III Connective and Supporting Tissues
Plate 48. Origin of Connective and Supporting Tissues

The mesenchyme, from which — with the exception of the notochord — all connective and supporting tissues develop, stems largely from the middle germ layer or mesoderm. Only a small part of the mesenchyme derives from the ectoderm of the neural crest (see embryology texts for further information).

In Fig. A, the trilaminar stage of an 18-day-old human embryo is illustrated at the level of the primitive streak (unshaded arrow). All three germ layers are visible in the section: ectoderm (1), endoderm (2), and the interjacent mesoderm (3).

The initially closed epithelium-like cell layer of the mesoderm becomes less compact due to the uptake of fluid and transforms into the embryonic connective tissue, the mesenchyme. The cells of the mesenchyme differentiate and form, among others:

- Stem cells (4) of all blood elements
- Practically all smooth muscle cells (5)
- Immature connective tissue cells, fibroblasts (6), which differentiate into mature connective tissue cells, fibrocytes (7)
- Immature bone-forming cells, osteoblasts (8), which become osteocytes (9) during the process of ossification. Fibroblasts (6) can also differentiate into osteoclasts. The dentin-forming elements, odontoblasts (10), similarly develop from mesenchymal cells
- All cartilage cells, chondrocytes, of hyaline (11), elastic (12), and fibrous (13) cartilage
- Polynuclear chondroclasts and osteoclasts (14)
- Mast cells (15)
- Lipoblasts (16) — immature — and adipocytes (17) — mature fat cells, which are able to differentiate into one another
- Reticular cells (18) of the reticular tissue [fat cells (16, 17) can develop by metaplastic transformation of reticular cells]
- Connective tissue macrophages or histiocytes (19); reticular cells also have the ability to transform into macrophages
- Endothelial cells (20) of blood and lymphatic vessels.

As is evident from the above examples, mesenchyme is a pluripotential tissue.

Magnifications: Fig. A, x 120; Figs. 4-20, x 800
Plate 49. Classification of Connective and Supporting Tissues

This plate provides a summary of the very varied forms of connective and supporting tissues. The main tissue-groups are shown in rectangles, and the subdivisions in circles.
Plate 50. Mesenchyme or Embryonic Connective Tissue from the Dorsal Mesogastrium of a 14-Day-Old Mouse Fetus

The low cells (1) at the upper edge of the illustration will in the course of development, after flattening, differentiate into mesothelium, i.e., epithelium of mesodermal origin. Like all surface epithelia, it forms a boundary to the underlying amorphous mesenchymal tissue.

The mesenchymal cells (2) are connected to one another by fine cell processes (3), invisible under the light microscope. Uptake of fluid into the intercellular spaces causes the structure to become less compact and a three-dimensional lattice develops, the interstices of which contain capillaries (4).

Mesenchymal tissue is characterized by large numbers of mitoses (5). Cells that are about to divide round themselves off, though they still remain connected to neighboring cells by fine processes, which can be observed in the electron microscope. After mitosis, the daughter cells adopt the form of other cells in the lattice.

The interstices in mesenchymal tissue are filled with an intercellular substance which does not contain specifically differentiated structures.

In addition to their ability to proliferate, mesenchymal cells tend to form localized clusters of cells, blastemas. All connective and supporting tissues, musculature, and other organs of mesodermal origin (e.g., part of the kidney, adrenal cortex) develop from these areas of tightly packed cells. Though morphologically very similar to gelatinous connective tissue, mesenchymal tissue is characterized by this special histoplastic ability to form other tissues. (See Plate 112 in Krsćić 1979.)

Magnification: $\times 2,500$
Mesenchymal cells are stellate elements. Their numerous, fairly regular cell processes (1) connect with those of other cells in the connective tissue meshwork. The great diversity in external appearance is in contrast to the primitive internal organization.

The nuclei of mesenchymal cells are large, predominantly ellipsoidal, and with deep indentations. The appearance of these nuclei is characteristic of very active cells, where the area of contact between nucleus and cytoplasm has to be as great as possible. The nuclei contain dispersed chromatin, though they do contain a large nucleolus, which is displaced toward the nuclear membrane.

Mesenchymal cells are very poor in organelles: Apart from a few mitochondria (2), some cisternae of rough endoplasmic reticulum (3), and a medium-sized Golgi apparatus (4), the cytoplasm only contains a small amount of free ribosomes. Sporadic lysosomes and lipid droplets occasionally appear.

The motility of mesenchymal cells is limited. They can leave the meshwork in order to accumulate at particular sites, where they serve as an anlage for other tissues or organs.

The intercellular substance of mesenchyme is fluid. It contains occasional microfibrils (5) and an amorphous, moderately osmiophilic material. (See Plate 166 in KRSTIČ 1979.)

Magnification: $\times 7,000$
Plate 52. Gelatinous or Mucous Connective Tissue.
Example: Umbilical Cord of a Human Neonate

Gelatinous tissue is morphologically very similar to mesenchyme. There is, however, a fundamental difference between the two: Whereas mesenchyme represents a pluripotential tissue, gelatinous tissue is already mature and incapable of further differentiation.

Gelatinous tissue occurs as Wharton's jelly in the umbilical cord (Fig. A1) and chorionic plate (Fig. A2), where it surrounds the fetal blood vessels (Fig. A3). At the bottom of the illustration, part of the placenta with the basal plate (Fig. A4) can be seen. Varicosities (Fig. A5), which are common in the umbilical vessels, can also be distinguished. The light-microscopic appearance of a section through the umbilical cord is shown in Fig. B.

The cells of gelatinous tissue (Fig. B1) are stellate like mesenchymal cells, though less numerous. It is not possible using the light microscope to discern whether the thin cell processes connect with one another.

In the spaces between the cells, there is a feltwork composed of delicate collagen fibrils (Fig. B2) and a proteoglycan ground substance. A section from Fig. B (inset), including the amniotic epithelium, is presented three-dimensionally in Fig. C.

Electron-microscopic studies have demonstrated that the stellate cells (Fig. C1) of gelatinous tissue form a three-dimensional lattice. The bundles of collagen microfibrils (Fig. C2), which cross in all directions, provide the tissue, and thus the umbilical cord, with a certain tensile strength. The ability of the very polymerized hyaluronic acid of the ground substance to absorb water imparts turgidity to the gelatinous tissue and thus increases the mechanical resistance of the cord. This helps to prevent kinking of the umbilical cord, which could lead to interruption of blood circulation.

The outer surface of the umbilical cord is lined with amniotic epithelium (Fig. C3). The epithelium is nonsecretory in this section since Wharton's jelly contains neither capillaries nor nerve fibers. The structure of adult dental pulp is reminiscent of gelatinous tissue, though the former is well vascularized and supplied with numerous nerve fibers.

Mesenchyme and gelatinous tissue occur only temporarily during the course of prenatal development.

Magnifications: Fig. A, ×1; Fig. B, ×450; Fig. C, ×1,000

REFERENCE
Reticular connective tissue forms the basic framework of and fulfills specific functions in the bone marrow, spleen, and lymph nodes. It also occurs in the tonsils, solitary lymphatic nodules, and Peyer's patches of the ileum. In addition, it separates the lobuli of glands and accompanies blood and lymph capillaries.

A lymph node (Fig. A) has been chosen to elucidate the structure of reticular tissue. The capsule (Figs. A1, B1) is composed of dense connective tissue, through which numerous afferent lymphatic capillaries (Figs. A2, B2) pass; they open into the subcapsular sinus (Figs. A3, B3).

