

Connective tissue

They responsible for **1-** providing and maintaining form in the body .

2- Provide a matrix that connects and binds the cells and organs to give support to the body . Is formed by cells , fibers and ground substance.

The major constituent of connective tissue is Extracellular matrix

A- different combination of protein fibers(collagen ,reticular ,and elastic) .

B- ground substance . Is hydrophilic ,viscous complex of

1- (glycosaminoglycans and proteoglycans)

2- glycoproteins (laminin and, fibronectin) , which are binding to receptor proteins (integrins) on the surface on cells and to other matrix Components.

The origin of connective tissue

Mesoderm (embryonic tissue) —————> Mesenchyme tissue —————> Mesodermal cell migrate from their origin site, surrounding and penetrating developing organs

□ Cells of connective tissue

Table 5–1. Functions of connective tissue cells.		
Cell Type	Representative Product or Activity	Representative Fun.
Fibroblast, chondroblast, osteoblast, odontoblast	Production of fibers and ground substance	Structural
Plasma cell	Production of antibodies	Immunologic (defense)
Lymphocyte (several types)	Production of immunocompetent cells	Immunologic (defense)
Eosinophilic leukocyte	Participation in allergic and vasoactive reactions, modulation of mast cell activities and the inflammatory process	Immunologic (defense)
Neutrophilic leukocyte	Phagocytosis of foreign substances, bacteria	Defense
Macrophage	Secretion of cytokines and other molecules, phagocytosis of foreign substances and bacteria, antigen processing and presentation to other cells	Defense
Mast cell and basophilic leukocyte	Liberation of pharmacologically active molecules (eg, histamine)	Defense (participate in allergic reactions)
Adipocyte	Storage of neutral fats	Energy reservoir, heat production

Fibroblasts

- 1- Synthesize collagen , elastin ,glycosaminoglycans ,proteoglycans & multiadhesive glycoproteins.
- 2- Involved in production of **Growth factors** that influence cell growth and differentiation

Two stages of activity

- 1- Active → Fibroblast
- 2- Quiescent → Fibrocyte

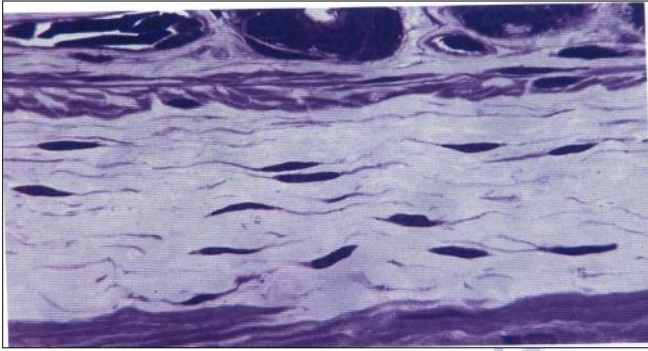


Figure 5-3. Quiescent fibroblasts are elongated cells with thin cytoplasmic extensions and condensed chromatin. Pararosaniline– toluidine blue (PT) stain. Medium magnification.

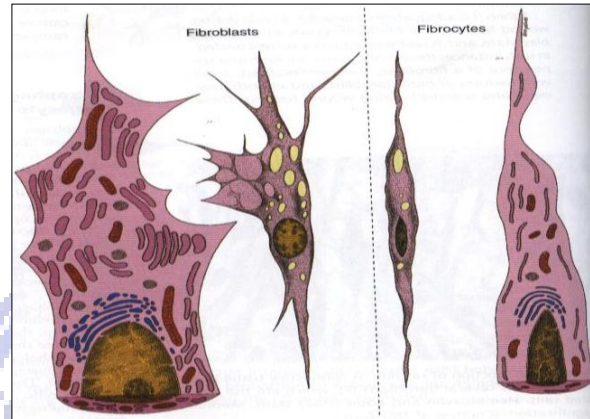
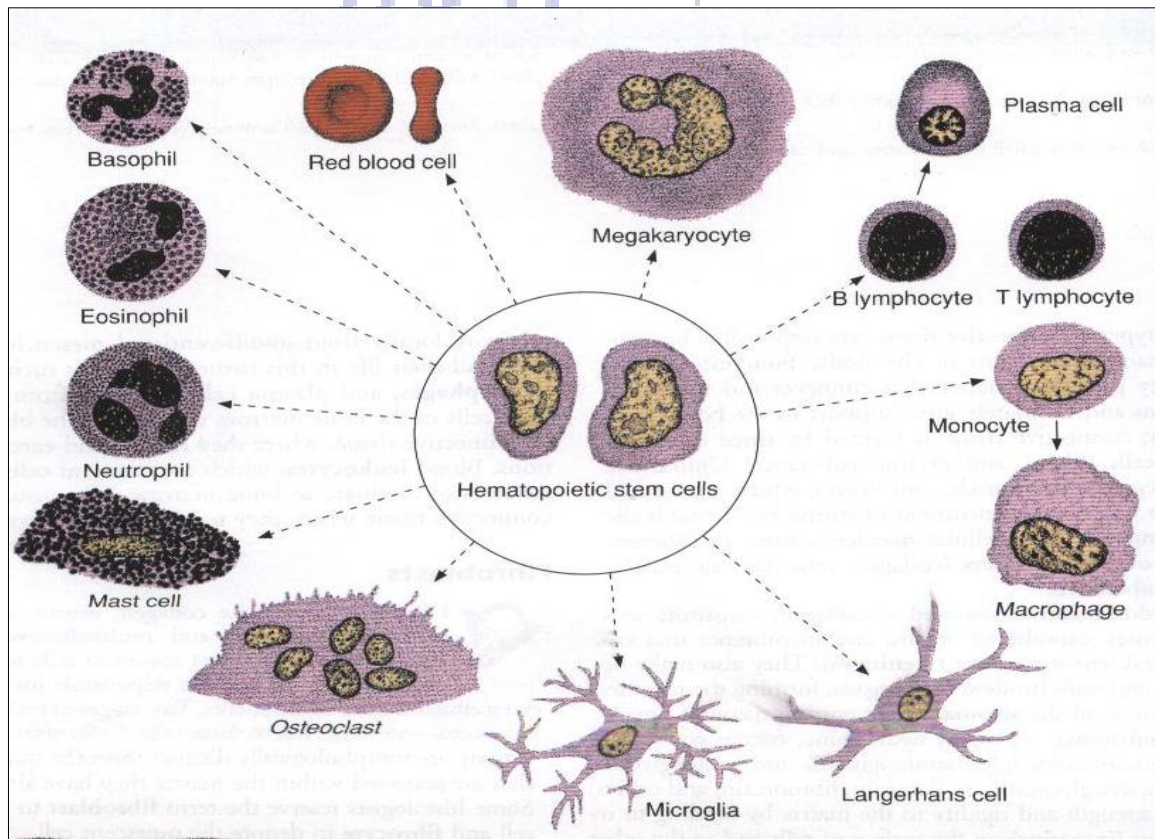
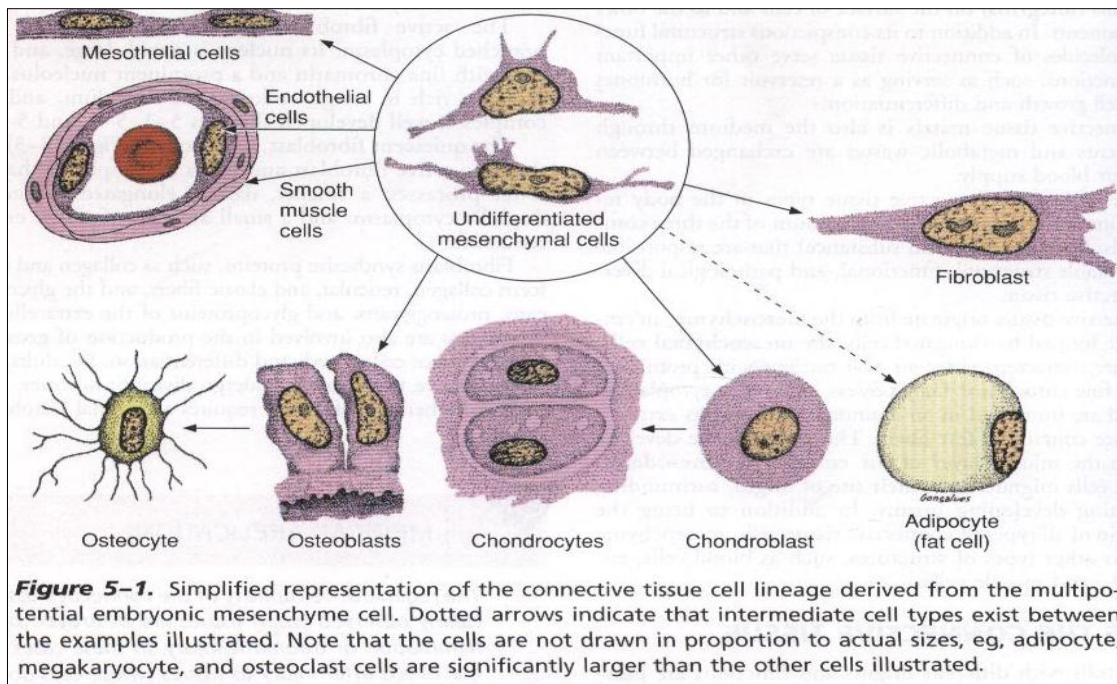


Figure 5-4. Active (left) and quiescent (right) fibroblasts. External morphological characteristics and ultrastructure of each cell are shown. Fibroblasts that are actively engaged in synthesis are richer in mitochondria, lipid droplets, Golgi complex, and rough endoplasmic reticulum than are quiescent fibroblasts (fibrocytes).





Medical application

When tissues are destroyed by inflammation or traumatic injury the main cell type involved in repair is Fibroblast.

