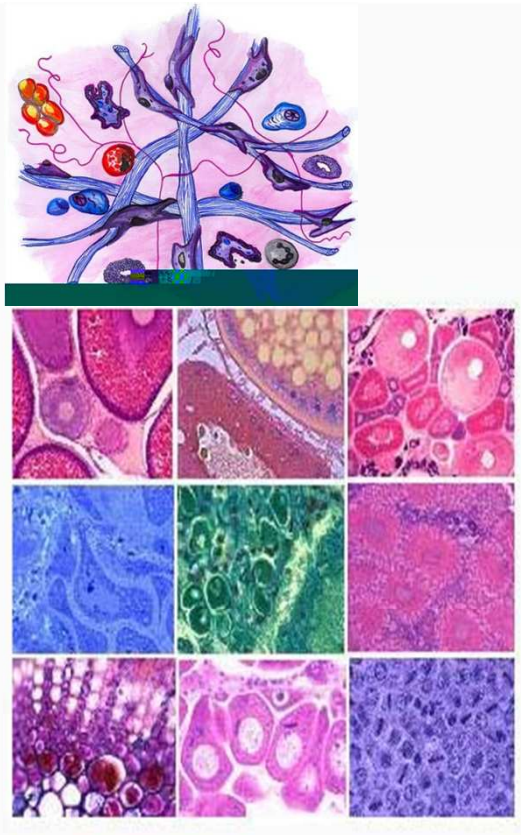
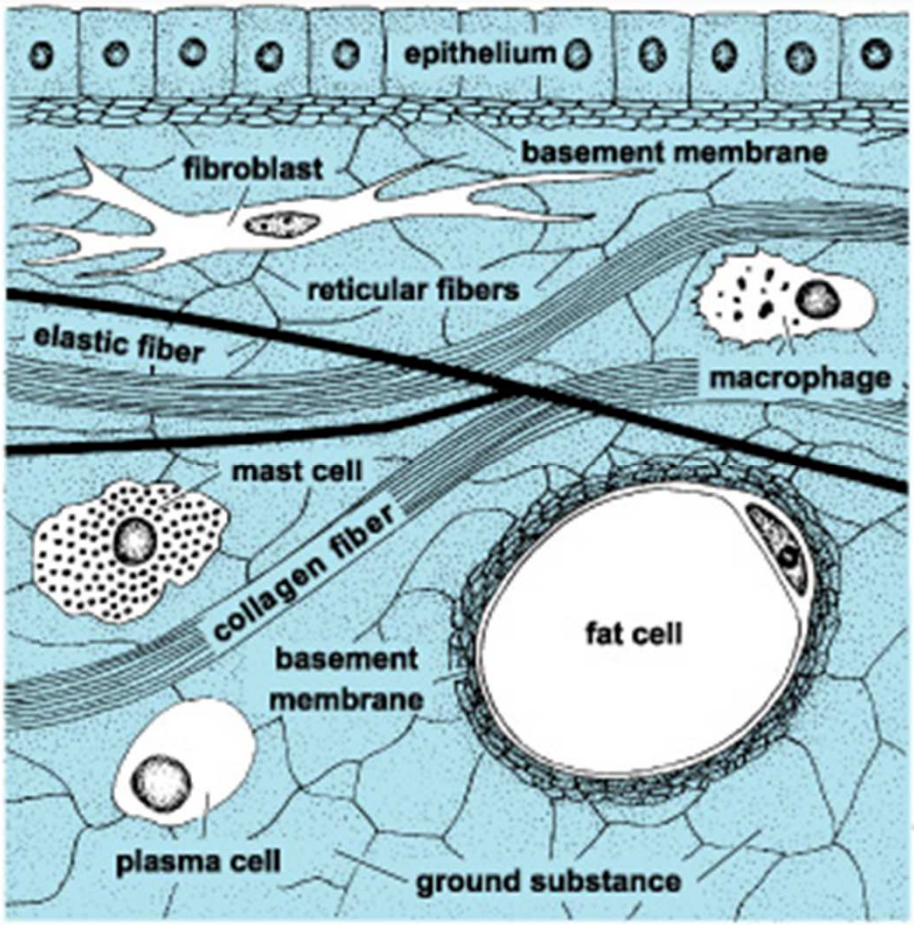


Connective tissue

1. Connective tissue – terminology and classification
2. Cells of the connective tissue
3. Extracellular matrix:
   - ✓ ground substance
   - ✓ protein fibers
4. Connective tissue proper:
   - ✓ loose connective tissue
   - ✓ dense connective tissue
     - ➢ regular
     - ➢ irregular
5. Mononuclear phagocyte system

- *Textus connectivus:*
  - ✓ cells of mesenchymal origin
  - ✓ extracellular matrix

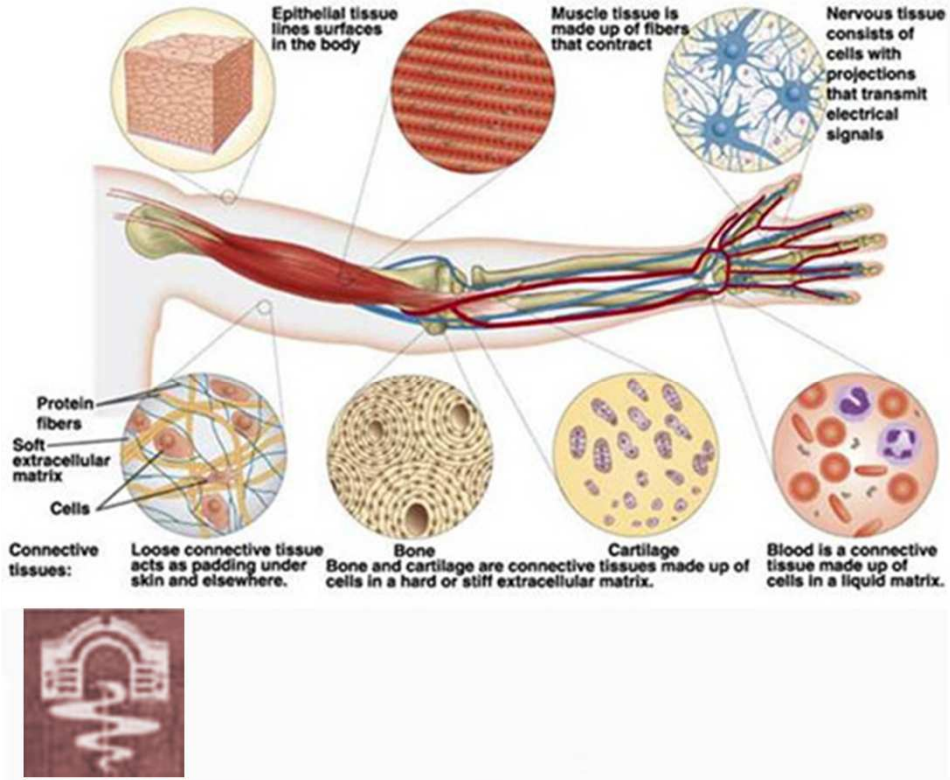
- connective tissue features:
  - ✓ interior location – never found at the surface
  - ✓ cellular polymorphism
  - ✓ abundant amounts of extracellular matrix – determines the species diversity
  - ✓ absence of cell polarity
  - ✓ high adaptive and regenerative capabilities
  - ✓ metaplastic abilities
  - ✓ specialized structures:
    - ➢ intracellular
    - ➢ extracellular

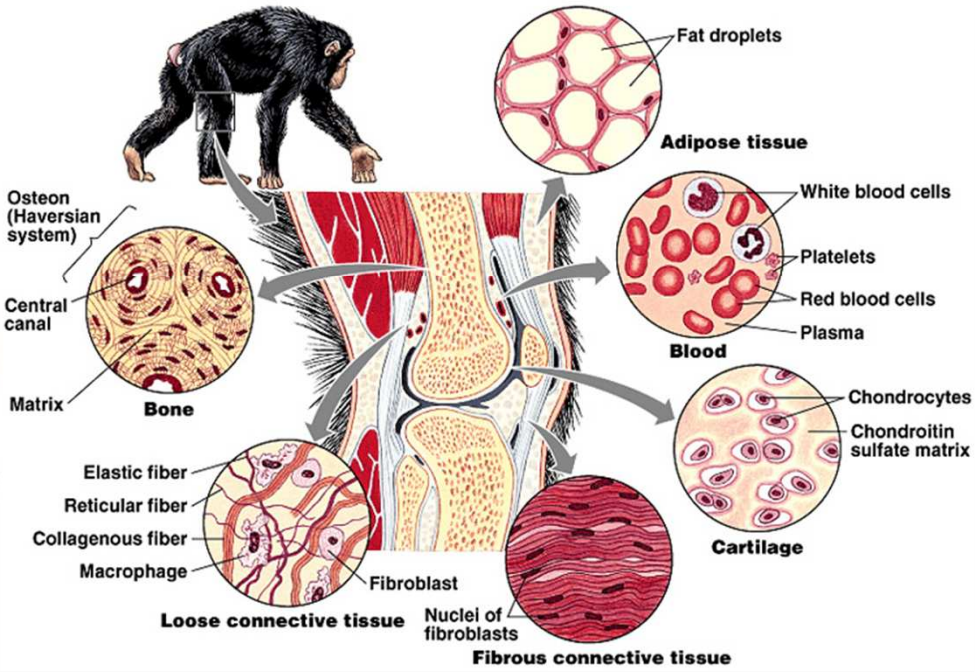


NB: most abundant of the basic tissues – ½ of the human body mass

Functions of connective tissue

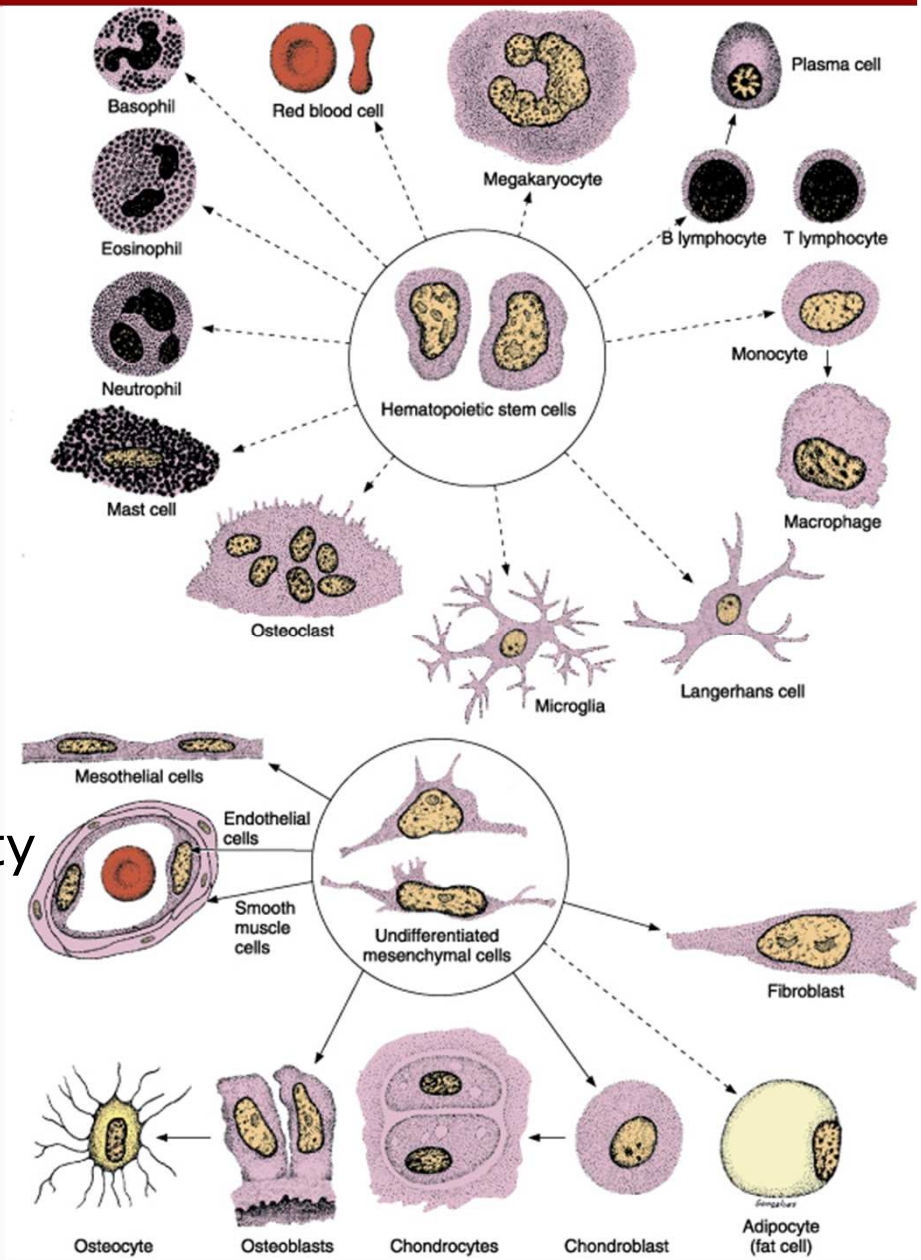
- ✓ binding together other tissues in the formation of organs – capsules
- ✓ structural support (mechanical role) – bones, ligaments and tendons
- ✓ nutritive role (homeostasis) – blood
- ✓ defensive functions (barrier and immunologic – antibodies)