The lymphatic or lymphoreticular tissue (lymphocytes + reticular tissue) of the organ is divided into two zones: a peripheral zone, the cortex characterized by large numbers of lymphatic follicles (Fig. A4); an inner zone, the medulla, distinguished by medullary cords (Fig. A5).

An artery (Fig. A6) enters the node at the hilus (Fig. A7), as veins (Fig. A8) and an efferent lymphatic vessel (Fig. A9) leave the organ at the same site. Thus, lymph streams constantly through the network of reticular cells in the direction of the arrows toward the hilus.

A detailed light-microscopic view of the capsule, subcapsular sinus, and cortex is illustrated in Fig. B. This zone of the lymph node is particularly suitable for a study of reticular tissue, since the reticular cells form here a loose cell union. An afferent lymphatic capillary (Fig. B2) with valves (Fig. B4) enters the capsule (Fig. B1) and brings lymph into the subcapsular sinus (Fig. B3), which is lined with a monolayer of littoral cells (Fig. B5). Stellate reticular cells (Fig. B6) are stretched transversely across the sinus, and a network of branching reticular fibers (Fig. B7) is in close contact with these cells. Large numbers of small lymphocytes (Fig. B8) and macrophages (Fig. B9) are present in the spaces between the reticular cells.

Part of Fig. B is three-dimensionally presented in Plate 54.

Magnifications: Fig. A, ×15; Fig. B, ×800

REFERENCES
The capsule (1) of the lymph node has been drawn thinner and with only a few collagen bundles so that the course of an afferent lymphatic capillary (2) and the point where it opens into the subcapsular sinus (3) can be seen more clearly. The capillary endothelial cells (4) are continuous with the very flattened reticular cells, littoral cells (5), which line all sinuses of the lymph node.

The ramified, stellate, reticular cells (6) are usually stretched transversely through the sinus. They are connected with neighboring cells of the same type by means of thin cell processes. Many bundles of reticular microfibrils (7), which can be visualized by silver staining, are in close contact with the reticular cells; such bundles are frequently surrounded by processes of the reticular cells.

Several wandering cells move freely in the lymph of the sinus: a monocyte (8; see Plate 51), a histiocyte (9; see Plate 56), a lymphocyte (10; see Plate 58), and a plasma cell (11; see Plate 72). A few lymphocytes (12) by virtue of their plasticity and a certain degree of ameboid movement are able to enter the sinus by passing between the littoral cells (13) that line the cortex. Some of these littoral cells cover the inner surface of a small drainage sinus (14), which allows the lymph to drain slowly in the direction of the arrow through the network of reticular cells to the efferent capillary. Lymph thus comes into contact with every reticular cell.

Magnification: x 3,500

REFERENCES


Plate 55. Reticular Connective Tissue. Continuation of Plate 54

The left drawing shows a section through a reticular cell, revealing the ultrastructure.

A large part of the cell body is occupied by a voluminous, spherical or ellipsoidal, indented nucleus (1) with a conspicuous nucleolus (2). Several mitochondria (3) and a simple or multiple Golgi apparatus (4) are found in the cytoplasm. The cisternae of rough endoplasmic reticulum (5) have moderately osmiophilic contents and are broad or narrow according to cytophysiological stage. Lysosomes (6), free ribosomes, fine bundles of microfilaments, and glycogen particles occur in variable amounts in reticular cells. The cell presented in this drawing corresponds to a poorly differentiated form because of its relative paucity of organelles.

If a reticular cell produces fibers, the rough endoplasmic reticulum becomes broader owing to the intensive protein synthesis. In this plate, the normally very fine reticular microfibrils (7) are depicted somewhat thicker. Reticular microfibrils combine to form bundles, i.e., reticular fibers, which are in close contact with the reticular cells. The bundles are frequently surrounded by very thin processes (arrows) of the reticular cells and a glycoprotein coating (not shown), probably responsible for special staining properties of the reticular fibers. Reticular cells do not possess a basal lamina.

Under certain circumstances, a reticular cell can transform into a phagocyte (cell on the right). Particles of dye (8) are phagocytized and stored by reticular cells when subject to vital staining (injection of stains into the connective tissue which penetrate or are taken up by the cells without causing damage), e.g., with trypan blue. During this process, the reticular cells detach themselves from the microfibrillar lattice (7) and, by means of an undulating membrane (9), migrate through the tissue. The cell forms several pseudopodia (10) with which it draws the particles of dye into the cytoplasm; it also develops a large number of microvilli (11) and filopodia (12). Phagocytosis of bacteria, viruses, cell debris, etc. proceeds according to the same mechanism. The majority of littoral cells have similar abilities.

Reticular cells of lymph nodes are also able to bind antigens to their cell membranes. The lymphocytes that are in contact with such cells differentiate into antibody-producing plasma cells (see Plates 72, 115).

Reticular cells of the spleen as macrophages, phagocytize old red blood cells. Bilirubin and iron result from disintegration of the erythrocytes. Bilirubin leaves the cell by diffusion; iron is transferred to the erythroblast (see Plate 68), from which red blood cells subsequently develop (see histology texts for further information).

Reticular tissue is thus primarily involved in defense of the organism.

Magnification: ×5,000

REFERENCES
Lobular reticular tissue of the so-called primitive organs forms the basis for adipose tissue. By the deposition of fat it becomes transformed into lobular adipose tissue; it can thus be regarded as a storage form of reticular tissue. The close similarity between reticular and adipose tissue explains the frequent metaplastic transformations that occur between the two (see Plate 5).

Adipose tissue consists of white and brown types (see Plates 59–61). Two kinds of white adipose tissue are found in the organism.

1. Structural adipose tissue fulfills several functions: It forms envelopes providing mechanical support for organs (e.g., kidneys, lymph nodes, eyes) and elastic pads in areas subject to pressure (e.g., palms, soles, buttocks, joints). Structural adipose tissue also occupies the space where unfixed organs will develop (e.g., mammary glands). A large reduction in weight has little influence on structural adipose tissue. The major sites in the human body where structural adipose tissue is found are marked black in Fig. A.

2. Storage adipose tissue functions as a caloric reserve material and provides thermal insulation. Through its ability to bind water it plays an important part in water balance. Storage adipose tissue is found particularly in the subcutis and abdominal cavity (subserosa, omenta, mesenteries, epiploic appendices, etc.).

In Fig. B, grapelike complexes of adipose tissue, epiploic appendices (Fig. B1), of the large intestine (Fig. B2) are illustrated. The inset is enlarged in Fig. C.

All epiploic appendices are covered with mesothelium (Fig. C1), visceral peritoneum. Lobules (Fig. C2) composed of groups of fat cells (adipocytes or lipocytes, Fig. C3) can be observed on the surface of the section. Several blood and lymphatic vessels run through the connective tissue septa. The light-microscopic image of the inset in Fig. C is shown in Fig. D.

Adipocytes (Fig. D1) are 40- to 120-μm large cells containing a voluminous fat droplet or vacuole, (Fig. D2). In unilocular (containing one droplet) adipocytes, the droplet displaces the cytoplasm and nucleus toward the plasmalemma. In routine histological preparations, the contents of the fat cells are dissolved due to the treatment with alcohol, benzene, xylene, etc. The fat cells then have the appearance of signet rings, with thin cytoplasm, flattened nuclei, and voluminous, empty vacuoles. To prevent dissolution of the fat, the adipose tissue is fixed in formalin, frozen, and cut with a freezing microtome. The sections are then treated with liposoluble dyes (scarlet red, Sudan III), which penetrate and stain the fat droplets.

