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# **CONNECTIVE TISSUES, BLOOD AND HEMATOPOESIS**

- \*It connects other tissues into larger morphofunctional units - organs and organ systems.

- \*All connective tissues originate from embryonic connective tissue - mesenchyme.

- \*In most connective tissues, the extracellular matrix predominates, although some tissues are dominated by cells.

- \*Certain tissues contain only one type of cell, while most tissues contain more than one type of cell.

- \*The base substance can be liquid, viscous or mineralized.

- \*In some tissues, the fibers are dense, in others less, and in others they are absent

- \*Composition of connective tissue:

- \*Cells

- \*Extracellular matrix

- a) basic substance

- b) protein fibers

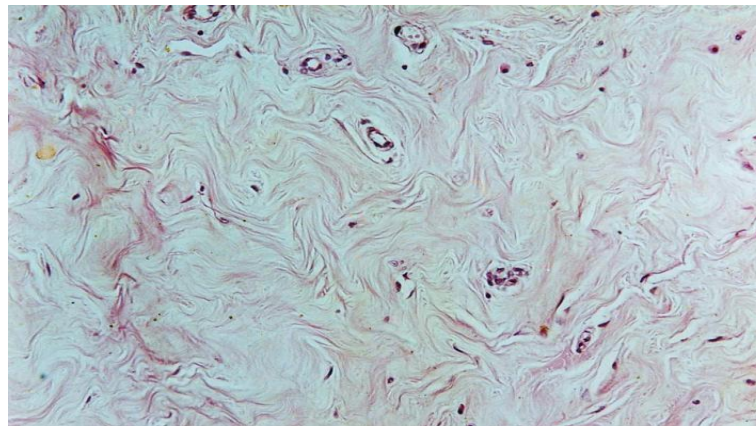
- collagen

- elastic

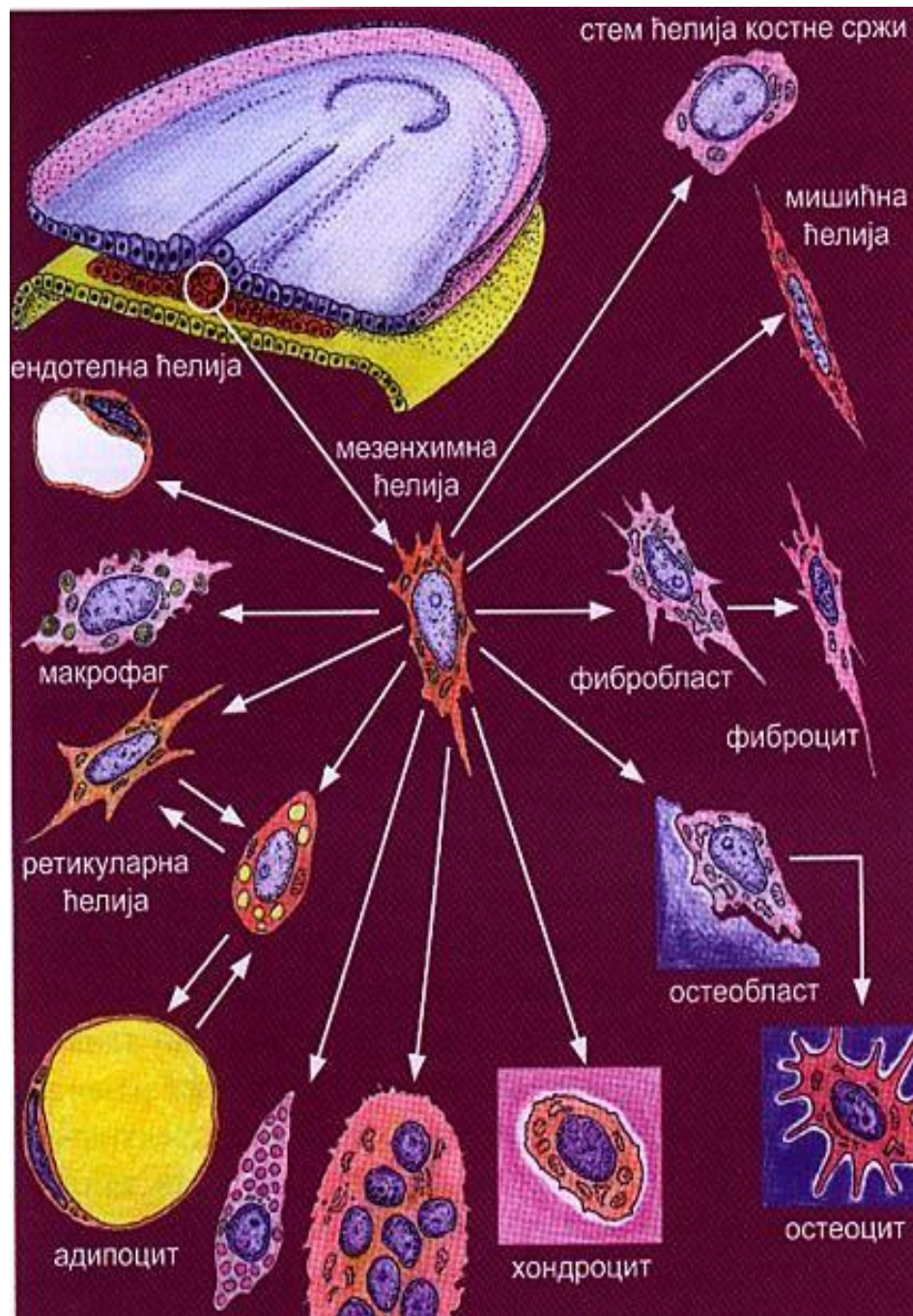
- reticular

# Basic roles of connective tissue

1. It provides support to organs by forming their stroma
2. It enables the exchange of gases and metabolites
3. It provides reparation of damaged tissues
4. It participates in the body's defense through:
  - phagocytosis
  - immunoglobulin production
  - production of inflammatory mediators.



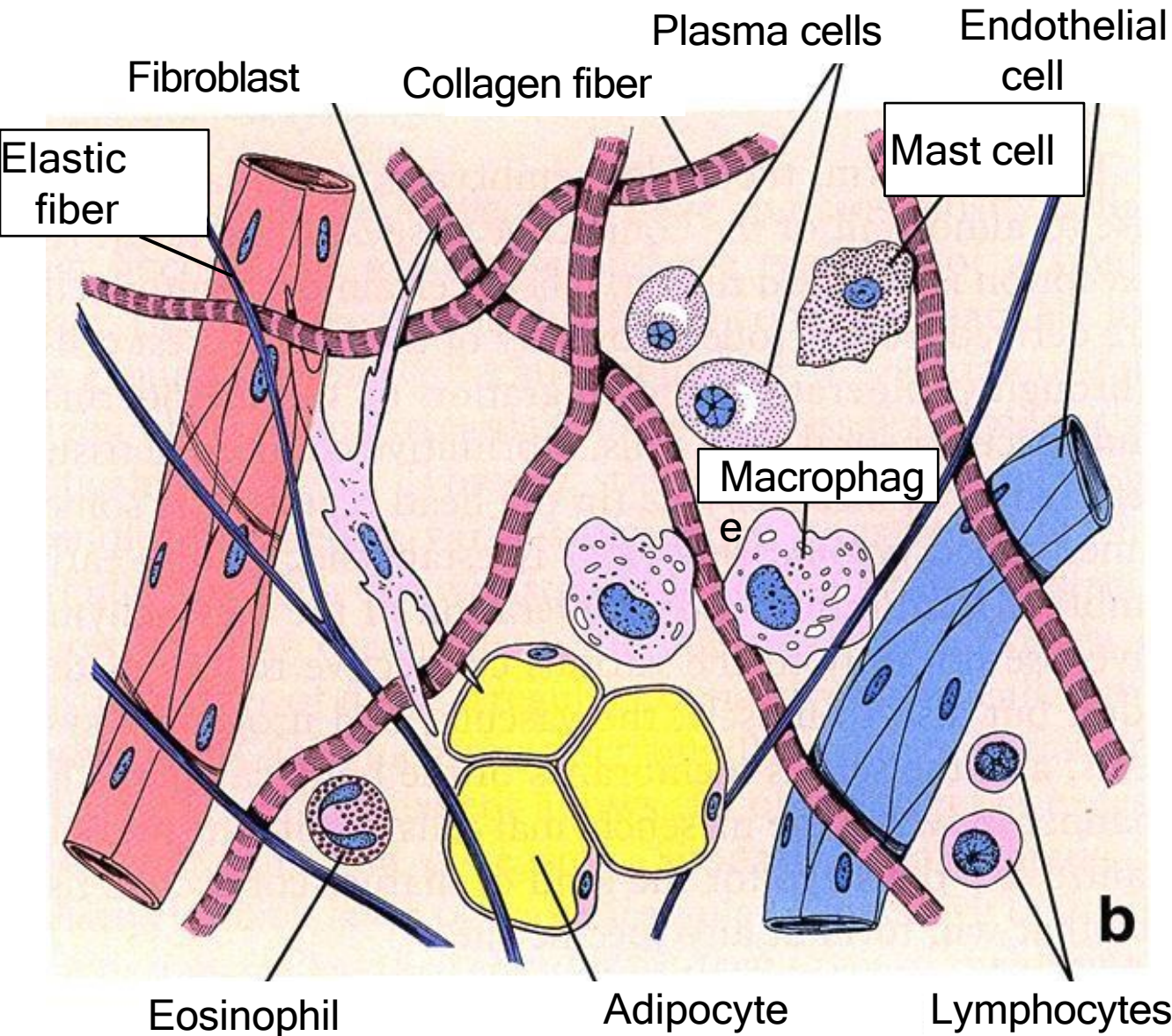
# Mesenchymal cell



- Bone marrow stem cells (blood cells)
- Fibroblast and fibrocyte
- Macrophage
- Reticular cell
- Adipocyte
- Mast cell
- Osteoblast and osteocyte
- Osteoclast
- Chondroblast and chondrocyte.