Fibrocyte reverts to Fibroblasts state and its synthetic activities are reactivated during wound healing .The **myofibroblast** ,a cell with features of both fibroblasts and smooth muscle observed during wound healing .Its activity is responsible for wound closure ,this process call **Wound contractio**

2---Macrophages & the mononuclear phagocyte system

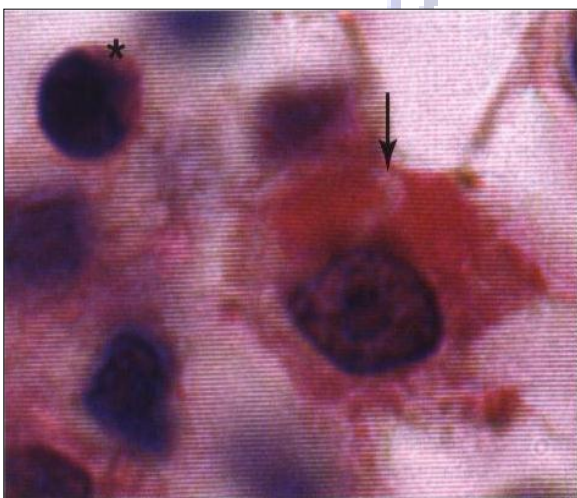
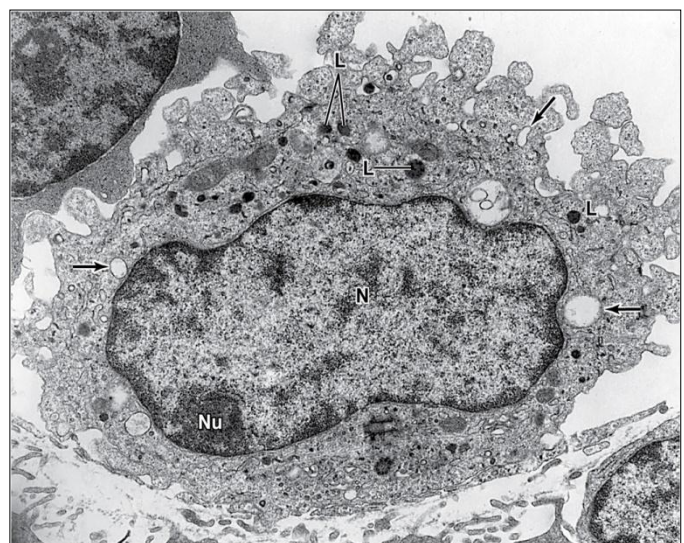


Figure 5-6. Section of lymph node showing blood cells (*) and macrophages. Note the cytoplasm of one of the macrophages (arrow). High magnification. (Courtesy of TMT Zorn.)



Characteristic features of macrophages seen in this TEM of one such cell are the prominent nucleus (N) and the nucleolus (Nu) and the numerous secondary lysosomes (L). The arrows indicate phagocytic vacuoles near the protrusions and indentations of the cel surface. X10,000.

- They are characterized by an irregular surface , a morphological expression of their active pinocytotic and phagocytic activities .They have a well–developed Golgi complex, many Lysosomes ,and R.E.R.
- Bone marrow → Monocyt → circulate in blood cross the wall of venules and capillaries to penetrate the connective tissue, where they mature and acquire morphological features of Macrophage

Medical application

- 1- When they are stimulated increase in size & clusters form Epithelioid cell
- 2- Several Macrophages may fuse to form multinuclear giant cells
- 3- Macrophages participate in cell- mediated resistance to infection by bacteria, viruses, protozoa, fungi ,and metazoans(parasitic worm)
- 4- Macrophages are also secretory cells that produce enzymes eg,collagenase & cytokiwhich they exhibit increased tumor cell –killingsnes
- 5- They participate in the processes of partial digestion and presentation of antigen to other cells ex. The langerhans cell in the dermis .

They have an important role in removing cell debris and damaged extracellular -o components formed during the physiological involution processes. Ex .during pregnancy the uterus increases in size and after parturition ,some of its tissue are destroyed by the action of macrophages

Table 5–2. Distribution and main functions of the cells of the mononuclear phagocyte system.		
Cell Type	Location	Main Function
Monocyte	Blood	Precursor of macrophages
Macrophage	Connective tissue, lymphoid organs, lungs, bone marrow	Production of cytokines, chemotactic factors, and several other molecules that participate in inflammation (defense), antigen processing and presentation
Kupffer cell	Liver	Same as macrophages
Microglia cell	Nerve tissue of the central nervous system	Same as macrophages
Langerhans cell	Skin	Antigen processing and presentation
Dendritic cell	Lymph nodes	Antigen processing and presentation
Osteoclast	Bone (fusion of several macrophages)	Digestion of bone
Multinuclear giant cell	Connective tissue (fusion of several macrophages)	Segregation and digestion of foreign bodies

Mast cells

- Are oval to round connective tissues cells ,cytoplasm is filled with basophilic granules that give a heterogeneous appearance with a prominent scroll-like substructure ,that contains Histamine & Heparin . They are abundant in the dermis & in the digestive & respiratory tracts.
- They originate from progenitor cells in bone marrow, circulate in the blood , cross the wall of venules & capillaries & penetrate the tissue , they proliferate & differentiate.
- The principal function of mast cells is the storage of chemical mediators of the inflammatory response .
- The surface of mast cells contains specific receptors for immunoglobulin E (IgE) ,which produced by plasma cells.

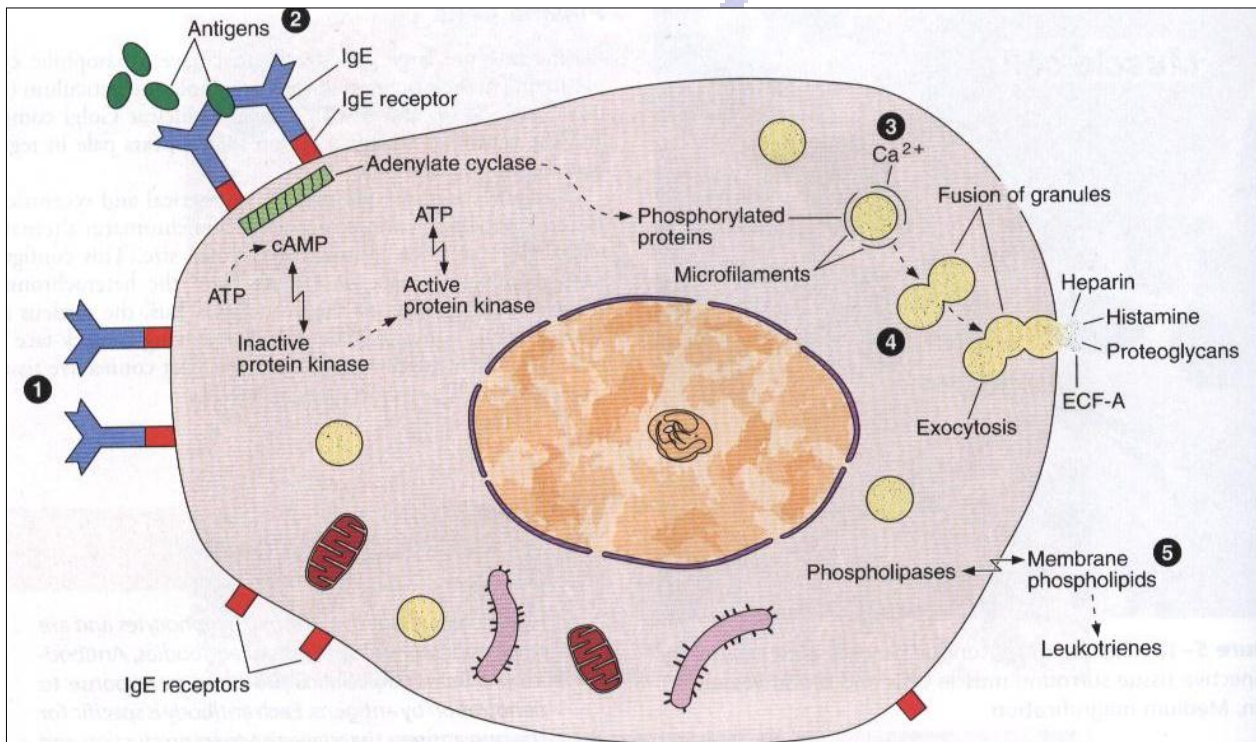
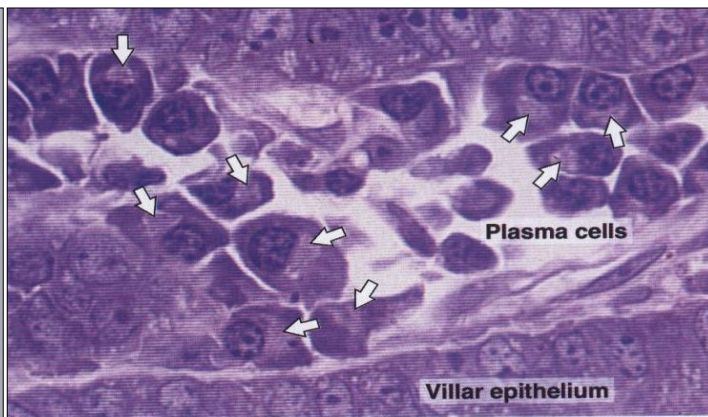


Figure 5-12. Mast cell secretion. (1) IgE molecules are bound to the surface receptors. (2) After a second exposure to an antigen (eg, bee venom), IgE molecules bound to surface receptors are cross-linked by the antigen. This activates adenylate cyclase and results in the phosphorylation of certain proteins. (3) At the same time, Ca²⁺ enters the cell. (4) These events lead to intracellular fusion of specific granules and exocytosis of their contents. (5) In addition, phospholipases act on membrane phospholipids to produce leukotrienes. The process of extrusion does not damage the cell, which remains viable and synthesizes new granules. ECF-A, eosinophil chemotactic factor of anaphylaxis.