Magnification: Fig. D, x 400

REFERENCES
Hausberger FX (1964) Influence of nutritional state on size and number of fat cells. Z Zellforsch 64:13–18
As indicated in the previous plate, the epiploic appendices are covered with simple squamous epithelium, the peritoneal mesothelium (1). Directly beneath this epithelium and connected only by a few reticular microfibrils (arrow) are the globular, densely packed adipocytes (2). They contain large, homogeneous, moderately osmiophilic lipid droplets (3), which develop during the histogenesis of adipose tissue by the fusion of several small intracellular lipid droplets. The cytoplasm is confined to a narrow, sickle-shaped border and contains the nucleus (4).

Unlike routine light-microscopic preparations, where the vacuoles of fat are dissolved, fixation with \( \text{OsO}_4 \) (osmium tetroxide) for electron microscopy preserves the vacuolar contents. In this process, the fat is stained dark as a result of the formation of osmium esters. Adipocytes are densely packed cells surrounded by a basal lamina (here omitted) and a well-developed basket of reticular microfibrils (5). These microfibrils and the plasticity of the fatty material together give adipose tissue its cushioning properties. When adipose tissue is compressed, the fat cells become ellipsoidal. The original globular form is reinstated by the feltwork of entwined reticular fibers upon removal of the mechanical stress. Tensile stress is largely absorbed by the interlobular collagen fibers.

Adipose tissue is very well vascularized, which makes substantial demands upon the circulation. Numerous capillaries (6), accompanied by nerve fibers (7), run between the fat cells. The thick accumulation of fat cells and rich supply of blood give adipose tissue a certain similarity to epithelial tissue (see Plate 44).

Adipose tissue is subject to hormonal influences like all tissues. Histogenesis, for example, is largely controlled by pituitary and sex hormones. Two hormones responsible for the metabolism of adipose tissue, lipotropins, have been isolated in the sheep. Epinephrine and norepinephrine exert similar mobilizing effects. Exophthalmos-producing factor (EPF), of pituitary origin, induces an increase in the volume of the orbital adipose tissue and this gives rise to abnormal protrusion of the eyeballs (exophthalmos). (See Plate 79 in Krstić 1979.)

Magnification: \( \times 2,000 \)

REFERENCES


Slavin BG (1979) Fine structural studies on white adipocyte differentiation. Anat Rec 195:63-72

The narrow cytoplasmic rim of fat cells contains the flattened nucleus (1), some mitochondria (2), flattened cisternae of rough endoplasmic reticulum (3), a Golgi apparatus, and a few tubules of smooth endoplasmic reticulum. A giant fat droplet (4) dominates the cell body. The droplet is separated from the cytoplasm by numerous microfilaments (5), which also stabilize the fatty mass in the cell body; large fat droplets do not possess a limiting membrane of their own.

Every adipocyte is surrounded by a basal lamina (6). In the upper part of the plate, the basal lamina has been folded back so that the micropinocytotic vesicles (7) can be discerned. A feltwork of ramified reticular microfibrils (8; drawn somewhat thicker than normal) surrounds the fat cell.

Adipose tissue is a very active, dynamic tissue, which is constantly being built up and broken down.

Fatty acids, which are formed by hydrolysis of triglycerides from chylomicrons (see Plate 31) or serum lipoproteins, are taken up by the fat cells and resynthesized to triglycerides. Adipocytes can also synthesize triglycerides from carbohydrates. Lipids are stored in the cells as neutral triglycerides. Animal and human fat comprises a mixture of oleic, palmitic, and stearic acids. Exogenous liposoluble pigments, e.g., lipochromes and carotenoids, which are ingested with the food, give adipose tissue a yellowish color. Reduction in body weight leads to fat depletion in the cells; the fat droplets become smaller or disappear completely from the cytoplasm, and several cell processes form of various length. Adipocytes that have lost their fat content thus come to resemble reticular cells. In extreme cases, the body of the emptied cell becomes filled with a viscous fluid (so-called serous fat cells).

The hormones epinephrine and norepinephrine influence lipolysis by means of cAMP (see Plate 163). Stimulation by these enzymes leads to activation of hormone-sensitive lipase, which affects hydrolysis of the stored triglycerides. Fatty acids are released, they enter the circulation, become attached to albumins, and are transported to other cells of the organism, where they are utilized as a high-calorie material. (See Plate 80 in Kastner 1979.)

Magnification: × 5,000

REFERENCES
Brown or multilocular adipose tissue is relatively infrequent in man and is found predominantly in newborns. It occurs in the neck, armpit (Fig. A1), in the vicinity of the subclavian artery (Fig. A2) and kidney (Fig. A3), dorsal skin, mediastinum (Fig. A4), and mesenteries. Brown adipose tissue is more widespread in many animals, particularly hibernators ("hibernation gland"). In addition to the retroperitoneal space it is regularly found as the interscapular fat organ (Fig. B1). An area from this organ is depicted light microscopically in Fig. C.

Brown adipose tissue is arranged in lobules, like white adipose tissue. Blood and lymphatic vessels and nerve fibers enter the tissue through interlobular septa (Fig. C1). Brown fat cells (Fig. C2) are polygonal elements with a central nucleus; the cytoplasm contains several small fat droplets, hence the name "multilocular" adipose tissue. White adipocytes (Fig. C3) are occasionally found in brown fat and are distinctly larger than the brown adipocytes. Numerous blood capillaries (Fig. C4) can be seen between the brown adipocytes.

Magnification: Fig. C, × 800

REFERENCES


Tazuma Y, Obata M, Ito T, Yokochi C (1976) Possible function of human brown adipose tissue as suggested by observation on perirenal brown fat from autopsy cases of variable age groups. Arch Pathol Lab Med 90:117–145
This plate presents a three-dimensional electron-microscopic image of a lobule of brown fat cells. The brown fat cells (1) are closely packed and form an epitheliumlike structure (see Plate 59). The cytoplasm is located by the nucleus (2) and contains a number of mitochondria (3). The previously mentioned multiple fat droplets (4) occur in the cell body as inclusion products. The blood vessels (5) ensure that each cell comes into contact with capillaries. The large numbers of unmyelinated nerve fibers (6) supply practically every cell with a club-like nerve ending (7). Brown adipocytes are surrounded by a basket of reticular and collagen microfibrils (8). For the sake of clarity, the basal laminae have not been drawn on this plate.

The major function of brown adipose tissue is thermogenesis, hence the wide distribution in the bodies of hibernators, where the tissue assists in maintaining body temperature during the winter. Oxidation of fatty acids in brown adipocytes leads to a local increase in temperature, such that brown adipose tissue acts as a heating element and warms the perfusing blood. In human neonates, brown adipose tissue is important in adaptation to environmental temperature.

Magnification: x 3,200

REFERENCES
Robison GA, Sutherland EW (1971) Cyclic AMP and the function of adrenergic cells. J Physiol (Lond) 223:539–534
A section through a brown adipocyte reveals a protruding nucleus (1) with several nuclear pores (2). The cytoplasm contains a large number of mitochondria (3), responsible for the intensive oxidation, and a few cisternae of rough (4) and tubules of smooth (5) endoplasmic reticulum. The distinctive feature of a brown adipocyte is the presence of several lipid droplets (6). These are similar to the droplets of white fat cells—confined within a small basket of microfibrils (7) which provide support for the lipid mass and prevent the fusion of several fat droplets into one large droplet. The contents of the droplets are moderately osmiophilic and homogeneous. Every multicellular cell possesses its own basal lamina (8), which is externally reinforced by a network of reticular and collagen microfibrils (9). Many micropinocytotic vesicles (10) form on the cell membrane.