# Composition of connective tissue (schematic view)



**Cells**

**Extracellular matrix**  
basic substance  
protein fibers.

# Connective tissue cells

```
graph TD; A[Connective tissue cells] --> B[fixed (stationary)]; A --> C[mobile (roaming)]; B --> B1[Fibrocyte]; B --> B2[Chondrocytes]; B --> B3[Osteocytes]; B --> B4[Adipocytes]; B --> B5[Mesenchymal cells]; B --> B6[Reticular cells]; C --> C1[Leukocytes]; C --> C2[Macrophages]; C --> C3[Plasma cells]; C --> C4[Mast cells]; C1 --> C1a[neutrophil granulocytes]; C1 --> C1b[eosinophilic granulocytes]; C1 --> C1c[basophilic granulocytes]; C1 --> C1d[monocytes]; C1 --> C1e[Lymphocytes];
```

## fixed (stationary)

**Fibrocyte**  
**Chondrocytes**  
**Osteocytes**  
**Adipocytes**  
**Mesenchymal cells**  
**Reticular cells**

## mobile (roaming)

### **Leukocytes**

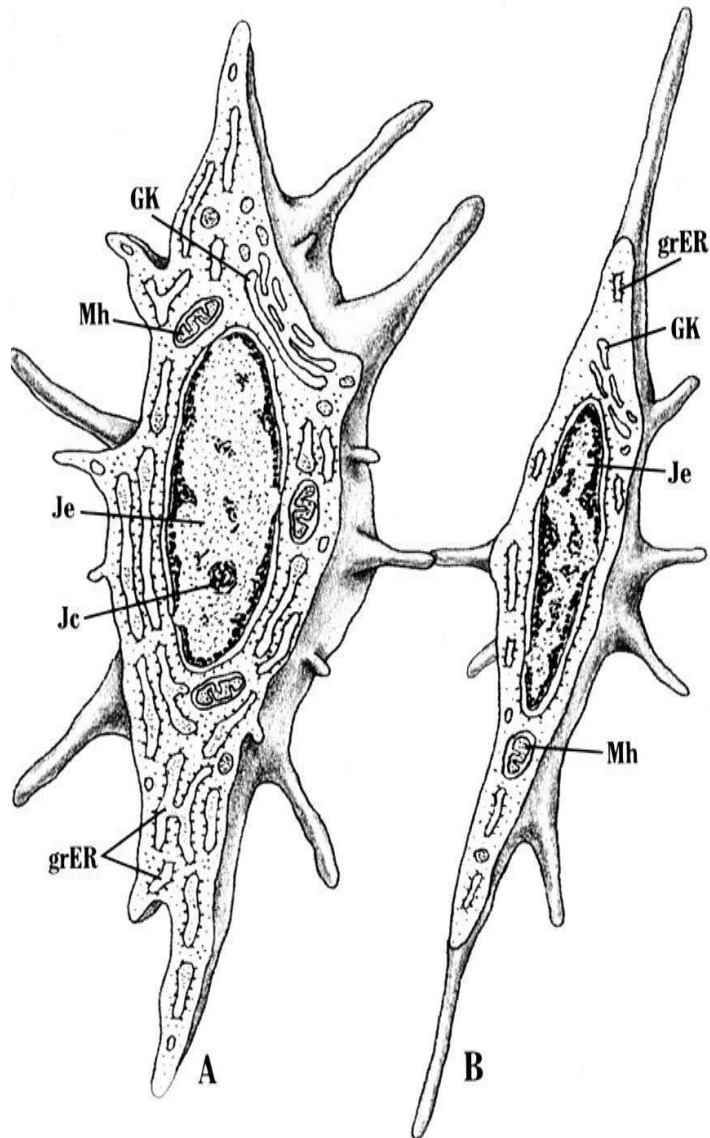
- neutrophil granulocytes
- eosinophilic granulocytes
- basophilic granulocytes
- monocytes
- Lymphocytes

### **Macrophages**

### **Plasma cells**

### **Mast cells**

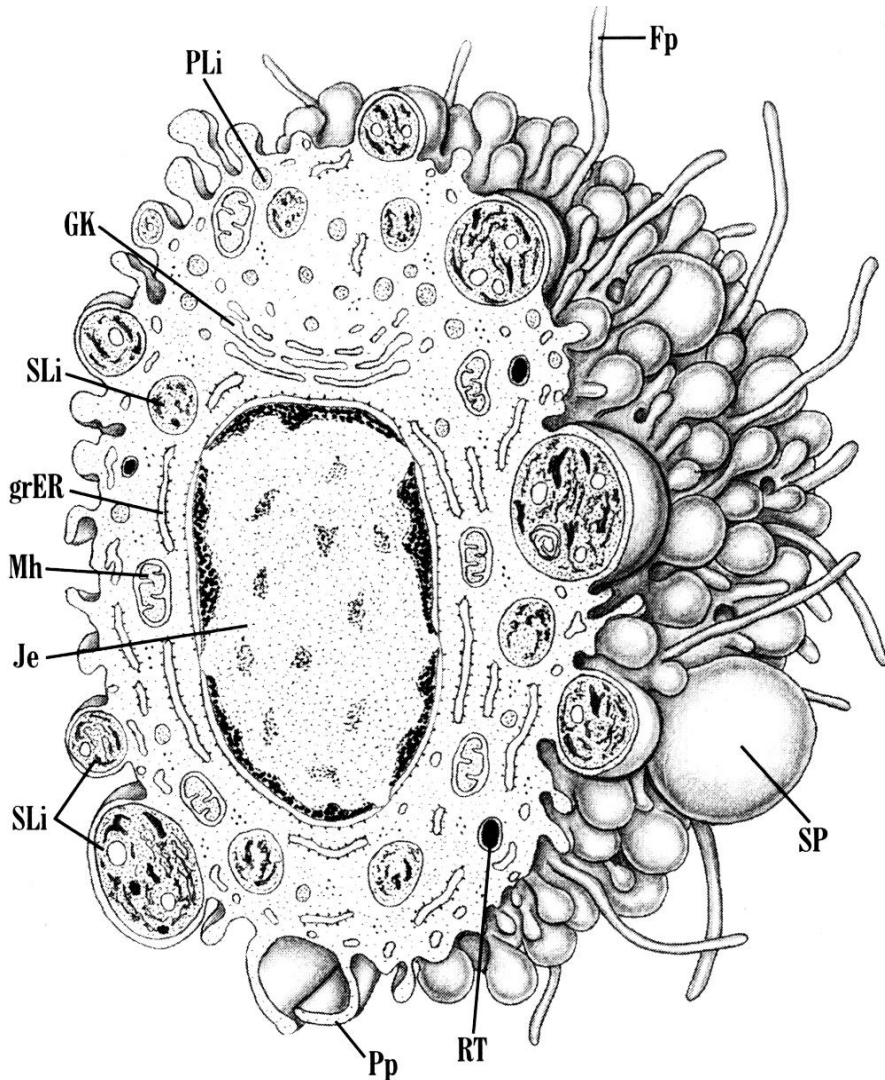
# Fibroblast and fibrocyte



- Fibroblast is a fixed cell, present in mucous, loose and dense connective tissue.
- A fibroblast is an active, and a fibrocyte is a resting (inactive) form of a cell.
- The role of fibroblasts: creates connective fibers and ground substance.
- Fibroblast has numerous extensions, light nucleus, basophilic cytoplasm, well-expressed grER and Golgi apparatus.
- Fibrocytes have a flattened shape, a dark core, eosinophilic cytoplasm, poorly developed organelles.
- A fibrocyte can be reactivated into a fibroblast, which occurs in
- cases of tissue regeneration.



# Macrophage



- A macrophage is a wandering connective tissue cell that derives from monocytes.
- Size 15-30  $\mu\text{m}$ , lifetime about 2 of the month.
- By moving into the connective tissue, the monocyte undergoes phenotypic modification into a macrophage, acquiring an oval shape with pseudopodia and filopodia on the surface.
- With pseudopodia, the macrophage captures and internalizes foreign particles in order to partially or completely break them down and then deposit them in lysosomes or thrown out of the cell.



# Macrophage

The cell nucleus is heterochromatic, organelles well developed, a cytoplasm filled with vacuoles and lysosomes.

It belongs to the mononucleus phagocytic system.

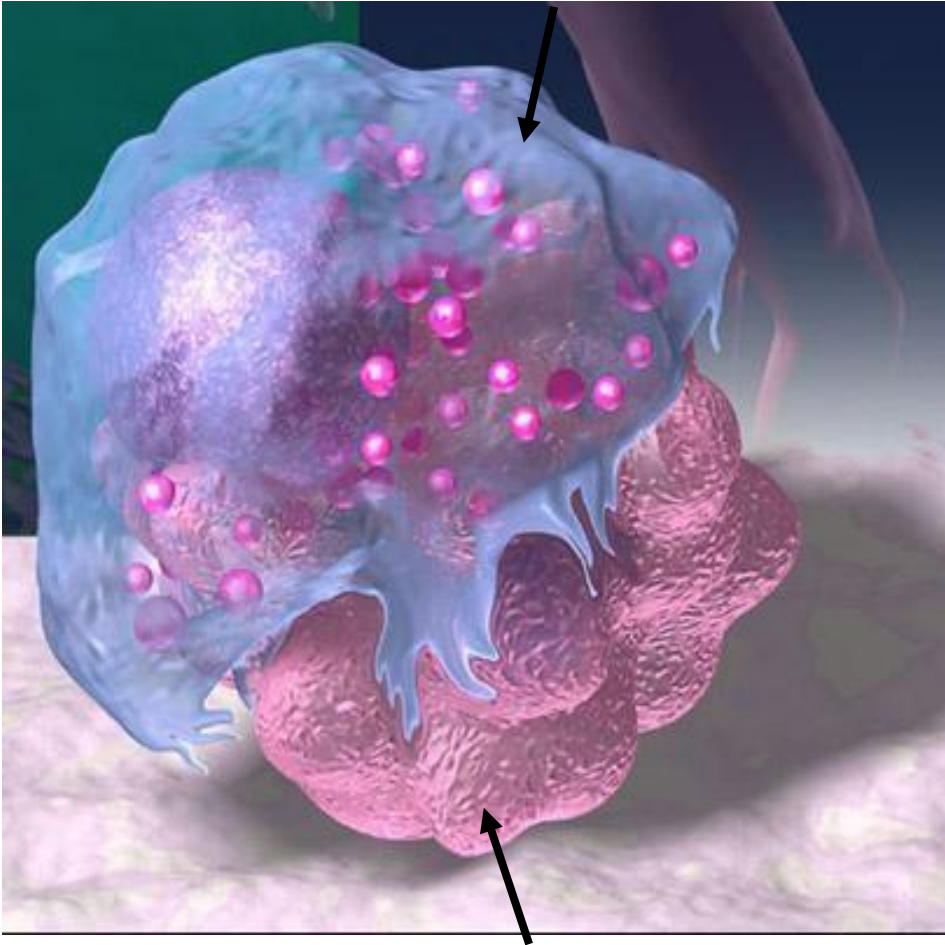
Roles:

phagocytosis

antigen presentation

secretion of active substances  
(enzymes, inflammatory  
mediators)

metabolic role (removal  
erythrocytes)

