secondary bone.

Primary Bone Tissue

Primary bone tissue is usually temporary and, except in a very few places in the body (eg, near the sutures of the flat bones of the skull, in tooth sockets, and in the insertions of some tendons), is replaced in adults by secondary bone tissue.

In addition to the irregular array of collagen fibers, other characteristics of primary bone tissue are a lower mineral content (it is more easily penetrated by x-rays) and a higher proportion of osteocytes than in secondary bone tissue.

Secondary Bone Tissue

Secondary bone tissue is usually found in adults. It characteristically shows collagen

fibers arranged in lamellae (3â€“7 m thick) that are parallel to each other or concentrically organized around a vascular canal. The whole complex of concentric lamellae of bone surrounding a canal containing blood vessels, nerves, and loose connective tissue is called a **haversian system,** or **osteon** (Figures 8â€“6 and 8â€“8). Lacunae containing osteocytes are found between, and occasionally within, the lamellae. In each lamella, collagen fibers are parallel to each other. Surrounding each haversian system is a deposit of amorphous material called the **cementing substance** that consists of mineralized matrix with few collagen fibers.

Figure 8â€“8.

Schematic drawing of two osteocytes and part of a haversian system. Collagen fibers of contiguous lamellae are sectioned at different angles. Note the numerous canaliculi that permit communication between lacunae and the haversian canals. Although it is not apparent in this simplified diagram, each lamella consists of multiple parallel

arrays of collagen fibers. In adjacent lamellae, the collagen fibers are oriented in different directions. The presence of large numbers of lamellae with differing fiber orientations provides the bone with great strength, despite its light weight. (Redrawn and reproduced, with permission, from Leeson TS, Leeson CR: *Histology,* 2nd ed. Saunders, 1970.)

In compact bone (eg, the diaphysis of long bones), the lamellae exhibit a typical organization consisting of **haversian systems, outer circumferential lamellae, inner circumferential lamellae,** and **interstitial lamellae** (Figures 8â€“6 and 8â€“9).

Figure 8â€“9.

Lamellar (secondary) bone in which the collagen fibers can be parallel to each other (at left) or organized concentrically around neurovascular channels, to constitute the haversian systems, or osteons (in most of the figure). Among the numerous haversian systems are some interstitial lamellae. PSP stain. Low magnification.

Inner circumferential lamellae are located around the marrow cavity, and outer circumferential lamellae are located immediately beneath the periosteum. There are more outer than inner lamellae.

Between the two circumferential systems are numerous haversian systems, including triangular or irregularly shaped groups of parallel lamellae called **interstitial** (or **intermediate**) **lamellae.** These structures are lamellae left by haversian systems destroyed during growth and remodeling of bone (Figure 8â€“10).

Each haversian system is a long, often bifurcated cylinder parallel to the long axis of the diaphysis. It consists of a central canal surrounded by 4â€“20 concentric lamellae (Figure 8â€“11). Each endosteum-lined canal contains blood vessels, nerves, and loose connective tissue. The haversian canals communicate with the marrow cavity, the periosteum, and one another through transverse or oblique Volkmann's canals (Figure 8â€“6). Volkmann's canals do not have concentric lamellae; instead, they perforate the lamellae. All vascular canals found in bone tissue come into existence when matrix is laid down around preexisting blood vessels.

Figure 8â€“11.

Section of a haversian system, or osteon. Note the alternation of clear and dark circles resulting from the alternation in the direction of the collagen fibers. The collagen fibers appear bright when cut longitudinally and dark when cross-sectioned. In the center of the osteon is a channel. PSP stain. Medium magnification.

Examination of haversian systems with polarized light shows bright anisotropic layers alternating with dark isotropic layers (Figure 8â€“11). When observed under polarized light at right angles to their length, collagen fibers are birefringent (anisotropic). The alternating bright and dark layers are due to the changing orientation of collagen fibers in the lamellae. In each lamella, fibers are parallel to each other and follow a helical course. The pitch of the helix is, however, different for different lamellae, so that at any given point, fibers from adjacent lamellae intersect at approximately right angles (Figure 8â€“6).

Because bone tissue is constantly being remodeled, there is great variability in the diameter of haversian canals. Each system is formed by successive deposits of lamellae, starting inward from the periphery, so that younger systems have larger canals. In mature haversian systems, the most recently formed lamella is the one closest to the central canal.
Histogenesis

Bone can be formed in two ways: by direct mineralization of matrix secreted by osteoblasts (**intramembranous ossification**) or by deposition of bone matrix on a preexisting cartilage matrix (**endochondral ossification**).

In both processes, the bone tissue that appears first is primary, or woven. Primary bone is a temporary tissue and is soon replaced by the definitive lamellar, or secondary, bone. During bone growth, areas of primary bone, areas of resorption, and areas of secondary bone appear side by side. This combination of bone synthesis and removal (**remodeling**) occurs not only in growing bones but also throughout adult life, although its rate of change in adults is considerably slower.

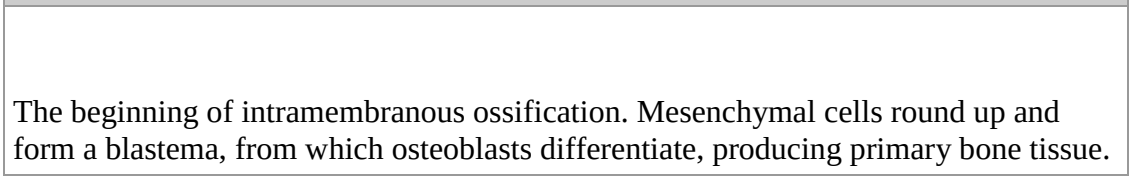
Intramembranous Ossification

Intramembranous ossification, the source of most of the flat bones, is so called because it takes place within condensations of mesenchymal tissue. The frontal and parietal bones of the skullâ€”as well as parts of the occipital and temporal bones and the mandible and maxillaâ€”are formed by intramembranous ossification. This process also contributes to the growth of short bones and the thickening of long bones.

In the mesenchymal condensation layer, the starting point for ossification is called a **primary ossification center.** The process begins when groups of cells differentiate into osteoblasts. Osteoblasts produce bone matrix and calcification follows, resulting in the encapsulation of some osteoblasts, which then become osteocytes (Figure 8â€“12). These islands of developing bone form walls that delineate elongated cavities containing capillaries, bone marrow cells, and undifferentiated cells. Several such groups arise almost simultaneously at the ossification center, so that the fusion of the

walls gives the bone a spongy structure. The connective tissue that remains among the bone walls is penetrated by growing blood vessels and additional undifferentiated mesenchymal cells, giving rise to the bone marrow cells.

Figure 8â€“12.



The beginning of intramembranous ossification. Mesenchymal cells round up and form a blastema, from which osteoblasts differentiate, producing primary bone tissue.

The ossification centers of a bone grow radially and finally fuse together, replacing the original connective tissue. The fontanelles of newborn infants, for example, are soft areas in the skull that correspond to parts of the connective tissue that are not yet ossified.

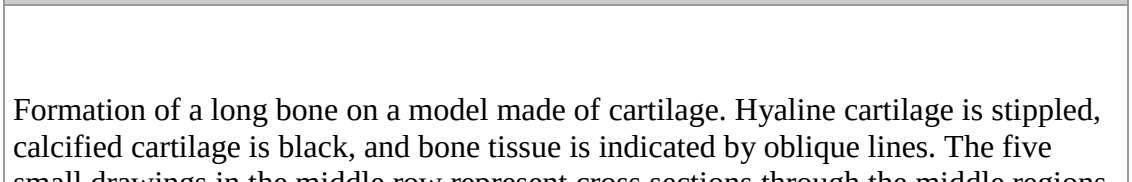
In cranial flat bones there is a marked predominance of bone formation over bone resorption at both the internal and external surfaces. Thus, two layers of compact bone (internal and external plates) arise, whereas the central portion (diploÃ«) maintains its spongy nature.

The portion of the connective tissue layer that does not undergo ossification gives rise to the endosteum and the periosteum of intramembranous bone.

Endochondral Ossification

Endochondral (Gr. *endon*, within, + *chondros*, cartilage) ossification takes place within a piece of hyaline cartilage whose shape resembles a small version, or model, of the bone to be formed. This type of ossification (Figures 8â€“13 and 8â€“14) is principally responsible for the formation of short and long bones.

Figure 8â€“13.



Formation of a long bone on a model made of cartilage. Hyaline cartilage is stippled, calcified cartilage is black, and bone tissue is indicated by oblique lines. The five small drawings in the middle row represent cross sections through the middle regions of the figures shown in the upper row. Note the formation of the bone collar and primary and secondary ossification centers. Epiphyseal fusion with diaphysis, with disappearance of the epiphyseal cartilage, occurs at different times in the same bone. (Redrawn and reproduced, with permission, from Bloom W, Fawcett DW: A Textbook of Histology, 9th ed. Saunders, 1968.)

Figure 8â€“14.

A small portion of an epiphyseal plate showing endochondral ossification. Remnants of calcified cartilage matrix (dark purple) appear covered by light-stained bone tissue. The newly formed bone is surrounded by osteoblasts. Some osteoblasts that were captured by the osseous matrix become osteocytes (arrowheads). Pararosanilineâ€“toluidine blue (PT) stain. Medium magnification.

Endochondral ossification of a long bone consists of the following sequence of events. Initially, the first bone tissue appears as a hollow bone cylinder that surrounds the mid portion of the cartilage model. This structure, the **bone collar,** is produced by intramembranous ossification within the local perichondrium. In the next step, the local cartilage undergoes a degenerative process of programmed cell death with cell enlargement (hypertrophy) and matrix calcification, resulting in a three-dimensional structure formed by the remnants of the calcified cartilage matrix (Figure 8â€“15). This process begins at the central portion of the cartilage model (diaphysis), where blood vessels penetrate through the bone collar previously perforated by osteoclasts, bringing osteoprogenitor cells to this region. Next, osteoblasts adhere to the calcified cartilage matrix and produce continuous layers of primary bone that surround the cartilaginous matrix remnants. At this stage, the calcified cartilage appears basophilic, and the primary bone is eosinophilic. In this way the **primary ossification center** is produced (Figure 8â€“13). Then, **secondary ossification centers** appear at the swellings in the extremities of the cartilage model (epiphyses). During their expansion and remodeling, the primary and secondary ossification centers produce cavities that are gradually filled with bone marrow.

Figure 8â€“15.

Schematic drawings showing the three-dimensional shape of bone in the epiphyseal plate area. Hyaline cartilage is stippled, calcified cartilage is black, and bone tissue is shown as yellow hatched areas. The upper drawing shows the region represented three-dimensionally in the lower drawing. (Redrawn and reproduced, with permission, from Ham AW: Histology, 6th ed. Lippincott, 1969.)

In the secondary ossification centers, cartilage remains in two regions: the **articular cartilage,** which persists throughout adult life and does not contribute to bone growth in length, and the **epiphyseal cartilage,** also called the **epiphyseal plate,** which connects the two epiphyses to the diaphysis (Figures 8â€“15 and 8â€“16). The

epiphyseal cartilage is responsible for the growth in length of the bone, and it disappears in adults, which is why bone growth ceases in adulthood.

Figure 8â€“16.

Photomicrograph of the epiphyseal plate, showing its five zones, the changes that take place in the cartilage, and the formation of bone. PT stain. Low magnification.

The closure of the epiphyses follows a chronological order according to each bone and is complete at about 20 years of age. Through x-ray examination of the growing skeleton, it is possible to determine the "bone age" of a young person, noting which epiphyses are open and which are closed. Once the epiphyses have closed, growth in length of bones becomes impossible, although widening may still occur.

Epiphyseal cartilage is divided into five zones (Figure 8â€“16), starting from the epiphyseal side of cartilage: (1) The **resting zone** consists of hyaline cartilage without morphological changes in the cells. (2) In the **proliferative zone,** chondrocytes divide rapidly and form columns of stacked cells parallel to the long axis of the bone. (3) The **hypertrophic cartilage zone** contains large chondrocytes whose cytoplasm has accumulated glycogen. The resorbed matrix is reduced to thin septa between the chondrocytes. (4) Simultaneous with the death of chondrocytes in the **calcified cartilage zone,** the thin septa of cartilage matrix become calcified by the deposit of hydroxyapatite (Figures 8â€“15 and 8â€“16). (5) In the **ossification zone,** endochondral bone tissue appears. Blood capillaries and osteoprogenitor cells formed by mitosis of cells originating from the periosteum invade the cavities left by the chondrocytes. The osteoprogenitor cells form osteoblasts, which are distributed in a discontinuous layer over the septa of calcified cartilage matrix. Ultimately, the osteoblasts deposit bone matrix over the three-dimensional calcified cartilage matrix (Figures 8â€“17, 8â€“18, 8â€“19, and 8â€“20).

Figure 8â€“17.

Higher magnification of the epiphyseal plate showing details of the endochondral ossification. Cartilage matrix (purple) is covered by recently formed bone tissue (red). Bone marrow and fat cells fill up the space left by the new bone. Picrosiriusâ€“hematoxylin (PSH) stain. Medium magnification.