High concentrations of cytochrome in mitochondria as well as the lipochrome pigment of the lipid droplets give the brown color to brown adipose tissue. Brown adipose tissue is richly innervated. The plate shows the terminal portion of an unmyelinated nerve fiber (11) with two axons (12). They are accompanied by a process of a Schwann's cell (13). The basal lamina is intercalated between the axons and the brown adipocyte. The axons contain numerous synaptic vesicles, some of which have highly osmiophilic contents. Norepinephrine is released at the axonal endings and, via cAMP, activates the previously mentioned hormone-sensitive lipase. This brings about hydrolysis of the triglycerides to glycerol and fatty acids, oxidation of which leads to thermogenesis. (See Plate 78 in Kastrić 1979.)

Magnification: ×7,000

REFERENCES
CONNECTIVE AND SUPPORTING TISSUES

Plate 62. Loose Connective Tissue

Loose connective tissue, or areolar tissue, is widely distributed in the organism. It fills the spaces between the skin and musculature, between the muscle fibers, and between the muscles; it surrounds vessels, nerves, and various organs, forms the stroma of the kidneys, liver, glands, testes, ovaries, etc., forms the leptomeninges, choroid of the eye, stratum papillare of the skin, and occurs in the omenta, pleura, and wherever gaps between organs have to be filled. Loose connective tissue also connects various organs or parts of organs. It is found in hollow organs (e.g., esophagus) between the epithelium (Fig. A 1) and lamina muscularis mucosae (Fig. A 2) as the lamina propria (Fig. A 3), as the tela submucosa (Fig. A 4), and as an organ envelope, the tunica adventitia (Fig. A 5).

The components of all connective tissues can be seen particularly well in loose connective tissue (Fig. B).

The following is a broad classification (after BUCHER 1980):

- Fixed cells in connective tissues consist of fibroblasts (Fig. B 1), fibrocytes (Fig. B 2), fat cells (Fig. B 3), and pericytes (Fig. B 4).
- Wandering cells comprise the histiocytes (Fig. B 5), mast cells (Fig. B 6), lymphocytes (Fig. B 7), plasma cells (Fig. B 8), eosinophilic granulocytes (Fig. B 9), and monocytes (Fig. B 10).

The insets in Fig. A correspond to Fig. B, which has been simplified for the sake of clarity.

Magnifications: Fig. A, × 5; Fig. B, × 850

REFERENCES

Deane HS (1964) Some electron microscopic observations on the lamina propria of the gut, with comments on the close association of macrophages, plasma cells and eosinophils. Anat Rec 149:453-474

The fixed cells, fibrocytes (1), form a network with their long, thin processes, and wandering connective tissue cells move in its interstices. In this slightly schematized illustration, it is possible to distinguish a histiocyte (2), a plasma cell (3), a monocyte (4), a lymphocyte (5), and an eosinophilic granulocyte (6). A mast cell (7) is in close contact with a sectioned capillary (8). A few granules (arrows) have been expelled from the mast cell. A pericyte (9) – also classified among the cells of loose connective tissue by many authors – embraces the capillary by means of its processes. Collagen fibers (10), with their interconnecting microfibrils (11), crisscross through the loose connective tissue. The collagen fiber bundles impart tensile strength to loose connective tissue. The ramifications of elastic fibers (12) in the interstices of loose connective tissue give it elasticity. Reticular microfibrils (13) are predominantly found around vessels. Capillaries are accompanied by unmyelinated nerve fibers (14). The fibers listed here are collectively referred to as the formed elements of the intercellular substance. The second intercellular component is a protein-poor, amorphous, transparent mass, the ground substance (not shown in this illustration). Its presence is of the greatest importance for the metabolism of the connective and supporting tissues, since it transports nutrients and waste products between the cells and capillaries.

The ground substance contains proteoglycans, the chemical composition and concentration of which vary from tissue to tissue: Depending on the type of tissue, the ground substance can be a thin sol (mesenchymal tissue; see Plate 50) or a viscous gel (gelatinous tissue; see Plate 52); it is plastic in cartilaginous tissue and hard in bony tissue. Hyaluronic acid is mainly evident in the ground substance and is responsible for the metachromasia (for definition see Plate 69), which is visible under the light microscope. Pathogenic bacteria that produce the enzyme hyaluronidase are able to spread through the host by depolymerizing hyaluronic acid and thus reducing the viscosity of the ground substance (for which reason hyaluronidase is also known as “spreading factor”).

Magnification: × 3,500

REFERENCES
Plate 64. Loose Connective Tissue. Fixed Cells: Fibroblast and Fibrocyte

The fibroblast (left) is an immature flattened cell which helps to make up the framework of loose connective tissue. On the surface, there are several, short, thick cell processes (1) and a variable number of microvilli. The nucleus of fibroblasts is ellipsoidal, frequently somewhat flattened, and contains finely dispersed chromatin and one or two nucleoli. Broad cisternae of rough endoplasmic reticulum (2) with moderately osmiophilic amorphous reticuloplasmin are the main morphological features of the cytoplasm. Several vacuoles occur in the vicinity of each Golgi apparatus. A few mitochondria are scattered in the cytoplasm. The presence of centrioles is indicative of the readiness of fibroblasts to divide. A number of free ribosomes in the cytoplasmic matrix and rough endoplasmic reticulum give the fibroblasts a light-microscopically evident basophilia.

The fibrocyte (right) is, compared with the fibroblast, a mature cell. According to the function of the connective tissue in which it occurs, the fibrocyte can be slender, spindle-shaped, or flattened. Several long, thin processes connect the fibrocytes and create a three-dimensional network. The nucleus of fibrocytes contains dispersed chromatin and is often a flattened ellipsoidal; its nucleolus is smaller than that of the fibroblast. The organelles of fibrocytes are not as well developed as in fibroblasts, and the difference is particularly apparent in the poorly developed rough endoplasmic reticulum (3) and Golgi apparatus. These features enable fibroblasts and fibrocytes to be distinguished.

Fibroblasts form various fibers and intercellular components (see Plate 65). Collagen microfibrils, both singly (4) and as bundled fibrils (5), are thus found near fibroblasts. Microfibrils (arrows) often interchange between one fibril and another.

Thick elastic fibers (6), which are also synthesized by fibroblasts, are found in the direct vicinity of the plasmalemma or within its surface depressions. As previously mentioned, these fibers are highly ramified and are contained within a finefibrillar material.

The ability of fibrocytes to produce amorphous, fibrillar, intercellular material is markedly limited. It is, however, very probable that mature fibrocytes can, under certain conditions (e.g., in regeneration), dedifferentiate into fibroblasts and thus recommence protein synthesis. In all connective tissues of adults, there remains a certain reserve of immature, pluripotential elements, which can as necessity arises transform into histiocytes, fibroblasts, chondroblasts, osteoblasts, etc.

Fixed connective tissue cells such as fibroblasts, fibrocytes, and pericytes possess the ability to phagocytize to a minor extent.

Pericytes are important in the exchange processes between the contents of the blood capillaries and connective tissue. They are of minor significance in regulating capillary diameter, since endothelial cells are themselves able to contract by means of their own microfilaments. Thus, pericytes can be regarded as a reserve of pluripotential cells since they are thought to be able to free themselves from the capillaries and migrate into the surrounding connective tissue. (See Plates 36, 112, 132, 133, 136 in Kasten 1979.)