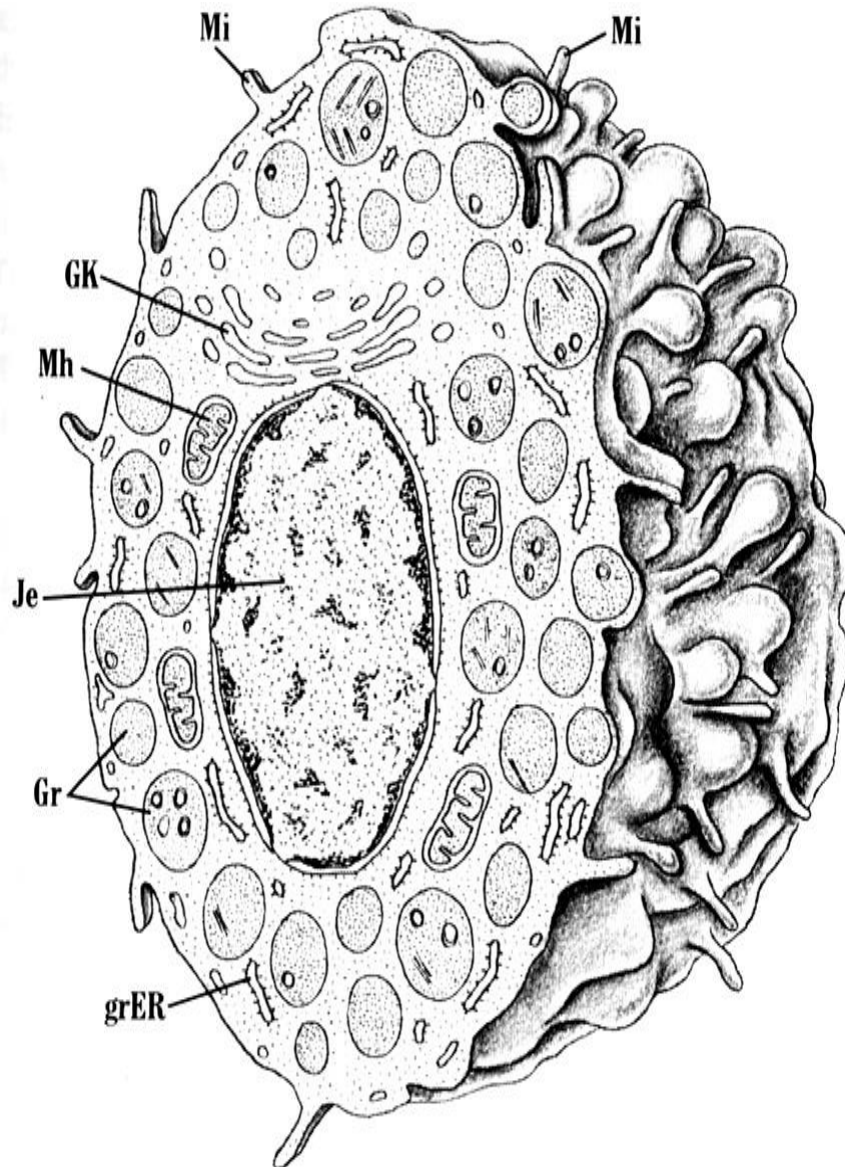


## Special names for macrophages

## Localization

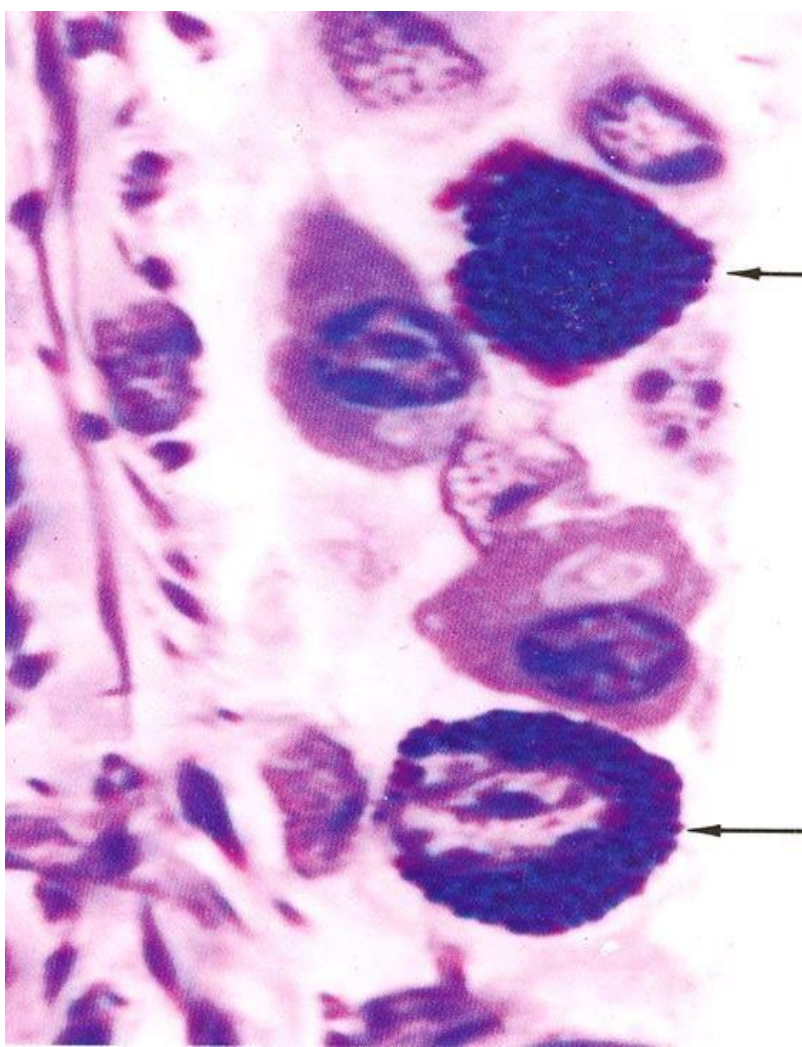
Histiocyte	Loose and dense connective tissue
Pleural and peritoneal macrophage	Serous cavities
Alveolar macrophage	Lungs
Kupffer's cell	Liver
Microglia	central nervous system
Synovial cell type A	Joints
Langerhans cell	Skin
Osteoclast	Bone

# Mast cell



- A mast cell is a wandering connective tissue cell localized along blood vessels, especially in the dermis and respiratory mucosa.
- Mast cells make up about 10% of connective tissue cells
- tissues and have a lifespan of several months.
- Division:
- loose connective tissue mast cells (heparin and neutral proteases are deposited in the granules)
- mast cells of the mucosa of the respiratory and digestive system (contain chondroitin sulfate and tryptase).

# Mast cell



- \* Appearance: oval cell with a diameter of 15-30  $\mu\text{m}$ ,
- \* with numerous growths on the surface and
- \* metachromatic granules up to 1  $\mu\text{m}$  in diameter in the cytoplasm.
- \* Some of the granules are filled with heparin.
- \* In addition to heparin, the granules also contain histamine, a strong vasodilator that increases the permeability of blood vessels even in acute cases
- \* inflammatory and allergic reactions lead to the appearance of edema.
- \* Mast cells participate in rapid allergic reactions.
- \* Antibodies of the IgE class are expressed in the mast cell membrane.
- \* Antigen binding to IgE leads to massive
- \* degranulation and release of allergic mediators.
- \* Role: synthesis of primary and secondary inflammatory mediators.



# MASTOCYTE

```
graph TD; MASTOCYTE --> Primary[Primary mediators]; MASTOCYTE --> Secondary[Secondary mediators]; Primary --> PList["Histamine (vasodilator, bronchoconstrictor), Heparin (anticoagulant), Chondroitin sulfate, Neutral proteases, Eosinophilic chemotactic factor, Neutrophil chemotactic factor, Aryl-sulfatase"]; Secondary --> SList["Leukotrienes (B4, C4, D4), Thromboxanes, Prostaglandins"];
```

## Primary mediators

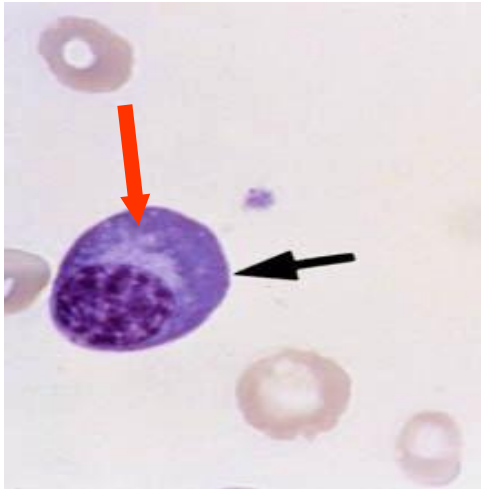
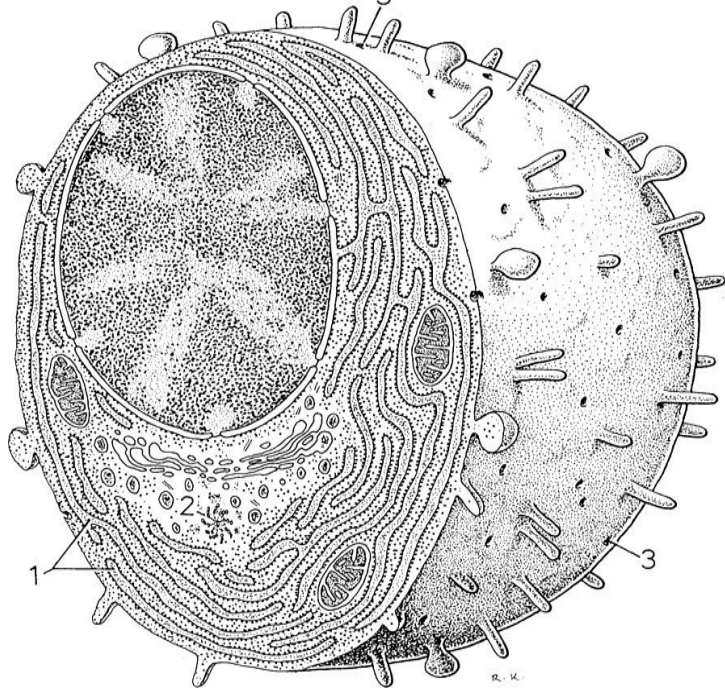
Histamine (vasodilator, bronchoconstrictor)  
Heparin (anticoagulant)  
Chondroitin sulfate  
Neutral proteases  
Eosinophilic chemotactic factor  
Neutrophil chemotactic factor  
Aryl-sulfatase

## Secondary mediators

Leukotrienes (B4, C4, D4)  
  
Thromboxanes  
  
Prostaglandins

- Primary mediators of inflammation are deposited in granules, and secondary mediators are released immediately after synthesis.
- Massive degranulation of mastocytes can cause anaphylactic shock.

# Plasmocyte



\*A plasma cell is a wandering connective tissue cell that arises from a B lymphocyte after its antigenic stimulation in the peripheral lymphatic organs.

\*Lifetime 10-30 days.

\*These cells are most represented in the connective tissue of the lymphatic organs, in the connective tissue of the mucous membrane of the respiratory and digestive tracts, as well as in the stroma of the exocrine glands.

\* Appearance: the cell has a round or oval shape, 10-20  $\mu\text{m}$  in diameter, a round eccentric nucleus with a characteristic arrangement of chromatin and many cisterns of grER and Golgi apparatus in the cytoplasm.