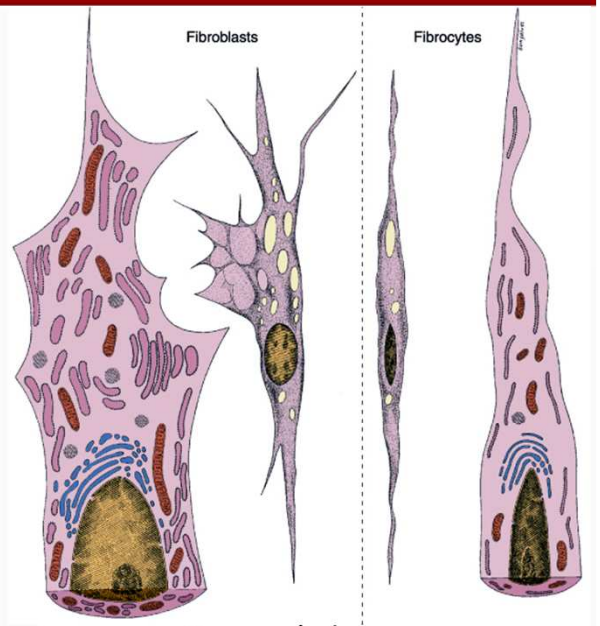
Cells of the connective tissue

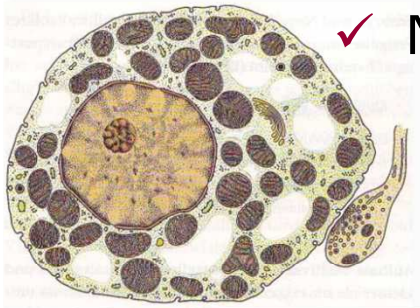
- ✓ productive and nutritive:
  - ➢ synthesize and secrete the extracellular matrix
  - ➢ regenerative and repair abilities
- ✓ defense cells:
  - ➢ motile and circulatory activity
- ✓ pigment cells:
  - ➢ presence of specialized structures

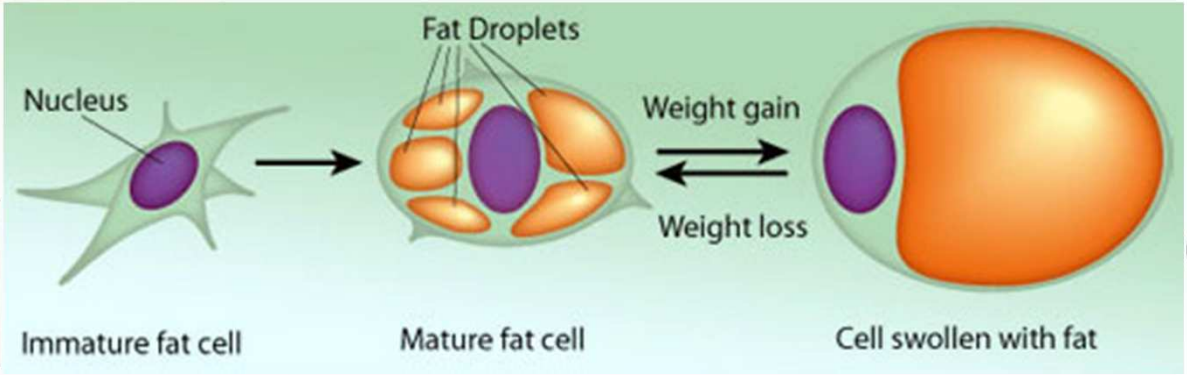


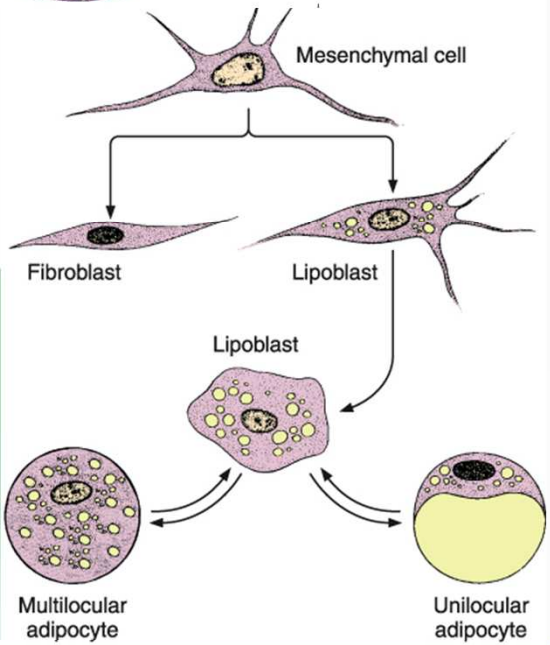
Productive and nutritive cells

- ✓ Productive cells:
  - ➢ fibroblasts, chondroblasts, osteoblasts, odontoblasts
  - ➢ fibrocytes, chondrocytes, osteocytes
- ✓ Undifferentiated mesenchymal cells – stem cells
- ✓ Nutritive cells:
  - ➢ lipocytes (adipocytes, fat cells)
    - unilocular
    - multilocular



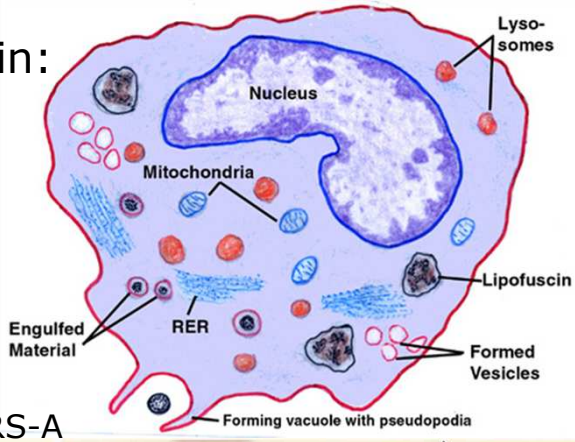


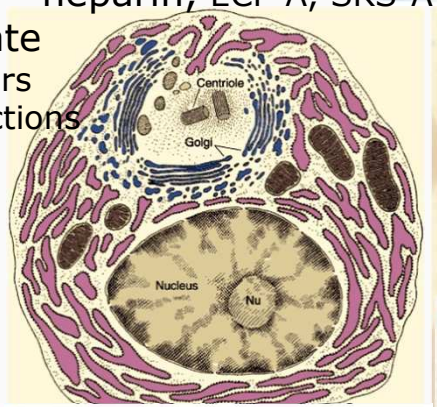


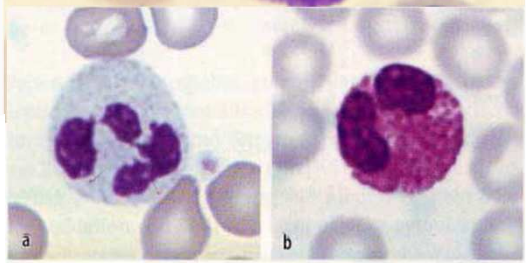


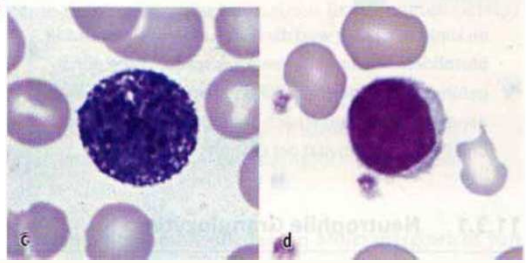
Defense cells

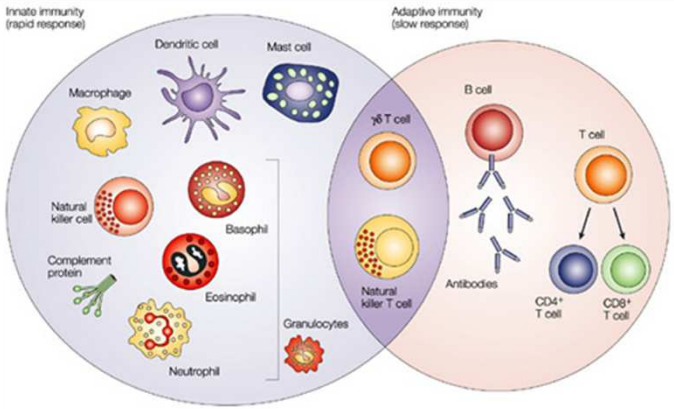
- ✓ macrophages (Gr. big eaters) – monocytic origin:
  - ➢ fixed (histiocytes) ⇨ tissue macrophages
  - ➢ migrated macrophages ⇨ dendritic cells
- ✓ plasma cells (plasmocytes) – differentiation from B-lymphocytes
  - ➢ produce antibodies (immunoglobulins)
- ✓ mast cells (mastocytes, Gr. *masto*, I feed) – metachromasia:
  - ➢ connective tissue mast cell – heparin, ECF-A, SRS-A
  - ➢ mucosal – chondroitin sulfate
  - ➢ primary and secondary mediators
  - ➢ immediate hypersensitivity reactions – anaphylactic shock
- ✓ blood cells:
  - ➢ granulocytes
    - neutrophilic – microphages
    - eosinophilic
    - basophilic
  - ➢ lymphocytes

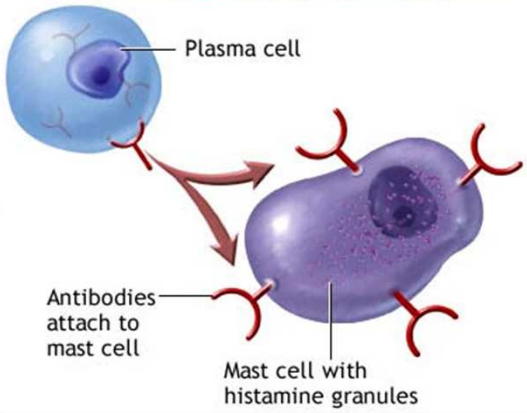






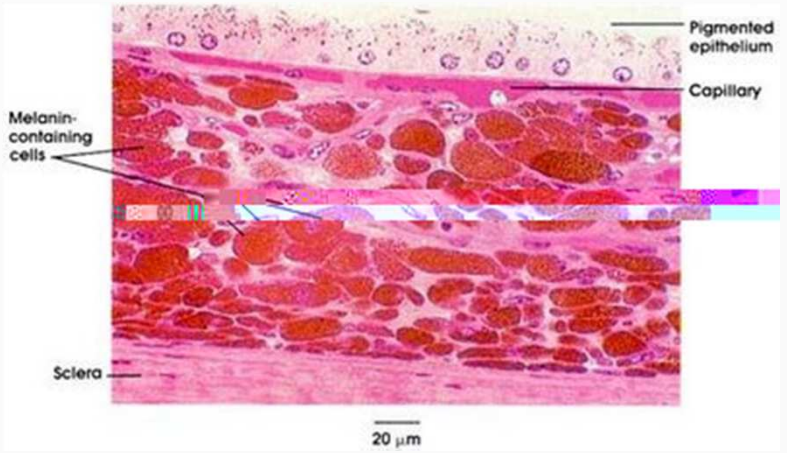


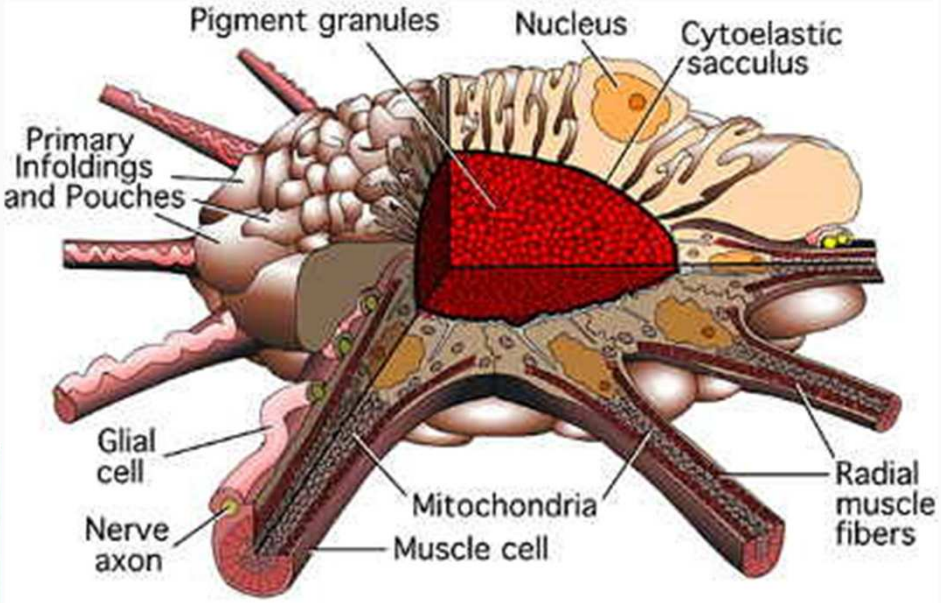


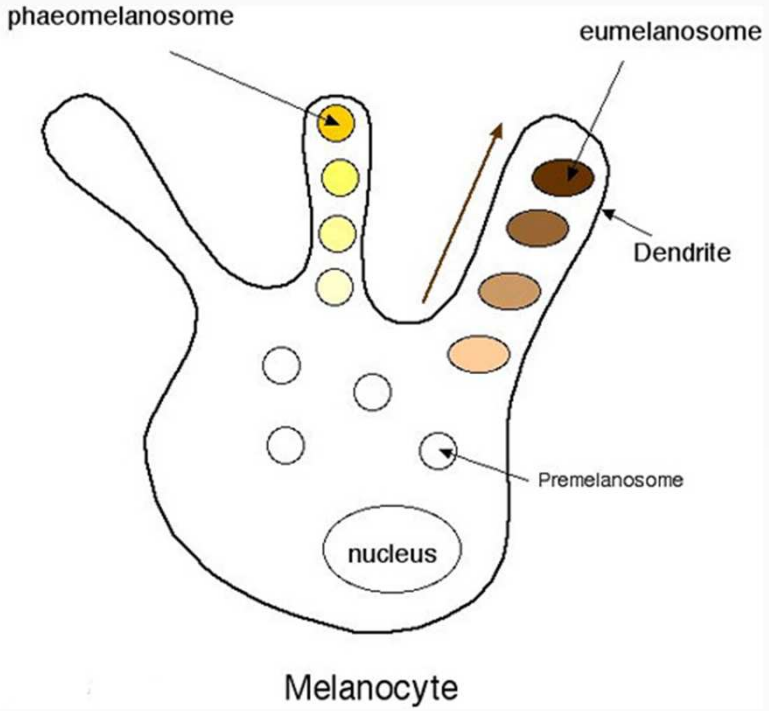


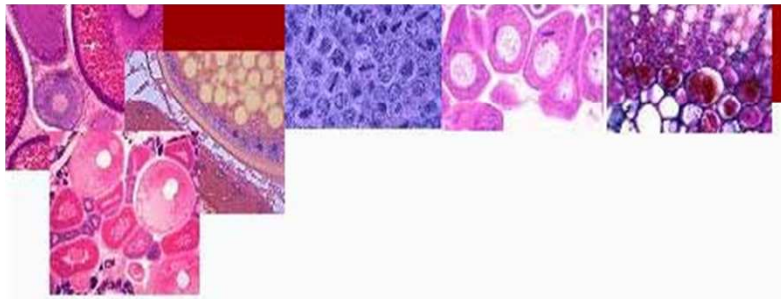
Pigment cells

- ✓ melanin-containing cells:
  - melanocytes – dermis, choroidea, meninges
  - melanophores – skin
- ✓ chromatophores:
  - chemosiderophores
  - lipochromophores