Magnitude: × 5,000
As previously mentioned, fibroblasts are above all protein-synthesizing cells. They form four kinds of protein-containing macromolecule:

A. Collagen
B. Microfibrillar proteins of elastic fibers and elastin
C. Proteoglycans
D. Structural glycoproteins (fibronectin and laminin)

A. Through the uptake of hydroxyproline (arrows) and other amino acids, the first peptides are synthesized on the ribosomes of rough endoplasmic reticulum (RER). These are incorporated into the pre- or pro-collagen polypeptide chains. The first 280-nm-long and 1.5-nm-wide tropocollagen molecules develop from three helically entwined chains. After incorporation of sugar components, they pass from the Golgi apparatus into collagen secretory granules. The tropocollagen is expelled from the cell into the intercellular space, where it is polymerized into collagen or reticular microfibrils. During this process, the heads of the molecules arrange themselves at a constant distance of 70 nm apart, which gives rise to the regular transverse striation of both fibrous elements.

Collagen microfibrils have a diameter of about 10-200 nm; reticular microfibrils are considerably thinner with a diameter of about 5-15 nm. The collagen structures unite to form fibrils, fibers, and fiber bundles, and the latter can attain a diameter of 12 pm. Recticular microfibrils combine to form reticular fibers, which are, unlike collagen fibers, thin, disposed in a network in the tissues, and argentophile, i.e., they can be impregnated and stained intensely black by silver nitrate. Reticular microfibrils occur between the basal laminae and collagen microfibrils (see Plates 24, 32). Biochemically and morphologically, there is a gradual transition between the two types of fiber.

B. After a process which has not been adequately investigated, fibroblasts produce elastic fibers. This occurs, according to the current understanding of events, by the expulsion of short microfibrillar proteins, which unite in the vicinity of the cell to form a feltlike structure (oxytalan fibers). The proelastin molecules also formed in the fibroblasts, accumulate within the feltwork, fuse, and become the electron-microscopically homogeneous elastic fibers.

C. Connective tissue cells synthesize the proteoglycans of the ground substance. The hypothetical picture of a highly enlarged detail from the circular inset is also shown in Fig. C. The proteoglycans are very large molecules, consisting of a core protein to which glycosaminoglycans are laterally connected. The latter are made up of repeating disaccharide units, chondroitin 4- and 6-sulfates, dermatan, heparan, and keratan sulfates. By a link glycoprotein, the proteoglycans are bound to a filiform hyaluronic acid molecule to form a dense molecular feltwork, which structures large volumes of extracellular water.

As a result of the water-binding properties of proteoglycans, the ground substance acts as a reserve of extracellular water. It also contains numerous ions, enzymes, hormones, vitamins, and antibodies. Increased water content in the ground substance caused by diseases of the heart and kidney as well as by damaged capillary permeability is termed edema. The ground substance acts as a filter in the diffusion of various substances from the capillaries into the cell and vice versa, retaining larger molecules and allowing smaller ones to pass through.

D. Fibronectin and laminin are involved in cell interactions as well as in the adhesion of cells to their collagen support via basal laminae. (See Plates 118, 132—137 in Kast's 1979.)

REFERENCES
Plate 66. Loose Connective Tissue. Wandering Cells: Histiocyte

The relatively large (10–20 μm) histiocye has an irregular outline and is a permanent component of loose connective tissue. The nucleus is mainly spherical or ellipsoidal and sometimes displays deep indentations. It contains finely dispersed chromatin and a distinct nucleolus. The cytoplasm contains a few mitochondria, sparse flattened cisternae of rough endoplasmic reticulum, a well-developed Golgi apparatus, and fairly abundant free ribosomes. Histiocytes are characterized by a variable number of lysosomes at various stages of development, depending on the functional state of the cell. In addition to small primary lysosomes (1), which are mainly found around the Golgi apparatus, secondary lysosomes (2), phagolysosomes (3), and residual bodies (4) are found in the interior of active histioocytes. The external morphology of these cells is extremely variable. The surface often bears a profusion of irregular microvilli (5) or globular protruberances (6), which correspond to the more extensive phagolysosomes in the cell interior. Invaginations in the plasmalemma are formed by thin folds (7) of cytoplasm. When these folds close, small amounts of intracellular fluid are engulfed by the cell, a process termed macropinocytosis. Histiocytes also contain of course large numbers of membranous vesicles (8). Histiocytes move vigorously by ameboidism. They usually follow the course of vessels and occur in large numbers where the penetration of foreign particles is likely, e.g., in the loose connective tissue of the subepithelial layer (lamina propria) of the intestinal tract.

Histiocytes are distinguished by their marked capacity to phagocytize and store. They are capable of engulfing large particles and/or dead cells and digesting them intracellularly, for which reason they are also termed macrophages. In vital staining with trypan blue (see Plate 55), dye particles are stored in the cytoplasm. (See Plates 32, 33, 47, 56–58, 168, 169 in Kristić 1979.)

Magnification: × 10,000

REFERENCES
Ten Cate AR, Deporter DA (1975) The degradative role of the fibroblast in the remodeling and turnover of collagen in soft connective tissue. Anat Rec 182:1–14
Macrophages from loose connective tissue can be easily cultivated and experimentally manipulated in vitro. The phagocytic process can be observed by adding a few red blood corpuscles to a macrophage culture. The macrophages soon develop a broad, thin, undulating membrane (4) and approach the erythrocytes (2). This veil of cytoplasm then glides over the red blood cell, which gradually becomes engulfed by the macrophage. Numerous microvilli (3) and filopodia (4) are evident on the prominent nuclear region of the macrophage. It is possible that the filopodia are important in the ameboid movement of macrophages.

Large phagolysosomes (5) or previously phagocytized erythrocytes can be easily observed in the very flattened body of the macrophage.

Magnification: \( \times 7,500 \)

REFERENCES
Carr I (1968) Some aspects of the fine structure of the reticuloendothelial system: the cells which clear colloids from the blood system. Z. Zellforsch 89:355-370
The reticuloendothelial system (RES), according to the classic interpretation of Aschhoff (1924), combines those cells of the body whose major functions are phagocytosis and storage. It thus represents a powerful defense system of the organism. The RES comprises the following cells.

- Reticular cells (1) and, deriving from the reticular cells, endothelial macrophages or littoral cells (2) lining various sinuses of the lymph nodes (3; see Plate 54), spleen (4), and bone marrow (5)
- Histiocytes (6) and monocytes (7) of loose connective tissue (8); because of the presence of histiocytes the RES is also termed the reticulohistiocytic (RHS) system
- Some endothelial cells (9) of the capillaries of the adrenal (10) and pituitary (11) glands
- Kupffer's cells (12) of the liver (13)
- In a broader sense, the microglia (14) of the central nervous system.

The main functions of the RES may be summarized as follows:

A. Phagocytosis and immunological activity (see Plate 115)
B. Storage of exogenous foreign bodies and/or vital dyes
C. Metabolism of hemoglobin and iron [old red blood cells are phagocytized; their iron is transferred (arrow) to the erythroblasts]
D. Extrabiliary synthesis of bile pigments. (Bile pigments develop as a result of digestion of erythrocytes and diffuse out of the phagocytes)
E. Lipid metabolism (reticular cells can store lipids and transform into adipocytes).

The above details represent a classic description of the RES. Recent electron-microscopic studies have revealed that phagocytosis is not performed by the sinus endothelia of the pituitary and adrenal capillaries but by perivascular macrophages. The phagocytic activity of spleen endothelia has also been questioned following new research. With the elimination of the endothelial components, the term “reticulohistiocytic system” becomes preferable to “reticuloendothelial system.”

Modern investigations have shown that macrophages originate from stem cells of the bone marrow (except microglia), for this reason and because of their morphological and functional similarities, a new concept of the mononuclear phagocyte system has been elaborated to replace the RES/RHS concept.