The bulky Golgi apparatus causes a perinuclear halo.

Role: secretion of immunoglobulins (antibodies). Sometimes Russell bodies are observed in the cytoplasm.

# Extracellular matrix



```
graph TD; A[Extracellular matrix] --> B[Basic substance]; A --> C[Protein fibers]; B --> D[Glycosaminoglycans]; B --> E[Proteoglycans]; B --> F[Adhesive glycoproteins]; C --> G[Collagen fibers]; C --> H[Elastic fibers]; C --> I[Reticular fibers];
```

The diagram is a hierarchical flowchart. At the top is a box labeled 'Extracellular matrix'. Two arrows point down from this box to two separate boxes: 'Basic substance' on the left and 'Protein fibers' on the right. From the 'Basic substance' box, a single arrow points down to a light gray box containing three items: 'Glycosaminoglycans', 'Proteoglycans', and 'Adhesive glycoproteins'. From the 'Protein fibers' box, a single arrow points down to a light gray box containing three items: 'Collagen fibers', 'Elastic fibers', and 'Reticular fibers'.

## Basic substance

**Glycosaminoglycans**

**Proteoglycans**

**Adhesive glycoproteins**

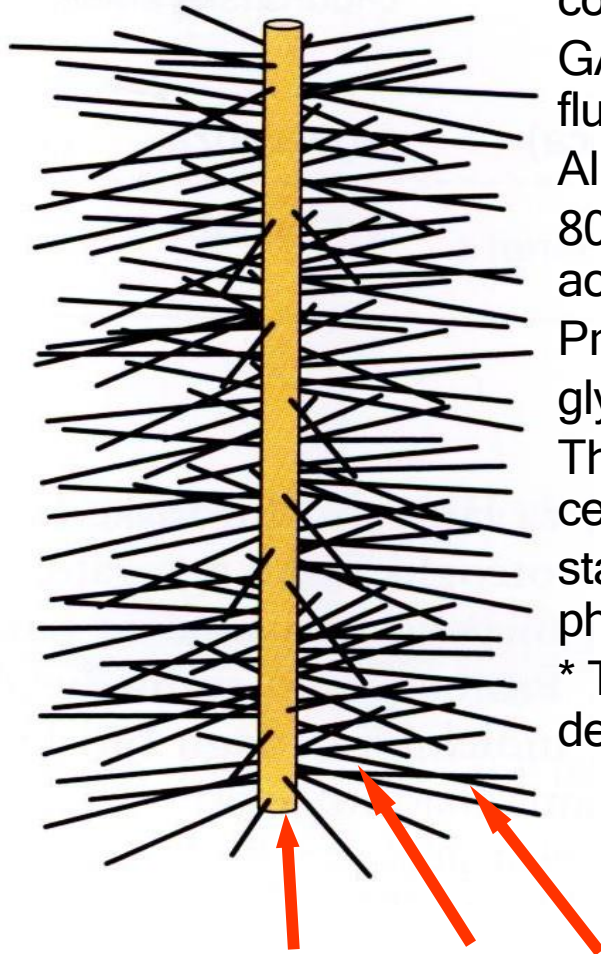
## Protein fibers

**Collagen fibers**

**Elastic fibers**

**Reticular fibers**

# Glycosaminoglycans and proteoglycans



Protein  
center

Glycosaminoglycans

\* GAGs are often referred to as mucopolysaccharides or mucins. GAGs are unbranched polysaccharide chains composed of hexuronic acid and hexosamine molecules. GAGs act as anions that attract cations and bind tissue fluid.

All GAGs are sulfated, except for hyaluronic acid. 80-90% of the molecular weight of glycoproteins is accounted for by GAGs.

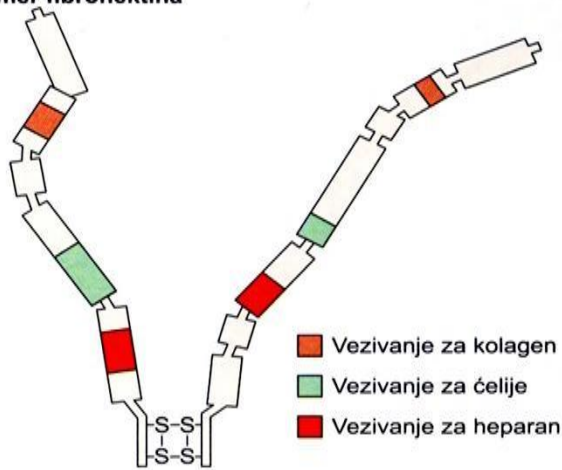
Proteoglycans are highly sulfated (acidic) glycosaminoglycans with a centrally placed protein core. They are synthesized by fibroblasts, mast cells, and in certain states and smooth muscle cells of the synthetic phenotype.

\* The degree of polymerization of these large molecules determines the degree of viscosity of the base substance.

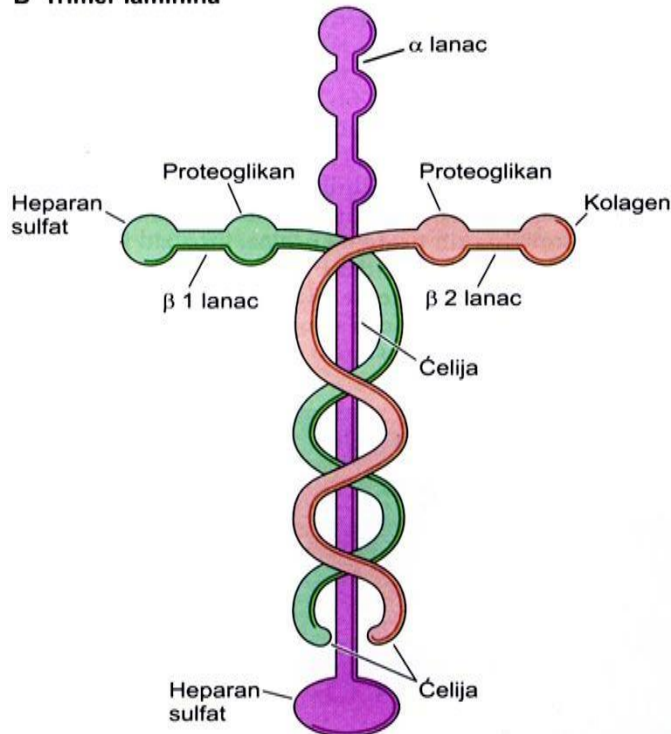


# Adhesive glycoproteins

A Dimer fibronektina



B Trimer laminina



- Adhesive glycoproteins are involved in cell-ECM interactions.
- Polysaccharide chains in proteoglycans are branched.
- Adhesive glycoproteins have binding sites for transmembrane proteins of cell membranes, then for collagen fibers of the extracellular matrix and, finally, for glycosaminoglycan basic substances.
- The most important proteoglycans: fibronectin, laminin, entactin, thrombospondin, chondronectin and osteonectin.

# Collagen fibers

- **Collagen fibers are the most common connective tissue fibers that**
- **they represent elements of solidity in the tissue, providing resistance to mechanical**
- **pressure and stretching forces.**
- **They are made of collagen protein, which in its composition has three polypeptide  $\alpha$  chains spirally twisted around each other, forming a triple helix.**
- **Collagen is synthesized by fibroblasts, but also by other fixed cells of connective tissue, as well as reticular cells and smooth muscle cells with a synthetic phenotype.**
- **There are about twenty types of collagen that differ by small variations in the composition of the  $\alpha$  chain. The first seven types are best studied.**

# Collagen

Collagen type I makes up about 90% of collagen and builds fibers in loose and dense connective tissue.

Type II collagen forms fibers in hyaline cartilage.

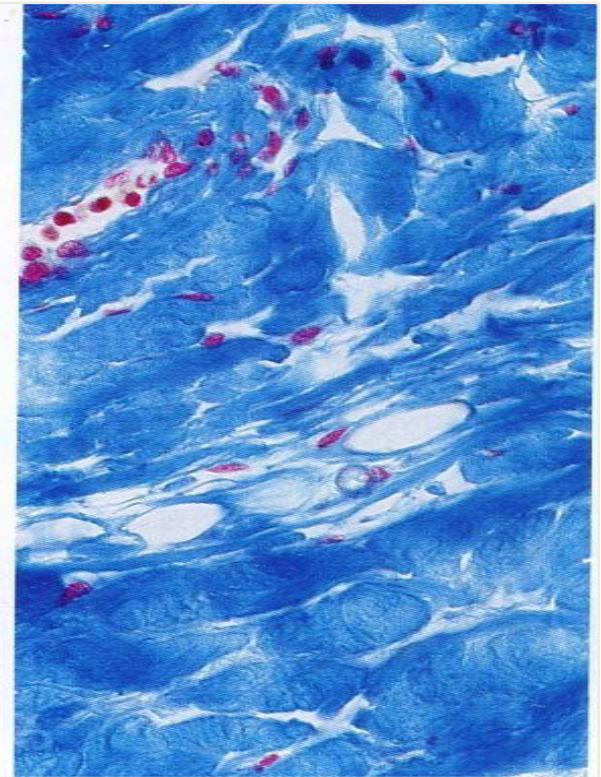
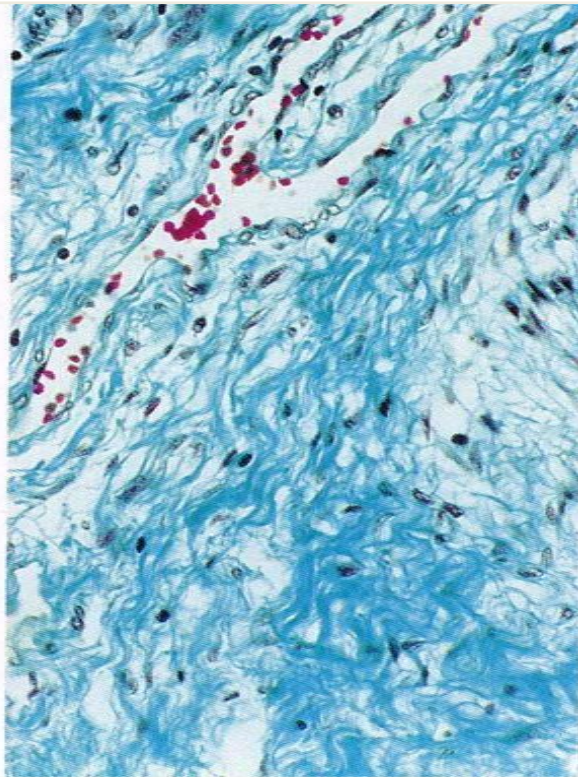
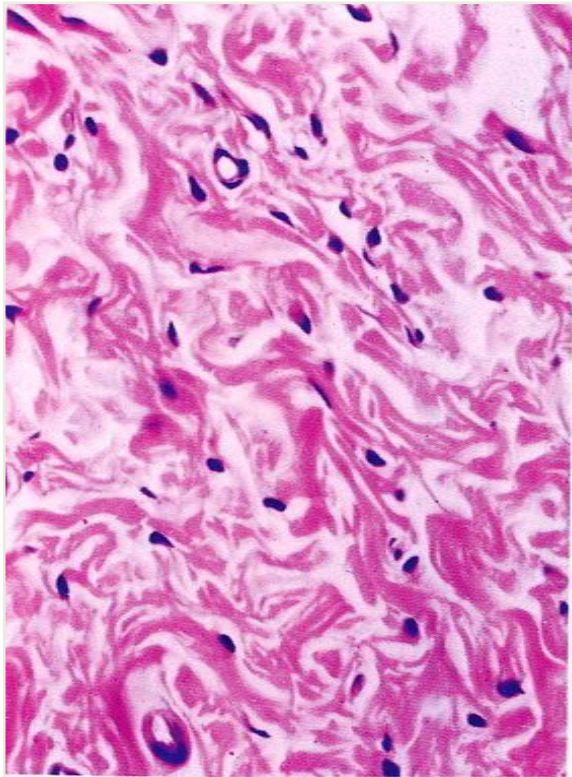
Collagen type III forms reticular fibers.