Figure 8â€“18.

Photomicrograph of endochondral ossification. In the upper region is a row of osteoblasts with intense cytoplasmic basophilia, a feature to be expected in cells synthesizing a glycoprotein (collagen). Note an osteoblast being captured in the bone matrix (arrow). Between the layer of osteoblasts and the calcified bone matrix is a pale region made of noncalcified bone matrix called osteoid. PT stain. Medium magnification.

Figure 8â€“19.

Section of endochondral ossification. The osseous matrix, rich in collagen type I, is specifically stained with picrosiriusâ€“hematoxylin. The cartilaginous matrix, containing collagen type II, stains blue with hematoxylin because of its high content of chondroitin sulfate. Medium magnification.

Figure 8â€“20.

Section of the extremity of a long bone showing the epiphysis, epiphyseal plate, and newly formed bone tissue. PSP stain. Low magnification.

In summary, growth in length of a long bone occurs by proliferation of chondrocytes in the epiphyseal plate adjacent to the epiphysis. At the same time, chondrocytes of the diaphyseal side of the plate hypertrophy; their matrix becomes calcified, and the cells die. Osteoblasts lay down a layer of primary bone on the calcified cartilage matrix. Because the rates of these two opposing events (proliferation and destruction) are approximately equal, the epiphyseal plate does not change thickness. Instead, it is displaced away from the middle of the diaphysis, resulting in growth in length of the bone.

Mechanisms of Calcification

There is still no generally accepted hypothesis to explain the events occurring during calcium phosphate deposition on bone matrix.

It is known that calcification begins by the deposition of calcium salts on collagen fibrils, a process induced by proteoglycans and high-affinity calcium-binding glycoproteins. The deposition of calcium salts is probably accelerated by the ability of

osteoblasts to concentrate them in intracytoplasmic vesicles and to release these vesicles, when necessary, to the extracellular medium (matrix vesicles).

Calcification is aided, in some unknown way, by alkaline phosphatase, which is produced by osteoblasts and is present at ossification sites.
Bone Growth & Remodeling

Bone growth is generally associated with partial resorption of preformed tissue and the simultaneous laying down of new bone (exceeding the rate of bone loss). This process permits the shape of the bone to be maintained while it grows. Bone remodeling (**bone turnover**) is very active in young children, where it can be 200 times faster than the rate in adults. Bone remodeling in adults is a dynamic physiological process that occurs simultaneously in multiple locations of the skeleton, not related to bone growth.

Cranial bones grow mainly because of the formation of bone tissue by the periosteum between the sutures and on the external bone surface. At the same time, resorption takes place on the internal surface. Because bone is an extremely plastic tissue, it responds to the growth of the brain and forms a skull of adequate size. The skull will be small if the brain does not develop completely and will be larger than normal in a person suffering from hydrocephalus, a disorder characterized by abnormal accumulation of spinal fluid and dilatation of the cerebral ventricles.

Fracture Repair

MEDICAL APPLICATION

When a bone is fractured, bone matrix is destroyed and bone cells adjoining the fracture die. The damaged blood vessels produce a localized hemorrhage and form a blood clot.

During repair, the blood clot, cells, and damaged bone matrix are removed by macrophages. The periosteum and the endosteum around the fracture respond with intense proliferation producing a tissue that surrounds the fracture and penetrates between the extremities of the fractured bone (Figure 8â€“21).

Primary bone is then formed by endochondral and intramembranous ossification, both processes contributing simultaneously to the healing of fractures. Repair progresses in such a way that irregularly formed trabeculae of primary bone temporarily unite the extremities of the fractured bone, forming a **bone callus** (Figure 8â€“21).

Stresses imposed on the bone during repair and during the patient's gradual return to activity serve to remodel the bone callus. If these stresses are identical to those that occurred during the growth of the boneâ€”and therefore influence its structureâ€”the primary bone tissue of the callus is gradually resorbed and replaced by secondary tissue, remodeling the bone and restoring its original structure (Figure 8â€“21). Unlike other connective tissues, bone tissue heals without forming a scar.

Figure 8â€“21.

Repair of a fractured bone by formation of new bone tissue through periosteal and endosteal cell proliferation.

Internal Structure of Bones

Despite its hardness, bone is capable of changes in its internal structure in response to the various stresses to which it is subjected. For example, the positions of the teeth in the jawbone can be modified by lateral pressures produced by orthodontic appliances. Bone is formed on the side where traction is applied and is resorbed where pressure is exerted (on the opposite side). In this way, teeth move within the jawbone while the alveolar bone is being remodeled.

Metabolic Role of Bone Tissue

The skeleton contains 99% of the total calcium of the body and acts as a reservoir of calcium and phosphate ions. The concentration of calcium ions in the blood and tissues is quite stable because of a continuous interchange between blood calcium and bone calcium.

Bone calcium is mobilized by two mechanisms, one rapid and the other slow. The first is the simple transfer of ions from hydroxyapatite crystals to interstitial fluidâ€”from which, in turn, calcium passes into the blood. This purely physical mechanism takes place mainly in spongy bone. The younger, slightly calcified lamellae that exist even in adult bone (because of continuous remodeling) receive and lose calcium more readily. These lamellae are more important for the maintenance of calcium concentration in the blood than are the older, greatly calcified lamellae, whose role is mainly that of support and protection.

The second mechanism for controlling blood calcium level depends on the action of hormones on bone. **Parathyroid hormone** promotes osteoclastic resorption of the bone matrix with the consequent liberation of calcium. This hormone acts primarily on osteoblast receptors. The activated osteoblasts stop producing bone and start the secretion of an **osteoclast-stimulating factor.**

Another hormone, **calcitonin,** which is synthesized mainly by the parafollicular cells of the thyroid gland, inhibits matrix resorption. Calcitonin has an inhibitory effect on osteoclast activity.

MEDICAL APPLICATION

Because the concentration of calcium in tissues and blood must be kept constant, nutritional deficiency of calcium results in decalcification of bones; decalcified bones are more likely to fracture and are more transparent to x-rays.

Decalcification of bone may also be caused by excessive production of parathyroid hormone (hyperparathyroidism), which results in increased osteoclastic activity, intense resorption of bone, elevation of blood Ca^{2+} and $PO_4^{3â€“}$ levels, and abnormal deposits of calcium in several organs, mainly the kidneys and arterial walls.

The opposite occurs in **osteopetrosis** (L. *petra,* stone), a disease caused by a defect in osteoclast function that results in overgrowth, thickening, and hardening of bones. This process produces obliteration of the bone marrow cavities, depressing blood cell formation with consequent anemia and frequent infections that may be fatal.

Effects of Nutritional Deficiencies on Bone Tissue

Bone is very sensitive to nutritional factors during growth. Deficiency of calcium leads to incomplete calcification of the organic bone matrix, due either to the lack of calcium in the diet or to the lack of the steroid prohormone vitamin D, which is important for the absorption of Ca^{2+} and $PO_4^{3â€“}$ by the small intestine.

Calcium deficiency in children causes **rickets,** a disease in which the bone matrix does not calcify normally and the epiphyseal plate becomes distorted by the normal strains of body weight and muscular activity. Ossification processes at this level are consequently hindered, and the bones not only grow more slowly but also become deformed.

Calcium deficiency in adults gives rise to **osteomalacia** (*osteon* + Gr. *malakia,* softness), which is characterized by deficient calcification of recently formed bone and partial decalcification of already calcified matrix. Osteomalacia should not be confused with **osteoporosis.** In osteomalacia, there is a decrease in the amount of calcium per unit of bone matrix. Osteoporosis, frequently found in immobilized patients and in postmenopausal women, is an imbalance in skeletal turnover so that bone resorption exceeds bone formation.

Hormones Acting on Bone Tissue

In addition to parathyroid hormone and calcitonin, several other hormones act on bone. The anterior lobe of the pituitary synthesizes growth hormone, which stimulates the liver to produce somatomedins. This, in turn, has an overall effect on growth, especially on the epiphyseal cartilage. Consequently, lack of growth hormone during the growing years causes **pituitary dwarfism;** an excess of growth hormone causes excessive growth of the long bones, resulting in **gigantism.** Adult bones cannot increase in length when stimulated by an excess of somatomedins because of the lack of epiphyseal cartilage, but they do increase in width by periosteal growth. In adults, an increase in growth hormone causes **acromegaly,** a disease in which the bonesâ€”mainly the long onesâ€”become very thick.

The sex hormones, both male (androgens) and female (estrogens), have a complex effect on bones and are, in a general way, stimulators of bone formation. They influence the time of appearance and development of ossification centers and accelerate the closure of epiphyses.

Precocious sexual maturity caused by sex hormone-producing tumors retards bodily growth, since the epiphyseal cartilage is quickly replaced by bone (closure of epiphysis). In hormone deficiencies caused by abnormal development of the gonads, epiphyseal cartilage remains functional for a longer period of time, resulting in tall stature. Thyroid hormone deficiency in children, as in **cretinism,** is associated with **dwarfism.** Recent evidence indicates that the central nervous system participates in the regulation of bone formation during bone remodeling in adult mice. This regulatory mechanism involves the hormone leptin produced by adipose tissue and may thus explain the observation that bones of obese people have an increased mass, containing a higher concentration of calcium.

Bone Tumors

Although bone tumors are uncommon (0.5% of all cancer deaths), bone cells may escape the normal controls of proliferation to become benign (eg, **osteoblastoma, osteoclastoma**) or malignant (eg, **osteosarcoma**) tumors. Osteosarcomas show pleomorphic (Gr. *pleion,* more, + *morphe,* form) and mitotically active osteoblasts associated with osteoid. Most cases of this aggressive malignant tumor occur in adolescents and young adults. The lower end of the femur, the upper tibia, and the upper humerus are the most common locations. In addition to the tumors originating from bone cells, the skeleton is often the site of metastases from malignant tumors originating in other organs. The most frequent bone metastases are from breast, lung, prostate, kidney, and thyroid tumors.
Joints

Joints are regions in which bones are capped and surrounded by connective tissues that hold the bones together and determine the type and degree of movement between them. Joints may be classified as **diarthroses,** in which there is free bone movement, or **synarthroses** (Gr. *syn,* together, + *arthrosis,* articulation), in which very limited or no movement occurs. There are three types of synarthroses, based on the type of tissue uniting the bone surfaces: **synostosis, synchondrosis,** and **syndesmosis.**

In synostosis (*syn* + *osteon* + Gr. *osis,* condition), bones are united by bone tissue and no movement takes place. In older adults, this type of synarthrosis unites the skull bones, which, in children and young adults, are united by dense connective tissue.

Synchondroses (*syn* + *chondros*) are articulations in which the bones are joined by hyaline cartilage. The epiphyseal plates of growing bones are one example, and in the adult human, synchondrosis unites the first rib to the sternum.

As with synchondrosis, a syndesmosis permits a certain amount of movement. The bones are joined by an interosseous ligament of dense connective tissue (eg, the pubic symphysis).

Diarthroses (Figures 8â€“22 and 8â€“23) are joints that generally unite long bones and have great mobility, such as the elbow and knee joints. In a diarthrosis, ligaments and a capsule of connective tissue maintain the contact at the ends of the bone. The capsule encloses a sealed **articular cavity** that contains **synovial fluid,** a colorless, transparent,

viscous fluid. Synovial fluid is a blood plasma dialysate with a high concentration of hyaluronic acid produced by cells of the synovial layer. The sliding of articular surfaces covered by hyaline cartilage (Figure 8â€“22) and having no perichondrium is facilitated by the lubricating synovial fluid, which also supplies nutrients and oxygen to the avascular articular cartilage.

Figure 8â€“22.

Schematic drawing of a diarthrosis. The capsule is formed by two parts: the external fibrous layer and the synovial layer (synovial membrane) that lines the articular cavity except for the cartilaginous areas (blue).

Figure 8â€“23.

Photomicrograph of a diarthrosis. Section of a guinea pig knee. PSH stain. Low magnification.

The collagen fibers of the articular surface cartilage are disposed as gothic arches, a convenient arrangement to distribute the forces generated by pressure in this tissue (Figure 8â€“24).

Figure 8â€“24.

Articular surfaces of a diarthrosis are covered by hyaline cartilage that is devoid of perichondrium. The upper drawing shows that in this cartilage, collagen fibers are first perpendicular and then bend gradually, becoming parallel to the cartilage surface. Deeply located chondrocytes are globular and are arranged in vertical rows. Superficially placed chondrocytes are flattened; they are not organized in groups. The lower left drawing shows the organization of collagen fibers in articular cartilage in three dimensions.