Figure 5-13. Portion of a chronically inflamed intestinal villus. The plasma cells are characterized by their size and abundant basophilic cytoplasm (rough endoplasmic reticulum) and are involved in the synthesis of antibodies. A large Golgi complex (arrows) is where the terminal glycosylation of the antibodies (glycoproteins) occurs. Plasma cells produce antibodies of importance in immune reactions. PT stain. Medium magnification.



There are two populations of mast cells

1- Connective tissue mast cell

Is found in the skin & peritoneal cavity ; their granules contain the anticoagulant heparin.

2- Mucosal mast cell

Is present in intestinal mucosa and in the lungs ; their granules contain chondroitin sulfate .

Medical application

Release of the chemical mediators stored in mast cells promotes the allergic reaction known as Mediate hypersensitivity reactions.

The surface of mast cells contains specific receptors for immunoglobulin E (IgE), a type of immunoglobulin produced by plasma cells .Most IgE molecules are bound to the surface of mast cells and blood basophiles ;very few remain in the plasma.

Plasma cells

Are large cells ,have a basophilic cytoplasm due to their richness in R.E.R.The nucleus is spherical and eccentrically placed ,containing compact ,coarse heterochromatin alternating with lighter areas of approximately equal size .this configuration resembles the face of a clock .

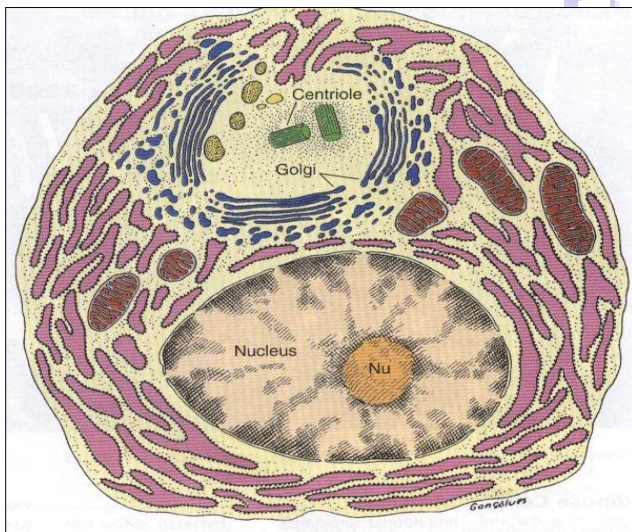


Figure 5-14. Ultrastructure of a plasma cell. The cell contains a well-developed rough endoplasmic reticulum, with dilated cisternae containing immunoglobulins (antibodies). In plasma cells, the secreted proteins do not aggregate into secretory granules. Nu, nucleolus. (Redrawn and reproduced, with permission, from Ham AW: *Histology*, 6th ed. Lippincott, 1969.)

Figure 5-15. Electron micrograph of a plasma cell showing an abundance of rough endoplasmic reticulum (R). Note that many cisternae are dilated. Four profiles of the Golgi complex (G) are observed near the nucleus (N). M, mitochondria. (Courtesy of PA Abrahamsohn.)

Medical application

They are responsible for the synthesis **of antibodies** is a glycoprotein that interacts specifically with an antigenic determinant.

antigens A molecule that is recognized by cells of the immune system **such as proteins, polysaccharides, and nucleoproteins**) or **molecules belonging to whole cells (bacteria, protozoa, tumor cells, or virus-infected cells)**.

The cells of the immune system do not recognize and react to the whole antigen molecule but instead react to small molecular domains of the antigen known **as antigenic determinants or epitopes**

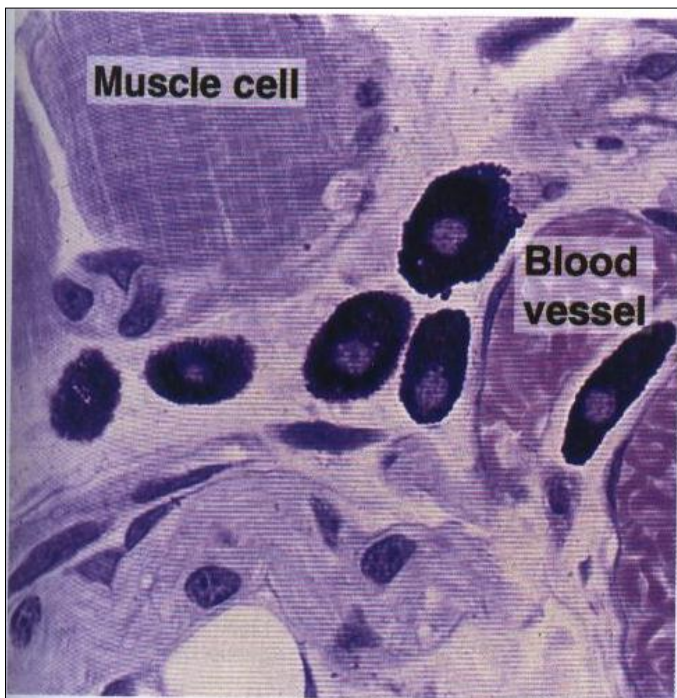


Figure 5-10. Section of rat tongue. Several mast cells in the connective tissue surround muscle cells and blood vessels. PT stain. Medium magnification.

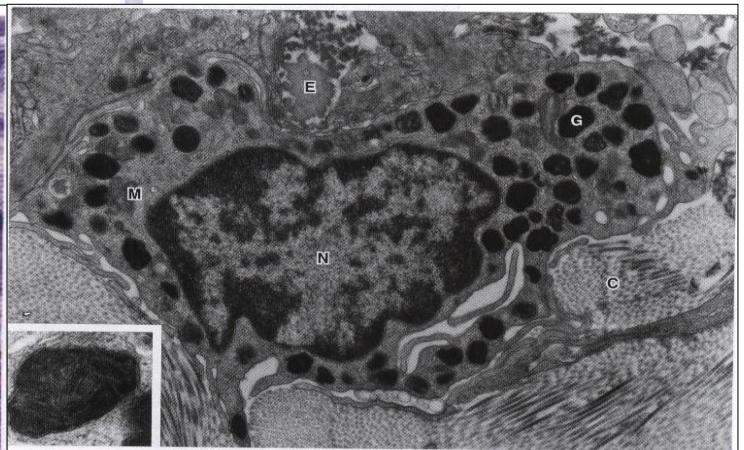
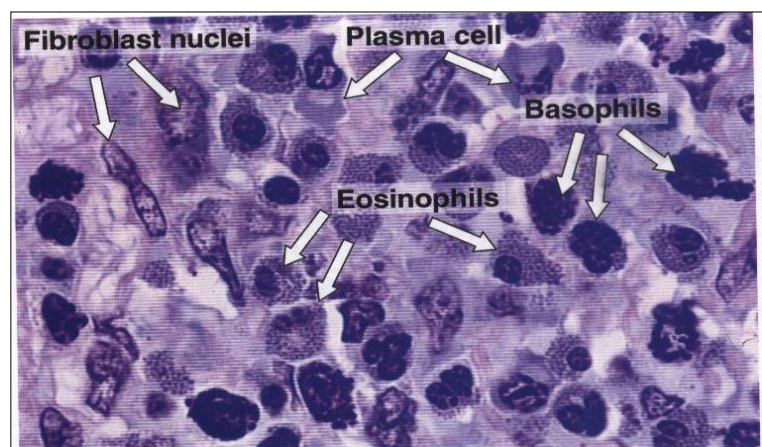


Figure 5-11. Electron micrograph of a human mast cell. The granules (G) contain heparin and histamine. Note the characteristic scroll-like structures within the granules. M, mitochondrion; C, collagen fibrils; E, elastic fibril; N, nucleus. $\times 14,700$. Inset: Higher magnification view of a mast cell granule. $\times 44,600$. (Courtesy of MC Williams.)

Figure 5-16. Section of an inflamed intestinal lamina propria. Inflammation was caused by nematode parasitism. Aggregated eosinophils and plasma cells function mainly in the connective tissue by modulating the inflammatory process. Giemsa stain. Low magnification.



Adipose Cells

Adipose cells (adipocytes; L. *adeps*, fat, + Gr. *kytos*) are connective tissue cells that have become specialized for storage of neutral fats or for the production of heat. Often called **fat cells**, they are discussed in detail in Chapter 6: Adipose Tissue.

Leukocytes

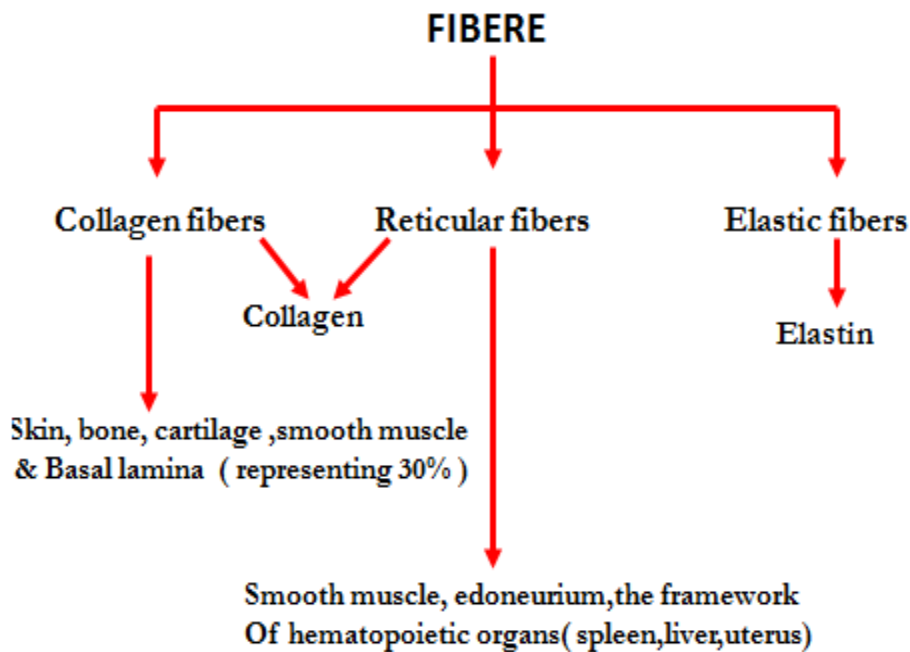
The normal connective tissue contains leukocytes that migrate from the blood vessels by diapedesis. Leukocytes (Gr. *leukos*, white, + *kytos*), or white blood corpuscles, are the wandering cells of the connective tissue. They migrate through the walls of capillaries and postcapillary venules from the blood to connective tissues by a process called **diapedesis**. This process increases greatly during inflammation (Figure 5–16). Inflammation is a vascular and cellular defensive reaction against foreign substances, in most cases pathogenic bacteria or irritating chemical substances. The classic signs of inflammation were first described by Celsus (first century A.D.) as redness and swelling with heat and pain (*rubor et tumor cum calore et dolore*). Much later, disturbed function (*functio laesa*) was added as the fifth cardinal sign.