Collagen type IV builds a network in the basal lamina.

Type V collagen forms the bond between cells and other tissue structures. Collagen type VI forms thin fibers mainly in the cornea.

Collagen type VII binds interstitial collagen fibers (type I and II) to non-collagenous elements in the tissue structure.

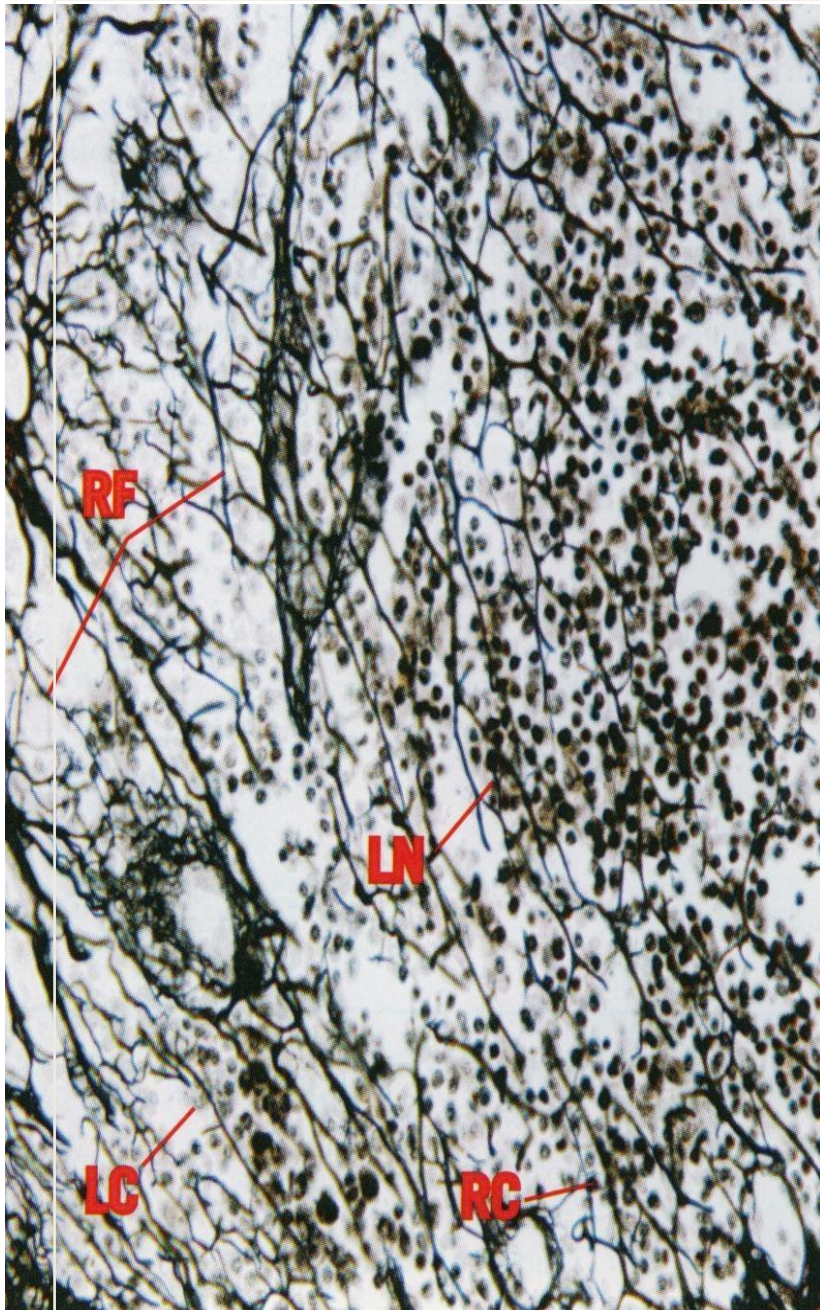
# Collagen fibers





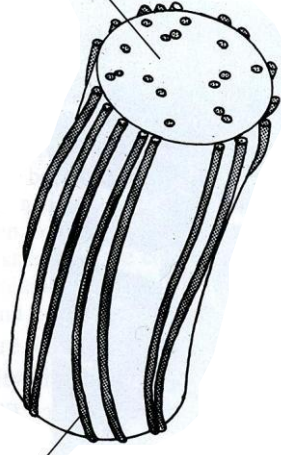
# Reticular fibers

- \* Fiber diameter 0.5-2  $\mu\text{m}$ .
- \* Made of collagen type III.
- \* Reticular fibers are found in tissues associated with stronger type I collagen fibers.
- \* They form a supportive three-dimensional network, which supports the cells.
- \* They are present in lymphatic organs, around glandular acini, fat and muscle cells.
- \* Type III collagen is often called "fetal" collagen, because fetal tissue
- \* contains more collagen III in its composition compared to the adult.



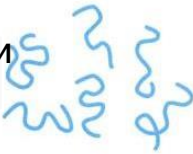


Еластин



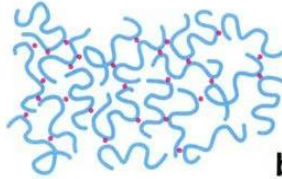
Микрофибрил

Еластински  
молекули



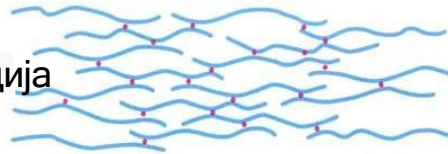
a

Релаксација



b

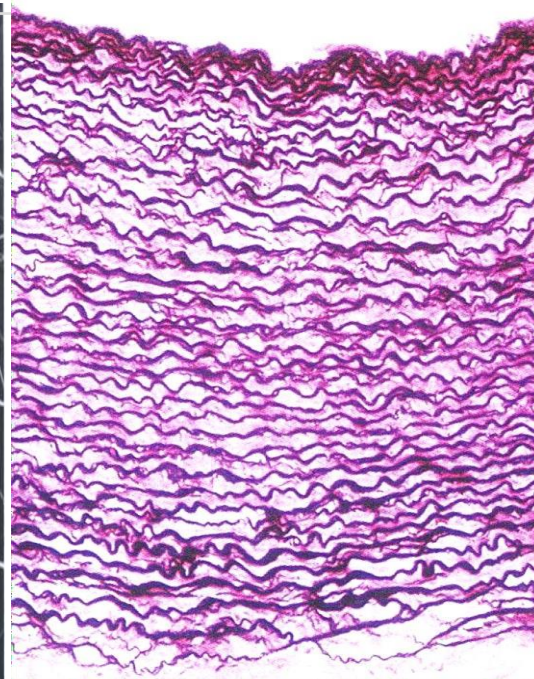
Контракција



c

# Elastic fibers

- Elastic fibers
- they are elements of connective tissue that ensure the elasticity of tissues and organs.
- These are thin and branched fibers.
- Composition: protein elastin + microfibrils.
- During synthesis, microfibrils are initially formed, and then amorphous elastin is embedded within their bundle.



# Elastic fibers



Бојење резорцином



Бојење орцеином

- Young elastic fibers contain a larger amount
- microfibrils, while with
- with age, the amount of elastin increases, which is why it is lost
- tissue quality and elasticity.
- Elastin contains specific amino acids desmosine and isodesmosine.
- Fibers stretch up to 150%.
- Oxytalan and elaunin fibers are immature forms of elastic fibers.
- Elastic fibers are synthesized by fibroblasts and smooth
- muscle cells of the synthetic phenotype.

# Connective tissue classification

```
graph TD; Root[Connective tissue classification] --> Embryonic[Embryonic]; Root --> Adult[Adult]; Embryonic --> EmbryonicList["Mesenchymal tissue (mesenchyme), Mucous connective tissue"]; Adult --> AdultList["a) With general properties: Loose tissue, Thick tissue (regularly, irregularly), b) Specialized connective tissues: Fat tissue (yellow, dark), Hematopoietic tissue, Cartilaginous tissue, Bone tissue, Blood"];
```

**Embryonic**

Mesenchymal tissue  
(mesenchyme)