The resilient articular cartilage is also an efficient absorber of the intermittent mechanical pressures to which many joints are subjected. A similar mechanism is seen in intervertebral disks (Figure 8â€“25). Proteoglycan molecules, found isolated or

aggregated in a network, contain a large amount of water. These matrix components, rich in highly branched hydrophilic glycosaminoglycans, function as a biomechanical spring. When pressure is applied, water is forced out of the cartilage matrix into the synovial fluid. When water is expelled, another mechanism that contributes to cartilage resilience enters into play. This is the reciprocal electrostatic repulsion of the negatively charged carboxyl and sulfate groups in the glycosaminoglycan molecules. These charges are also responsible for separating the glycosaminoglycan branches and thus creating spaces to be occupied by water. When the pressure is released, water is attracted back into the interstices of the glycosaminoglycan branches. These water movements are brought about by the use of the joint. They are essential for nutrition of the cartilage and for facilitating the interchange of O_2, CO_2, and other molecules between the synovial fluid and the articular cartilage.

Figure 8â€“25.

Example of a special type of joint. Section of a rat tail showing in the center the intervertebral disk consisting of concentric layers of fibrocartilage (annulus fibrosus) surrounding the nucleus pulposus (see Chapter 7: Cartilage). The nucleus pulposus is formed by residual cells of the notochord immersed in abundant viscous intercellular matrix. PSH stain. Low magnification.

The capsules of diarthroses (Figure 8â€“22) vary in structure according to the joint. Generally, however, this capsule is composed of two layers, the external **fibrous layer** and the internal **synovial layer** (Figure 8â€“26).

Figure 8â€“26.

Histological structure of the synovial membrane, with its lining cells in epithelioid arrangement. There is no basal lamina between the lining cells and the underlying connective tissue. This tissue is rich in blood capillaries and contains a variable number of adipose cells (AD). (Reproduced, with permission, from Cossermelli W: Reumatologia Basica. Sarvier, 1971.)

The synovial layer is formed by two types of cells. One resembles fibroblasts and the other has the aspect and behavior of macrophages (Figure 8â€“27). The fibrous layer is made of dense connective tissue.

Figure 8â€“27.

Schematic representation of the ultrastructure of synovial membrane. The two covering cell types are separated by a small amount of connective tissue ground substance. No basal lamina is seen separating the lining cells from the connective tissue. Blood capillaries are of the fenestrated type, which facilitates exchange of substances between blood and synovial fluid.

MEDICAL APPLICATION

Obesity imposes significant strain on the articular cartilage, accelerating its degeneration. Joint problems are far more frequent in obese individuals.
References

Demers C, Handy RC: Bone morphogenetic proteins. Sci Med 1999;6(6):8.

Ducy P et al: The osteoblast: a sophisticated fibroblast under central surveillance. Science 2000;289:1421.

Ducy P et al: Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. Cell 2000;100:197. [PMID: 10660043]

Ghadially FN: *Fine Structure of Synovial Joints.* Butterworth, 1983.

Gunness M, Hock JM: Anabolic effect of parathyroid hormone on cancellous and cortical bone histology. Bone 1993;14:277. [PMID: 8363868]

Levick JR: Synovial fluid hydraulics. Sci Med 1996;3(5):52.

Mundy GR et al: The effects of cytokines and growth factors on osteoblastic cells. Bone 1995;17:71S.

Roach HI, Clark NM: Physiological cell death of chondrocytes in vivo is not confined to apoptosis. New observations on the mammalian growth plate. J Bone Joint Surg Br 2000;82:601. [PMID: 10855892]

Ross PD et al: Bone mass and beyond: risk factors for fractures. Calcif Tissue Int 1993;53:S134.

Teltelbaum SL: Bone resorption by osteoclasts. Science 2000;289:1504.

Urist MR: *Fundamental and Clinical Bone Physiology*. Lippincott, 1980.

Note: Large images and tables on this page may necessitate printing in landscape mode.

Nerve Tissue & the Nervous System: Introduction

The human nervous system, by far the most complex system in the human body, is formed by a network of more than 100 million nerve cells (**neurons**), assisted by many more glial cells. Each neuron has, on average, at least 1000 interconnections with other neurons, forming a very complex system for communication.

Neurons are grouped as **circuits.** Like electronic circuits, neural circuits are highly specific combinations of elements that make up systems of various sizes and complexities. Although a neural circuit may be single, in most cases it is a combination of two or more circuits that interacts to generate a function. A neural function is a set of coordinated processes intended to produce a definite result. A number of elementary circuits may be combined to form higher-order systems.

Nerve tissue is distributed throughout the body as an integrated communications network. Anatomically, the nervous system is divided into the **central nervous system,** consisting of the brain and the spinal cord, and the **peripheral nervous system,** composed of nerve fibers and small aggregates of nerve cells called **nerve ganglia** (Figure 9–1).

Figure 9–1.

The general functional organization of the central and peripheral nervous systems.

Structurally, nerve tissue consists of two cell types: **nerve cells,** or **neurons,** which usually show numerous long processes, and several types of **glial cells** (Gr. *glia,* glue), which have short processes, support and protect neurons, and participate in neural activity, neural nutrition, and the defense processes of the central nervous system.

The study of nerve tissue has recently progressed rapidly, due to the use of markers that identify neurons and glia cells and the use of molecules that flow in a retrograde direction, permitting a more precise study of neuronal circuits.

Neurons respond to environmental changes (**stimuli**) by altering electrical potentials that exist between the inner and outer surfaces of their membranes. Cells with this property (eg, neurons, muscle cells, some gland cells) are called **excitable,** or **irritable.** Neurons react promptly to stimuli with a modification of electrical potential that may be restricted to the place that received the stimulus or may be spread (propagated) throughout the neuron by the plasma membrane. This propagation, called the **action potential,** or **nerve impulse,** is capable of traveling long distances; it transmits information to other neurons, muscles, and glands.

By creating, analyzing, identifying, and integrating information, the nervous system generates two great classes of functions: stabilization of the intrinsic conditions (eg, blood pressure, O_2 and CO_2 content, pH, blood glucose levels, and hormone levels) of the organism within normal ranges and behavioral patterns (eg, feeding, reproduction, defense, interaction with other living creatures).

Development of Nerve Tissue

Nerve tissues develop from embryonic ectoderm that is induced to differentiate by the underlying notochord. First, a neural plate forms; then the edges of the plate thicken, forming the neural groove. The edges of the groove grow toward each other and ultimately fuse, forming the neural tube. This structure gives rise to the entire central nervous system, including neurons, glial cells, ependymal cells, and the epithelial cells of the choroid plexus.

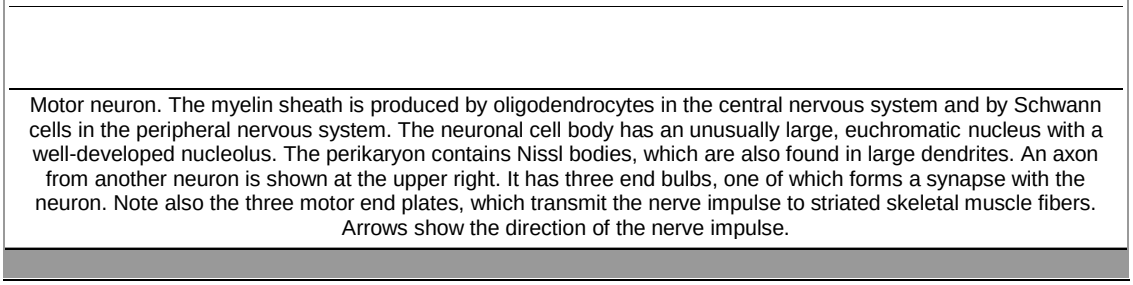
Cells lateral to the neural groove form the **neural crest.** These cells undergo extensive migrations and contribute to the formation of the peripheral nervous system, as well as a number of other structures. Neural crest derivatives include (1) chromaffin cells of the adrenal medulla (see Chapter 20: Endocrine Glands), (2) melanocytes of skin and subcutaneous tissues (see Chapter 18: Skin), (3) odontoblasts (see Chapter 15: Digestive Tract), (4) cells of the pia mater and the arachnoid, (5) sensory neurons of cranial and spinal sensory ganglia, (6) postganglionic neurons of sympathetic and parasympathetic ganglia, (7) Schwann cells of peripheral axons, and (8) satellite cells of peripheral ganglia.

Neurons

Nerve cells, or neurons, are responsible for the reception, transmission, and processing of stimuli; the triggering of certain cell activities; and the release of neurotransmitters and other informational molecules.

Most neurons consist of three parts (Figure 9–2): the **dendrites,** which are multiple elongated processes specialized in receiving stimuli from the environment, sensory epithelial cells, or other neurons; the **cell body,** or **perikaryon** (Gr. *peri,* around, + *karyon,* nucleus), which is the trophic center for the whole nerve cell and is also receptive to stimuli; and the **axon** (from Greek, meaning axis), which is a single process specialized in generating or conducting nerve impulses to other cells (nerve, muscle, and gland cells). Axons may also receive information from other neurons; this information mainly modifies the transmission of action potentials to other neurons. The distal portion of the axon is usually branched and constitutes the **terminal arborization.** Each branch of this arborization terminates on the next cell in dilatations called **end bulbs** (**boutons**), which interact with other neurons or nonnerve cells, forming structures called **synapses.** Synapses transmit information to the next cell in the circuit.

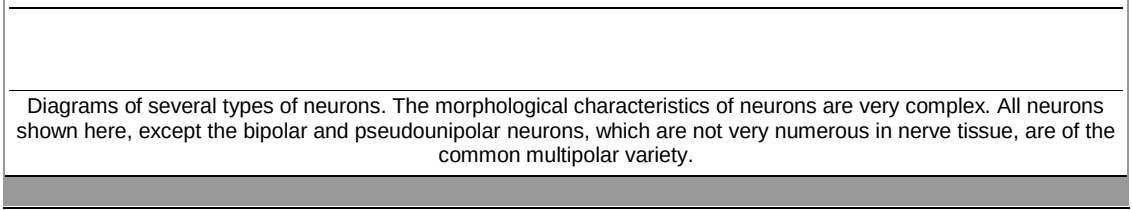
Figure 9–2.



Motor neuron. The myelin sheath is produced by oligodendrocytes in the central nervous system and by Schwann cells in the peripheral nervous system. The neuronal cell body has an unusually large, euchromatic nucleus with a well-developed nucleolus. The perikaryon contains Nissl bodies, which are also found in large dendrites. An axon from another neuron is shown at the upper right. It has three end bulbs, one of which forms a synapse with the neuron. Note also the three motor end plates, which transmit the nerve impulse to striated skeletal muscle fibers. Arrows show the direction of the nerve impulse.

Neurons and their processes are extremely variable in size and shape (Figure 9–3). Cell bodies can be spherical, ovoid, or angular; some are very large, measuring up to 150 m in diameter—large enough to be visible to the naked eye. Other nerve cells are among the smallest cells in the body; for example, the cell bodies of granule cells of the cerebellum are only 4–5 m in diameter.

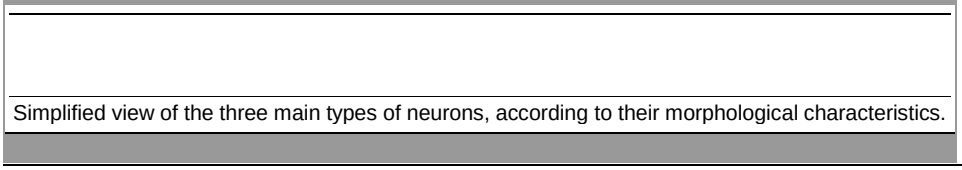
Figure 9–3.



Diagrams of several types of neurons. The morphological characteristics of neurons are very complex. All neurons shown here, except the bipolar and pseudounipolar neurons, which are not very numerous in nerve tissue, are of the common multipolar variety.

Based on the size and shape of their processes, most neurons can be placed in one of the following categories (Figures 9–3 and 9–4): **multipolar neurons,** which have more than two cell processes, one process being the axon and the others dendrites; **bipolar neurons,** with one dendrite and one axon; and **pseudounipolar neurons,** which have a single process that is close to the perikaryon and divides into two branches. The process then forms a T shape, with one branch extending to a peripheral ending and the other toward the central nervous system (Figure 9–4). In pseudounipolar neurons, stimuli that are picked up by the dendrites travel directly to the axon terminal without passing through the perikaryon.

Figure 9–4.



Simplified view of the three main types of neurons, according to their morphological characteristics.

During the maturation process of pseudounipolar neurons, the central (axon) and the peripheral (dendrite) fibers fuse, becoming one single fiber. In these neurons, the cell body does not seem to be involved in the conduction of impulses, although it does synthesize many molecules, including neurotransmitters that migrate to the peripheral fibers.

Most neurons of the body are multipolar. Bipolar neurons are found in the cochlear and vestibular ganglia as well as in the retina and the olfactory mucosa. Pseudounipolar neurons are found in the spinal ganglia (the sensory ganglia located in the dorsal roots of the spinal nerves). They are also found in most cranial ganglia.

Neurons can also be classified according to their functional roles. **Motor** (**efferent**) **neurons** control effector organs such as muscle fibers and exocrine and endocrine glands. **Sensory** (**afferent**) **neurons** are involved in the reception of sensory stimuli from the environment and from within the body. **Interneurons** establish relationships among other neurons, forming complex functional networks or circuits (as in the retina).