Functions of connective tissue cells

Connective tissue cells & functions

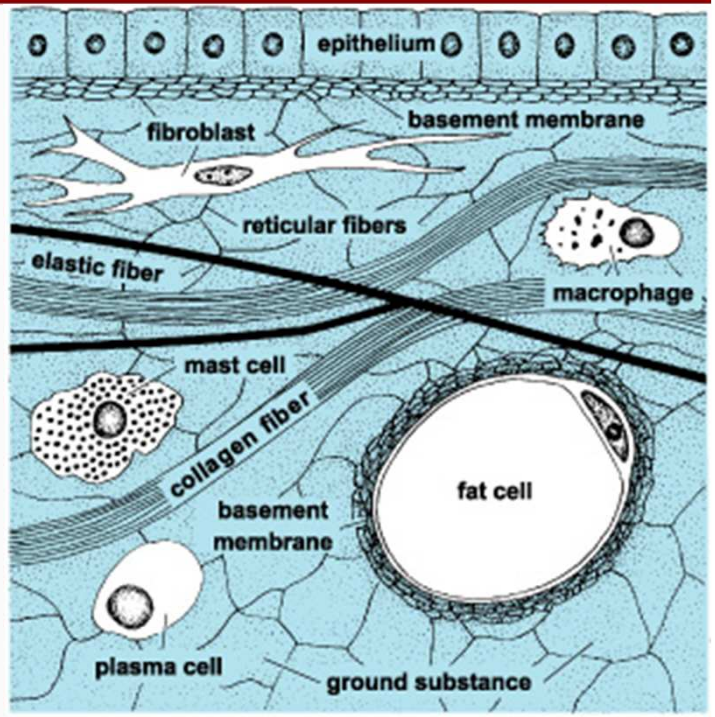
Fibroblast (res)	ECM production/structural
Macrophage	Phagocytosis/defense
Plasma cell	Antibody production/immuno
Mast cell	Chemical mediators/defense
Adipose cell (res)	Fat storage/energy, heat
White blood cells	Immuno & defense
lymphocyte, neutrophil, basophil, eosinophil (later lecture)	
Reticular cell* (res)	reticular fib/delicate support
Mesenchymal cell*(res)	precursor to CT, mainly embryo

Table 5–1. Functions of Connective Tissue Cells.

Cell Type	Representative Product or Activity	Representative Function
Fibroblast, chondroblast, osteoblast	Production of fibers and ground substance	Structural
Plasma cell	Production of antibodies	Immunological (defense)
Lymphocyte (several types)	Production of immunocompetent cells	Immunological (defense)
Eosinophilic leukocyte	Participation in allergic and vasoactive reactions, modulation of mast cell activities and the inflammatory process	Immunological (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)
Adipose (fat) cell	Storage of neutral fats	Energy reservoir, heat production

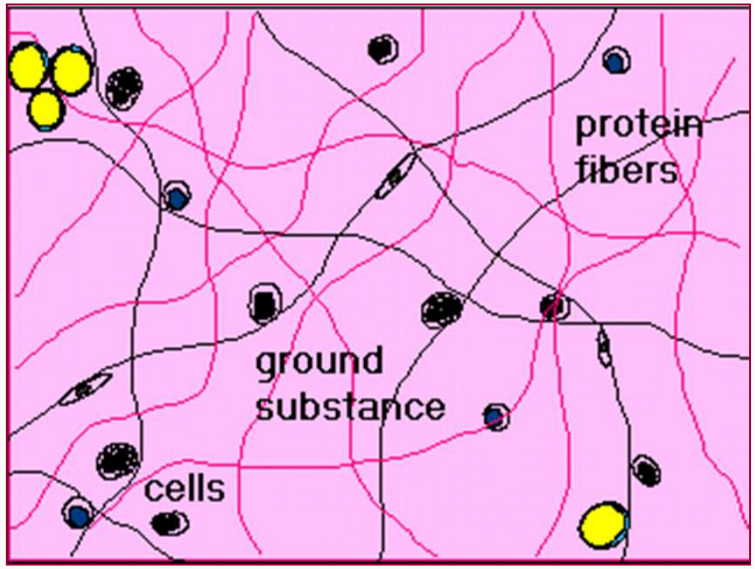
Extracellular matrix

- Extracellular matrix:
  - ✓ amorphous substance (ground substance, tissue fluid)
  - ✓ connective tissue fibers – protein fibers – types:
    - ➢ collagen fibers
    - ➢ elastic fibers
    - ➢ reticular fibers

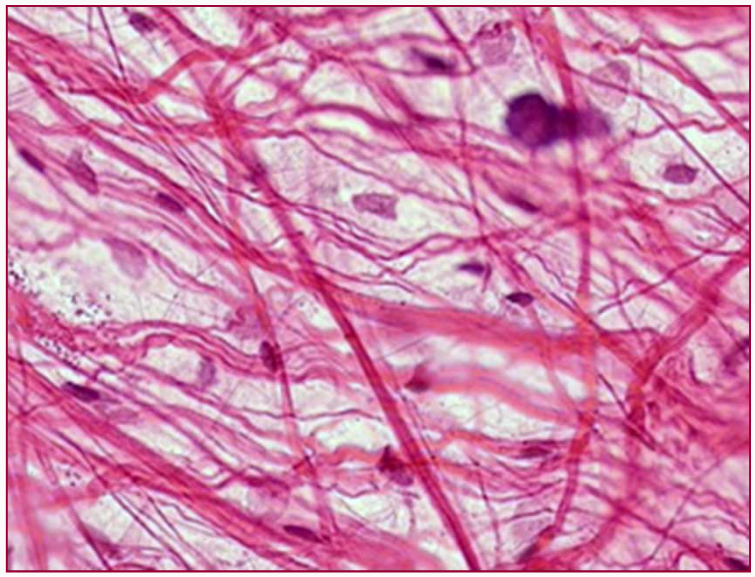


Amorphous intercellular substance

- ground substance – the non-cellular component of the matrix:
  - ✓ viscous, gel-like
  - ✓ highly hydrated
  - ✓ transparent
  - ✓ colorless complex mixture



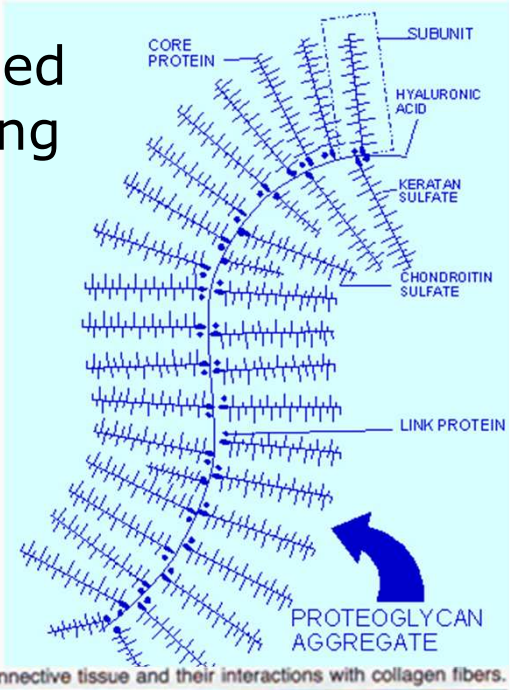
- molecular components:
  - ✓ **glycosaminoglycans** (acid mucopolysaccharides)
  - ✓ **proteoglycans**
  - ✓ structural **glycoproteins**



- tissue fluid

Ground substance

- glycosaminoglycans – long unbranched polysaccharides consisting of a repeating disaccharide unit:
  - ✓ non-sulfated – hyaluronic acid
  - ✓ sulfated:
    - heparan sulfate
    - chondroitin-4-sulfate
    - chondroitin-6-sulfate
    - dermatan sulfate
    - keratan sulfate



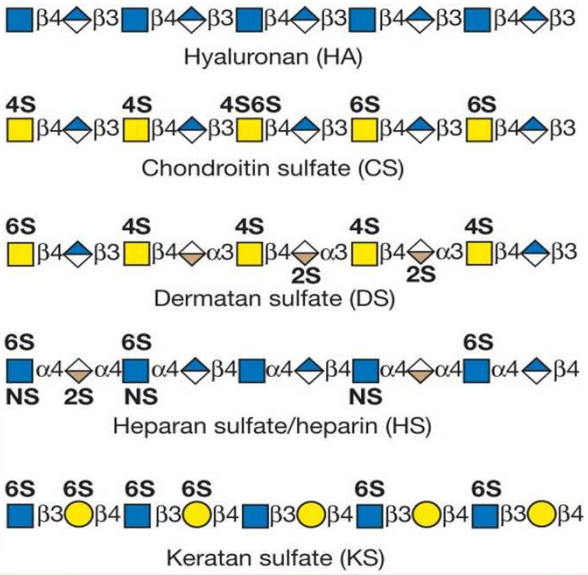
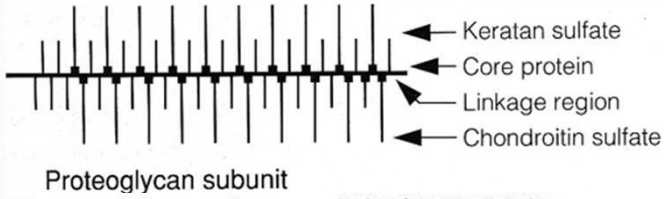


Table 5–1. Composition and distribution of glycosaminoglycans in connective tissue and their interactions with collagen fibers.

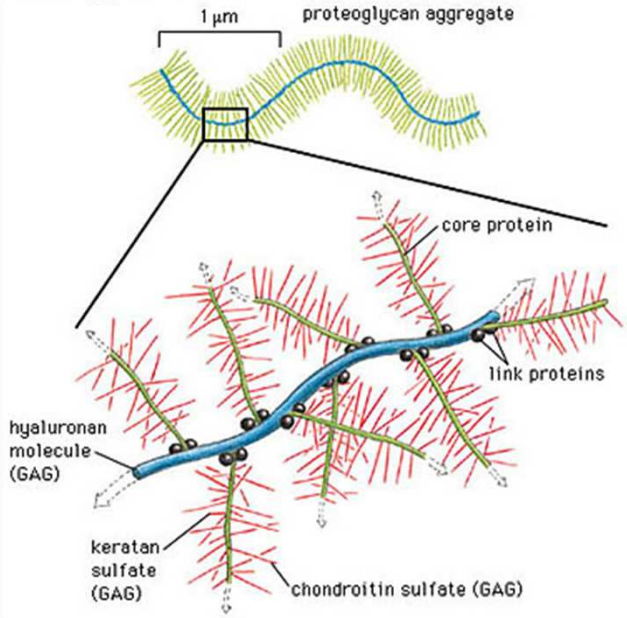
Glycosaminoglycan	Repeating Disaccharides		Distribution	Electrostatic Interaction with Collagen
	Hexuronic Acid	Hexosamine		
Hyaluronic acid	D-Glucuronic acid	D-Glucosamine	Umbilical cord, synovial fluid, vitreous humor, cartilage	. . .
Chondroitin 4-sulfate	D-Glucuronic acid	D-Galactosamine	Cartilage, bone, cornea, skin, notochord, aorta	High levels of interaction, mainly with collagen type II
Chondroitin 6-sulfate	D-Glucuronic acid	D-Galactosamine	Cartilage, umbilical cord, skin, aorta (media)	High levels of interaction, mainly with collagen type II
Dermatan sulfate	L-iduronic acid or D-glucoronic acid	D-Galactosamine	Skin, tendon, aorta (adventitia)	Low levels of interaction, mainly with collagen type I
Heparan sulfate	D-Glucuronic acid or L-iduronic acid	D-Galactosamine	Aorta, lung, liver, basal laminae	Intermediate levels of interaction, mainly with collagen types III and IV
Keratan sulfate (cornea)	D-Galactose	D-Galactosamine	Cornea	. . .
Keratan sulfate (skeleton)	D-Galactose	D-Glucosamine	Cartilage, nucleus pulposus, annulus fibrosus	. . .