**REFERENCES**

Mast cells are wandering cells found largely along the small vessels of loose connective tissue (see Plates 62, 63). Occasionally, they occur in small groups in the stroma of various organs. They are relatively large cells (up to 20 μm) which can adopt a globular or elongated form. Mast cells are not evident in normally stained histological sections. Special techniques, involving basic dyes, such as methylene blue, toluidine blue, azure II, are required, whereby the granules appear metachromatic. Metachromasia signifies a substrate staining a different color to that of the dye applied. Thus, e.g., the blue solutions of the above dyes stain mast cell granules reddish-violet.

Mast cells usually contain an ellipsoidal nucleus. The cells are characterized by numerous large (up to 2 μm), electron-dense granules (Figs. A1, B), surrounded by a unit membrane. In many animals, these granules are filled with crystalline inclusions; in man, they contain odd, rolled cylindrical structures termed “scrolls” (Fig. B1). The intergranular cytoplasm of mast cells comprises a few cisternae of rough endoplasmic reticulum, a well-developed Golgi apparatus, and some mitochondria and ribosomes. The external morphology of mast cells is very variable. At rest, the surface is smooth and bears only a few cell processes. In an active mast cell, the plasma membrane forms numerous irregular microvilli (Fig. A2), folds (Fig. A3), invaginations (Fig. A4), and large numbers of protruding globular structures. The openings (Fig. A5) between the processes are probably residual traces of expelled granules.

Mast cell granules contain:

- Heparin, a proteoglycan inhibiting blood coagulation, which is also responsible for the metachromasia of the connective tissue ground substance
- Histamine, a low-molecular-weight tissue hormone that is involved in local inflammatory reactions and edema by increasing capillary permeability
- Serotonin (5-hydroxytryptamine, 5-HT; only in the rat and mouse) effects a constriction of the small blood vessels. Mast cells also produce leukotrienes, prostaglandins, and other important factors in immunity and regulation of the composition of the ground substance. (See Plate 165 in Kastner 1979 and physiology texts for further details.)

**REFERENCES**


Lympocytes, with a diameter of 7–10 \( \mu \)m, are the smallest mobile cells of the loose connective tissue. Histochemical evidence has long suggested that there are two types of lymphocyte. Unfortunately, studies employing transmission and scanning electron microscopy were unable to provide definitive confirmation of these suspicions. Immunological studies were the first to prove that there are in fact two functionally different types of lymphocyte—B and T lymphocytes. B lymphocytes in mammals stem from the bone marrow and in birds from the bursa of Fabricius, whence the term “B” lymphocyte derives. During development, T lymphocytes spend a short amount of time in the thymus (hence “T”) lymphocyte, where they receive programmed information that enables them to recognize substances foreign to the body. Both types of lymphocyte contain a large spherical nucleus with very dense chromatin. In the thin belt of cytoplasm are found only a few mitochondria, cisternae of rough endoplasmic reticulum, and a poorly developed Golgi apparatus. The diplosome is indicative of the high mitotic activity of these cells. Large numbers of free ribosomes are also scattered in the cytoplasm.

According to the functional condition, the surface of the lymphocyte is smooth or covered with numerous microvilli. Small lymphocytes account for about 20%–35% of white blood cells. They are able to leave the blood capillaries and enter the connective tissue by virtue of their plasticity. From the connective tissue, they penetrate the lymph capillaries and finally reenter the blood circulation. The number of lymphocytes in the interstices of connective tissue is small; upon the appearance of foreign elements or substances, however, they increase considerably. T lymphocytes are the carriers of so-called cellular or cell-bound immunity (see Plate 115). Under certain circumstances, B cells can transform into gamma-globulin-producing plasma cells and thus are important in humoral immune reactions.

Magnification: \( \times 10,000 \)

REFERENCES


Plate 71. Loose Connective Tissue. Wandering Cells: Monocyte

Monocytes are 12- to 20-μm-large, basophilic, spherical cells with a voluminous, kidney-shaped nucleus, which is rich in chromatin and has one or two conspicuous nucleoli. The Golgi apparatus is frequently located in the nuclear concavity. Several small, dense granules (1), just visible under the light microscope, are found in the vicinity of the Golgi apparatus. Following combined May-Grünwald and Giemsa staining, they appear purple-red (azurophilic). Electron-microscopic investigations have shown these granules to be primary lysosomes. Centrioles (2) are also seen near the Golgi apparatus. Several mitochondria and flattened cisternae of rough endoplasmic reticulum are scattered throughout the cell body.

The outer surface of inactive monocytes is smooth apart from the presence of a few microvilli. With increased activity, the plasmalemma forms numerous globular, digitiform, and microvillous protuberances, such that the monocyte can no longer be differentiated from a histiocyte (see Plate 66).

Monocytes are definite macrophages. They wander through the interstices of connective tissue by means of vigorous ameboid movements and phagocytize bacteria as well as larger particles and dead cells. Like histiocytes, monocytes store vital dyes.

Monocytes comprise about 2%–8% of all white blood cells. As a result of their mobility, they are able to leave the blood circulation and enter the connective tissue. They subsequently alter their morphology, for which reason they are also termed polyblasts. Since monocytes cannot ultimately be differentiated from histiocytes, they can be regarded as a reserve of macrophagic elements in the connective tissue.

Magnification: × 10,000

REFERENCES
Plate 72. Loose Connective Tissue. Wandering Cells: Plasma Cell

Plasma cells are 10- to 20-μm-large, ovoid, basophilic elements that predominantly occur in the vicinity of small vessels, stroma of several glands (e.g., salivary and lacrimal glands), bone marrow, lymphatic system, omenta, lamina propria of the intestinal tract, and remnant of the endometrium of the uterus during menstruation. Exceptionally, they appear in the blood (rubella).

The nucleus of plasma cells is spherical and eccentric. The clumps of chromatin adopt a characteristic wheel-like pattern ("cartwheel nucleus"). This morphological property is useful in the light-microscopic identification of these cells.

The ultrastructure of plasma cells is distinguished by highly developed parallel cisternae of rough endoplasmic reticulum, ergastoplasm (1), which contains a moderately osmiophilic, fine-granular material (reticuloplasm).

A well-developed Golgi apparatus, flanked by several smaller vacuoles and the centriole (2), is found close to the nucleus. Under the light microscope, the Golgi complex appears as a pale zone. Several mitochondria and vast numbers of free ribosomes are found between the cisternae of the ergastoplasm. The ribosomes, together with the ergastoplasm, are responsible for the basophilia of plasma cells, visible with the light microscope.

Plasma cells are capable of weak ameboid movement. It is probably for this reason that the surface bears only a few microvilli and globular processes.

Plasma cells are important producers of protein. They synthesize and secrete serum albumins and gamma globulins (immunoglobulins) by a kind of reverse microinocytosis, i.e., in small vesicles (3). Plasma cells are thus intensively involved in the defense of the organism.

Overproduction of proteins as a result of an inflammation leads to distension of the ergastoplasmic cisternae. This is caused by the accumulation of a material termed Russell bodies, which can be visualized light-microscopically after eosin or fuchsin staining.

Plasma cells can develop from B lymphocytes in the lymph nodes (see Plate 115) and from lymphoeyteliike elements in the region of blood vessels. (See Plates 35, 45, 54, 55 in Krstic 1979.)

Magnification: × 10,000

REFERENCES
Plate 73. Loose Connective Tissue. Wandering Cells: Eosinophilic Granulocyte

Eosinophilic granulocytes, which are about 11–14 μm in diameter, comprise approximately 1%–4% of all white blood cells in the circulation. They are easily identified since the cytoplasm contains granules (Fig. A1) that stain red with eosin and are visible under the light microscope.