During mammalian evolution a great increase in the number and complexity of interneurons has occurred. Highly developed functions of the nervous system cannot be ascribed to simple neuron circuits; rather, they depend on complex interactions established by the integrated functions of many neurons.

In the central nervous system, nerve cell bodies are present only in the gray matter. White matter contains neuronal processes but no nerve cell bodies. In the peripheral nervous system, cell bodies are found in ganglia and in some sensory regions (eg, olfactory mucosa).

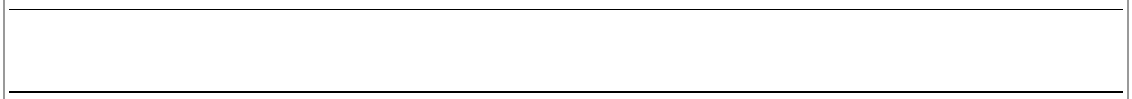
Cell Body

The cell body, also called **perikaryon,** is the part of the neuron that contains the nucleus and surrounding cytoplasm, exclusive of the cell processes (Figure 9–2). It is primarily a trophic center, although it also has receptive capabilities. The perikaryon of most neurons receives a great number of nerve endings that convey excitatory or inhibitory stimuli generated in other nerve cells.

Most nerve cells have a spherical, unusually large, euchromatic (pale-staining) nucleus with a prominent nucleolus. Binuclear nerve cells are seen in sympathetic and sensory ganglia. The chromatin is finely dispersed, reflecting the intense synthetic activity of these cells.

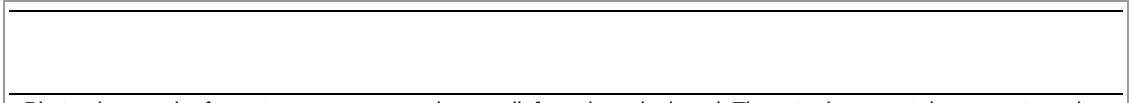
The cell body (Figure 9–5) contains a highly developed rough endoplasmic reticulum organized into aggregates of parallel cisternae. In the cytoplasm between the cisternae are numerous polyribosomes, suggesting that these cells synthesize both structural proteins and proteins for transport. When appropriate stains are used, rough endoplasmic reticulum and free ribosomes appear under the light microscope as basophilic granular areas called **Nissl bodies** (Figures 9–2 and 9–6). The number of Nissl bodies varies according to neuronal type and functional state. They are particularly abundant in large nerve cells such as motor neurons (Figure 9–6). The **Golgi complex** is located only in the cell body and consists of multiple parallel arrays of smooth cisternae arranged around the periphery of the nucleus (Figure 9–5). Mitochondria are especially abundant in the axon terminals. They are scattered throughout the cytoplasm of the cell body.

Figure 9–5.



Ultrastructure of a neuron. The neuronal surface is completely covered either by synaptic endings of other neurons or by processes of glial cells. At synapses, the neuronal membrane is thicker and is called the postsynaptic membrane. The neuronal process devoid of ribosomes (lower part of figure) is the axon hillock. The other processes of this cell are dendrites.

Figure 9–6.



Photomicrograph of a motor neuron, a very large cell, from the spinal cord. The cytoplasm contains a great number of Nissl bodies. The large cell process is a dendrite. Note the large, round, stained nucleus, with a central dark-stained nucleolus. Pararosaniline–toluidine blue (PT) stain. Medium magnification.

Neurofilaments (intermediate filaments with a diameter of 10 nm) are abundant in perikaryons and cell processes. Neurofilaments bundle together as a result of the action of certain fixatives. When impregnated with silver, they form **neurofibrils** that are visible with the light microscope. The neurons also contain microtubules that are identical to those found in many other cells. Nerve cells occasionally contain inclusions of pigments, such as **lipofuscin,** which is a residue of undigested material by lysosomes.

Dendrites

Dendrites (Gr. *dendron,* tree) are usually short and divide like the branches of a tree (Figure 9–4). They receive many synapses and are the principal signal reception and processing sites on neurons. Most nerve cells have numerous dendrites, which considerably increase the receptive area of the cell. The arborization of dendrites allows one neuron to receive and integrate a great number of axon terminals from other nerve cells. It has been estimated that up to 200,000 axonal terminations establish functional contact with the dendrites of a Purkinje cell of the cerebellum (Figure 9–3). That number may be even higher in other nerve cells. Bipolar neurons, with only one dendrite, are uncommon and are found only in special sites. Unlike axons, which maintain a constant diameter from one end to the other, dendrites become thinner as they subdivide into branches. The cytoplasmic composition of the dendrite base, close to the neuron body, is similar to that of the perikaryon but is devoid of Golgi complexes. Most synapses impinging on

neurons are located in **dendrite spines,** which are usually mushroom-shaped structures (an expanded head

connected to the dendrite shaft by a narrower neck) measuring 1–3 m long and less than 1 m in diameter. These spines, which play relevant functions, occur in vast numbers, estimated to be on the order of 10^{14} for the human cerebral cortex. Dendrite spines are the first processing locale for synaptic signals arriving on a neuron. The processing apparatus is contained in a complex of proteins attached to the cytosolic surface of the postsynaptic membrane, which is visible under the electron microscope and received the name postsynaptic membrane long before its function was disclosed. Dendritic spines participate in the plastic changes that underlie adaptation, learning, and memory. They are dynamic structures with a morphological plasticity based on the cytoskeletal protein actin, which is related to the development of the synapses and their functional adaptation in adults.

Axons

Most neurons have only one axon; a very few have no axon at all. An axon is a cylindrical process that varies in length and diameter according to the type of neuron. Although some neurons have short axons, axons are usually very long processes. For example, axons of the motor cells of the spinal cord that innervate the foot muscles may be up to 100 cm (about 40 inches) in length. All axons originate from a short pyramid-shaped region, the **axon hillock,** that usually arises from the perikaryon (Figure 9–5). The plasma membrane of the axon is called the **axolemma** (*axon* + Gr. *eilema,* sheath); its contents are known as **axoplasm**.

In neurons that give rise to a myelinated axon, the portion of the axon between the axon hillock and the point at which myelination begins is called the **initial segment.** This is the site at which various excitatory and inhibitory stimuli impinging on the neuron are algebraically summed, resulting in the decision to propagate—or not to propagate—an action potential, or nerve impulse. It is known that several types of ion channels are localized in the initial segment and that these channels are important in generating the change in electrical potential that constitutes the action potential. In contrast to dendrites, axons have a constant diameter and do not branch profusely. Occasionally, the axon, shortly after its departure from the cell body, gives rise to a branch that returns to the area of the nerve cell body. All axon branches are known as **collateral branches** (Figure 9–2). Axonal cytoplasm (axoplasm) possesses mitochondria, microtubules, neurofilaments, and some cisternae of smooth endoplasmic reticulum. The absence of polyribosomes and rough endoplasmic reticulum emphasizes the dependence of the axon on the perikaryon for its maintenance. If an axon is severed, its peripheral parts degenerate and die.

There is a lively bidirectional transport of small and large molecules along the axon.

Macromolecules and organelles that are synthesized in the cell body are transported continuously by an **anterograde flow** along the axon to its terminals.

Anterograde flow occurs at three distinct speeds. A slow stream (a few millimeters per day) transports proteins and actin filaments. A flow of intermediate speed transports mitochondria, and a fast stream (100 times more rapid) transports the substances contained in vesicles that are needed at the axon terminal during neurotransmission.

Simultaneously with anterograde flow, a **retrograde flow** in the opposite direction transports several molecules, including material taken up by endocytosis (including viruses and toxins), to the cell body. This process is used to study the pathways of neurons; peroxidase or another marker is injected in regions with axon terminals, and its distribution is followed after a certain period of time.

Motor proteins related to axon flow include **dynein,** a protein with ATPase activity present in microtubules (related to retrograde flow), and **kinesin,** a microtubule-activated ATPase that, when attached to vesicles, promotes anterograde flow in the axon.

Membrane Potentials

The nerve cells have molecules in their membranes that act as pumps and channels, transporting ions into and out of the cytoplasm. The axolemma or limiting membrane of the axon pumps Na^+ out of the axoplasm, maintaining a concentration of Na^+ that is only a tenth of that in the extracellular fluid. In contrast, the concentration of K^+ is maintained at a level many times greater than that prevailing in the extracellular environment. Therefore, there is a potential difference across the axolemma of –65 mV with the inside negative to the outside. This is the **resting membrane potential.** When a neuron is stimulated, ion channels open and there is a sudden influx of extracellular Na^+ (an ion whose concentration is much higher in the extracellular fluid than in the cytoplasm) that changes the resting potential from –65 mV to +30 mV. The cell interior becomes positive in relation to the extracellular environment, which determines the beginning of the **action potential** or **nerve impulse.** However, the +30 mV potential closes the sodium channels, and the axonal membrane again becomes impermeable to this ion. In axons, in a few milliseconds, the opening of potassium channels modifies this ionic situation. As a result of the elevated intracellular concentration of potassium, this ion leaves the axon by diffusion, and the membrane potential returns to –65 mV, ending the action potential. The duration of these events is very short (about 5 ms) and takes place in a very small membrane area. However, the action potential propagates along the membrane, that is, the electrical disturbance opens neighboring sodium channels and, in sequence, potassium channels. In this way the action potential propagates at high speed along the axon. When the action potential arrives at the nerve ending, it promotes discharge of stored neurotransmitter that stimulates or inhibits another neuron or a nonneural cell, such as a muscle or gland cell.

MEDICAL APPLICATION

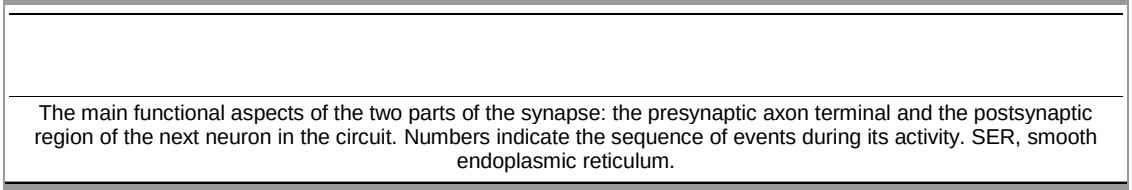
Local anesthetics are hydrophobic molecules that bind to sodium channels, inhibiting sodium transport and, consequently, also the action potential responsible for the nerve impulse.

Synaptic Communication

The synapse (Gr. *synapsis,* union) is responsible for the unidirectional transmission of nerve impulses. Synapses are sites of functional contact between neurons or between neurons and other effector cells (eg, muscle and gland cells). The function of the synapse is to convert an electrical signal (impulse) from the presynaptic cell into a chemical signal that acts on the **postsynaptic** cell. Most synapses transmit information by releasing **neurotransmitters** during the signaling process. Neurotransmitters are chemicals that, when combined with a receptor

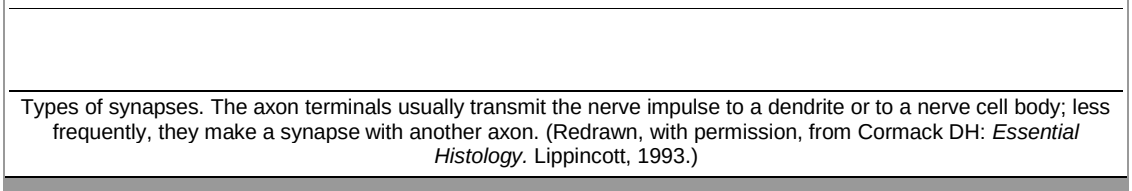
protein, either open or close ion channels or initiate second-messenger cascades. **Neuromodulators** are chemical messengers that do not act directly on synapses but modify neuron sensitivity to synaptic stimulation or inhibition. Some neuromodulators are neuropeptides or steroids produced in the nerve tissue; others are circulating steroids. The synapse itself is formed by an axon terminal (**presynaptic terminal**) that delivers the signal, a region on the surface of another cell at which a new signal is generated (**postsynaptic terminal**), and a thin intercellular space called the **synaptic cleft** (Figure 9–7). If an axon forms a synapse with a cell body, the synapse is called **axosomatic;** if it forms a synapse with a dendrite, it is called **axodendritic;** and if it forms a synapse with an axon, it is called **axoaxonic** (Figure 9–8).

Figure 9–7.



The main functional aspects of the two parts of the synapse: the presynaptic axon terminal and the postsynaptic region of the next neuron in the circuit. Numbers indicate the sequence of events during its activity. SER, smooth endoplasmic reticulum.

Figure 9–8.