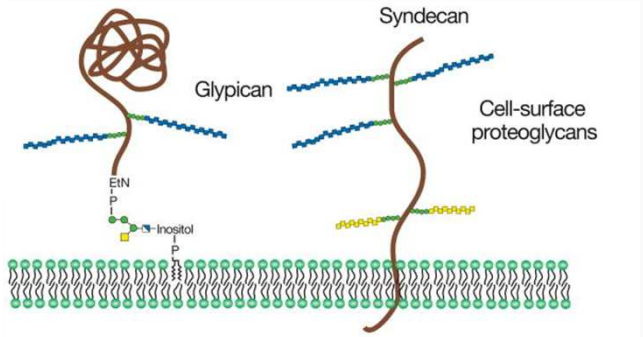
Ground substance

- proteoglycans – glycoproteins that are heavily glycosylated:
  - ✓ a core protein
  - ✓ one or more covalently attached glycosaminoglycan(s) – 80-90%:
    - ➢ heparan sulfate
    - ➢ chondroitin-4-sulfate
    - ➢ chondroitin-6-sulfate
    - ➢ dermatan sulfate
    - ➢ keratan sulfate

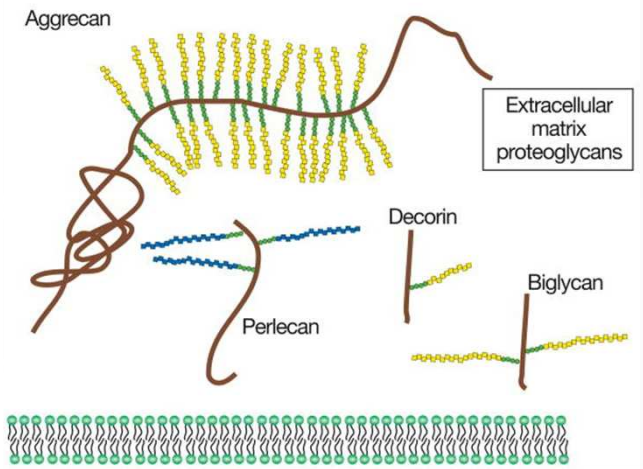


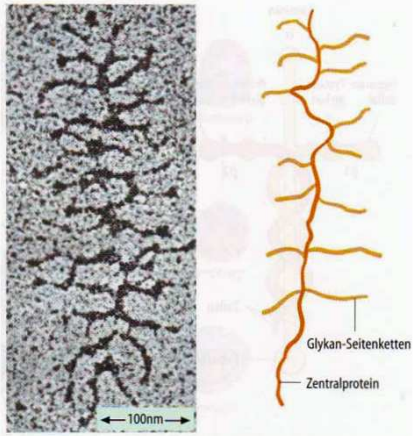
Proteoglycan subunit





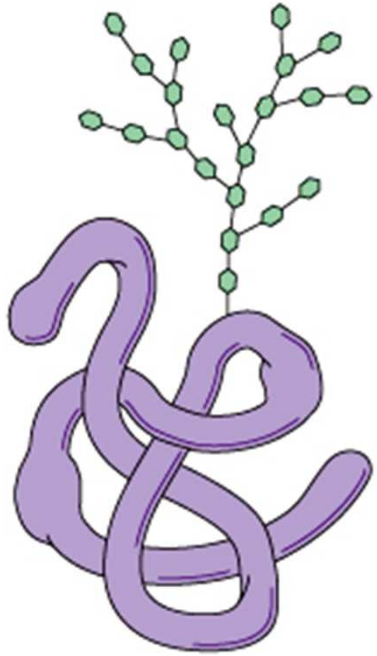
- extracellular matrix proteoglycans:
  - ✓ aggrecan
  - ✓ perlecan
  - ✓ decorin
  - ✓ biglycan
- cell-surface proteoglycans:
  - ✓ syndecan
  - ✓ fibroglycan
  - ✓ glypican

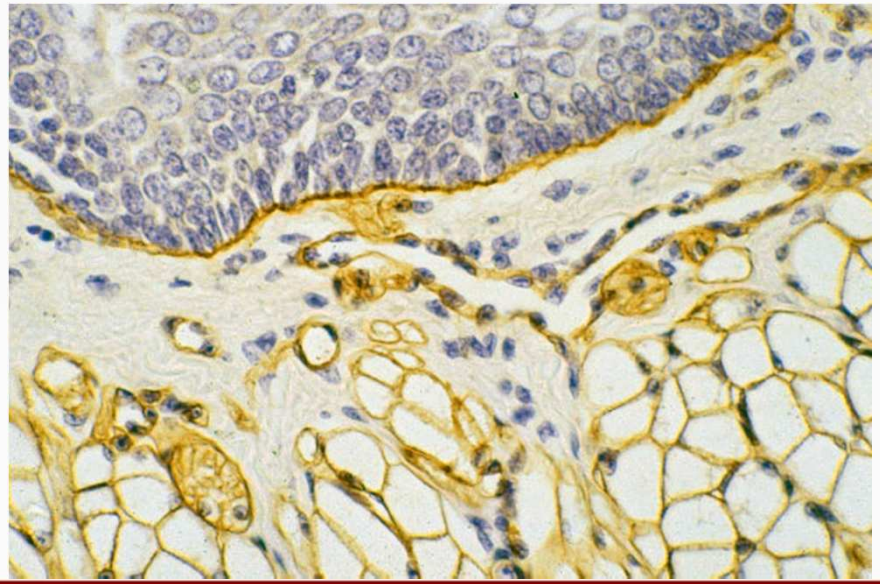


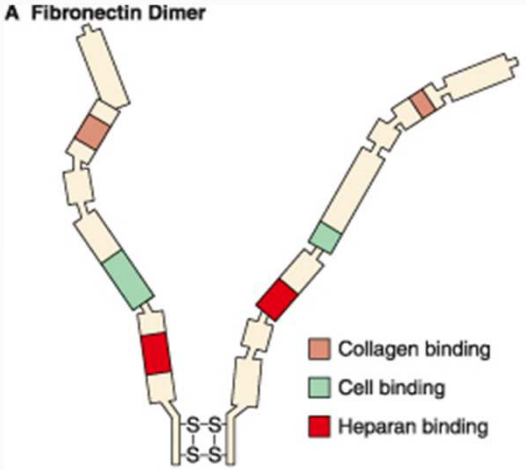


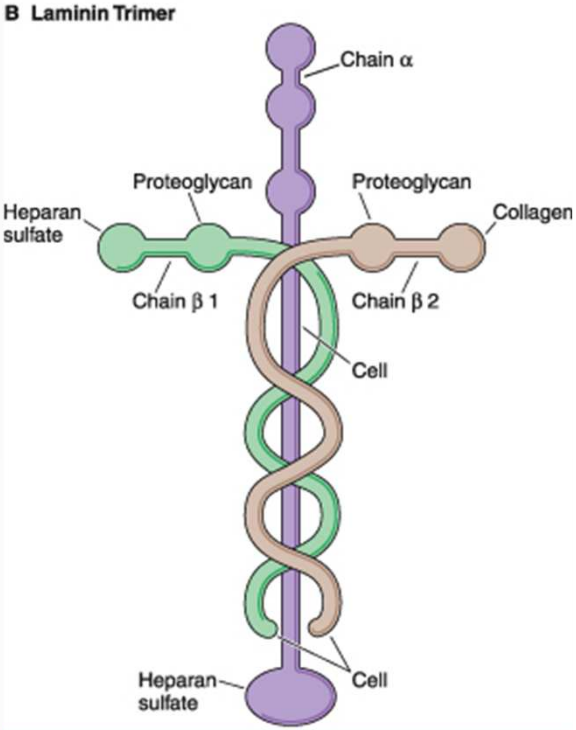
Ground substance

- multiadhesive glycoproteins – proteins that contain oligosaccharide chains (glycans) covalently attached to polypeptide side-chains:
  - ✓ a protein moiety – predominant
  - ✓ attached carbohydrate
    - ➢ fibronectin (Lat. *fibra,* fiber + *nexus,* interconnection)
    - ➢ chondronectin
    - ➢ laminin