Mucous connective tissue

**Adult**

a) With general properties

Loose tissue

Thick tissue

regularly

irregularly

b) Specialized connective tissues

Fat tissue

yellow

dark

Hematopoietic tissue

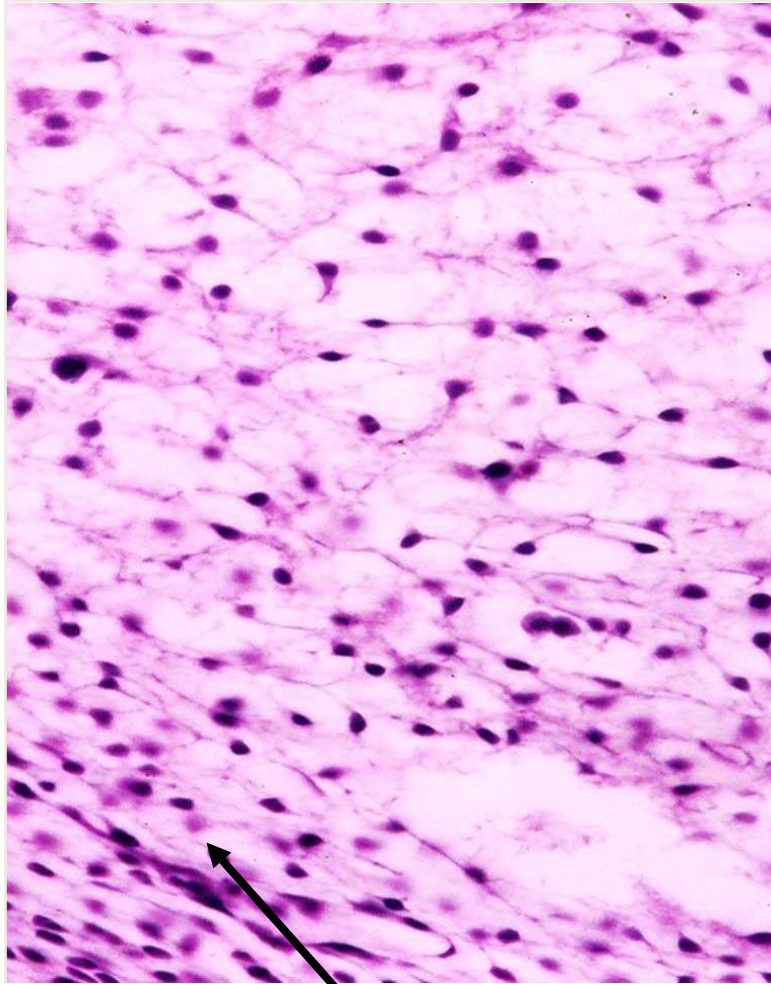
Cartilaginous tissue

Bone tissue

Blood



# Mesenchymal tissue



Бластем

**Mesenchyme represents the original, embryonic connective tissue that mostly originates from the mesoderm.**

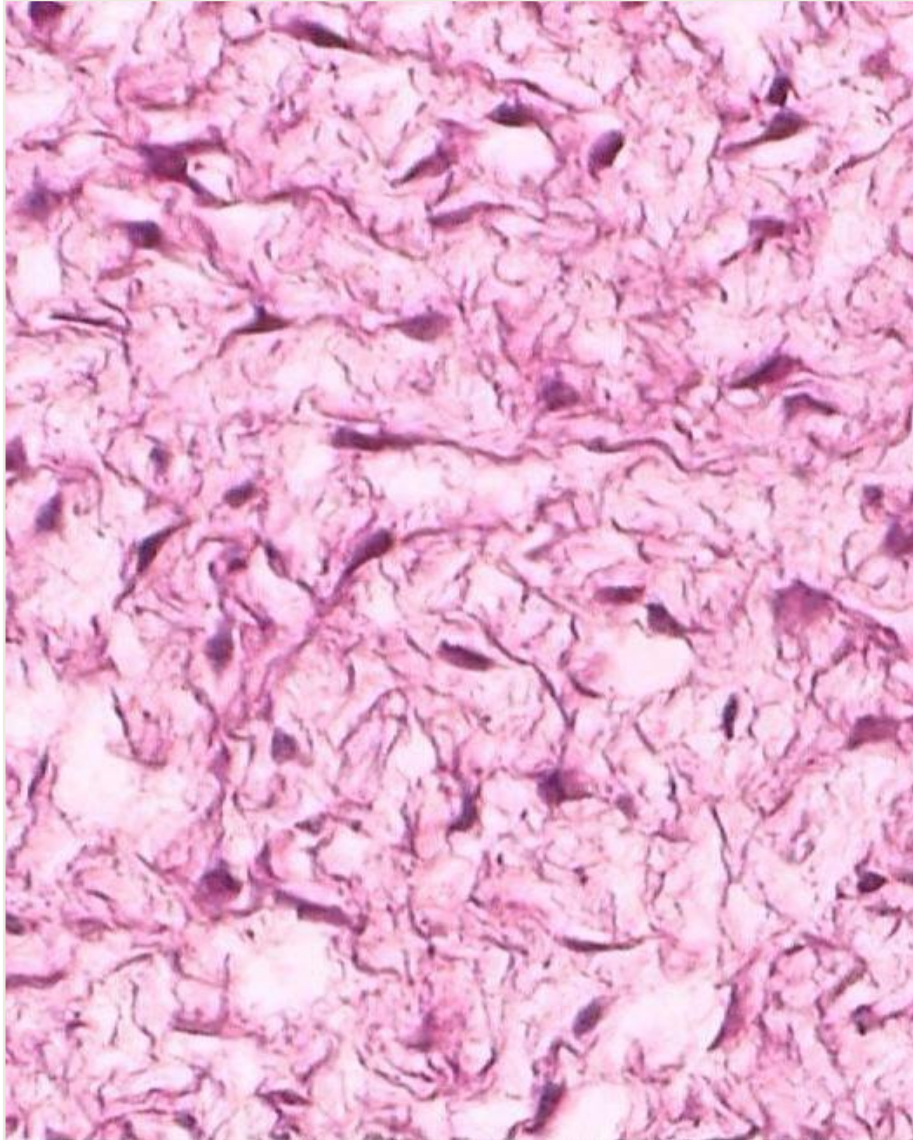
**Present only in the embryonic period. It contains mesenchymal cells, a lot of ground substance and rare reticular fibers.**

**Mesenchymal cells are characterized by large proliferative potential and frequent mitoses.**

**Mesenchymal migration and compaction cells, blastemas are formed, from which skeletal and muscle tissue are later differentiated.**

**Adult connective tissue is formed from the mesenchyme tissues.**

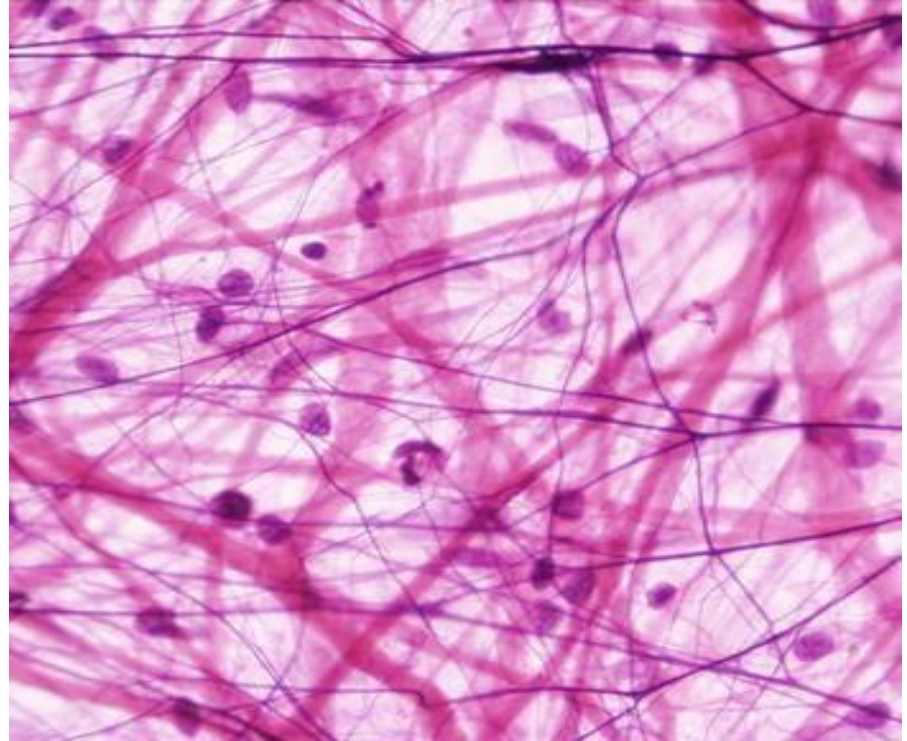
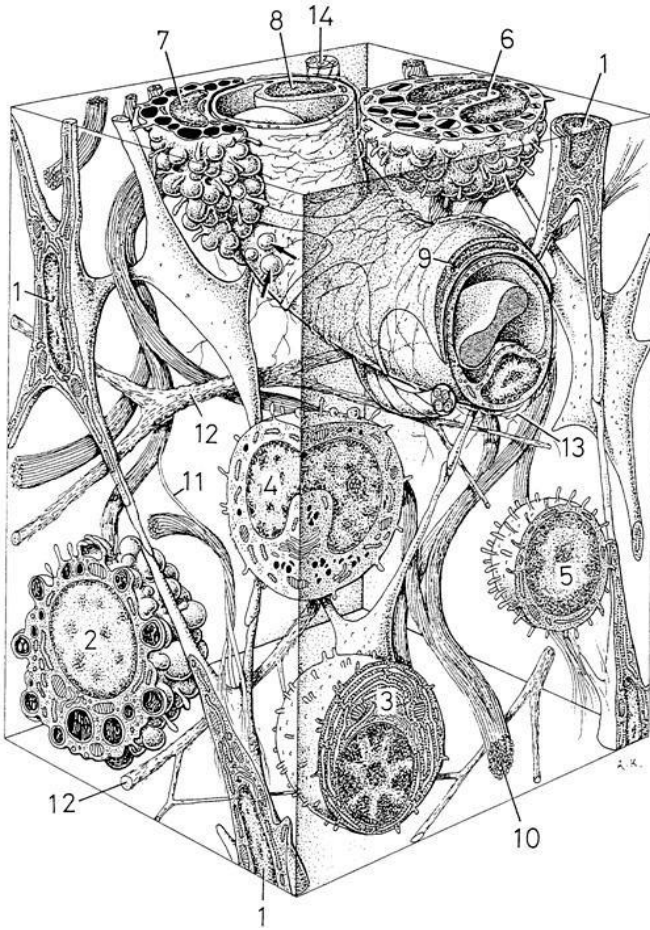
# Mucous connective tissue



- **Mucous connective tissue is found in the umbilical cord and is known as Wharton's.**
- **The tissue has no capacity for further differentiation and is not bloodied.**
- **It contains fibroblasts, ground substance and collagen fibers.**
- **Hyaluronic acid is present in the basic substance, which gives the tissue viscosity.**



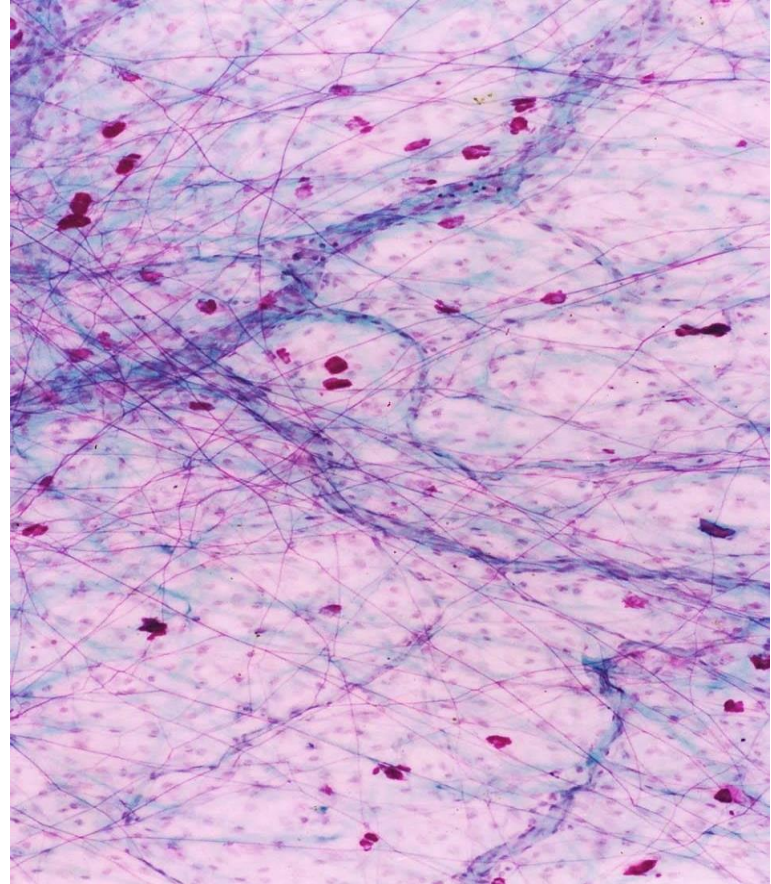
# Loose connective tissue



- It is found in the dermis, in the mucous membranes under the epithelium, blood and lymphatic vessels, etc.
- It contains a multitude of cell types, an extensive intercellular substance, and all three type of connective fibers in a loose arrangement.