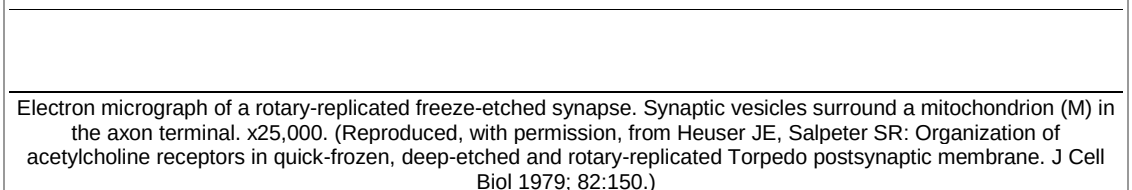


Types of synapses. The axon terminals usually transmit the nerve impulse to a dendrite or to a nerve cell body; less frequently, they make a synapse with another axon. (Redrawn, with permission, from Cormack DH: *Essential Histology.* Lippincott, 1993.)

Although most synapses are **chemical synapses** and use chemical messengers, a few synapses transmit ionic signals through gap junctions that cross the pre- and postsynaptic membranes, thereby conducting neuronal signals directly. These synapses are called **electrical synapses.**

The presynaptic terminal always contains **synaptic vesicles** with neurotransmitters and numerous **mitochondria** (Figures 9–7 and 9–9).

Figure 9–9.



Electron micrograph of a rotary-replicated freeze-etched synapse. Synaptic vesicles surround a mitochondrion (M) in the axon terminal. x25,000. (Reproduced, with permission, from Heuser JE, Salpeter SR: Organization of acetylcholine receptors in quick-frozen, deep-etched and rotary-replicated Torpedo postsynaptic membrane. J Cell Biol 1979; 82:150.)

Neurotransmitters are generally synthesized in the cell body; they are then stored in vesicles in the presynaptic region of a synapse. During transmission of a nerve impulse, they are released into the synaptic cleft by **exocytosis.** The extra membrane that collects at the presynaptic region as a result of exocytosis of the synaptic vesicles is recycled by **endocytosis.** Retrieved membrane fuses with the smooth endoplasmic reticulum of the presynaptic compartment to be reused in the formation of new synaptic vesicles (Figure 9–7). Some neurotransmitters are synthesized in the presynaptic compartment, using enzymes and precursors brought by axonal transport.

The first neurotransmitters to be described were acetylcholine and norepinephrine. A norepinephrine-releasing axon terminal is shown in Figure 9–10. Most neurotransmitters are amines, amino acids, or small peptides (neuropeptides). Inorganic substances such as nitric oxide have also been shown to act as neurotransmitters. Several peptides that act as neurotransmitters are used elsewhere in the body, eg, as hormones in the digestive tract. Neuropeptides are important in regulating feelings and drives, such as pain, pleasure, hunger, thirst, and sex (Figure 9–11).

Figure 9–10.

Adrenergic nerve ending. There are many 50-nm-diameter vesicles (arrow) with dark, electron-dense cores containing norepinephrine. x40,000. (Courtesy of A Machado.)

Figure 9–11.

Amino acid sequence of some neuropeptides and the sensations and drives in which they probably participate. (Reproduced, with permission, from Alberts B et al: *Molecular Biology of the Cell,* 2nd ed. Garland Press, 1993.)

Sequence of Events during Chemical Synapse Transmission

The events that take place during chemical synapse transmission are illustrated in Figure 9–7. Nerve impulses that sweep rapidly (in milliseconds) along the cell membrane promote an explosive electrical activity (depolarization) that is propagated along the cell membrane. This impulse briefly opens calcium channels in the presynaptic region, promoting a calcium influx that triggers the exocytosis of synaptic vesicles. The neurotransmitters released at the sites of exocytosis react with receptors present at the postsynaptic region, promoting a transient electrical activity (depolarization) at the postsynaptic membrane. These synapses are called **excitatory,** because their activity promotes impulses in the postsynaptic cell membrane. In some synapses the neurotransmitter–receptor interaction has an opposite effect, promoting **hyperpolarization** with no transmission of the nerve impulse. These are called **inhibitory** synapses. Thus, synapses can excite or inhibit impulse transmission and thereby regulate nerve activity (Figure 9–12).

Figure 9–12.

Examples of excitatory and inhibitory synapses in a motor neuron. (Redrawn, with permission, from Ganong WF: *Review of Medical Physiology,* 15th ed. Appleton & Lange, 1991. Copyright © 2001 by the McGraw-Hill Companies, Inc.)

Once used, neurotransmitters are quickly removed by enzymatic breakdown, diffusion, or endocytosis mediated by specific receptors on the presynaptic membrane. This removal of neurotransmitters is functionally important because it prevents an undesirable sustained stimulation of the postsynaptic neuron.

Glial Cells & Neuronal Activity

Glial cells are 10 times more abundant in the mammalian brain than neurons; they surround both cell bodies and their axonal and dendritic processes that occupy the interneuronal spaces.

Nerve tissue has only a very small amount of extracellular matrix, and glial cells (Table 9–1) furnish a microenvironment suitable for neuronal activity.

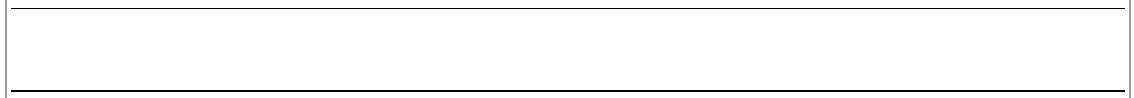
Table 9–1. Origin and Principal Functions of Neuroglial Cells.

Glial Cell Type	Origin	Location	Main Functions
Oligodendrocyte	Neural tube	Central nervous system	Myelin production, electric insulation
Schwann cell	Neural tube	Peripheral nerves	Myelin production, electric insulation
Astrocyte	Neural tube	Central nervous system	Structural support, repair processes
			Blood–brain barrier, metabolic exchanges
Ependymal cell	Neural tube	Central nervous system	Lining cavities of central nervous system
Microglia	Bone marrow	Central nervous system	Macrophagic activity

Oligodendrocytes

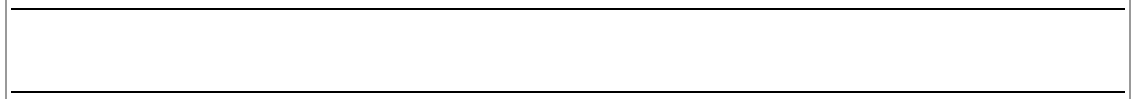
Oligodendrocytes (Gr. *oligos,* small, + *dendron* + *kytos,* cell) produce the myelin sheath that provides the electrical insulation of neurons in the central nervous system (Figures 9–13 and 9–14). These cells have processes that wrap around axons, producing a myelin sheath as shown in Figure 9–15.

Figure 9–13.



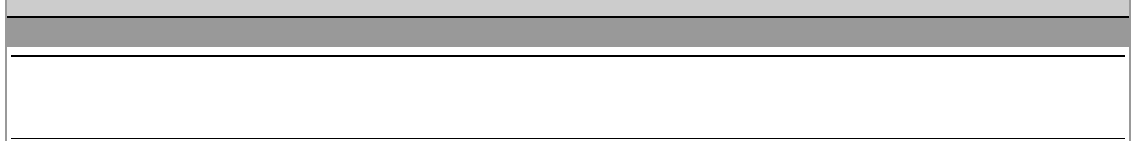
Drawings of neuroglial cells as seen in slides stained by metallic impregnation. Note that only astrocytes exhibit vascular end-feet, which cover the walls of blood capillaries.

Figure 9–14.



Photomicrographs (prepared with Golgi stain) of glial cells from the cerebral cortex. **A:** Fibrous astrocytes, showing blood vessels (BV). x1000. **B:** Protoplasmic astrocyte showing brain surface (arrow). x1900. **C:** Microglial cell. x1700. **D:** Oligodendrocytes. x1900. (Reproduced, with permission, from Jones E, Cowan WM: The nervous tissue. In: *Histology: Cell and Tissue Biology,* 5th ed. Weiss L [editor]. Elsevier, 1983.)

Figure 9–15.

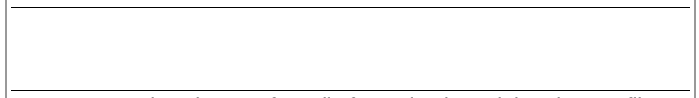


Myelin sheath of the central nervous system. The same oligodendrocyte forms myelin sheaths for several (3–50) nerve fibers. In the central nervous system, processes of other cells sometimes cover the nodes of Ranvier, or there is considerable extracellular space (ES) at that point. The axolemma shows a thickening where the cell membrane of the oligodendrocyte comes into contact with it. This limits the diffusion of materials into the periaxonal space between the axon and the myelin sheath. At upper left is a surface view of the cell body of an oligodendrocyte. Cyt, cytoplasm of the oligodendrocyte. (Redrawn and reproduced, with permission, from Bunge MB et al: Ultrastructural study of remyelination in an experimental lesion in adult cat spinal cord. J Biophys Biochem Cytol 1961;10:67.)

Schwann Cells

Schwann cells have the same function as oligodendrocytes but are located around axons in the peripheral nervous system. One Schwann cell forms myelin around a segment of one axon, in contrast to the ability of oligodendrocytes to branch and serve more than one neuron and its processes. Figure 9–27 shows how the Schwann cell membrane wraps around the axon.

Figure 9–27.

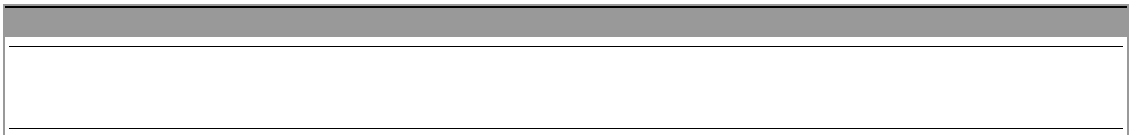


Four consecutive phases of myelin formation in peripheral nerve fibers.

Astrocytes

Astrocytes (Gr. *astron,* star, + *kytos*) are star-shaped cells with multiple radiating processes. These cells have bundles of intermediate filaments made of **glial fibrillary acid protein** that reinforce their structure. Astrocytes bind neurons to capillaries and to the pia mater (a thin connective tissue that covers the central nervous system). Astrocytes with few long processes are called **fibrous astrocytes** and are located in the white matter; **protoplasmic astrocytes,** with many short-branched processes, are found in the gray matter (Figures 9–13, 9–14, and 9–16). Astrocytes are by far the most numerous glial cells and exhibit an exceptional morphological and functional diversity.

Figure 9–16.



Brain section prepared with Rio Hortega silver stain showing fibrous astrocytes with their processes ending on the external surface of blood vessels. Medium magnification.

In addition to their supporting function, astrocytes participate in controlling the ionic and chemical environment of neurons. Some astrocytes develop processes with expanded **end feet** that are linked to endothelial cells. It is believed that through the end feet, astrocytes transfer molecules and ions from the blood to the neurons. Expanded processes are also present at the external surface of the central nervous system, where they make a continuous layer. Furthermore, when the central nervous system is damaged, astrocytes proliferate to form cellular scar tissue. Astrocytes also play a role in regulating the numerous functions of the central nervous system. Astrocytes *in vitro*

exhibit adrenergic receptors, amino acid receptors (eg, -aminobutyric acid [GABA]), and peptide receptors (including natriuretic peptide, angiotensin II, endothelins, vasoactive intestinal peptide, and thyrotropin-releasing hormone). The presence of these and other receptors on astrocytes enables them to respond to several stimuli. Astrocytes can influence neuronal survival and activity through their ability to regulate constituents of the extracellular environment, absorb local excess of neurotransmitters, and release metabolic and neuroactive molecules. The latter molecules include peptides of the angiotensinogen family, vasoactive endothelins, opioid precursors called **enkephalins,** and the potentially neurotrophic somatostatin. On the other hand, there is some evidence that astrocytes transport energy-rich compounds from the blood to the neurons and also metabolize glucose to lactate, which is then supplied to the neurons.

Finally, astrocytes are in direct communication with one another via gap junctions, forming a network through which information can flow from one point to another, reaching distant sites. For example, by means of gap junctions and the release of various cytokines, astrocytes can interact with oligodendrocytes to influence myelin turnover in both normal and abnormal conditions.

Ependymal Cells

Ependymal cells are low columnar epithelial cells lining the ventricles of the brain and central canal of the spinal cord. In some locations, ependymal cells are ciliated, which facilitates the movement of cerebrospinal fluid.

Microglia

Microglia (Gr. *micros,* small, + *glia*) are small elongated cells with short irregular processes (Figures 9–13 and 9–14). They can be recognized in routine hematoxylin and eosin (H&E) preparations by their dense elongated nuclei, which contrast with the spherical nuclei of other glial cells. Microglia, phagocytic cells that represent the mononuclear phagocytic system in nerve tissue, are derived from precursor cells in the bone marrow. They are involved with inflammation and repair in the adult central nervous system, and they produce and release neutral proteases and oxidative radicals. When activated, microglia retract their processes and assume the morphological characteristics of macrophages, becoming phagocytic and acting as antigen-presenting cells (see Chapter 14: Lymphoid Organs). Microglia secrete a number of immunoregulatory cytokines and dispose of unwanted cellular debris caused by central nervous system lesions.