Eosinophilic granulocytes are particularly numerous in the lamina propria of the intestinal tract, especially when parasites (worms) are present. With the exception of the thymus, these cells are less common in the connective tissue of other organs. Under the light or electron microscope, the nucleus is seen to be in the shape of a dumbbell or a pair of glasses since it is made up of two interconnected lobes. The nucleus contains condensed chromatin and one or two nucleoli. A well-developed Golgi apparatus is located in the space between the nuclear lobes; here are also found smaller vesicles with a low osmophilic content. Mitochondria and rough endoplasmic reticulum are moderately developed.

The granules, which are up to 1.5 μm in diameter and surrounded by a unit membrane (Fig. B1), contain one or two protein crystals (Figs. A2, B2) embedded in a dense, osmophilic matrix. These granules are now considered lysosomes.

Eosinophilic granulocytes can leave the capillaries by virtue of their ameboid movement and enter the connective tissue. They are apparently also able to differentiate in situ directly from immature, pluripotential cells. Recent studies have shown that eosinophilic granulocytes are capable of weak phagocytosis.

Eosinophilic granulocytes are sensitized to the tissue hormone histamine. Adrenocorticotropic hormone (ACTH) and cortisol reduce the number of these cells in the blood and tissues. (See Plate 59 in Krstić 1979.)

Magnifications: Fig. A, × 10,000; Fig. B, × 40,000

REFERENCES
Pigment connective tissue is a type of loose connective tissue. In man, it is found in the iris (Fig. A1), choroid (Fig. A2), leptomeninges, and genital skin. A section from the iris is presented in Fig. B.

Pigment connective tissue is partly built up of stellate, serrated, or lobular pigment cells of ectodermal origin, melanocytes (Fig. B1, see Plate 24). These cells contain large numbers of granules of the endogenous pigment melanin and frequently contact one another by means of their processes. The framework thus created also accommodates numerous fibrocytes (Fig. B2).

Collagen (Fig. B3) and elastic (Fig. B4) fibers, lymphatic and blood capillaries (Fig. B5), and nerve fibers (Fig. B6) run through the interstices of the pigment connective tissue. Thus, it has all the features of a loose fibrous connective tissue, whose intercellular fluid also contains wandering cells.

The genetically determined number of melanocytes in the iris is responsible for the color of the eyes. Many densely packed pigment cells give the iris a dark-brown to black color. The appearance of green or brown shades is due to fewer numbers of melanocytes. Blue and gray eyes do not contain pigment cells; the iris stroma in front of the black pigment epithelium (see Plate 13) of the retina appears bluish. In albinos, this retinal layer is also free of melanin, and the iris appears pink owing to reflection of the many choroidal blood vessels of the fundus of the eye.

Magnification: Fig. B, ×2,500

REFERENCES
Plate 75. Loose Connective Tissue.
Special Form: Pigment Connective Tissue.
Melanocyte of the Human Iris

Melanocytes (1) are, as seen in the previous plate, stellate or spindle-shaped cells similar to fibrocytes. Numerous collagen microfibrils (2) are in contact with the cell body and its processes (3). Melanocytes are basically fixed cells. The nucleus of a melanocyte is indented, ellipsoidal, and appears under the light microscope as a pale zone in the pigment-rich cell body. The unit membrane-bound, 1- to 2-μm-wide granules (4) are mostly made up of mature melanin. Melanosomes (5), precursors of the melanin granules, also occur in melanocytes (see Plate 24).

Magnification: ×7,000

REFERENCE
A special form of loose connective tissue is found in the cortical zone of the ovary (Fig. A1). Beneath the germinal epitheliun (Fig. A 2), a fibrous layer or tunica albuginea (Fig. A3) is found, followed by an exceptionally cell-rich loose connective tissue, which is represented three-dimensionally in Fig. B. The spindle-shaped fibrocytes of this tissue, which have a plump appearance owing to the small number of processes, and the intervening reticular and collagen fibers are arrayed in irregular whorls (Figs. A 4, B). The narrow intercellular spaces contain fibrous structures and permit only a small degree of movement for any free elements of connective tissue (Fig. B). It is unclear whether the cells of this tissue are able to transform into steroid hormone-producing cells of the theca interna (Fig. A5). Another, similarly cell-rich, loose connective tissue is found in the endometrium (see Plate 47). Its cells differentiate during pregnancy into large, epithelioid, pale, glycogen-rich decidual cells. The term "cellular" in the context of this kind of loose connective tissue is only intended to signify its richness in fixed cells.

Magnifications: Fig. A, × 250; Fig. B, × 2,500

REFERENCES
Kivirikko KI; Risteli L (1976) Biosynthesis of collagen and its alteration in pathological states. Med Biol 54:159–186
The loose connective tissue of the omenta (Fig. A1) of the abdominal cavity displays a special type of organization, shown at low magnification in Fig. B. It is a loose connective tissue comprised of strands (Fig. B1) of various thicknesses, connected to one another in a kind of network. Blood and lymphatic vessels (Fig. B2) run through the broad strands. A section from Fig. B is enlarged in Fig. C and shows the three-dimensional structure of this tissue.

Collagen (Fig. C1), elastic (Fig. C2), and reticular (Fig. C3) fibers form the skeleton of the strands, which are covered with polygonal, flattened mesothelial cells (Fig. C4), bearing large numbers of microvilli. The interior of the strands contains fibrocytes (Fig. C5), histiocytes (Fig. C6), adipocytes (Fig. C7), mast cells (Fig. C8), and other cellular elements of loose connective tissue. In addition, there are capillaries (Fig. C9) with pericytes (Fig. C10), lymphatic vessels (not shown), and nerve fibers (Fig. C11).

The lymphocytes and histiocytes of this special form of loose connective tissue can be concentrated along vessels in groups which have a milky appearance in fresh specimens (so called milky spots). The histiocytes and lymphocytes of this tissue become active upon the penetration of microorganisms into the abdominal cavity. They then wander over the surface of the strands, where they phagocytize the bacteria or produce antibodies against the pathogen. Histiocytes that die in the process are replaced by differentiation of fibroblasts or pericytes.

Mesothelial cells react to toxic effects by mitosis and by swelling and loosening of the cell union. Some of the elements that develop as a consequence of the action of toxins differentiate into fibrocytes, others into polynuclear giant cells. Gaps in the strands brought about by death of mesothelial cells are filled by histiocytes. Whether mesothelial cells are capable of phagocytosis is open to debate.

The leptomeninges (pia mater and arachnoid; see Plate 153) are also classed as loose connective tissue.

Magnifications: Fig. B, x 150; Fig. C, x 2,000

REFERENCE
As a result of an increase in fibrillar structures and a reduction in cells and ground substance, a dense fiber-rich connective tissue forms over areas subject to a high degree of mechanical stress. Dense connective tissue forms various organ capsules (testis, kidney, spleen, liver, etc.), the dura mater, the sclera, the stratum reticulare of the corium, the periosteum, and perichondrium, the pericardium, the skeleton of the cardiac valves, and the articular capsules. This tissue is characterized by very thick interwoven collagen fibers and fiber bundles (1). These fibers are accompanied by occasional elastic fibers (2), which are responsible for dense connective tissue reverting to its original form following deformation. A few, very flattened fibrocytes (3) are found in the spaces between the fibrous structures. Both cells and ground substance are quantitatively reduced in this tissue.

Dense fibrous connective tissue only contains a small number of blood and lymphatic vessels and nerve fibers. These histological properties are typical of a bradytrophic tissue, i.e., one with slow metabolism.