Inflammation begins with the local release of **chemical mediators of inflammation**, substances of various origin (mainly from cells and blood plasma proteins) that induce some of the events characteristic of inflammation, eg, **increase of blood flow** and **vascular permeability, chemotaxis, and phagocytosis**.

Chemotaxis

Is the phenomena by which specific cell types are attracted by some molecules ,is responsible for the migration of large quantities of specific cell types to regions of inflammation .as leukocytes ,cross the venules and capillaries by **Diapedesis** ,invading the inflamed area.

□ Fibers of connective tissue



Collagen

Based on their structure and function ,they can be classified into the following groups:

- 1- Collagens that form fibers : They form structures such as bones ,dentin ,tendons ,organ capsules and dermis .
- 2- Fibrile-associated collagen : Short structures that bind collagen fibrils to one another and other components of extracellular matrix
- 3- Collagen that form networks : Assemble in a meshwork that constitutes the structural component of the basal lamina.
- 4- Collagen that form anchoring fibrils : Is present in anchoring fibrils that bind collagen fibers to the basal lamina

Collagen synthesis

- Fibroblast ,Chondroblast , Osteoblast , and Odontoblast producing collagen protein. The protein unit that form collagen fibrils is elongated molecule called **Tropocollagen** (280 nm in length and 1.5 nm in width) .Tropocollagen consist of three sub unit polypeptide chain intertwined in a triple helix

- Differences in chemical structure of these polypeptide chains are responsible for the various type of collagen

The transverse striations of collagen fibrils are determined by overlapping arrangement of the tropocollagen molecules

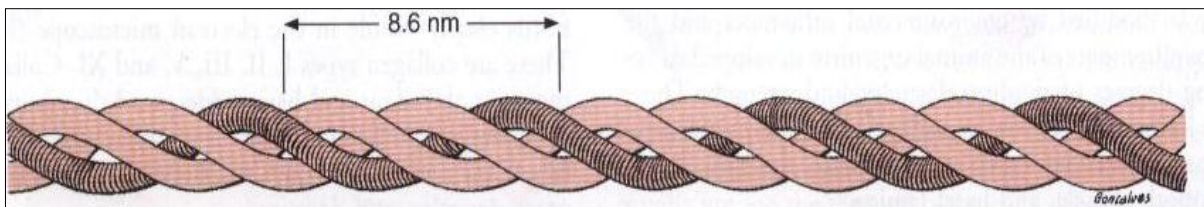
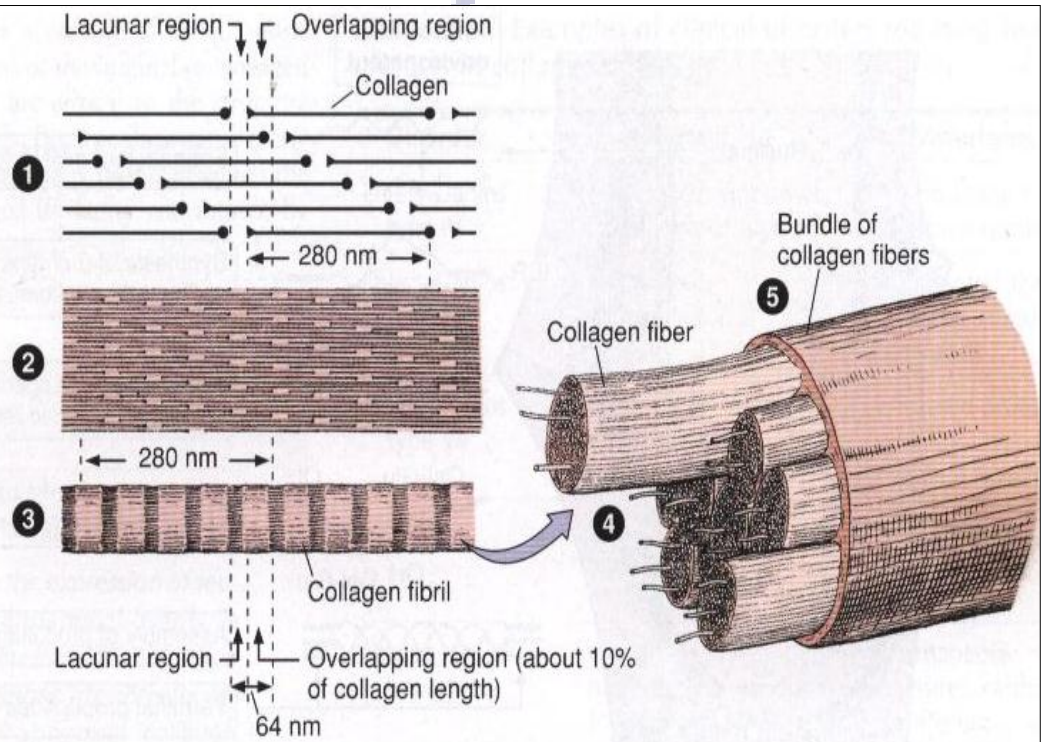


Figure 5-18. In the most abundant form of collagen, type I, each molecule (tropocollagen) is composed of two $\alpha 1$ and one $\alpha 2$ peptide chains, each with a molecular mass of approximately 100 kDa, intertwined in a right-handed helix and held together by hydrogen bonds and hydrophobic interactions. Each complete turn of the helix spans a distance of 8.6 nm. The length of each tropocollagen molecule is 280 nm, and its width is 1.5 nm.

Figure 5-19. Schematic drawing of an aggregate of collagen molecules, fibrils, fibers, and bundles. There is a stepwise overlapping arrangement of rodlike tropocollagen subunits, each measuring 280 nm (1). This arrangement results in the production of alternating lacunar and overlapping regions (2) that cause the cross-striations characteristic of collagen fibrils and confer a 64-nm periodicity of dark and light bands when the fibril is observed in the electron microscope (3). Fibrils aggregate to form fibers (4), which aggregate to form bundles (5) routinely called collagen fibers. Collagen type III usually does not form bundles.



Medical application

A large number of pathological conditions are directly attributable to insufficient or abnormal collagen synthesis

1- progressive systemic sclerosis: Result from an excessive accumulation of collagen (fibrosis) .It occurs in skin ,digestive tract muscle and kidney ,causing hardening and functional impairment of implicated organ

2- Keloid: Is a local swelling caused by abnormal amounts of collagen that form in scars of the skin ,especially in individuals of black African descent

Others disorders are illustrated in table 5-4.,

Table 5-4. Examples of clinical disorders resulting from defects in collagen synthesis.

Disorder	Defect	Symptoms
Ehlers-Danlos type IV	Faulty transcription or translation of type III	Aortic and/or intestinal rupture
Ehlers-Danlos type VI	Faulty lysine hydroxylation	Augmented skin elasticity, rupture of eyeball
Ehlers-Danlos type VII	Decrease in procollagen peptidase activity	Increased articular mobility, frequent luxation
Scurvy	Lack of vitamin C (cofactor for proline hydroxylase)	Ulceration of gums, hemorrhages
Osteogenesis imperfecta	Change of one nucleotide in genes for collagen type I	Spontaneous fractures, cardiac insufficiency

Reticular fibers

- They consist of collagen type III, in association with other types of collagen, glycoprotein and proteoglycans.
- Reticular fibers contain 6-12% hexoses. These fibers are called argyrophilic, because of their affinity for silver salts.
- They are formed by loosely packed, thin fibrils bound together by interfibrillar bridges. They are found in smooth muscle, endoneurium, and Hematopoietic organs.