MEDICAL APPLICATION

In multiple sclerosis, the myelin sheath is destroyed by an unknown mechanism with severe neurological consequences. In this disease, microglia phagocytose and degrade myelin debris by receptor-mediated phagocytosis and lysosomal activity. In addition, AIDS dementia complex is caused by human immunodeficiency virus type 1 (HIV-1) infection of the central nervous system. Overwhelming experimental evidence indicates that microglia are infected by

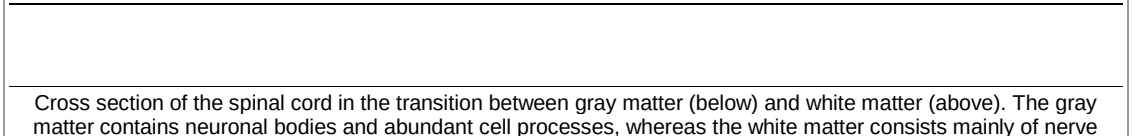
HIV-1. A number of cytokines, such as interleukin-1 and tumor necrosis factor- , activate and enhance HIV replication in microglia.

The Central Nervous System

The central nervous system consists of the **cerebrum, cerebellum,** and **spinal cord.** It has almost no connective tissue and is therefore a relatively soft, gel-like organ.

When sectioned, the cerebrum, cerebellum, and spinal cord show regions that are white (**white matter**) and that are gray (**gray matter**). The differential distribution of myelin in the central nervous system is responsible for these differences: The main component of white matter is myelinated axons (Figure 9–17) and the myelin-producing oligodendrocytes. White matter does not contain neuronal cell bodies.

Figure 9–17.



Cross section of the spinal cord in the transition between gray matter (below) and white matter (above). The gray matter contains neuronal bodies and abundant cell processes, whereas the white matter consists mainly of nerve fibers whose myelin sheath was dissolved by the histological procedure. PT stain. Medium magnification.

Gray matter contains neuronal cell bodies, dendrites, and the initial unmyelinated portions of axons and glial cells. This is the region at which synapses occur. Gray matter is prevalent at the surface of the cerebrum and cerebellum, forming the **cerebral and cerebellar cortex** (Figures 9–18, 9–19, and 9–20), whereas white matter is present in more central regions. Aggregates of neuronal cell bodies forming islands of gray matter embedded in the white matter are called **nuclei.** In the **cerebral cortex,** the gray matter has six layers of cells with different forms and sizes. Neurons of some regions of the cerebral cortex register **afferent** (**sensory**) impulses; in other regions, **efferent** (**motor**) neurons generate motor impulses that control voluntary movements. Cells of the cerebral cortex are related to the integration of sensory information and the initiation of voluntary motor responses.

Figure 9–18.

Silver-stained section of cerebral cortex showing many pyramid-shaped neurons with their processes and a few glial cells. Medium magnification.

Figure 9–19.

Photomicrograph of the cerebellum. The staining procedure used (H&E) does not reveal the unusually large dendritic arborization of the Purkinje cell, which is illustrated in Figure 9–3. Low magnification.

Figure 9–20.

Section of the cerebellum with distinct Purkinje cells. One Purkinje cell shows part of its rich dendritic arborization. H&E stain. Medium magnification.

The **cerebellar cortex** has three layers (Figures 9–19 and 9–20): an outer molecular layer, a central layer of large Purkinje cells, and an inner granule layer. The Purkinje cells have a conspicuous cell body and their dendrites are highly developed, assuming the aspect of a fan (Figure 9–3). These dendrites occupy most of the molecular layer and are the reason for the sparseness of nuclei. The granule layer is formed by very small neurons (the smallest in the body), which are compactly disposed, in contrast to the less cell-dense molecular layer (Figure 9–19).

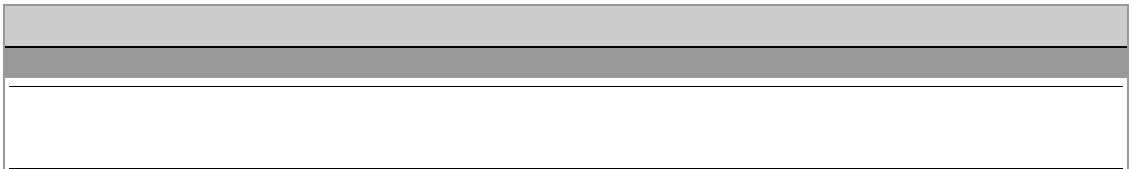
In cross sections of the **spinal cord,** white matter is peripheral and gray matter is central, assuming the shape of an **H** (Figure 9–21). In the horizontal bar of this **H** is an opening, the **central canal,** which is a remnant of the lumen of the embryonic neural tube. It is lined with ependymal cells. The gray matter of the legs of the **H** forms the **anterior horns.** These contain motor neurons whose axons make up the ventral roots of the spinal nerves. Gray matter also forms the posterior horns (the arms of the **H**), which receive sensory fibers from neurons in the spinal ganglia (dorsal roots).

Figure 9–21.

Cross section through the spinal cord.

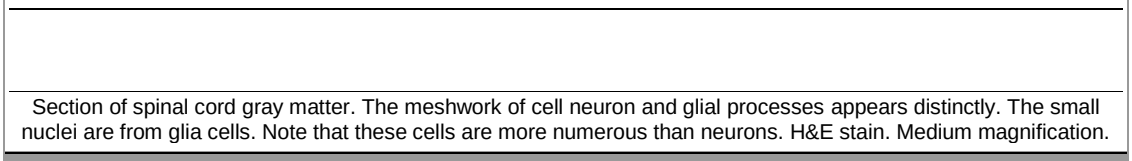
Spinal cord neurons are large and multipolar, especially in the anterior horns, where large motor neurons are found (Figures 9–22 and 9–23).

Figure 9–22.



Section of the gray matter of the spinal cord showing several motor neurons with their basophilic bodies (Nissl bodies). Nucleoli are seen in some nuclei. The neurons are surrounded by a mesh of neuronal and glial processes. PT stain. Medium magnification.

Figure 9–23.

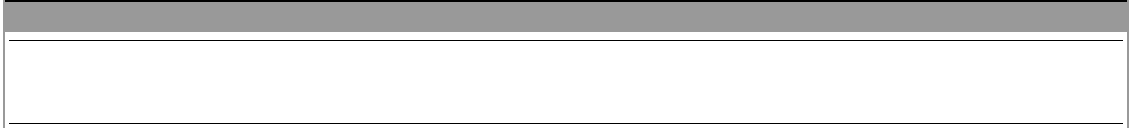


Section of spinal cord gray matter. The meshwork of cell neuron and glial processes appears distinctly. The small nuclei are from glia cells. Note that these cells are more numerous than neurons. H&E stain. Medium magnification.

Meninges

The skull and the vertebral column protect the central nervous system. It is also encased in membranes of connective tissue called the **meninges** (Figure 9–24). Starting with the outermost layer, the meninges are the **dura mater, arachnoid,** and **pia mater.** The arachnoid and the pia mater are linked together and are often considered a single membrane called the **pia-arachnoid.**

Figure 9–24.



The structure of the meninges, with the superposition of pia mater, arachnoid, and dura mater. Astrocytes form a three-dimensional net around the neurons (not shown). Note that the footlike processes of the astrocytes form a continuous layer that involves the blood vessels that contribute to the blood–brain barrier. (Reproduced, with permission, from Krstíc RV: *Microscopic Human Anatomy.* Springer-Verlag, 1991.)

Dura Mater

The dura mater is the external layer and is composed of dense connective tissue continuous with the periosteum of the skull. The dura mater that envelops the spinal cord is separated from the periosteum of the vertebrae by the epidural space, which contains thin-walled veins, loose connective tissue, and adipose tissue.

The dura mater is always separated from the arachnoid by the thin subdural space. The internal surface of all dura mater, as well as its external surface in the spinal cord, is covered by simple squamous epithelium of mesenchymal origin.

Arachnoid

The arachnoid (Gr. *arachnoeides,* cobweblike) has two components: a layer in contact with the dura mater and a system of trabeculae connecting the layer with the pia mater. The cavities between the trabeculae form the **subarachnoid space,** which is filled with cerebrospinal fluid and is completely separated from the **subdural space.** This space forms a hydraulic cushion that protects the central nervous system from trauma. The subarachnoid space communicates with the ventricles of the brain.

The arachnoid is composed of connective tissue devoid of blood vessels. The same type of simple squamous epithelium that covers the dura mater covers its surfaces. Because the arachnoid has fewer trabeculae in the spinal cord, it can be more clearly distinguished from the pia mater in that area.

In some areas, the arachnoid perforates the dura mater, forming protrusions that terminate in venous sinuses in the dura mater. These protrusions, which are covered by endothelial cells of the veins, are called **arachnoid villi.** Their function is to reabsorb cerebrospinal fluid into the blood of the venous sinuses.

Pia Mater

The pia mater is a loose connective tissue containing many blood vessels. Although it is located quite close to the nerve tissue, it is not in contact with nerve cells or fibers. Between the pia mater and the neural elements is a thin layer of neuroglial processes, adhering firmly to the pia mater and forming a physical barrier at the periphery of the central nervous system. This barrier separates the central nervous system from the cerebrospinal fluid (Figure 9–24).

The pia mater follows all the irregularities of the surface of the central nervous system and penetrates it to some extent along with the blood vessels. Squamous cells of mesenchymal origin cover pia mater.

Blood vessels penetrate the central nervous system through tunnels covered by pia mater—the **perivascular spaces.** The pia mater disappears before the blood vessels are transformed into capillaries. In the central nervous system, the blood capillaries are completely covered by expansions of the neuroglial cell processes (Figure 9–24).

Blood–brain Barrier

The blood–brain barrier is a functional barrier that prevents the passage of some substances, such as antibiotics and chemical and bacterial toxic matter, from the blood to nerve tissue.

The blood–brain barrier results from the reduced permeability that is characteristic of blood capillaries of nerve tissue. Occluding junctions, which provide continuity between the endothelial cells of these capillaries, represent the main structural component of the barrier. The cytoplasm of these endothelial cells does not have the fenestrations found in many other locations, and very few pinocytotic vesicles are observed. The expansions of neuroglial cell processes that envelop the capillaries are partly responsible for their low permeability.

Choroid Plexus & Cerebrospinal Fluid

The choroid plexus consists of invaginated folds of pia mater, rich in dilated fenestrated capillaries, that penetrate the interior of the brain ventricles. It is found in the roofs of the third and fourth ventricles and in part in the walls of the lateral ventricles.

The choroid plexus is composed of loose connective tissue of the pia mater, covered by a simple cuboidal or low columnar epithelium (Figure 9–25) made of ion-transporting cells (see Chapter 4: Epithelial Tissue).

Figure 9–25.

Photomicrograph of choroid plexus section. The choroid plexus presents a core of loose connective tissue rich in blood capillaries (BC) covered by a simple cubic epithelium (arrowhead). H&E stain. Medium magnification.

The main function of the choroid plexus is to elaborate cerebrospinal fluid, which contains only a small amount of solids and completely fills the ventricles, central canal of the spinal cord, subarachnoid space, and perivascular space. Cerebrospinal fluid is important for the metabolism of the central nervous system and acts as a protective device against mechanical shocks.

Cerebrospinal fluid is clear, has a low density (1.004–1.008 g/ mL), and is very low in protein content. A few desquamated cells and two to five lymphocytes per milliliter are also present. Cerebrospinal fluid is continuously produced and circulates through the ventricles, from which it passes into the subarachnoid space. There, arachnoid villi provide the main pathway for absorption of cerebrospinal fluid into the venous circulation. (There are no lymphatic vessels in brain nerve tissue.)

MEDICAL APPLICATION

A decrease in the absorption of cerebrospinal fluid or a blockage of outflow from the ventricles results in the condition known as **hydrocephalus** (Gr. *hydro,* water, + *kephale,* head). Hydrocephalus describes any condition in which an excess quantity of cerebrospinal fluid is present in the central nervous system cavity, increasing intracranial pressure. Congenital hydrocephalus results in an enlargement of the head, followed by mental impairment and muscular weakness. In adults, there are multiple neurological symptoms also caused by damage to brain nervous tissue.

Peripheral Nervous System

The main components of the peripheral nervous system are the **nerves, ganglia,** and **nerve endings.** Nerves are bundles of nerve fibers surrounded by connective tissue sheaths.

Nerve Fibers

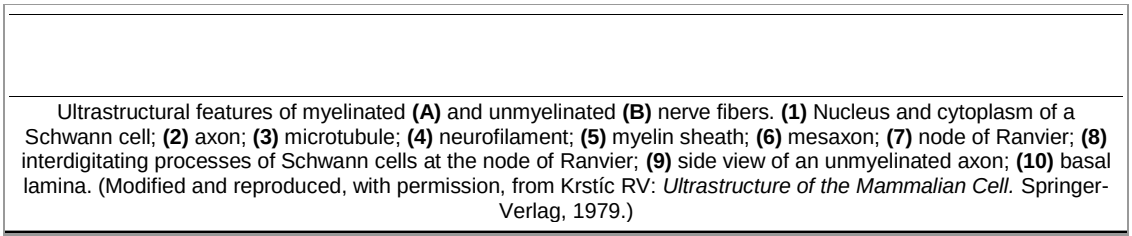
Nerve fibers consist of axons enveloped by a special sheath derived from cells of ectodermal origin. Groups of nerve fibers constitute the tracts of the brain, spinal cord, and peripheral nerves. Nerve fibers exhibit differences in their enveloping sheaths, related to whether the fibers are part of the central or the peripheral nervous system.