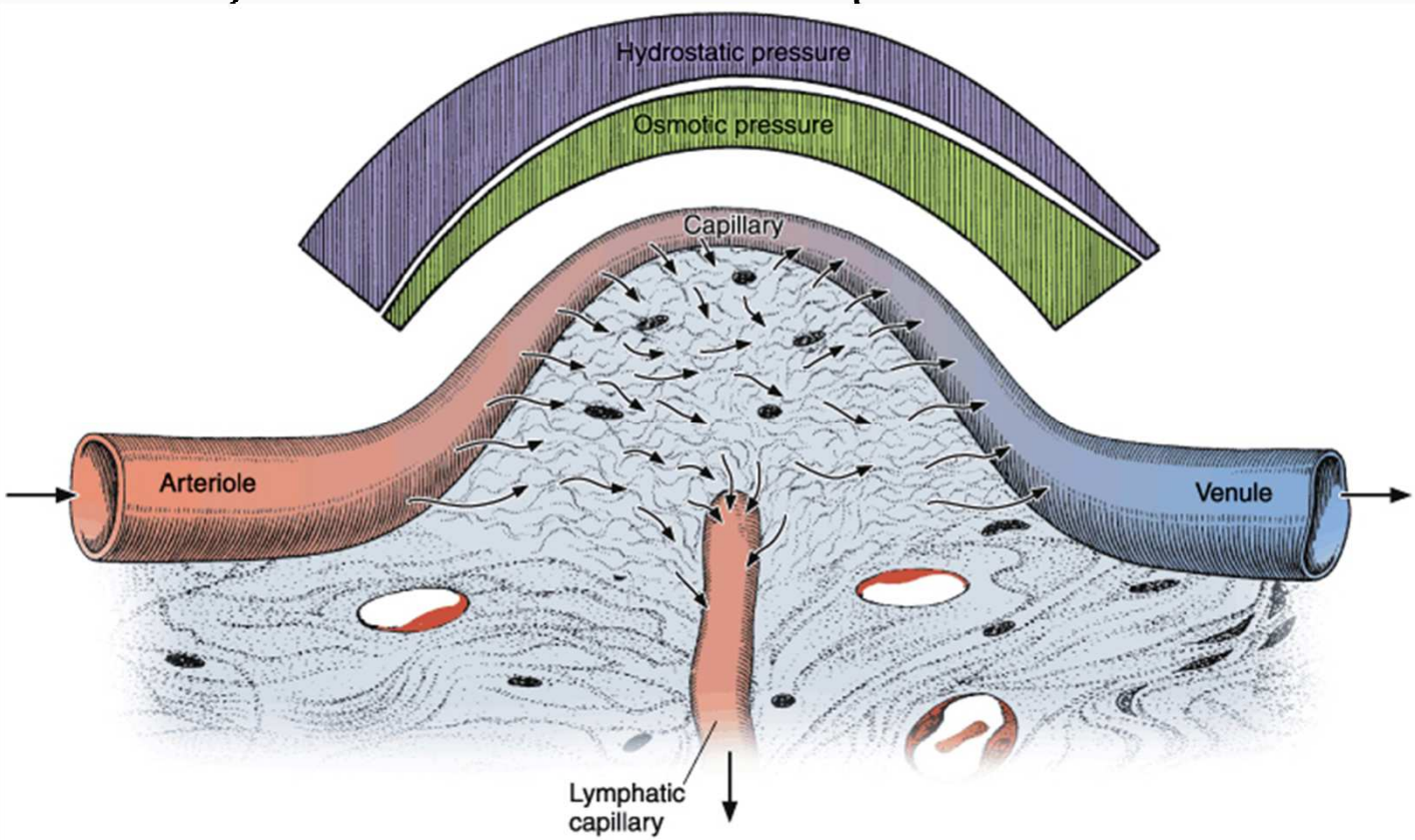






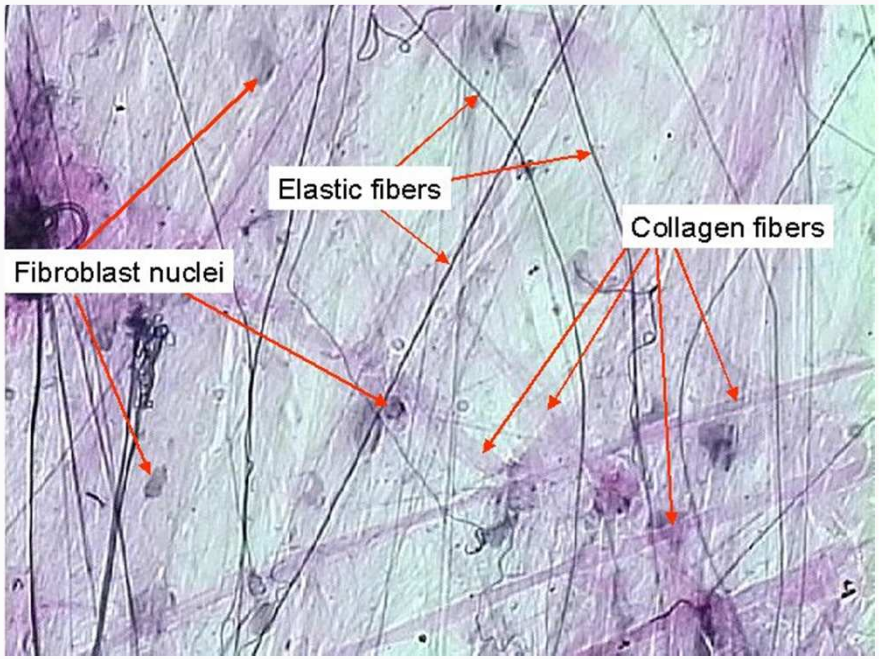
Tissue fluid

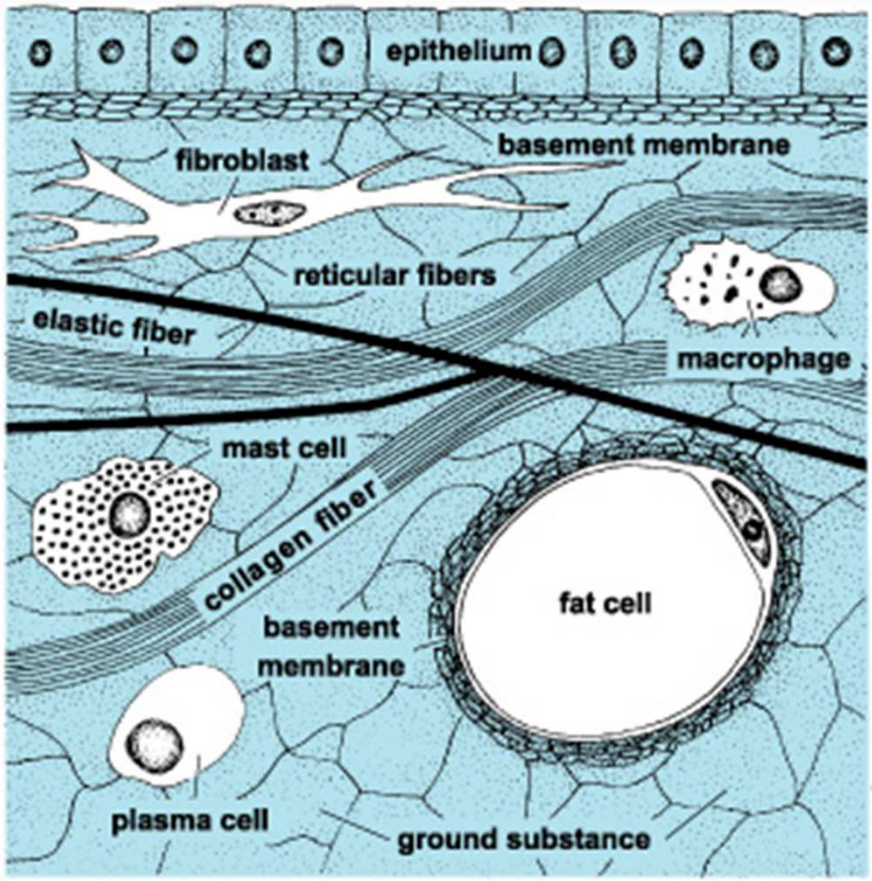
- tissue fluid – 10-12 l (60-70% of the matrix):
  - ✓ similar to blood plasma
  - ✓ contains:
    - ➢ plasma proteins of low molecular weight
    - ➢ ions and diffusible substances
  - ✓ hydrostatic and osmotic pressure ⇨ edema



Protein fibers

- Connective tissue fibers:
  - ✓ collagen
  - ✓ elastic
  - ✓ reticular

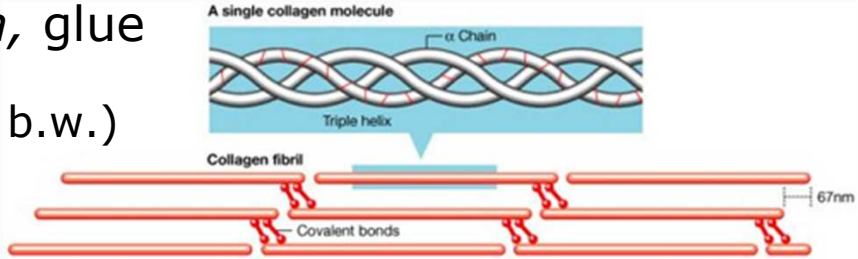


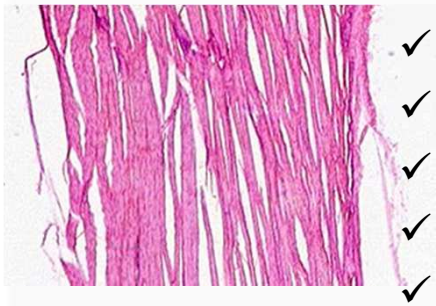


NB: in many cases, the predominant fiber type is responsible for conferring specific properties on the tissue!

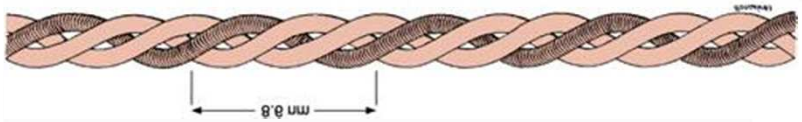
Collagen fibers

- *fibra collagenosa:* Gr. *kolla,* glue

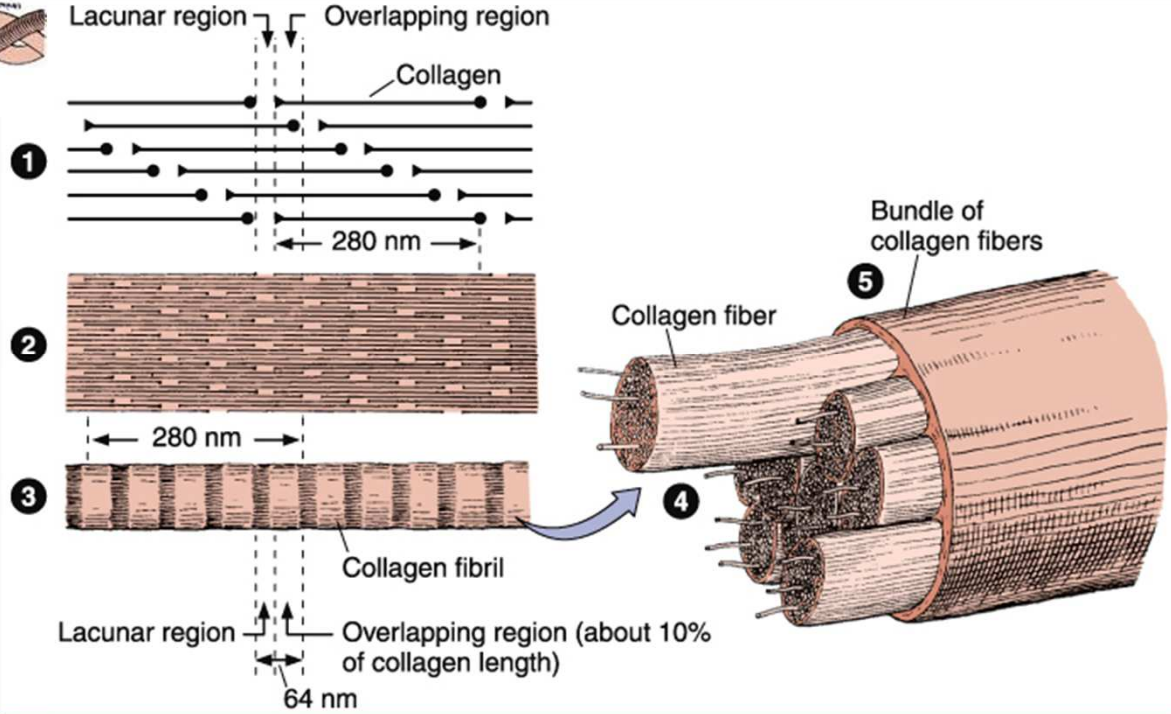




- ✓ most abundant (30% of dry b.w.)
- ✓ low elasticity – 5%
- ✓ strength – sustain 500 kg/cm^2
- ✓ acidophilic collagen fibers – 1-20 μm thick
- ✓ collagen fibrils – 0.1-0.5 μm in diameter
- ✓ collagen microfibrils – 50-90 nm; 68 nm periodicity
- ✓ collagen molecules – molecular mass 360000 Da

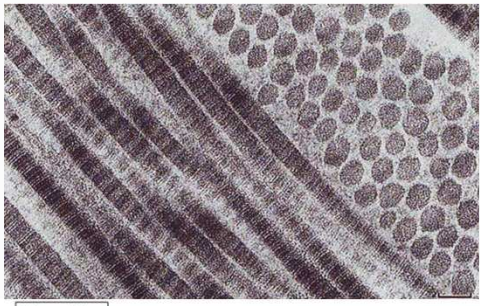


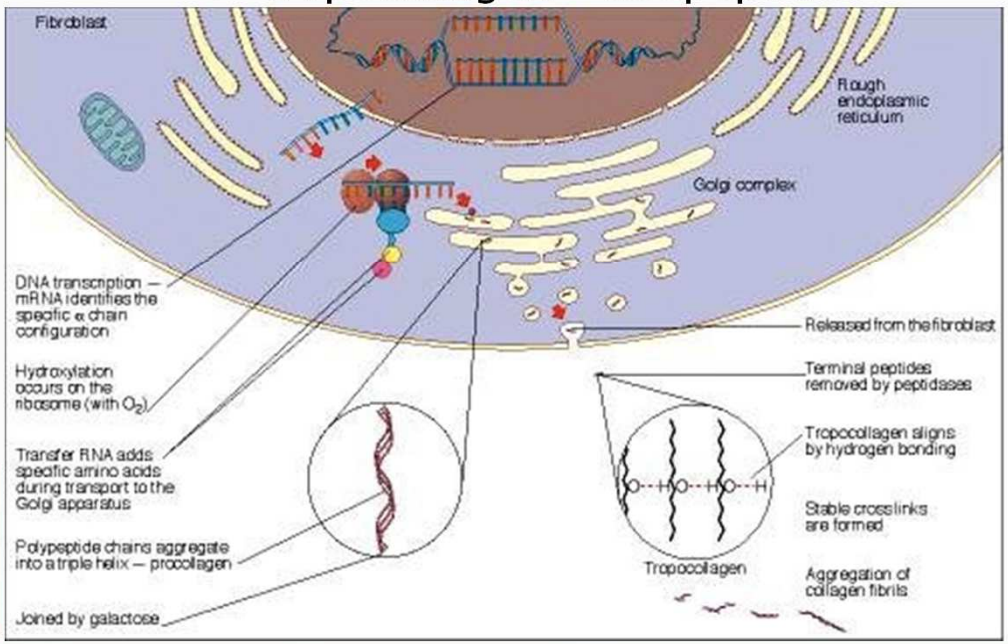
- collagen:
  - tropocollagen – 280 nm/1.5 nm
  - 3 subunit α-polypeptide chains – triple helix
  - amino acid content:
    - glycine (33.5%)
    - proline (12%)
    - hydroxyproline (10%)
    - hydroxylysine

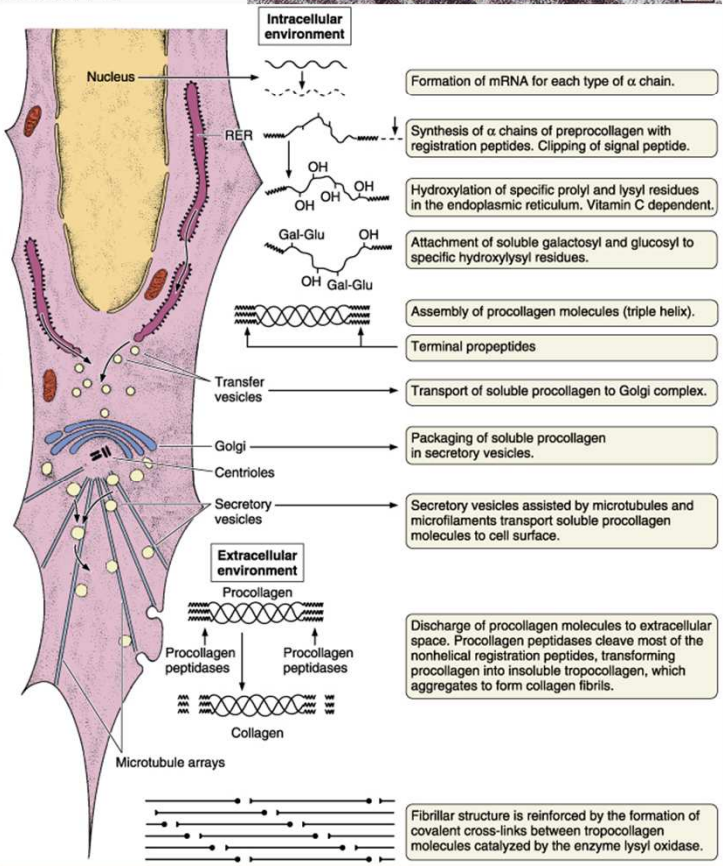


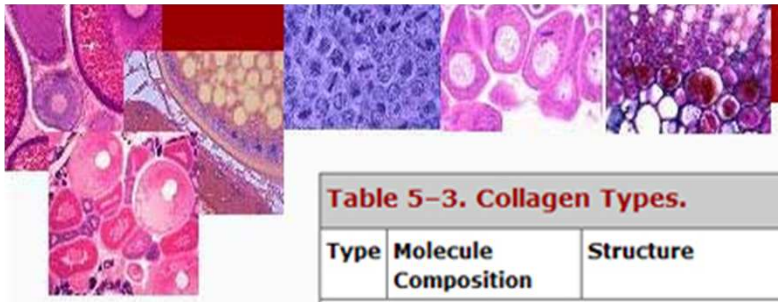
Collagen biosynthesis

- producing cells – fibroblasts, chondroblasts, osteoblasts etc.
- Steps of collagenogenesis:
  - ✓ intracellular synthesis – rough ER
    - hydroxylation of prolyl and lysyl residues
    - glycosylation of hydroxylysine
    - pro-alpha chains ⇨ procollagen molecule
  - ✓ secretion ⇨ exocytosis
  - ✓ extracellular assembling:
    - propeptide removal ⇨ peptidases
    - tropocollagen – telopeptides