# Loose connective tissue



- The cell population consists of fibroblasts, as fixed cells of loose connective tissue, but also a large number of wandering cells whose number and composition change during inflammatory and allergic reactions.
- The tissue is flexible and less resistant to mechanical stress.



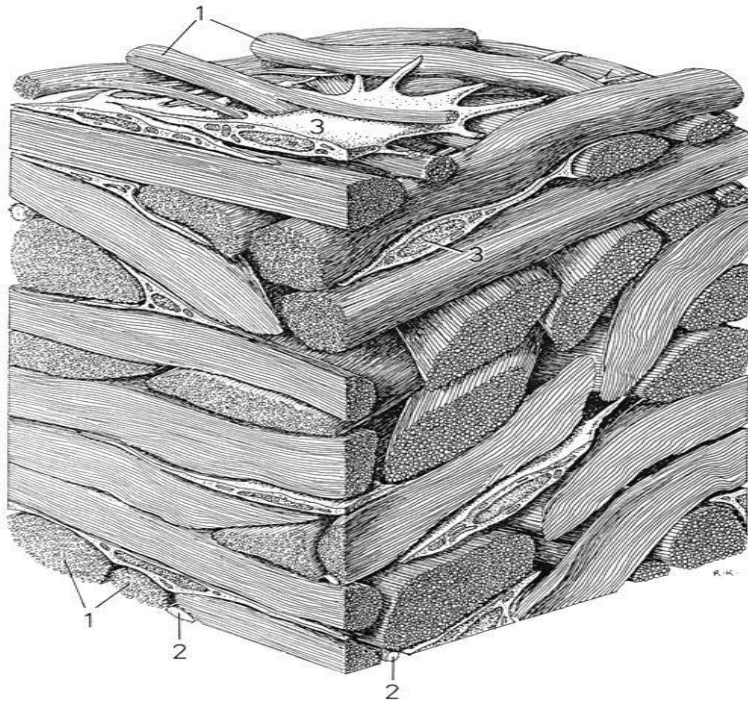
# Pigmented connective tissue



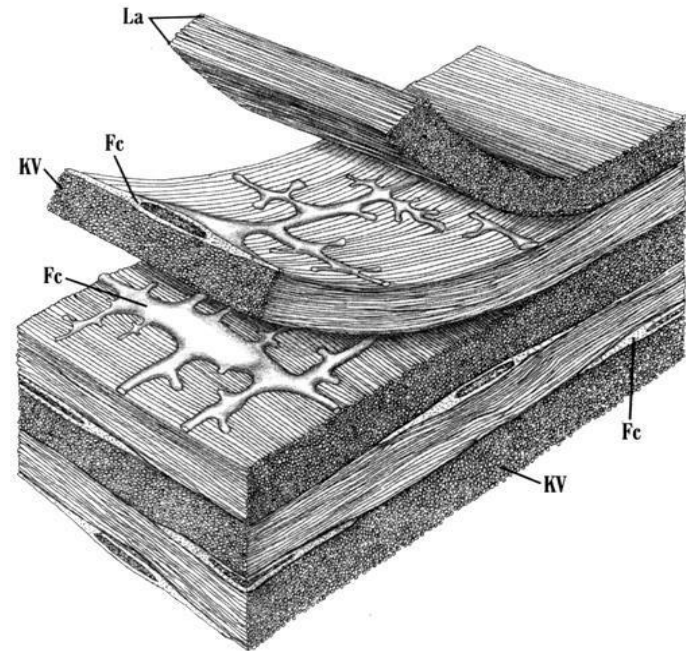
- Variant of loose binder with a lot of pigment cells.
- It is located in the lens, ciliary body and part of the choroid.

# Dense connective tissue

\* The tissue is dominated by a fibrous component (fibers), which is why it is called a fibrous binder. Among the cells, rare fibrocytes and even rarer macrophages are represented. It is divided into irregular and regular connective tissue.



**Irregular dense connective tissue contains bundles of collagen fibers directed in different directions with little intercellular substance and rare fibroblasts and macrophages between them.**

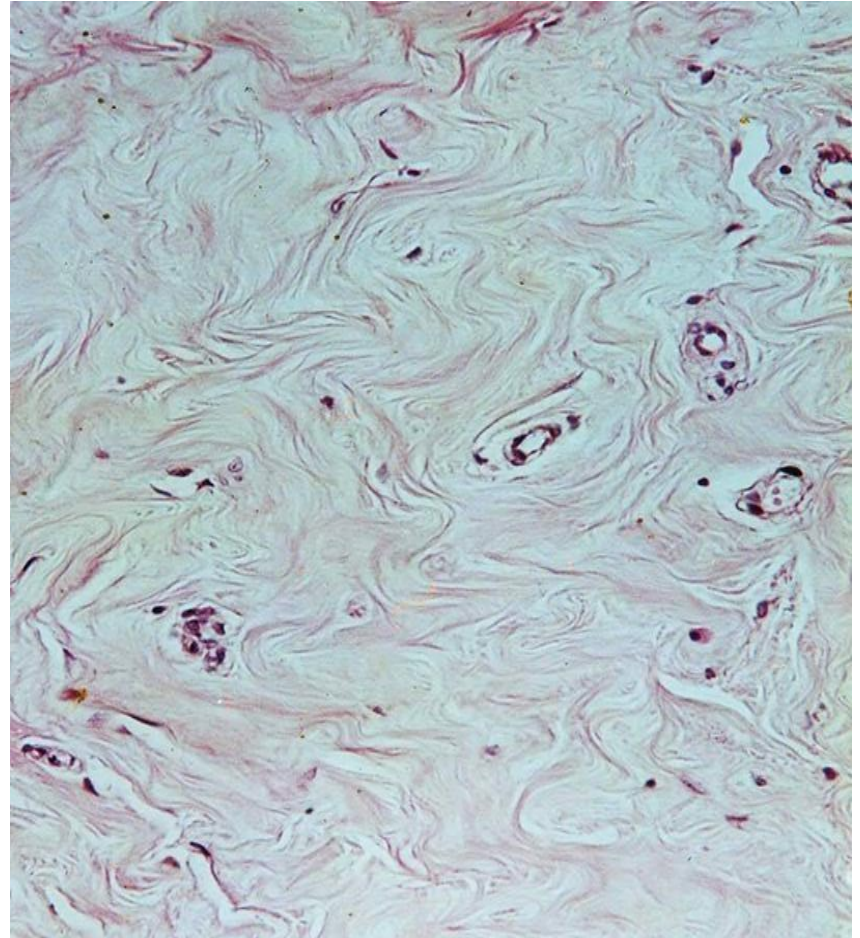


**Regular dense connective tissue contains properly oriented collagens and elastic fibers. Depending on which fibers dominate, the tissue is divided into regular collagenous and elastic connective tissue.**



# Irregular dense connective tissue

It is found in the submucosa of the stomach and intestines, in the depth of the dermis, around larger nerves, in the capsule and septa of numerous organs, etc.



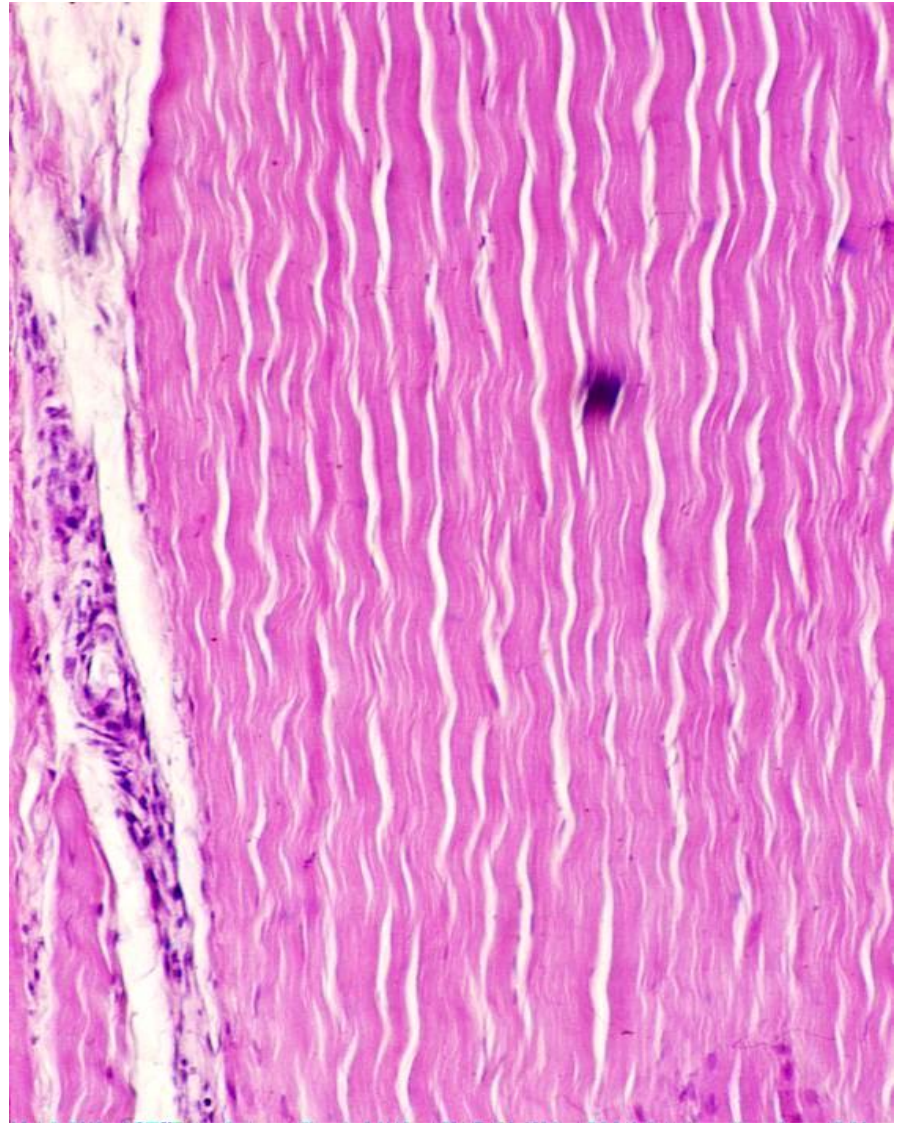
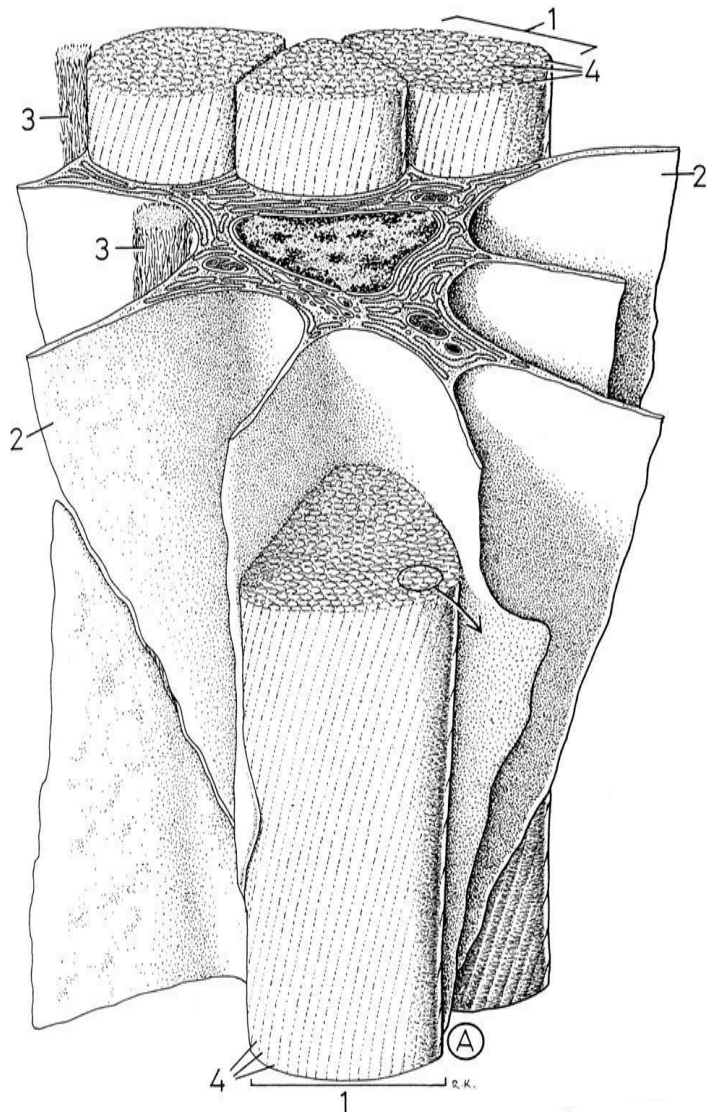
ХЕ бојење