Single or multiple folds of a sheath cell cover most axons in adult nerve tissue. In peripheral nerve fibers, the sheath cell is the **Schwann cell,** and in central nerve fibers it is the **oligodendrocyte.** Axons of small diameter are usually **unmyelinated nerve fibers** (Figures 9–26, 9–28, and 9–29). Progressively thicker axons are generally sheathed by increasingly numerous concentric wrappings of the enveloping cell, forming the **myelin sheaths.** These fibers are known as **myelinated nerve fibers** (Figures 9–27, 9–28, and 9–29).

Figure 9–26.

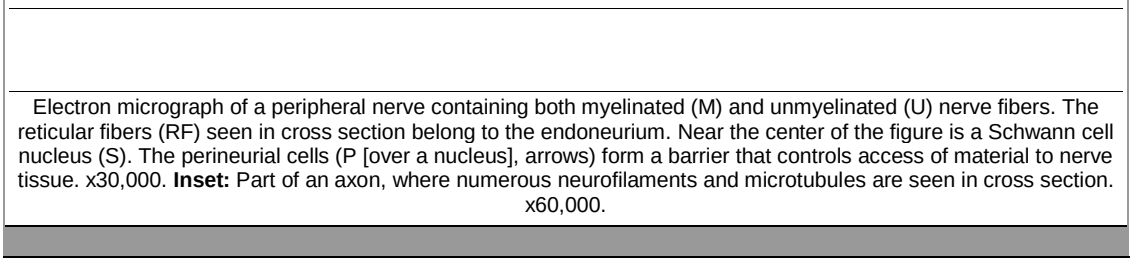
A: The most frequent type of unmyelinated nerve fiber, in which isolated axons are surrounded by a Schwann cell and each axon has its own mesaxon. **B:** Many very thin axons are sometimes found together, surrounded by the Schwann cell. In such cases, there is one mesaxon for several axons.

Figure 9–28.



Ultrastructural features of myelinated **(A)** and unmyelinated **(B)** nerve fibers. **(1)** Nucleus and cytoplasm of a Schwann cell; **(2)** axon; **(3)** microtubule; **(4)** neurofilament; **(5)** myelin sheath; **(6)** mesaxon; **(7)** node of Ranvier; **(8)** interdigitating processes of Schwann cells at the node of Ranvier; **(9)** side view of an unmyelinated axon; **(10)** basal lamina. (Modified and reproduced, with permission, from Krstíc RV: *Ultrastructure of the Mammalian Cell.* Springer-Verlag, 1979.)

Figure 9–29.

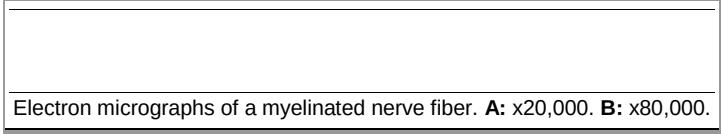


Electron micrograph of a peripheral nerve containing both myelinated (M) and unmyelinated (U) nerve fibers. The reticular fibers (RF) seen in cross section belong to the endoneurium. Near the center of the figure is a Schwann cell nucleus (S). The perineurial cells (P [over a nucleus], arrows) form a barrier that controls access of material to nerve tissue. x30,000. **Inset:** Part of an axon, where numerous neurofilaments and microtubules are seen in cross section. x60,000.

Myelinated Fibers

In myelinated fibers of the peripheral nervous system, the plasmalemma of the covering Schwann cell winds and wraps around the axon (Figures 9–27, 9–28, and 9–30). The layers of membranes of the sheath cell unite and form **myelin,** a whitish lipoprotein complex whose lipid component can be partly removed by standard histological procedures.

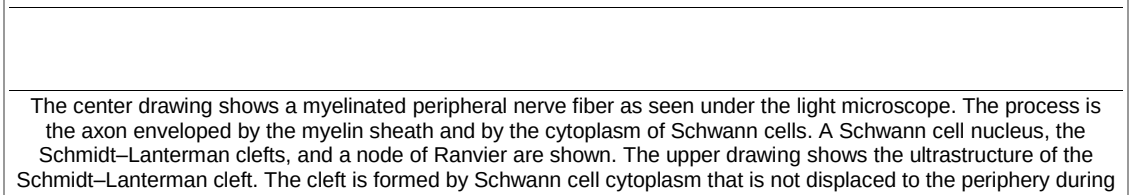
Figure 9–30.



Electron micrographs of a myelinated nerve fiber. **A:** x20,000. **B:** x80,000.

Myelin consists of many layers of modified cell membranes. These membranes have a higher proportion of lipids than do other cell membranes. The myelin sheath shows gaps along its path called the **nodes of Ranvier** (Figures 9–28 and 9–31); these represent the spaces between adjacent Schwann cells along the length of the axon. Interdigitating processes of Schwann cells partially cover the node. The distance between two nodes is called an **internode** and consists of one Schwann cell. The length of the internode varies between 1 and 2 mm.

Figure 9–31.



The center drawing shows a myelinated peripheral nerve fiber as seen under the light microscope. The process is the axon enveloped by the myelin sheath and by the cytoplasm of Schwann cells. A Schwann cell nucleus, the Schmidt–Lanterman clefts, and a node of Ranvier are shown. The upper drawing shows the ultrastructure of the Schmidt–Lanterman cleft. The cleft is formed by Schwann cell cytoplasm that is not displaced to the periphery during myelin formation. The lower drawing shows the ultrastructure of a node of Ranvier. Note the appearance of loose interdigitating processes of the outer leaf of the Schwann cells' cytoplasm (SC) and the close contact of the axolemma. This contact acts as a type of barrier to the movement of material in and out of the periaxonal space between the axolemma and the membrane of the Schwann cell. The basal lamina around the Schwann cell is continuous. Covering the nerve fiber is a connective tissue layer—mainly reticular fibers—that belongs to the endoneurial sheath of the peripheral nerve fibers.

There are no Schwann cells in the central nervous system; there, the processes of the oligodendrocytes form the myelin sheath. Oligodendrocytes differ from Schwann cells in that different branches of one cell can envelop segments of several axons (Figure 9–15).

Unmyelinated Fibers

In both the central and peripheral nervous systems, not all axons are sheathed in myelin. In the peripheral system, all unmyelinated axons are enveloped within simple clefts of the Schwann cells (Figure 9–26). Unlike their association

with individual myelinated axons, each Schwann cell can sheathe many unmyelinated axons. Unmyelinated nerve fibers do not have nodes of Ranvier, because abutting Schwann cells are united to form a continuous sheath. The central nervous system is rich in unmyelinated axons; unlike those in the peripheral system, these axons are not sheathed. In the brain and spinal cord, unmyelinated axonal processes run free among the other neuronal and glial processes.

Nerves

In the peripheral nervous system, the nerve fibers are grouped in bundles to form the nerves. Except for a few very thin nerves made up of unmyelinated fibers, nerves have a whitish, homogeneous, glistening appearance because of their myelin and collagen content.

Nerves (Figures 9–32, 9–33, 9–34, 9–35, and 9–36) have an external fibrous coat of dense connective tissue called **epineurium,** which also fills the space between the bundles of nerve fibers. Each bundle is surrounded by the **perineurium,** a sleeve formed by layers of flattened epitheliumlike cells. The cells of each layer of the perineurial sleeve are joined at their edges by tight junctions, an arrangement that makes the perineurium a barrier to the passage of most macromolecules and has the important function of protecting the nerve fibers from aggression. Within the perineurial sheath run the Schwann cell-sheathed axons and their enveloping connective tissue, the **endoneurium** (Figure 9–33). The endoneurium consists of a thin layer of reticular fibers, produced by Schwann cells.

Figure 9–32.

Schematic representation of a nerve and a reflex arc. In this example, the sensory stimulus starts in the skin and passes to the spinal cord via the dorsal root ganglion. The sensory stimulus is transmitted to an interneuron that activates a motor neuron that innervates skeletal muscle. Examples of the operation of this reflex are withdrawal of the finger from a hot surface and the knee-jerk reflex. (Modified, redrawn, and reproduced, with permission, from Ham AW: *Histology,* 6th ed. Lippincott, 1969.)

Figure 9–33.

Electron micrograph of a cross section through a nerve, showing the epineurium, the perineurium, and the endoneurium. The epineurium is a dense connective tissue rich in collagen fibers (Col) and fibroblasts (arrow). The perineurium is composed of several layers of flat cells tightly joined together to form a barrier to the penetration of the nerve by macromolecules. The endoneurium is composed mainly of reticular fibers (RF) synthesized by Schwann cells (SC). x1200.

Figure 9–34.

Cross section of a thick nerve showing the epineurium, perineurium, and endoneurium. The myelin sheath that envelops each axon was partially removed by the histological technique. PT stain. Medium magnification.

Figure 9–35.

Cross section of a thick nerve stained to show its collagenous components. Picrosirius–polarized light stain. Medium magnification.

Figure 9–36.

Cross sections of two small nerves with a thin covering layer. Note the Schwann cell nuclei (arrowheads) and the axons (arrows). PT stain. Medium magnification.

The nerves establish communication between brain and spinal cord centers and the sense organs and effectors (muscles, glands, etc). They possess afferent and efferent fibers to and from the central nervous system. **Afferent** fibers carry the information obtained from the interior of the body and the environment to the central nervous system. **Efferent** fibers carry impulses from the central nervous system to the effector organs commanded by these centers. Nerves possessing only sensory fibers are called **sensory nerves;** those composed only of fibers carrying impulses to the effectors are called **motor nerves.** Most nerves have both sensory and motor fibers and are called **mixed nerves;** these nerves have both myelinated and unmyelinated axons (Figure 9–29).

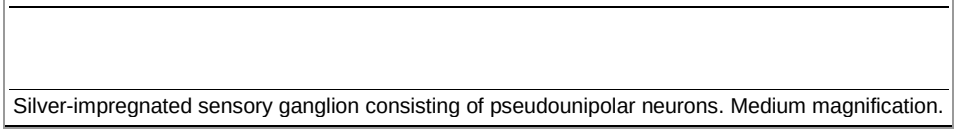
Ganglia

Ganglia are ovoid structures containing neuronal cell bodies and glial cells supported by connective tissue. Because they serve as relay stations to transmit nerve impulses, one nerve enters and another exits from each ganglion. The direction of the nerve impulse determines whether the ganglion will be a **sensory** or an **autonomic** ganglion.

Sensory Ganglia

Sensory ganglia receive afferent impulses that go to the central nervous system. Two types of sensory ganglia exist. Some are associated with cranial nerves (**cranial ganglia**); others are associated with the dorsal root of the spinal nerves and are called **spinal ganglia.** The latter comprise large neuronal cell bodies (Figure 9–37) with prominent fine Nissl bodies surrounded by abundant small glial cells called **satellite cells.**

Figure 9–37.



Silver-impregnated sensory ganglion consisting of pseudounipolar neurons. Medium magnification.

A connective tissue framework and capsule support the ganglion cells. The neurons of these ganglia are pseudounipolar and relay information from the ganglion's nerve endings to the gray matter of the spinal cord via synapses with local neurons.

Autonomic Ganglia

Autonomic ganglia appear as bulbous dilatations in autonomic nerves. Some are located within certain organs, especially in the walls of the digestive tract, where they constitute the **intramural ganglia.** These ganglia are devoid of connective tissue capsules, and their cells are supported by the stroma of the organ in which they are found. Autonomic ganglia usually have multipolar neurons. As with craniospinal ganglia, autonomic ganglia have neuronal perikaryons with fine Nissl bodies.

A layer of satellite cells frequently envelops the neurons of autonomic ganglia. In intramural ganglia, only a few satellite cells are seen around each neuron.

Autonomic Nervous System

The autonomic (Gr. *autos,* self, + *nomos,* law) nervous system is related to the control of smooth muscle, the secretion of some glands, and the modulation of cardiac rhythm. Its function is to make adjustments in certain activities of the body to maintain a constant internal environment (**homeostasis**). Although the autonomic nervous system is by definition a motor system, fibers that receive sensation originating in the interior of the organism accompany the motor fibers of the autonomic system.

The term "autonomic" is not correct—although it is widely used—inasmuch as most of the functions of the autonomic nervous system are not autonomous; they are organized and regulated in the central nervous system. The concept of the autonomic nervous system is mainly functional. Anatomically, it is composed of collections of nerve cells located in the central nervous system, fibers that leave the central nervous system through cranial or spinal nerves, and nerve ganglia situated in the paths of these fibers. The term "autonomic" covers all the neural elements concerned with visceral function. In fact, the so-called autonomic functions are as dependent on the central nervous system as are the motor neurons that trigger muscle contractions.