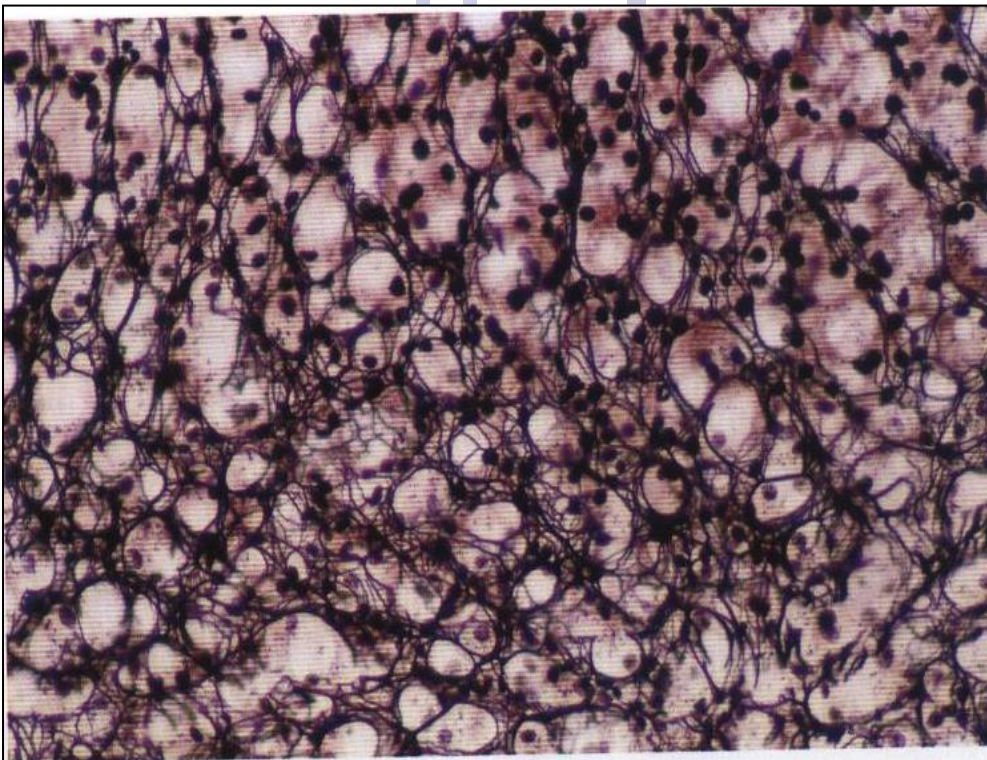
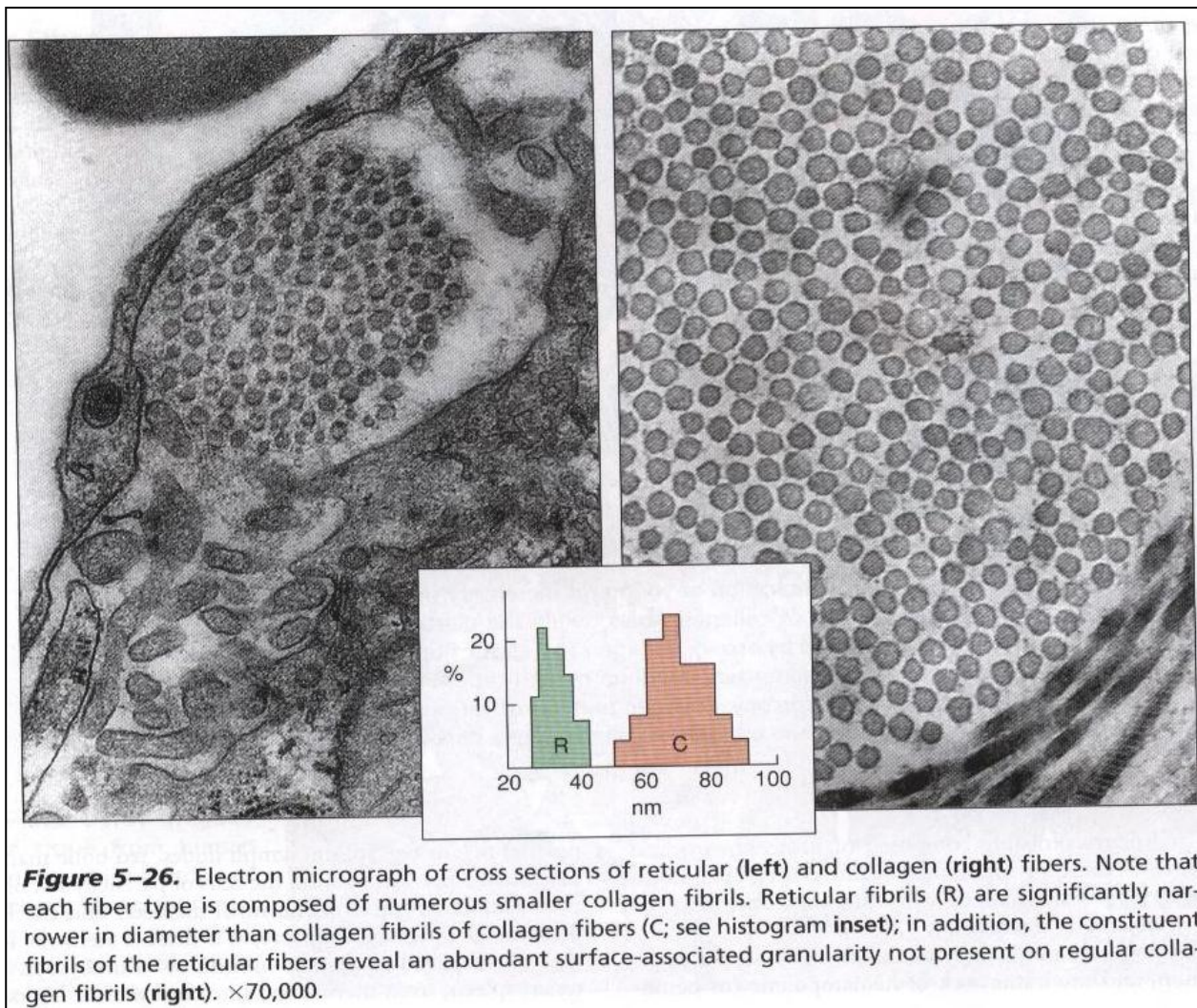


Figure 5-25. Section of an adrenal cortex, silver stained to show reticular fibers. This is a thick section made to emphasize the networks formed by these fibers, which consist of collagen type III. Nuclei are black, and cytoplasm is unstained. Medium magnification.



The elastic fiber system

I-Oxytalan fibers

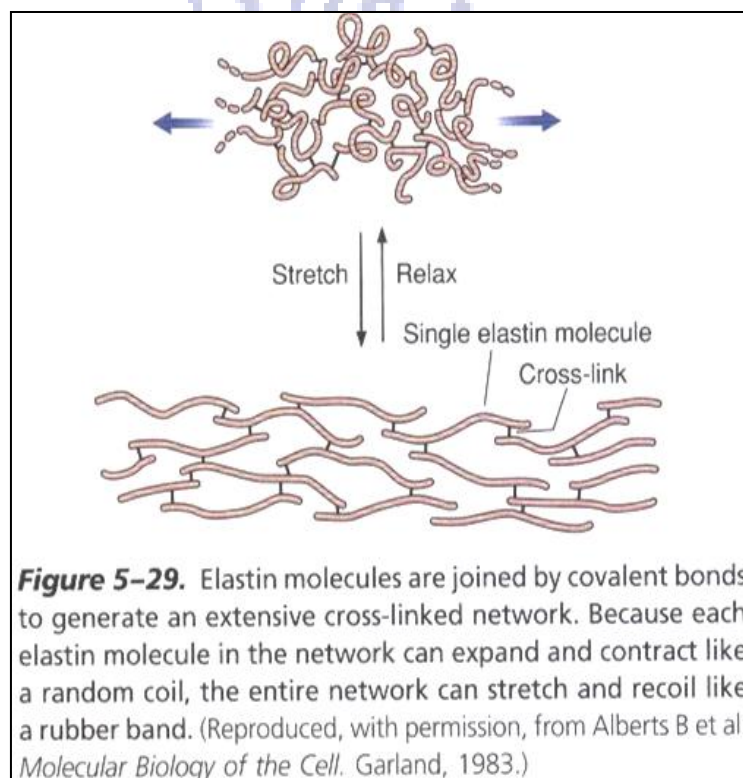
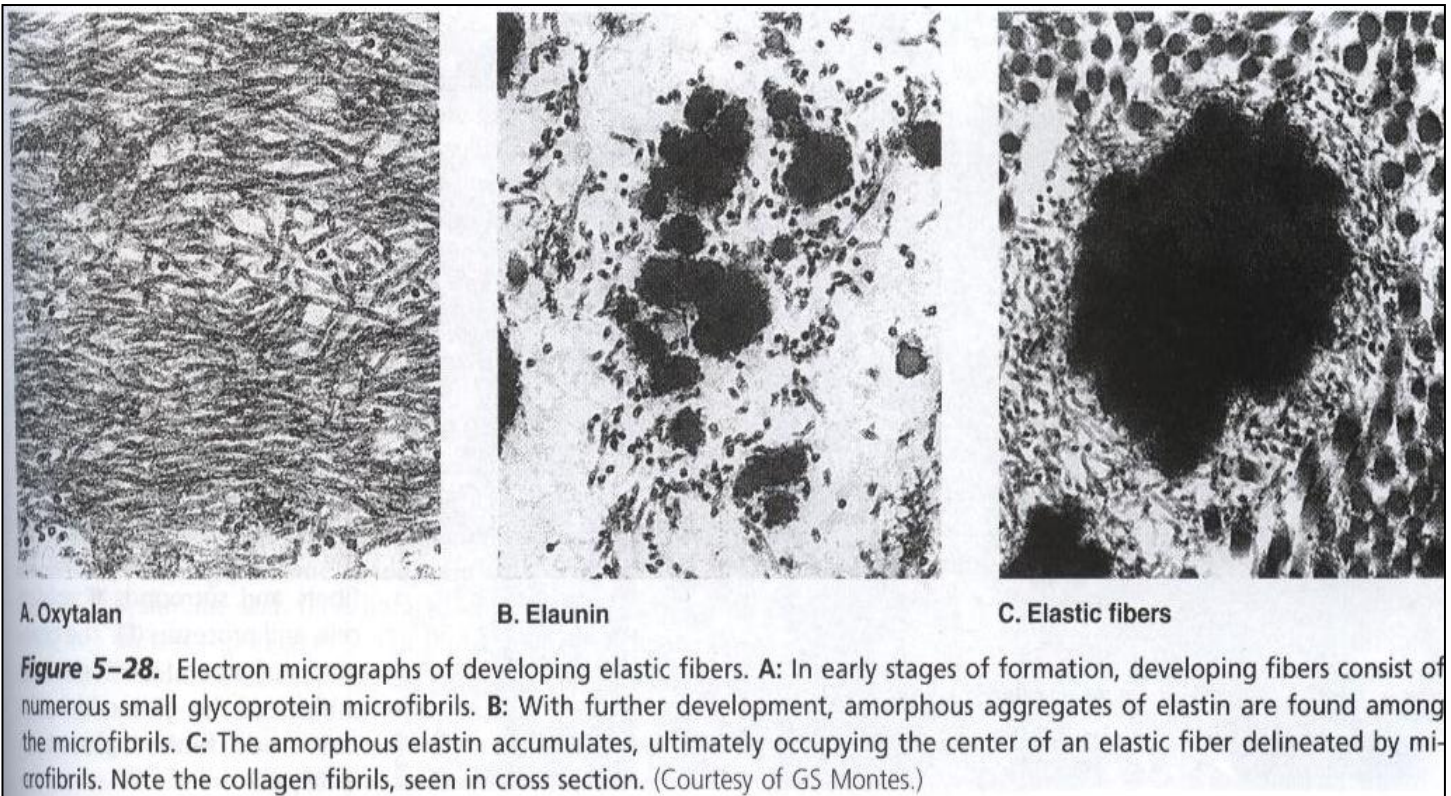
- 1- They are not elastic ,do not have elastin protein
- 2- Found in the zonule fibers of the eye & dermis.
- 3- They consist of a bundl of micro fibrils composed of glycoproteins, including fibromodulin & molecule fibrilin

II-Elaunin fibers

An irregular deposition of the protein Elastin, appear between the Oxytalan fibers ,forming Elaunin .They are found around sweat glands & in dermis .