Magnification: x 3,500

REFERENCES
The structure of tendons results from the particular organization of fibrillar material in response to tension exerted in one defined direction.

Macroscopically, the large number of collagen bundles give tendons the appearance of whitish cables stretched between the muscles and bones (see Plate 125). Tendons can lie on a bony base, and this gives rise to synovial vaginae. Such a case is presented in Fig. A.

The majority of tendons are surrounded by a loose fibrous connective tissue, the paratendineum (Figs. A 1, B 1). This material serves to connect the tendon with its synovial vagina (Fig. A 2), which facilitates sliding of the tendon over the hard base.

On the outer surface, the synovial vagina is covered by a fibrous layer, called the fibrous vagina (Fig. A 3). The inner surface of the synovial vagina is lined by simple squamous epithelium, similar to mesothelium and rich in nerves and vessels. Each synovial vagina consists of two sheets - an inner sheet (Fig. A 4), directly in contact with the tendon, and an outer sheet (Fig. A 5), lining the fibrous vagina. Both layers are continuous with one another at the ends of the synovial vagina.

The serous cavity delimited by the two sheets is a narrow cleft, containing only a small amount of synovial fluid. In Fig. A, the width of this cavity has been exaggerated for the sake of clarity.

Lymphatic and blood vessels (Fig. A 6) and nerve fibers (Fig. A 7) supplying the synovial vagina and the tendon run through a connective tissue plate enveloped by mesothelium, termed the mesotendineum (Fig. A 8).

A tendon is made up of many primary fascicles (Fig. A 9), each consisting of numerous tendon fibers (fibrac tendineae). Figure B shows a detail of the transverse section from the circular inset at higher magnification. The paratendineum (Fig. B 1) envelops the outer surface of the tendon and is continuous with a connective tissue layer, the epitendineum (Fig. B 2), on its inner surface. The primary fascicles (Fig. B 3) are separated from one another by the endotendineum (Fig. B 4), which contains blood vessels and nerve fibers. Several primary fascicles constitute a secondary fascicle. The tendon cells (Fig. B 5) appear as small stellate structures compressed by the tendon fibers (Fig. B 6).

Part of the paratendineum and epitendineum in the rectangular inset in Fig. A is enlarged in Fig. C to show the light-microscopic structure of a longitudinal section of the tendon.

The primary fascicles (Fig. C 1) of tendon fibers that are not stretched run in a wavelike manner. This is of great importance in movements which need to be initiated smoothly, since the tendon fibers have to be taut before muscular contraction can exert its effect on the bones. The endotendineum (Fig. C 2) and the tendon cells (Fig. C 3) arranged in rows, are also evident in longitudinal section.

Magnifications: Fig. A, × 10; Fig. B, × 800; Fig. C, × 550

REFERENCE
As a result of the highly developed tendon fibers (Fig. A1), tendon cells are laterally compressed, and this leads to the formation of thin, winglike cytoplasmic processes (Fig. A2). Tendon cells are fibrocytes which have predominantly adapted to synthesize collagen. The cell body contains an ovoid nucleus with condensed chromatin. The cytoplasm displays the features of a cell highly involved in protein synthesis, i.e., well-developed rough endoplasmic reticulum and great numbers of free ribosomes.

In addition to collagen tendon microfibrils (Figs. A4, B1), which run in a helicoidal fashion, unite and form tendon fibers, tendon cells also synthesize elastic fibers (Fig. A3), which, as described in Plate 65, are enveloped by a felterwork of 10-nm-thick microfibrils.

In man, tendon microfibrils with diameters of 65–175 nm are not uncommon. The microfibrils are connected to one another by means of interfibrillar bridges (Fig. B2), which occasionally extend into the interior of the microfibrils (Fig. B3). Collagenous material is practically inextensible (it can only be stretched up to 4%–5% of its original length), and this gives tendons very high tensile strength (500–1,000 kg/cm²). Consequently, the danger of rupture in tendons is considerably lower than in muscles.

Tendons are mainly connected to the fibrous layer of the periosteum (see Plate 106). Many tendon fibers also penetrate the bony substance in a brushlike manner (Sharpey's fibers).

Bone formation is occasionally found to a limited extent in tendons (so-called sesamoid bone). The best-known example is the knee cap (patella).

Tendons are basically good at regeneration and being transplanted (see Plate 114). The parts of the tendon surrounded by the synovial vaginae are technically more difficult to graft and do not functionally adapt so well because the mesothelial layers tend to fuse together. Fibroblasts, which are necessary for regeneration and synthesis of tendon fibers, originate from the connective tissue of the epitendineum and endotendineum.

Magnifications: Fig. A, ×19,000; Fig. B, ×26,500

REFERENCES
Plate 81. Regular Dense Connective Tissue. Aponeurosis. Example: Stroma of the Cornea

In the "tensile tendons" just described, the traction lies only in one direction of muscular contraction, unlike the flattened tendons or aponeuroses which are exposed to traction from several directions. The structure of these flattened tendons is demonstrated here in the stroma of the cornea, which, though without muscular connections, is an example of a very specialized aponeurosis.

Figure A is a transverse section through the cornea. Between the corneal epithelium (Fig. A 1) and corneal endothelium (Fig. A 2) is located the connective tissue of the corneal stroma (Fig. A 3). The structures in the rectangular inset correspond to those in Fig. B.

Nonkeratinized stratified squamous epithelium (Fig. B 1), as described in Plate 22, lies on the thick Bowman's membrane (Fig. B 2). The densely packed, collagen microfibrils (Fig. B 3), arranged in layers, cross practically at right angles in the corneal stroma. Extremely flattened cells, keratocytes (Fig. B 4), are flattened between the layers. These cells are fibrocytes differentiated to synthesize collagen and ground substance. Seen in plan view, keratocytes are characterized by long processes, giving rise to smaller branches, which follow the intersection of the collagen layers.

Keratocytes also form elastic fibers (Fig. B 5) in addition to collagen microfibrils. The cytophysiological differences between keratocytes and fibrocytes are due to the different properties of the secreted proteoglycans of the ground substance.

REFERENCES
Plate 82. Elastic Connective Tissue or Elastic Ligaments

The major elements of the elastic connective tissue (yellow ligaments) are the densely packed elastic fibers. The strongest elastic ligament is the ligamentum nuchae (Fig. AI) of ungulates, from which the heavy head of these animals "hangs." In humans, elastic connective tissue is less widely distributed; it occurs largely as the ligamenta flava (Fig. B1) between the vertebrae and in the vocal cords (Fig. C1).

In transverse section (Fig. D1), the elastic connective tissue is seen to be made up of large numbers of homogeneous polygonal structures between which are scattered a few fibrocytes (Fig. D2), some collagen fibrils, and occasional blood vessels. With resorcin-fuchsin andorcein, elastic fibers can be stained blue-black and dark brown, respectively (see Plate 86).

On the basis of electron-microscopic observations, part of an elastic ligament is reconstructed in Fig. E. The strong elastic fibers (Fig. EI) are, as previously described (see Plates 65, 80), surrounded by a microfibrillar feltwork and run almost parallel as a result of constant tension. At many sites, however, the fibers branch or run into one another at oblique angles. Between the fibers, there is a network of reticular and collagen fibrils and microfibrils (Fig. E2) and a small number of fibrocytes (Fig. E3).

The function of elastic ligaments is to reduce the work of the whole organism, or of certain muscles when parts of the body are maintained in a particular position. Elastic connective tissue regenerates poorly since its synthesis demands a high degree of cellular differentiation.

Magnifications: Fig. D, × 300; Fig. E, × 2,000

REFERENCES