Collagen types

- 28 types of collagen:

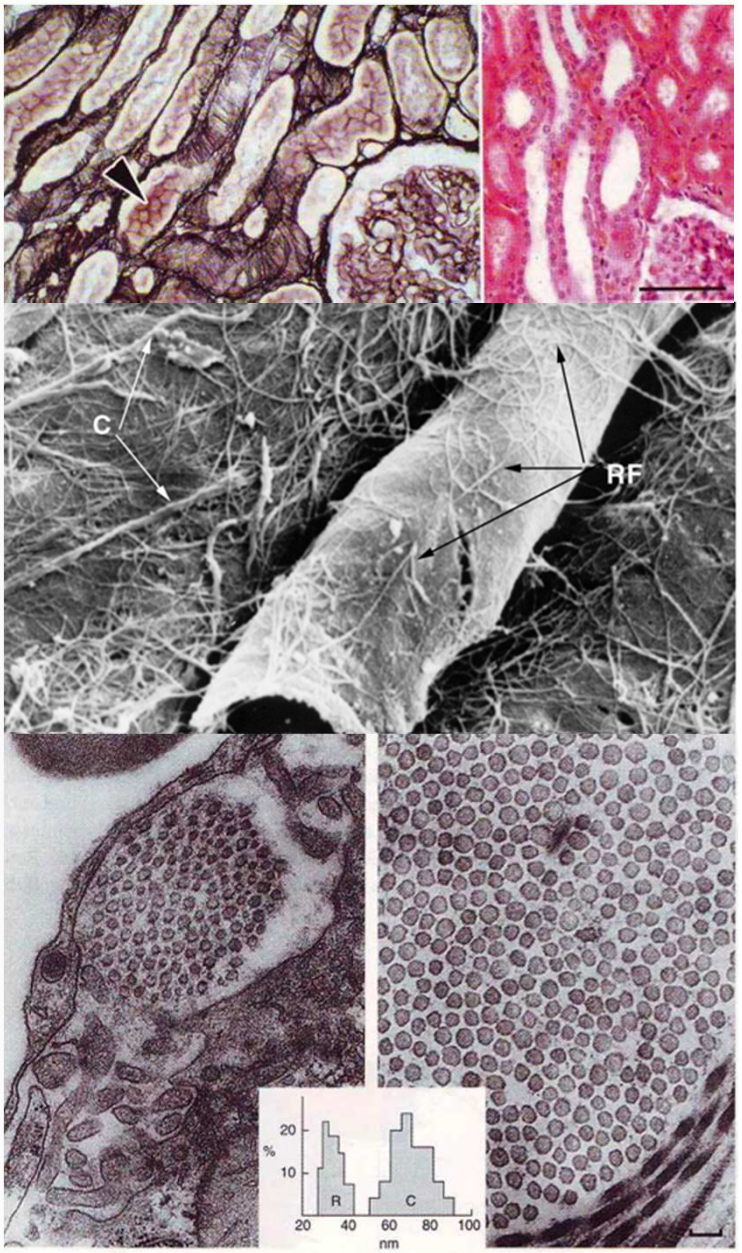
Table 5–3. Collagen Types.

Type	Molecule Composition	Structure	Optical Microscopy	Representative Tissues	Main Function
Collagen that forms fibrils					
I	$[\alpha 1\ (I)]_2\ [\alpha 2\ (I)]$	300-nm molecule, 67-nm banded fibrils	Thick, highly picrosirius birefringent, nonargyrophilic fibers	Skin, tendon, bone, dentin	Resistance to tension
II	$[\alpha 1\ (II)]_3$	300-nm molecule, 67-nm banded fibrils	Loose aggregates of fibrils, birefringent	Cartilage, vitreous body	Resistance to pressure
III	$[\alpha 1\ (III)]_3$	67-nm banded fibrils	Thin, weakly birefringent, argyrophilic fibers	Skin, muscle, blood vessels, frequently together with type I	Structural maintenance in expansible organs
V	$[\alpha 1\ (V)]_3$	390-nm molecule, N-terminal globular domain	Frequently forms fiber together with type I	Fetal tissues, skin, bone, placenta, most interstitial tissues	Participates in type I collagen function
XI	$[\alpha 1\ (XI)]\ [\alpha 2\ (XI)]\ [\alpha 3\ (XI)]$	300-nm molecule	Small fibers	Cartilage	Participates in type II collagen function
Fibril-associated collagen					
IX	$[\alpha 1\ (IX)]\ [\alpha 2\ (IX)]\ [\alpha 3\ (IX)]$	200-nm molecule	Not visible, detected by immunocytochemistry	Cartilage, vitreous body	Bound glycosaminoglycans; associated with type II collagen
XII	$[\alpha 1\ (XII)]_3$	Large N-terminal domain; interacts with type I collagen	Not visible, detected by immunocytochemistry	Embryonic tendon and skin	Interacts with type I collagen
XIV	$[\alpha 1\ (XIV)]_3$	Large N-terminal domain; cross-shaped molecule	Not visible; detected by immunocytochemistry	Fetal skin and tendon	
Collagen that forms anchoring fibrils					
VII	$[\alpha 1\ (VII)]_3$	450 nm, globular domain at each end	Not visible, detected by immunocytochemistry	Epithelia	Anchors skin epidermal basal lamina to underlying stroma
Collagen that forms networks					
IV	$[\alpha 1\ (IV)]_2\ [\alpha 1\ (IV)]$	Two-dimensional cross-linked network	Not visible, detected by immunocytochemistry	All basement membranes	Support of delicate structures, filtration

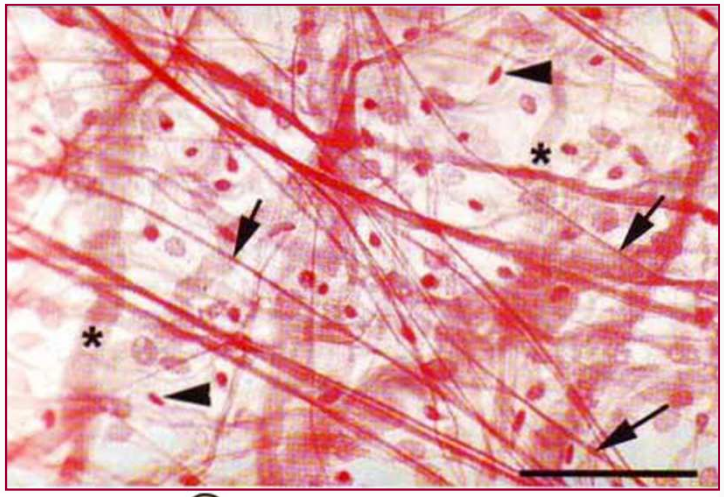
Reticular fibers

- *fibra reticulares:*

✓ extremely thin – diameter 0.2-2 μm
✓ form a network (*rete* = network)
✓ resistant to acids and trypsin
✓ PAS-positive – carbohydrates
✓ argyrophilic – selective affinity for silver salts (Gr. *argyros*, silver + *philein,* to love)
✓ 68 nm periodicity
✓ loosely packed thin (45 nm) fibrils
✓ content:
  - collagen type III
    - rich in cystine, poor of proline and hydroxyproline
    - 6-12% hexoses
    - glycoproteins
    - proteoglycans
✓ build up the reticular tissue:
  - framework of hemopoietic organs
  - smooth muscles, endoneurium



Elastic fibers



- *fibra elastica:*

✓ thinner – diameter 0.2-4 μm

✓ highly resistant to tension – 150%

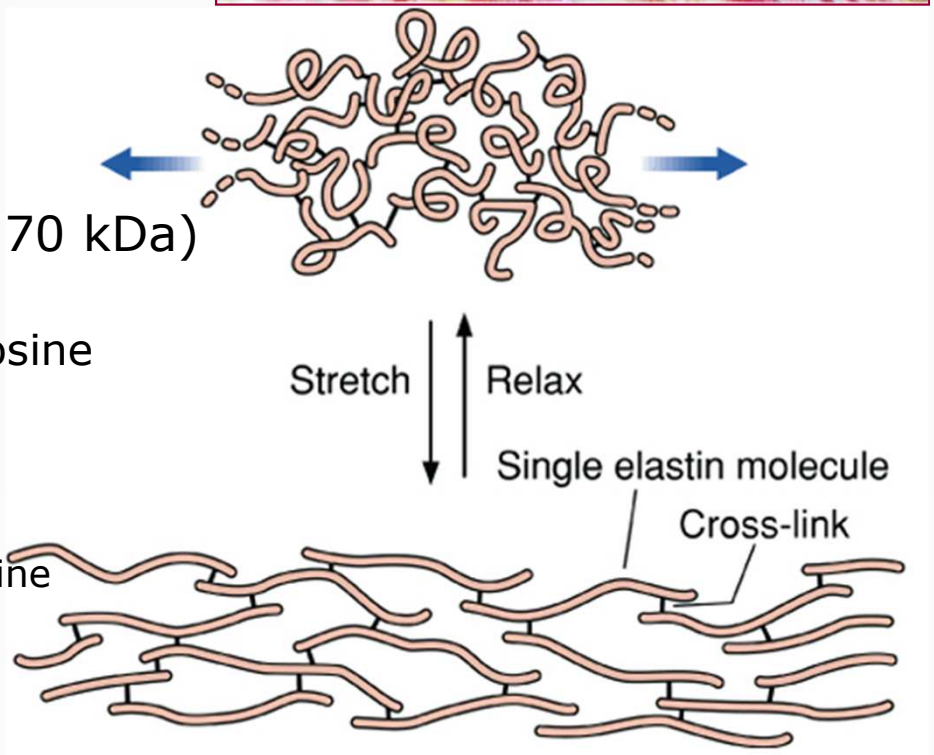
✓ lower force of strain – sustain 20-30 kg/cm^2

✓ resistant to boiling, acid and alkali extraction, digestion by proteases

✓ selective staining – orcein, resorcin-fucsin

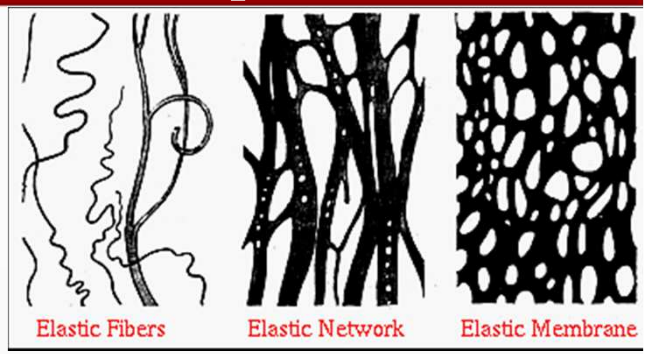
✓ content:

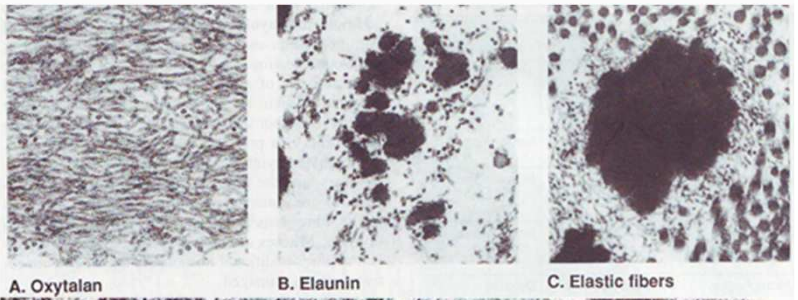
- elastin (750 amino acids; 70 kDa)
  - glycine and proline
  - desmosine and isodesmosine (4 lysine residues)
- microfibrils – 10-12 nm
  - polar amino acids
  - absent OH-lysine and -proline
  - fibrillin ~5%
  - fibromoduline I and II
  - 0.5-2% proteoglycans

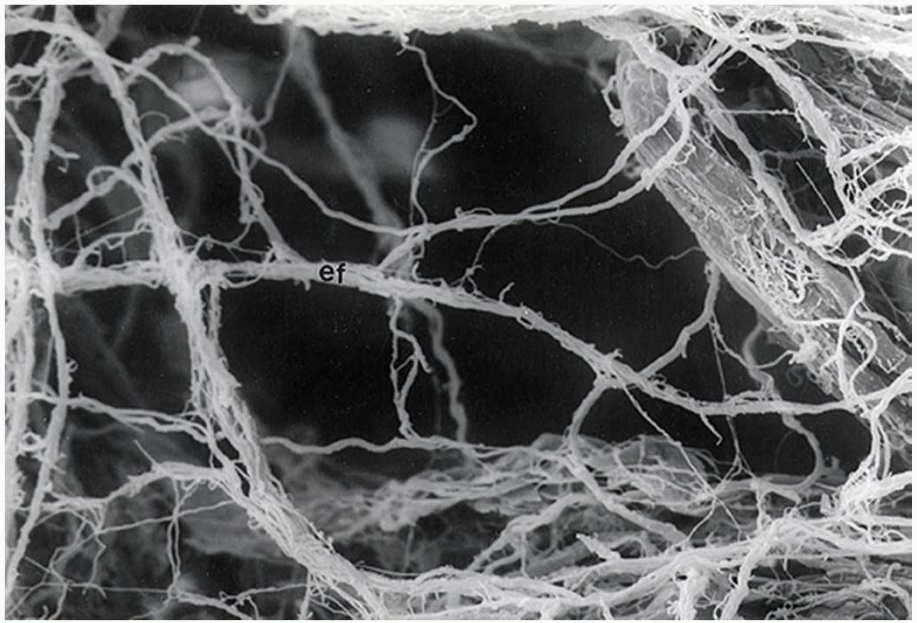


Elastic fiber system

- producing cells – fibroblasts
- 3 types of fibers – stages of development:
  - ✓ oxytalan fibers – 10 nm (Gr. *oxys,* thin)
    - *fibrae zonulares* of the eye
    - dermis
    - glycoprotein-containing microfibrils (fibrillin)
  - ✓ elaunin fibers (Gr. *elaunem,* to drive)
    - around sweat glands, dermis
    - aorta
    - elastic cartilage
    - secretion of proelastin
  - ✓ elastic fibers:
    - centrally – elastin
    - peripherally – microfibrils







Classification of connective tissue

CLASSIFICATION OF CONNECTIVE TISSUE

The connective tissues are classified into various types depending on the following Four Factors.