III-Elastic fibers

Elastin gradually accumulates until it occupies the center of the fiber bundles, which are further surrounded by a thin sheath of micro fibrils .They are rich in protein elastin ,they stretch easily in response to tension



Medical application

Mutation in the fibrillin gene which is necessary for deposition of elastin result in MARFAN SYNDROM, a disease characterized by a lack of resistance in the tissues rich in elastic fibers . Because the large arteries are in components of elastic system and because the blood pressure is high in the aorta patients with disease often experience aortic rupture.

□ Ground substance

- Is a highly hydrated, colorless and transparent complex mixture of macromolecules. It fills the space between cells & fibers of connective tissue
- Act as both a lubricate & a barrier to penetration of invaders, because of its viscosity.

The ground substance: Is formed mainly of three classes of components;

1- glycosaminoglycan (GAG) 2- proteoglycan 3- multiadhesive glycoproteins



Figure 5-30. Electron micrograph showing the structural organization of the connective tissue matrix. The ground substance is a fine granular material that fills the spaces between the collagen (C) and elastic (E) fibers and surrounds fibroblast cells and processes (F). The granularity of ground substance is an artifact of the glutaraldehyde-tannic acid fixation procedure. $\times 100,000$.

Glycosaminoglycan (GAG)

- Are linear polysaccharides formed by repeating disaccharide unit usually composed of a uronic acid & a hexosamine. This linear chains (exception of hyaluronic acid) are bound covalently to protein core forming a proteoglycan molecule.

- These molecule are hydrophilic because of the abundance of hydroxyl, carboxyl & sulfat groups in the carbohydrate moiety.

Proteoglycans

Are composed of a core protein associated with the four main GAG s ; Dermatan sulfate ; Chondroitin sulfate ; Keratan sulfate ;& Heparan sulfate. They are distinguished by their molecular diversity and can be located in cytoplasmic granules such Heparin of mast cells, in the cell surface, and the extracellular matrix

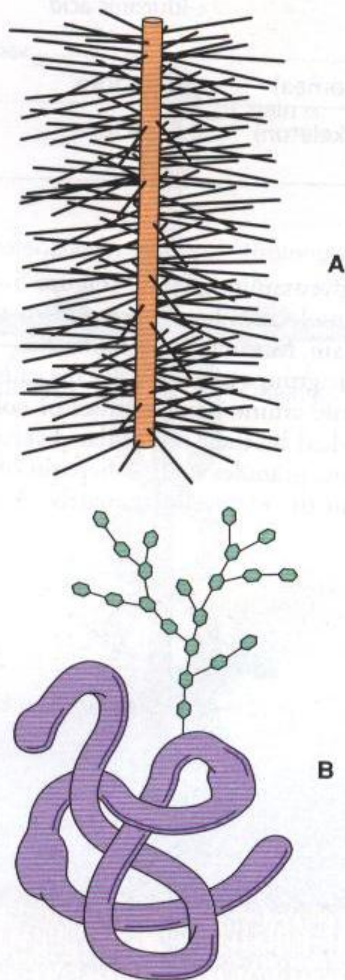


Figure 5-32. The molecular structure of proteoglycans and glycoproteins. **A:** Proteoglycans contain a core of protein (vertical rod in drawing) to which molecules of glycosaminoglycans (GAGs) are covalently bound. A GAG is an unbranched polysaccharide made up of repeating disaccharides; one component is an amino sugar and the other is uronic acid. Proteoglycans contain a greater amount of carbohydrate than do glycoproteins. **B:** Glycoproteins are globular protein molecules to which branched chains of monosaccharides are covalently attached. (Reproduced, with permission, from Junqueira LCU, Carneiro J: *Biologia Celular e Molecular*, 7th ed. Editora Guanabara Koogan, 2000.)

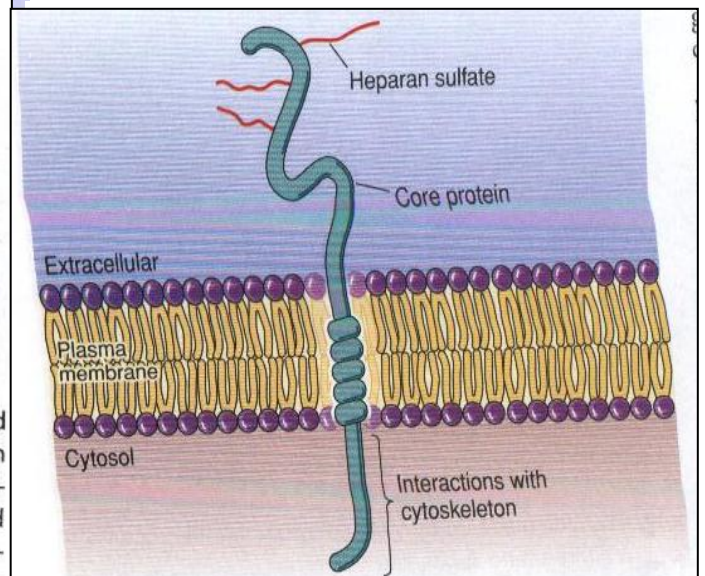


Figure 5-33. Schematic diagram of cell-surface syndecan proteoglycan. The core protein spans the plasma membrane through the cytoplasmic domain. The syndecan proteoglycans possess three heparan sulfate chains and sometimes chondroitin sulfate.

Proteoglycans functions

- 1- Structural components of the extracellular matrix .
- 2- Anchoring cells to the matrix .
- 3- Both extracellular & and surface proteoglycan also bind many protein growth factor .
- 4- Because of their viscosity , they are acted as barrier to the penetration of bacteria and others microorganism . Bacteria that produce hyaluronidase ,an enzyme that hydrolyzed hyaluronic acid and other glycosaminoglycan, have great invasive power because they reduce the viscosity of connective tissue ground substance

Multiadhesive glycoproteins

- Are compounds that contain a protein moiety to which carbohydrates are attached .
- 1- The protein moiety usually predominates and do not contain the linear polysaccharides
- 2- The carbohydrate moiety is frequently a branched structure .
- Glycoprotein has an important in the adhesion of cells to their substrate and interaction between neighboring adult and embryonic cells.

- Several glycoprotein have been isolated from connective tissues .

1- **Fibronectin** : Is a glycoprotein synthesized by fibroblasts and some epithelial cells. It has binding sites for cells ,collagen ,and GAG.

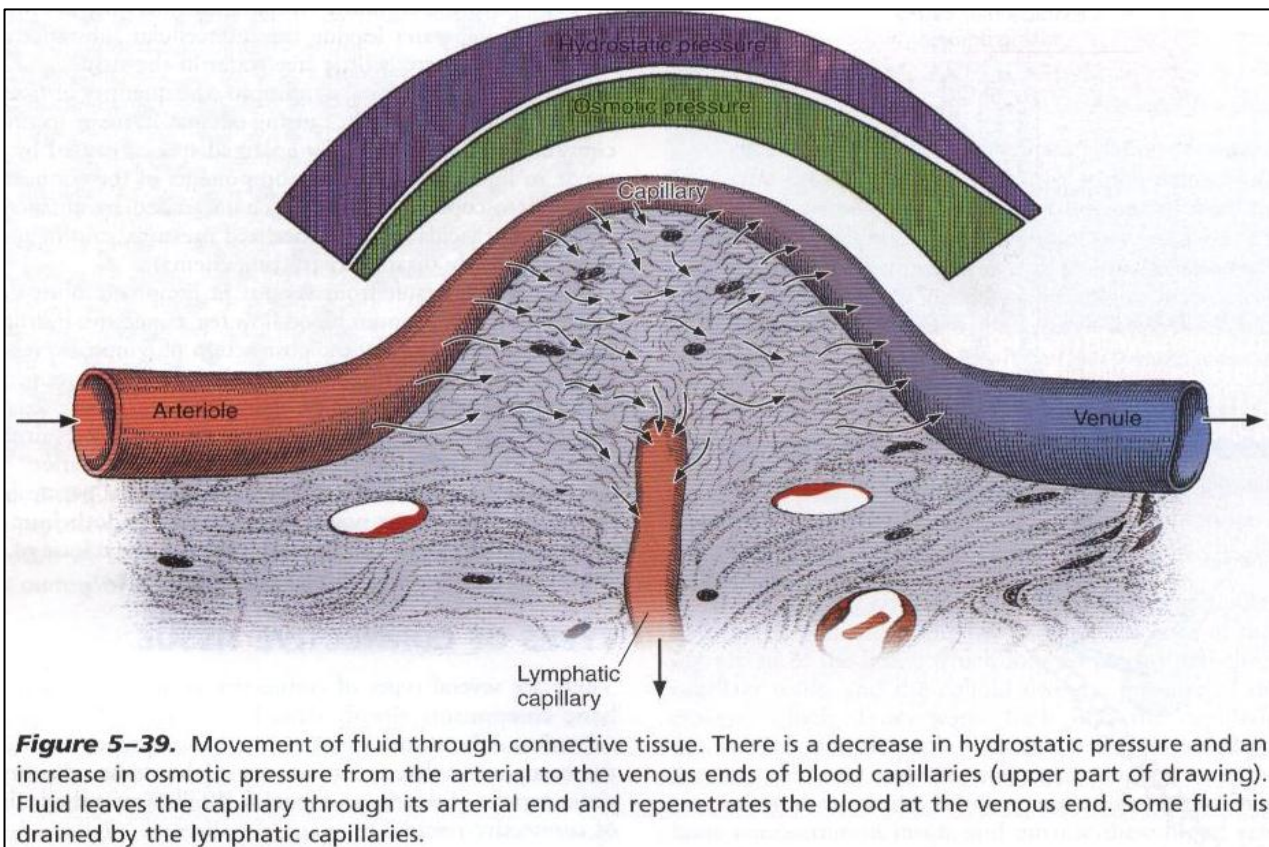
2- **Laminins** : Is a large glycoprotein that participates in the adhesion of epithelial cells to the basal lamina a structure rich in laminins