The autonomic nervous system is a two-neuron network. The first neuron of the autonomic chain is located in the central nervous system. Its axon forms a synapse with the second multipolar neuron in the chain, located in a ganglion of the peripheral nervous system. The nerve fibers (axons) of the first neuron are called **preganglionic fibers;** the axons of the second neuron to the effectors—muscle or gland—are called **postganglionic fibers.** The chemical mediator present in the synaptic vesicles of all preganglionic endings and at anatomically parasympathetic postganglionic endings is **acetylcholine,** which is released from the terminals by nerve impulses.

The adrenal medulla is the only organ that receives preganglionic fibers, because the majority of the cells, after migration into the gland, differentiate into secretory cells rather than ganglion cells.

The autonomic nervous system is composed of two parts that differ both anatomically and functionally: the sympathetic system and the parasympathetic system (Figure 9–38). Nerve fibers that release acetylcholine are called **cholinergic.**

Cholinergic fibers include all the preganglionic autonomic fibers (sympathetic as well as parasympathetic) and postganglionic parasympathetic fibers to smooth muscles, heart, and exocrine glands (Figure 9–38).

Figure 9–38.

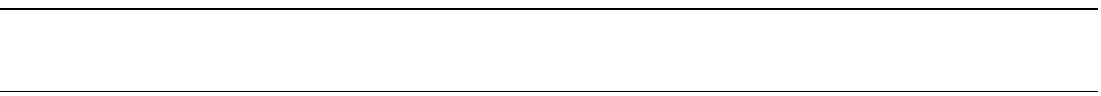


Diagram of the efferent autonomic pathways. Preganglionic neurons are shown as solid lines and postganglionic neurons as dotted lines. The blue lines are parasympathetic fibers; the red lines are sympathetic fibers. (Modified and reproduced, with permission, from Youmans W: *Fundamentals of Human Physiology,* 2nd ed. Year Book, 1962.)

Sympathetic System

The nuclei (formed by a collection of nerve cell bodies) of the sympathetic system are located in the thoracic and lumbar segments of the spinal cord. Therefore, the sympathetic system is also called the **thoracolumbar division** of the autonomic nervous system. The axons of these neurons—preganglionic fibers—leave the central nervous system by way of the ventral roots and white communicating rami of the thoracic and lumbar nerves. The chemical mediator of the postganglionic fibers of the sympathetic system is **norepinephrine,** which is also produced by the adrenal medulla. Nerve fibers that release norepinephrine are called **adrenergic** (a word derived from noradrenalin, another term for norepinephrine). Adrenergic fibers innervate sweat glands and blood vessels of skeletal muscle. Cells of the adrenal medulla release epinephrine and norepinephrine in response to preganglionic sympathetic stimulation.

Parasympathetic System

The parasympathetic system has its nuclei in the medulla and midbrain and in the sacral portion of the spinal cord. The preganglionic fibers of these neurons leave through four of the cranial nerves (III, VII, IX, and X) and also through the second, third, and fourth sacral spinal nerves. The parasympathetic system is therefore also called the craniosacral division of the autonomic system.

The second neuron of the parasympathetic series is found in ganglia smaller than those of the sympathetic system; it is always located near or within the effector organs. These neurons are usually located in the walls of organs (eg, stomach, intestines), in which case the preganglionic fibers enter the organs and form a synapse there with the second neuron in the chain.

The chemical mediator released by the pre- and postganglionic nerve endings of the parasympathetic system, **acetylcholine,** is readily inactivated by acetylcholinesterase—one of the reasons parasympathetic stimulation has both a more discrete and a more localized action than does sympathetic stimulation.

Distribution

Most of the organs innervated by the autonomic nervous system receive both sympathetic and parasympathetic fibers (Figure 9–38). Generally, in organs in which one system is the stimulator, the other has an inhibitory action.

Degeneration & Regeneration of Nerve Tissue

Although it has been shown that neurons can divide in the brain of adult birds, mammalian neurons usually do not divide, and their degeneration represents a permanent loss. Neuronal processes in the central nervous system are, within very narrow limits, replaceable by growth through the synthetic activity of their perikaryons. Peripheral nerve fibers can also regenerate if their perikaryons are not destroyed.

Death of a nerve cell is limited to its perikaryon and processes. The neurons functionally connected to the dead neuron do not die, except for those with only one link. In this latter instance, the isolated neuron undergoes **transneuronal degeneration.**

In contrast to nerve cells, neuroglia of the central nervous system—and Schwann cells and ganglionic satellite cells of the peripheral nervous system—are able to divide by mitosis. Spaces in the central nervous system left by nerve cells lost by disease or injury are invaded by neuroglia.

MEDICAL APPLICATION

Because nerves are widely distributed throughout the body, they are often injured. When a nerve axon is transected, degenerative changes take place, followed by a reparative phase.

In a wounded nerve fiber, it is important to distinguish the changes occurring in the proximal segment from those in the distal segment. The proximal segment maintains its continuity with the trophic center (perikaryon) and frequently regenerates. The distal segment, separated from the nerve cell body, degenerates (Figure 9–39).

Axonal injury causes several changes in the perikaryon: **chromatolysis,** ie, dissolution of Nissl substances with a consequent decrease in cytoplasmic basophilia; an increase in the volume of the perikaryon; and migration of the nucleus to a peripheral position in the perikaryon. The proximal segment of the axon degenerates close to the wound for a short distance, but growth starts as soon as debris is removed by macrophages. Macrophages produce interleukin-1, which stimulates Schwann cells to secrete substances that promote nerve growth.

In the nerve stub distal to the injury, both the axon (now separated from its trophic center) and the myelin sheath degenerate completely, and their remnants, excluding their connective tissue and perineurial sheaths, are removed by macrophages. While these regressive changes take place, Schwann cells proliferate within the remaining connective tissue sleeve, giving rise to solid cellular columns. These rows of Schwann cells serve as guides to the sprouting axons formed during the reparative phase.

After the regressive changes, the proximal segment of the axon grows and branches, forming several filaments that progress in the direction of the columns of Schwann cells. Only fibers that penetrate these Schwann cell columns will continue to grow and reach an effector organ (Figure 9–39).

When there is an extensive gap between the distal and proximal segments, or when the distal segment disappears altogether (as in the case of amputation of a limb), the newly grown nerve fibers may form a swelling, or **neuroma,** that can be the source of spontaneous pain (Figure 9–39).

Regeneration is functionally efficient only when the fibers and the columns of Schwann cells are directed to the correct place. The possibility is good, however, since each regenerating fiber gives origin to several processes, and each column of Schwann cells receives processes from several regenerating fibers. In an injured mixed nerve, however, if regenerating sensory fibers grow into columns connected to motor end plates that were occupied by motor fibers, the function of the muscle will not be reestablished.

Figure 9–39.

Main changes that take place in an injured nerve fiber. **A:** Normal nerve fiber, with its perikaryon and effector cell (striated skeletal muscle). Note the position of the neuron nucleus and the quantity and distribution of Nissl bodies. **B:** When the fiber is injured, the neuronal nucleus moves to the cell periphery, and Nissl bodies become greatly reduced in number. The nerve fiber distal to the injury degenerates along with its myelin sheath. Debris is phagocytosed by macrophages. **C:** The muscle fiber shows a pronounced denervation atrophy. Schwann cells proliferate, forming a compact cord penetrated by the growing axon. The axon grows at a rate of 0.5–3 mm/day. **D:** Here, the regeneration of the nerve fiber was successful. Note that the muscle fiber was also regenerated after receiving nerve stimuli. **E:** When the axon does not penetrate the cord of Schwann cells, its growth is not organized. (Redrawn and reproduced, with permission, from Willis RA, Willis AF: *The Principles of Pathology and Bacteriology,* 3rd ed. Butterworth, 1972.)

Neuronal Plasticity

Despite its general stability, the nervous system exhibits some plasticity in adults. Plasticity is very prominent during embryonic development, when an excess of nerve cells is formed, and the cells that do not establish correct synapses with other neurons are eliminated. Several studies conducted in adult mammals have shown that after an injury, the neuronal circuits may be reorganized by the growth of neuronal processes, forming new synapses to replace the ones lost by injury. Thus, new communications are established with some degree of functional recovery. This property of nerve tissue is known as **neuronal plasticity.** The regenerative processes in the nervous system are controlled by several growth factors produced by neurons, glial cells, Schwann cells, and target cells. These growth factors form a family of molecules called **neurotrophins.**

Neural Stem Cells

In several tissues of adult organs, there is a stem cell population that may generate new cells continuously or in response to injury. This population remains constant in the tissues: After cell divisions, only some daughter cells differentiate, whereas others remain as stem cells, thereby maintaining a stable pool of stem cells. Because neurons do not divide to replace the ones lost by accident or disease, the subject of neural stem cells is now under intense investigation. The pool of neural stem cells may constitute a reserve of cells that under correct stimulation could replace lost neurons. Some regions of the brain and spinal cord of adult mammals retain stem cells that can generate astrocytes, neurons, and oligodendrocytes. Recently, it was shown that neural stem cells can even generate cells not related to the nerve tissue. This observation demonstrates that neural stem cells have a great potential for differentiation.

Tumors of the Nervous System

MEDICAL APPLICATION

Virtually all cells of the nerve tissue generate tumors. Glial cells produce gliomas, immature nerve cells produce **medulloblastomas,** and Schwann cells produce **schwannomas.** Because adult neurons do not divide, they do not produce tumors.

References

Bothwell M: Functional interactions of neurotrophins and neurotrophin receptors. Annu Rev Neurosci 1995;18:223. [PMID: 7605062]

Clarke DL et al: Generalized potential of adult neural stem cells. Science 2000;288:1660. [PMID: 10834848]

Compagnone NA, Mellon SH: Neurosteroids: biosynthesis and function of these novel neuromodulators. Front Neuroendocrinol 2000;21:1. [PMID: 10662535]

Gage FH: Mammalian neural stem cell. Science 2000;287:1433. [PMID: 10688783]

Giulian D, Carpuz M: Neuroglial secretion products and their impact on the nervous system. Adv Neurol 1993;59:315. [PMID: 8420117]

Halpain S: Actin and the agile spine: how and why do dendritic spines dance Trends Neurosci 2000;23(4):141.

Häusser M et al: Diversity and dynamics of dendritic signaling. Science 2000;290:739. [PMID: 15900627]

Heuser JE, Reese TS: Structural changes after transmitter release at the frog neuromuscular junction. J Cell Biol 1981;88:564. [PMID: 6260814]

Kahn MA, de Vellis J: Growth factors in the CNS and their effects on oligodendroglia. Prog Brain Res 1995;105:145. [PMID: 7568872]

Kempermann G, Gage FH: New nerve cells for the adult brain. Sci Am 1999;280:38.

Kennedy MB: Signal-processing machines at the postsynaptic density. Science 2000;290:750. [PMID: 11052931]

Lancaster IC Jr: Nitric oxide in cells. Am Sci 1992;80:248.

Matus A: Actin-based plasticity in dendritic spines. Science 2000;290:754. [PMID: 11052932]

McKay R: Stem cells and the cellular organization of the brain. J Neurosci Res 2000;59:298. [PMID: 10679764]

Momma S et al: Get to know your stem cells. Curr Opin Neurobiol 2000;10:45. [PMID: 10679437]

Morell P, Norton WT: Myelin. Sci Am 1980;242:88. [PMID: 6154973]

Murphy S (editor): *Astrocytes: Pharmacology and Function.* Academic Press, 1993.

Patterson PH: Cytokines in Alzheimers disease and multiple sclerosis. Curr Opin Neurobiol 1995;5:642. [PMID: 8580716]

Reichardt LF, Kelly RB: A molecular description of nerve terminal function. Annu Rev Biochem 1983;52:871. [PMID: 6137190]

Rodgers RJ et al: Animal models of anxiety: an ethological perspective. Braz J Med Biol Res 1997;30:289. [PMID: 9246227]

Saffell JL et al: Axonal growth mediated by cell adhesion molecules requires activation of fibroblast growth factor receptors. Biochem Soc Trans 1995;23:469. [PMID: 8566363]

Sears TA (editor): *Neuronal–Glial Cell Interrelationships.* Springer-Verlag, 1982.

Thoenen H: Neurotrophins and neuronal plasticity. Science 1995;270:593. [PMID: 7570017]

Tsutsui K et al: Novel brain function: biosynthesis and actions of neurosteroids in neurons. Neurosci Res 2000;36:261. [PMID: 10771104]

Waxman SG: The neuron as a dynamic electrogenic machine: modulation of sodium-channel expression as a basis for functional plasticity in neurons. Philos Trans R Soc London B Biol Sci 2000;355:199. [PMID: 10724456]

Zigova T, Sanberg PR: Neural stem cell for brain repair. Sci Med 1999;6:18.