1. Relative proportion of the various fibers present
2. Compactness and arrangement of fibers
3. Nature of ground substance (matrix)
4. Types of cells

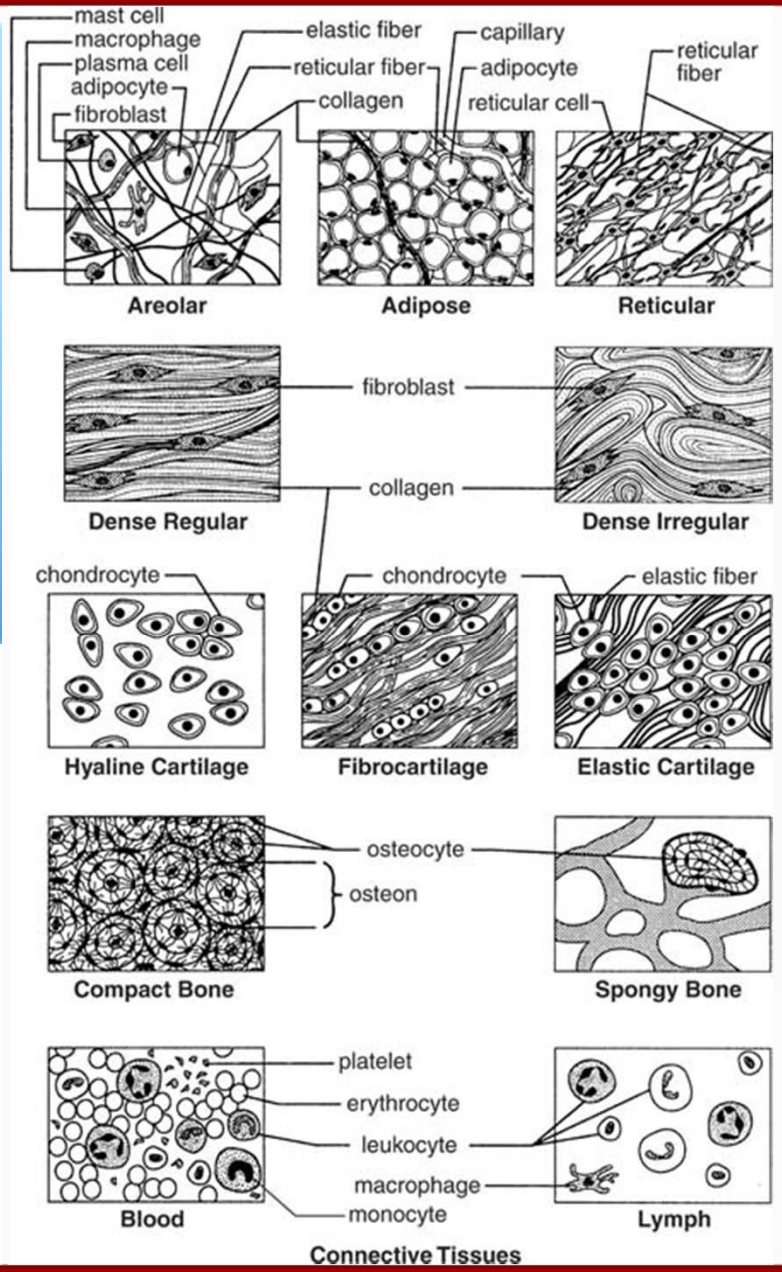
On these ground the connective tissues are divided into basic Groups

A. Embryonal Connective Tissue
B. Adult Connective Tissues

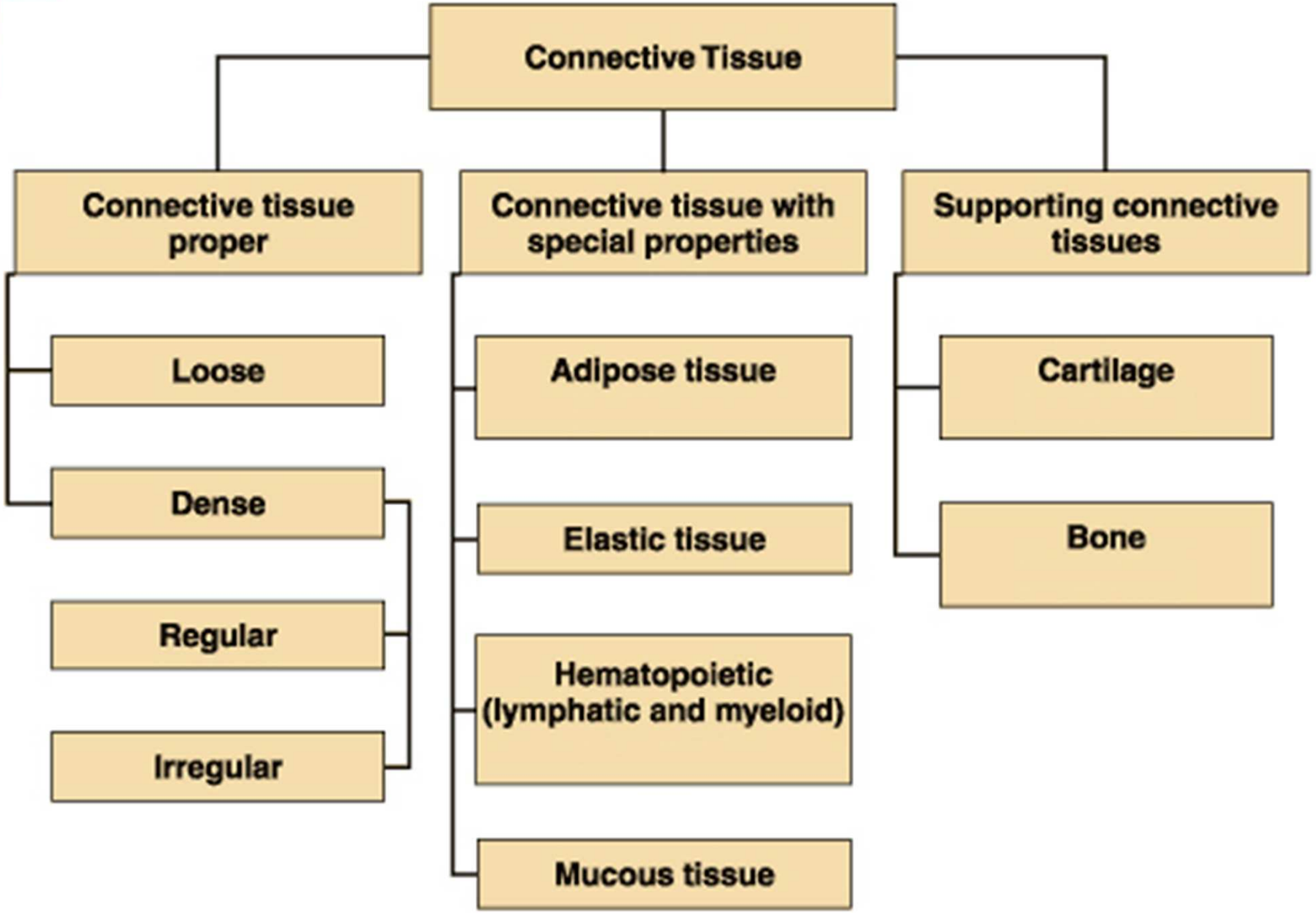
Classification of Connective Tissues

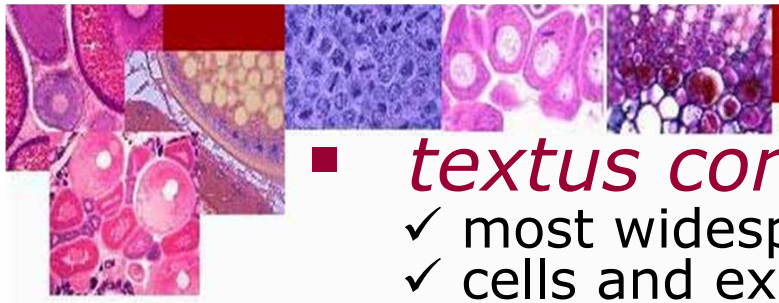
Embryonic Connective Tissues
- Mesenchymal connective tissue
- Mucous connective tissue

Adult Connective Tissues (Connective Tissues Proper)
- Loose (areolar) connective tissue
- Dense irregular connective tissue
- Dense regular connective tissue
- Elastic connective tissue
- Adipose connective tissue
- Reticular connective tissue



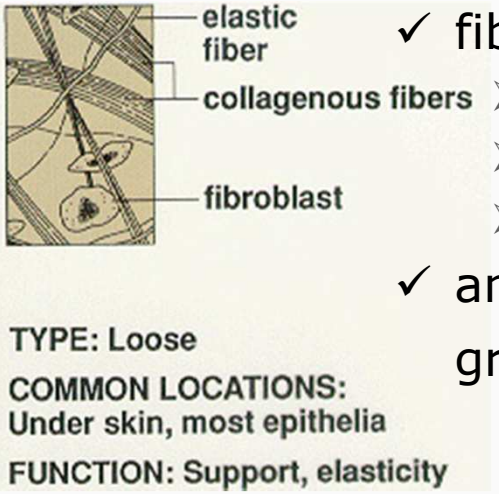
Classification of connective tissue



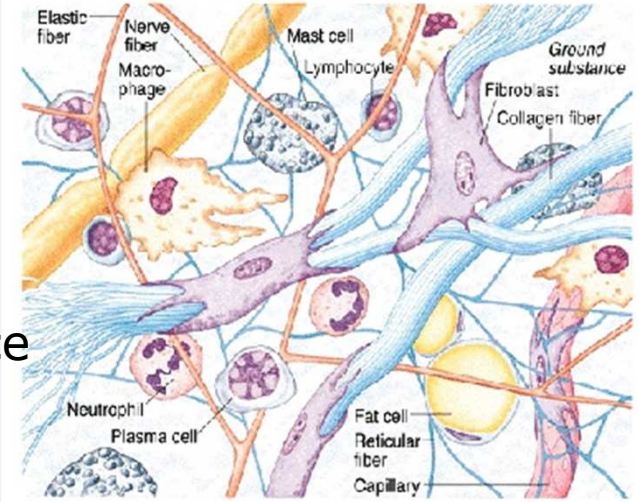


Loose (areolar) connective tissue

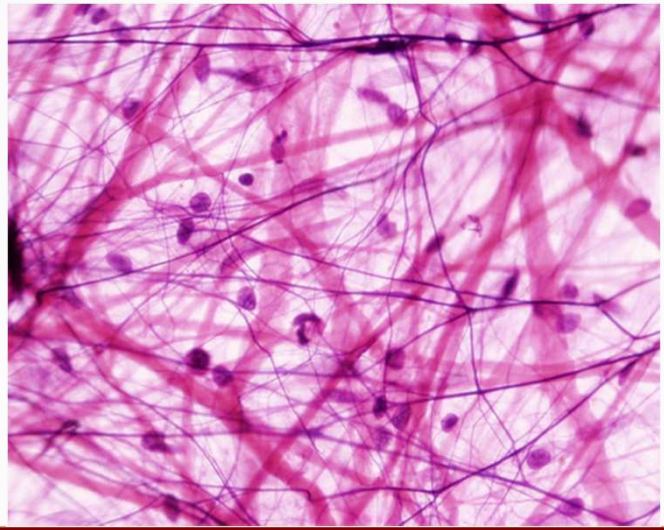
- *textus connectivus fibrosus laxus:*
  - ✓ most widespread type of connective tissue
  - ✓ cells and extracellular matrix:



- ✓ fibers:
  - ➢ collagen
  - ➢ elastic
  - ➢ reticular
- ✓ amorphous ground substance