Medical application

- Both Fibronectin & Laminin participate in embryonic development and the increased ability of cancer cells to invade other tissues has been postulate
- In addition to ground substance ,there is a very small quantity of Tissue fluid –
- Which it is similar to blood plasma in it content ion and diffusible substances.
- In some pathological conditions ,the quantity of tissue fluid may increase ,causing
- **Edema** ,which characterized by enlarged spaces ,caused by the increased in liquid ,between the components of connective tissue .

Edema may result from

- 1- Venous or lymphatic obstruction .
- 2- Decrease in venous blood flow (eg. congestive heart failure)
- 3- Obstruction of lymphatic vessels due to parasitic plugs or tumor cells and chronic starvation.
- 4- Protein deficiency in a lack of plasma protein and a decrease in colloid pressure.
- 5- Increased permeability of the blood capillary or post capillary venule endothelium resulting from chemical or mechanical injury

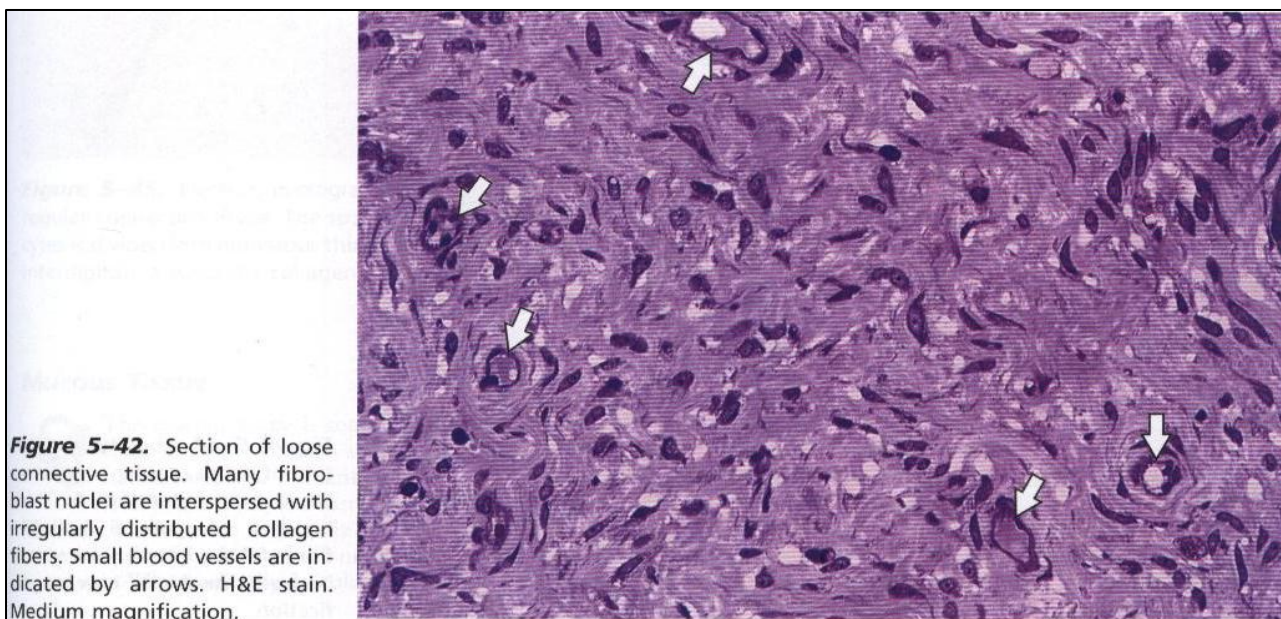


❖ Types of connective tissue

1- connective tissue proper

A- loose connective tissue

- 1- Supports many structures that are normally under pressure and low friction .
- 2- It fills spaces between groups of muscle cells .
- 3- Supports epithelial tissue .
- 4- Forms a layer that sheathes the lymphatic and blood vessels .
- 5- It is found in Papillary layer of the dermis , in the hypodermis , in glands & mucous membranes supporting to epithelial cells.



B- dense connective tissue

It adapted to offer resistance and protection ,it is the same components of loose c .t., .There are fewer cell and a clear predominance of collagen fibers .Is less flexible and far more resistant to stress than is loose c. t.

It is known as:

1- Dense irregular :

- The collagen fibers are arranged in bundles without a definite orientation .
- The collagen fibers form a three dimensional network .
- Provide resistance to stress from all directions .It is found in DERMIS.

2- Dense regular:

- The collagen fibers aligned with the linear orientation of fibroblasts .
- Provide resistance to stresses exerted in same direction

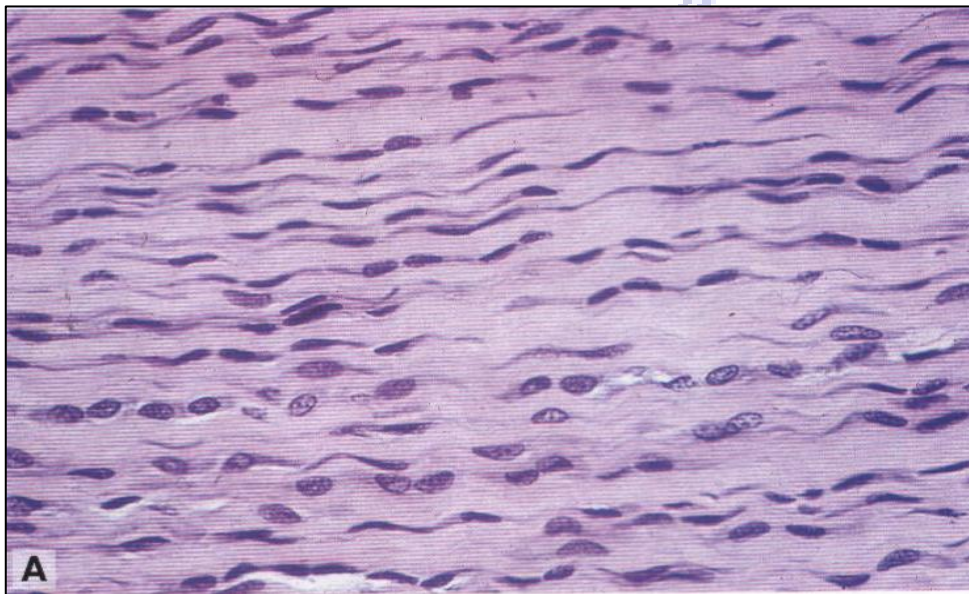


Figure 5-44. Longitudinal section of dense regular connective tissue from a tendon. **A:** Thick bundles of parallel collagen fibers fill the intercellular spaces between fibroblasts. Low magnification.

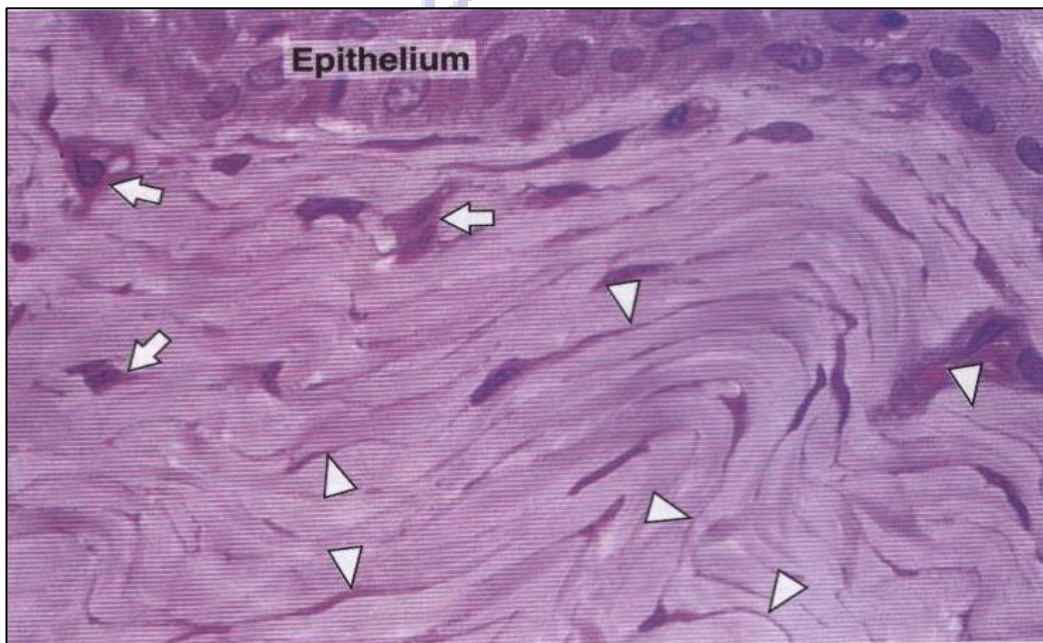
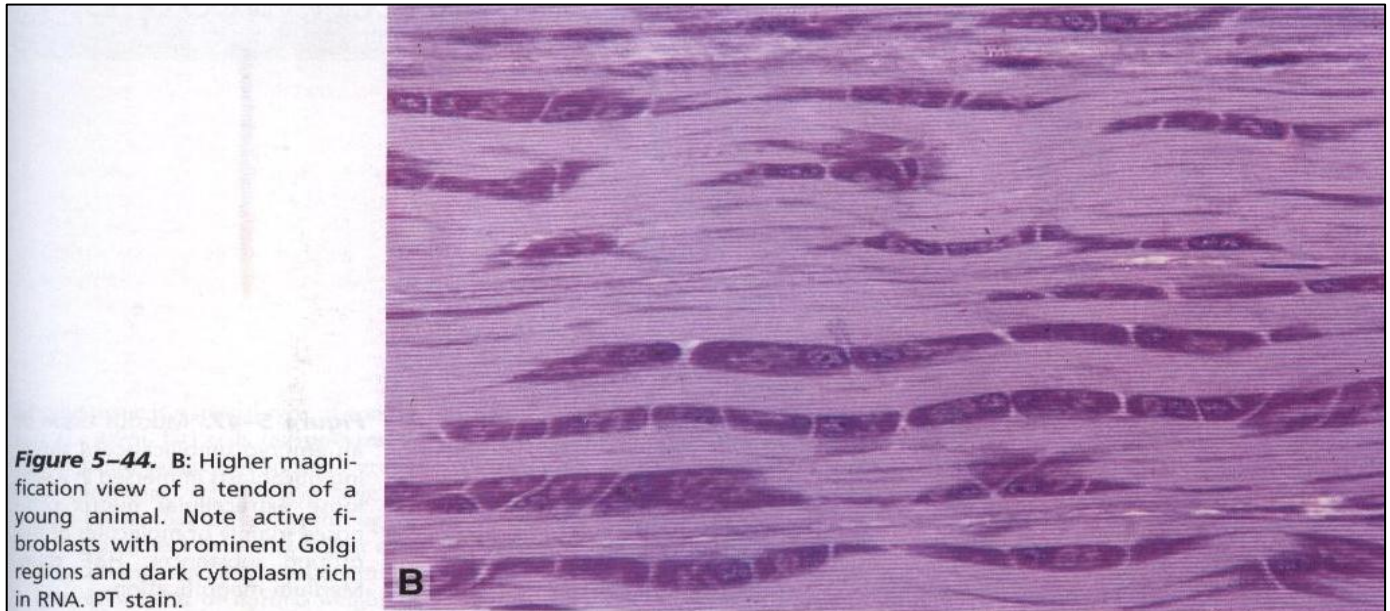


Figure 5-43. Section of immature dense irregular collagen tissue. This figure shows numerous fibroblasts (arrow) with many thin cytoplasmic extensions (arrowheads). As these cells are pressed by collagen fibers, the appearance of their cytoplasm depends on the section orientation; when the section is parallel to the cell surface, parts of the cytoplasm are visible. PT stain. Medium magnification.

Tendons are the most common example of dense regular C. T.

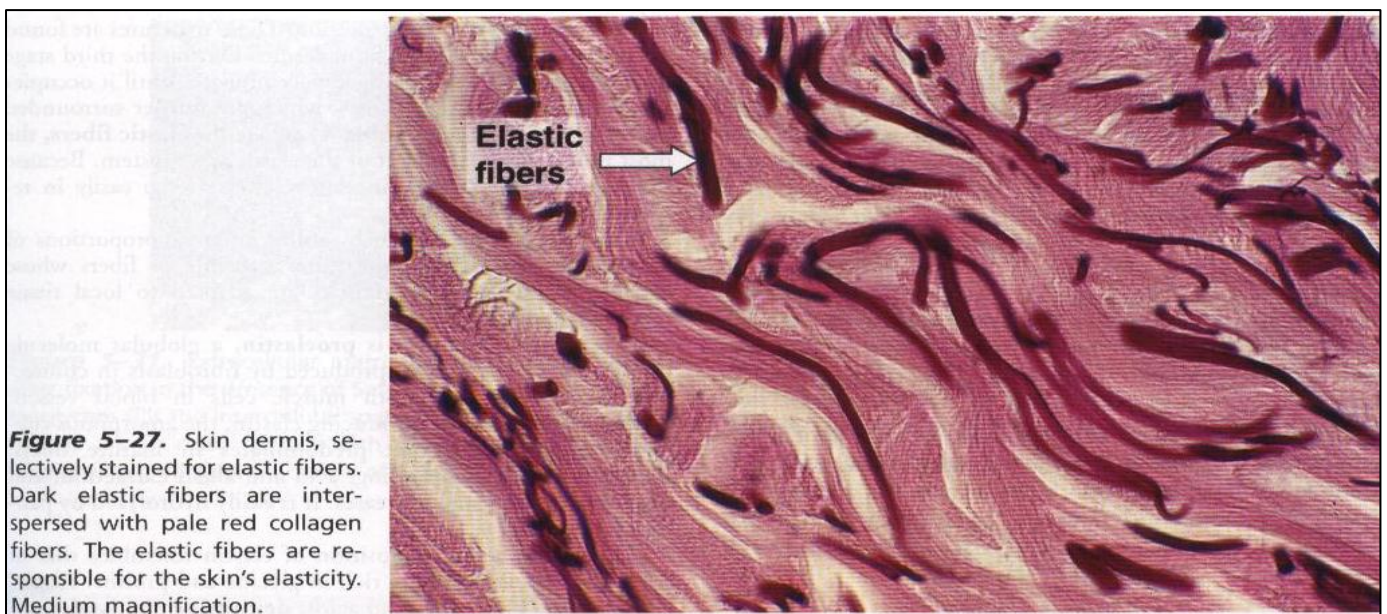
- 1- A re elongated cylindrical strictures attach striated muscle to bone .
- 2- They are white and inextensible .
- 3- They have parallel ,closely packed bundles of collagen.
- 4- Their fibroblasts contain elongated nuclei parallel to fibers.

The collagen bundles of the tendons (primary bundles) aggregate into larger bundles (secondary bundles) ,that are enveloped by loose connective tissue.



Elastic tissue

- Is composed of bundles of thick ,parallel elastic fibers ,between these fibers is occupied thin collagen fibers and flattened fibroblasts .
- It is yellow color , great elasticity .
- It is present in the yellow liquiments of the vertebral column.



Reticular tissue

- 1- It forms three dimensional networks that support cells .
 - 2- Specialized loose connective tissue consisting of reticular fibers associated with specialized fibroblasts called Reticular cells It forms three dimensional networks that support cells.
 - 3- Provides the architectural framework for hematopoietic organs & lymphoid organs (bone marrow ,lymph nodules ,and nodes and spleen)
- Reticular cells are dispersed along this framework and cover the reticular fibers and ground substance within cytoplasmic processes.

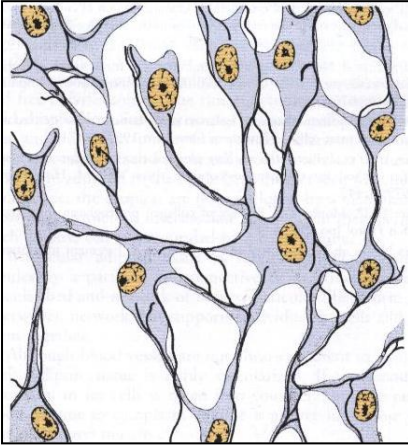


Figure 5-46. Reticular connective tissue showing only the attached cells and the fibers (free cells are not represented). Reticular fibers are enveloped by the cytoplasm of reticular cells; the fibers, however, are extracellular, being separated from the cytoplasm by the cell membrane. Within the sinus-like spaces, cells and tissue fluids of the organ are freely mobile.

Mucous tissue

- 1- It is found in **umbilical cord** Where it is referred to as **Wharton's jelly** & found in the pulp of young teeth.
- 2- Has an abundance of ground substance composed of hyaluronic acid .
- 3- It is a jelly tissue containing very few fibers .
- 4-The cells are mainly fibroblasts

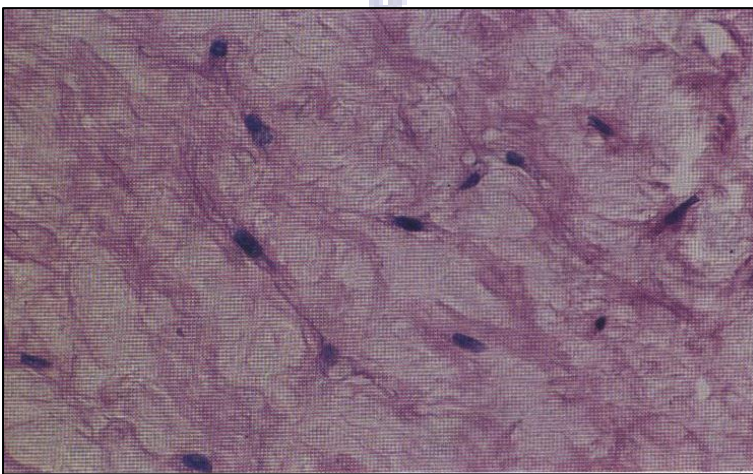


Figure 5-47. Mucous tissue of an embryo umbilical cord showing fibroblasts immersed in a very loose extracellular matrix composed mainly of molecules of the ground substances. H&E stain. Medium magnification.