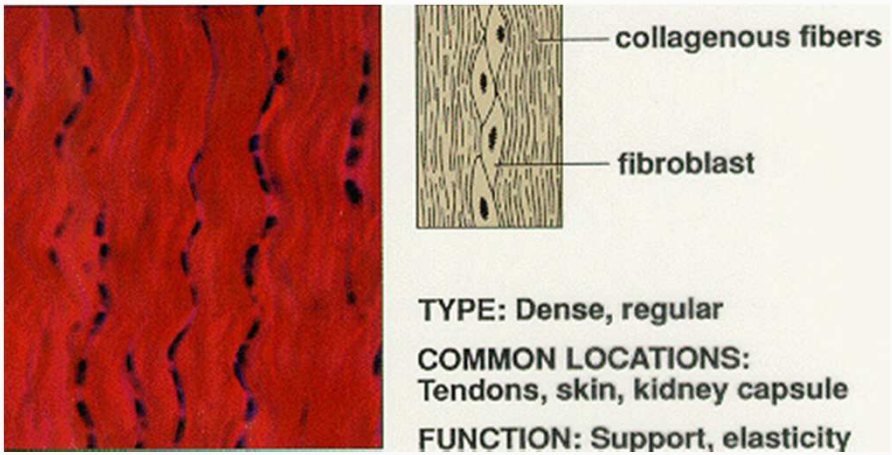


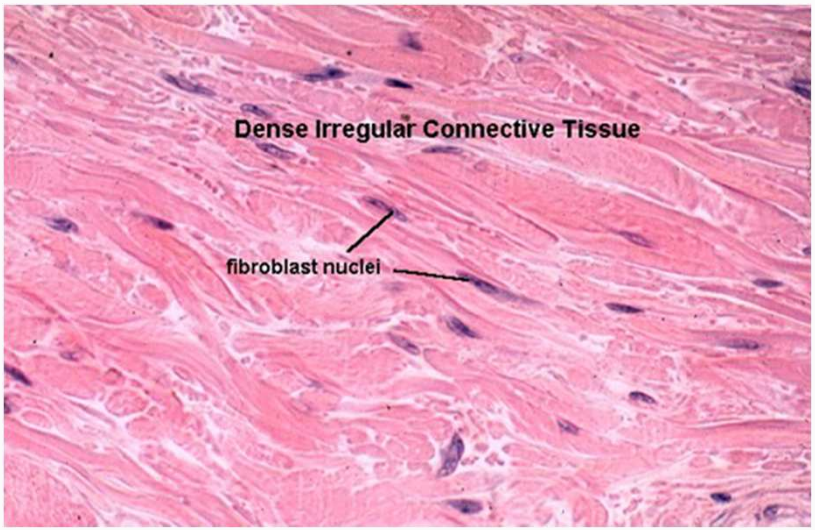
- Cells – productive, nutritive and defense:
  - ✓ proper (fixed):
    - ➢ fibroblasts and fibrocytes
  - ✓ free:
    - ➢ macrophages (histiocytes) – phagocytosis
    - ➢ plasma cells – unmature and mature (Russell bodies)
    - ➢ mast cells
    - ➢ leukocytes – granular and agranular
    - ➢ melanocytes



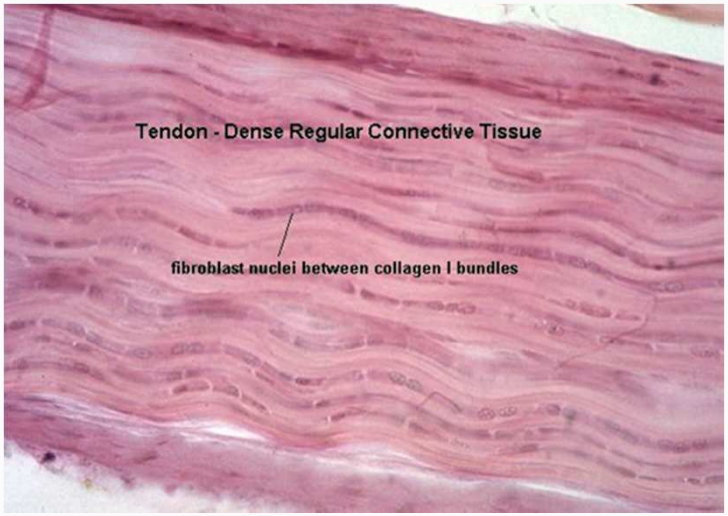
Compact dense connective tissue

- *textus connectivus fibrosus compactus:*
  - ✓ widely distributed – resistant to stress
  - ✓ cells and extracellular matrix – **collagen** fibers



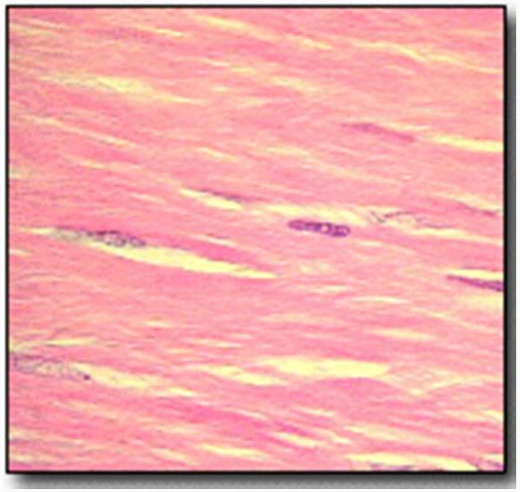


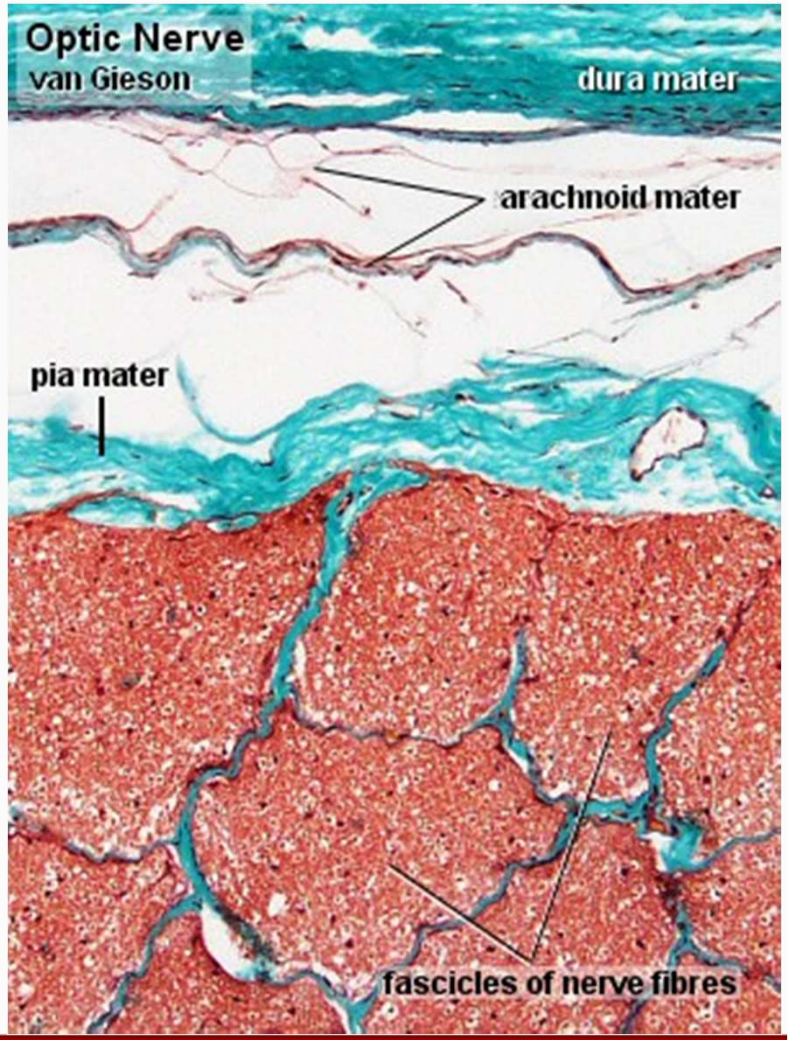
- Cells – relatively few:
  - ✓ fibroblasts and fibrocytes
- Types:
  - ✓ dense irregular connective tissue:
    - ➢ sclera
    - ➢ reticular layer of the dermis
    - ➢ capsules of the organs
  - ✓ dense regular connective tissue:
    - ➢ tendons
    - ➢ ligaments
    - ➢ parallel, closely packed bundles of collagen
    - ➢ fibrocytes ⇨ alar cells



Lamellar dense connective tissue

- *textus connectivus fibrosus lamellaris:*
  - ✓ widespread distribution – aponeuroses and fascia of the muscles, dura mater





- Cells – relatively few:
  - ✓ fibroblasts and fibrocytes
- Intercellular matrix:
  - ✓ numerous collagen fibers
  - ✓ lesser elastic fibers:
    - ➢ layers
    - ➢ lamellae

Reticuloendothelial system

- ✓ ***Systema reticuloendothelialis s. macrophagorum – Aschoff, 1924***
- ✓ **Synonym: Reticulohistiocyte system**

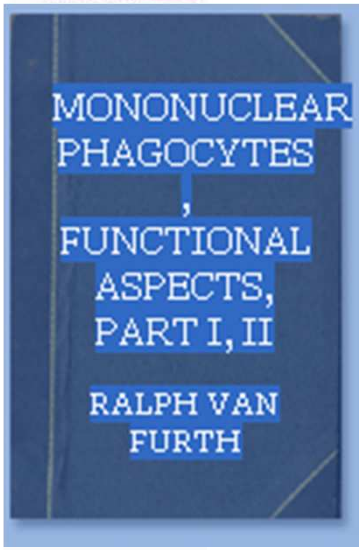
Karl Albert Ludwig Aschoff (1866-1942)

Table 5–4 Components of the Reticuloendothelial System

Sinus lining macrophages
Lymph sinuses
Blood sinuses
Liver (Kupffer cells)
Spleen
Bone marrow
Adrenal cortex
Anterior pituitary
Microglia (central nervous system)
Reticular cells of lymphatic tissues
Tissue macrophages (histiocytes)
Blood macrophages (monocytes)

Mononuclear phagocyte system

✓ **Mononuclear phagocyte system – Van Furth, 1969**



Mononuclear phagocyte system

Macrophages in different organs
Derived from stem cells of the bone marrow
Intense phagocytic activity
Activity mediated by Igs or serum complement
Characteristic morphology

irregular surface, well-formed Golgi,
RER, many lysosomes

Generally long-lived cells

Includes: macrophages of CT, lymph nodes, spleen, lung, serous cavities, Kupfer cells of liver, osteoclasts of bone, microglial cells of CNS

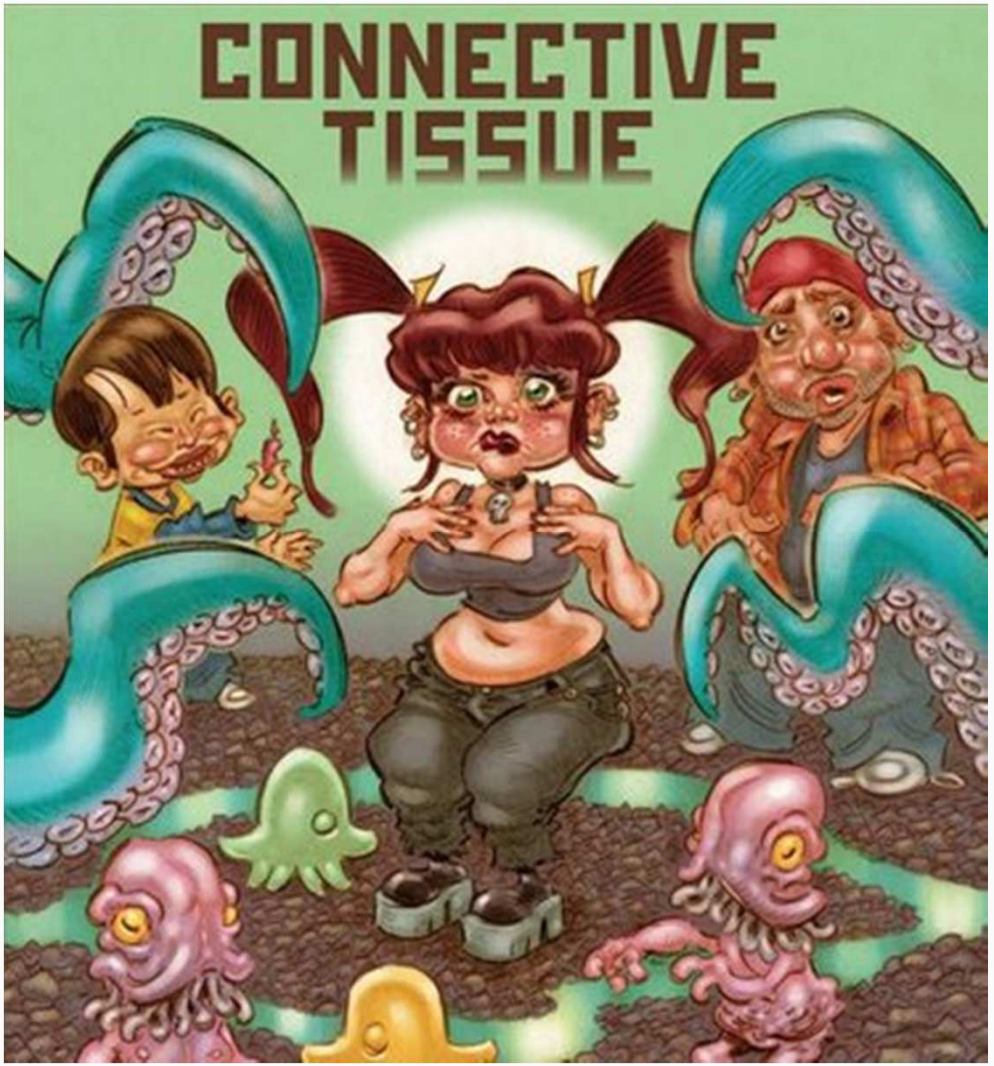
Mononuclear phagocyte system

- ✓ Reticuloendothelial System (RES)
  - ➢ *Ludwig Aschoff*, 1924
- ✓ Reticulohistiocyte System (RHS)
- ✓ Mononuclear Phagocyte System (MPS)
  - ➢ *Van Furth*, 1969

1866-1942

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



to be continued ...

Thank you ...