# **Regular collagen dense binder**

- **Regular collagen dense connective tissue can be composed of:**
- **bundles of collagen fibers that have a parallel arrangement, such as**
- **is the case with tendons and ligaments,**
- **bundles or densely packed collagen fibers, where the fibers in one layer are oriented parallel, but the layers are stacked at different angles, which is the case with fascia, aponeurosis, corneal stroma, periosteum, perichondrium, centrum tendineum of the diaphragm, as well as dura mater and skeleton heart valves.**
- **Between the collagen fibrils there is very little basic substance i**
- **rare fibrocytes that are specifically called tendons**
- **tendinocytes.**

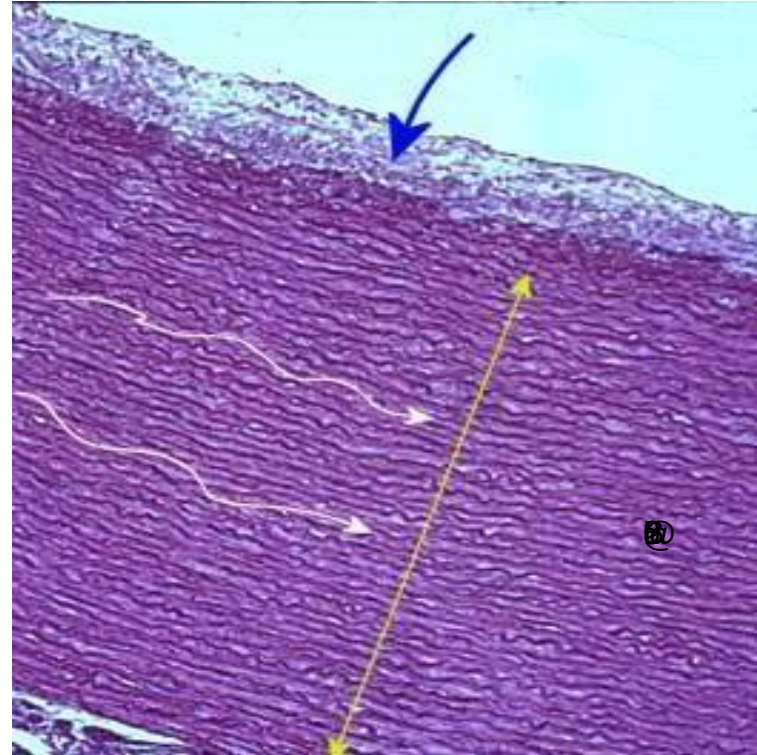
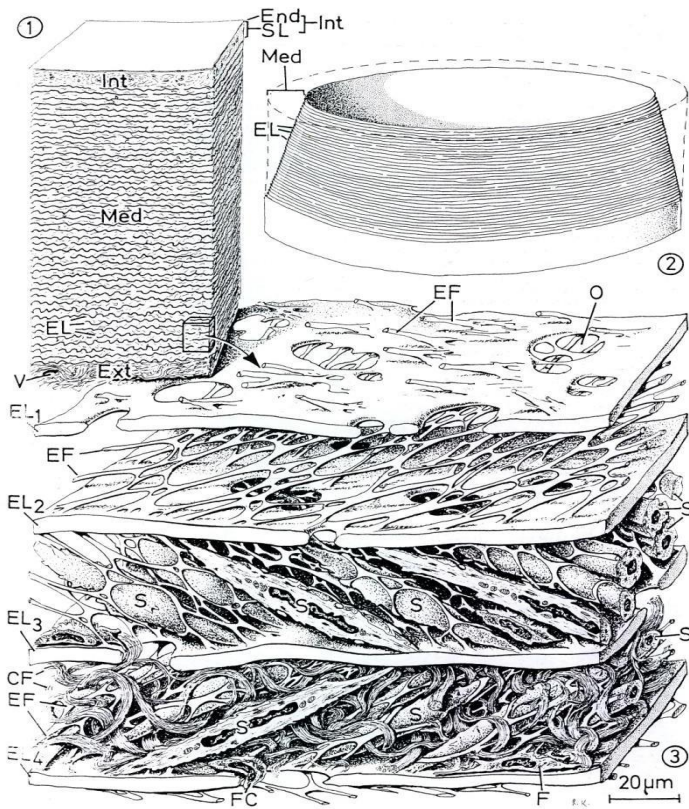


# Tendon





# Elastic connective tissue



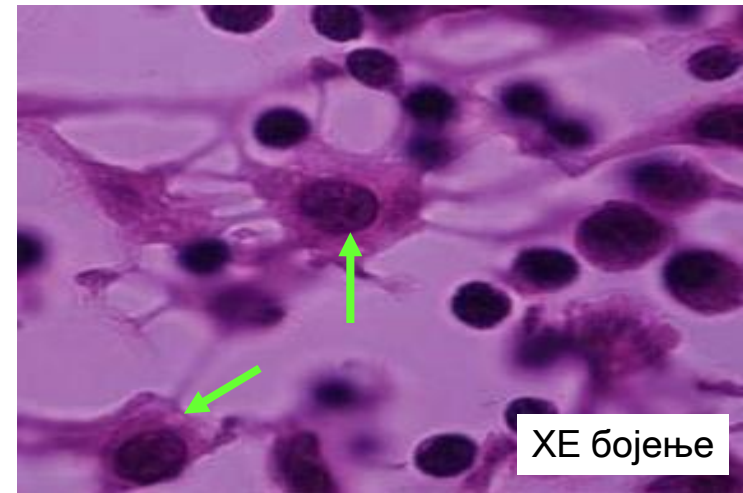
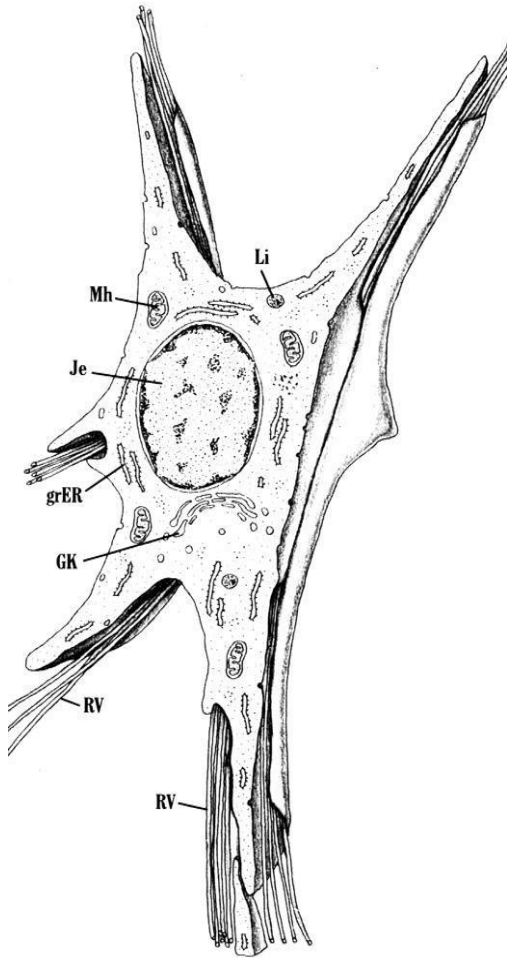
Aorta

**Regular elastic dense connective tissue contains thick elastic fibers, between which there is a little ground substance with rare fibrocytes and few reticular and collagen fibers. It is located in the wall of large blood vessels and certain ligaments (lig. flava, ligg. vocalia, lig. nuche).**

# Hematopoietic connective tissue

- Specialized in blood cell production and lymphocyte maturation.
- The tissue is highly cellular and has a soft consistency.
- It is found in hematopoietic and lymphatic organs, and is divided into myeloid and lymphatic tissue.
- Myeloid tissue is found in the bone marrow and dominates it
- immature blood cells, i.e. precursors of mature blood cells.
- Lymphatic tissue is found in the thymus, spleen, lymph nodes and mucosa of the digestive tract. It is dominated by lymphocytes. Lymphatic tissue is divided into lymphoepithelial and lymphoreticular tissue.
- Myeloid and lymphoreticular tissue contain reticular cells and
- reticular fibers and are often referred to by one name -
- reticular connective tissue.

# Reticular cells

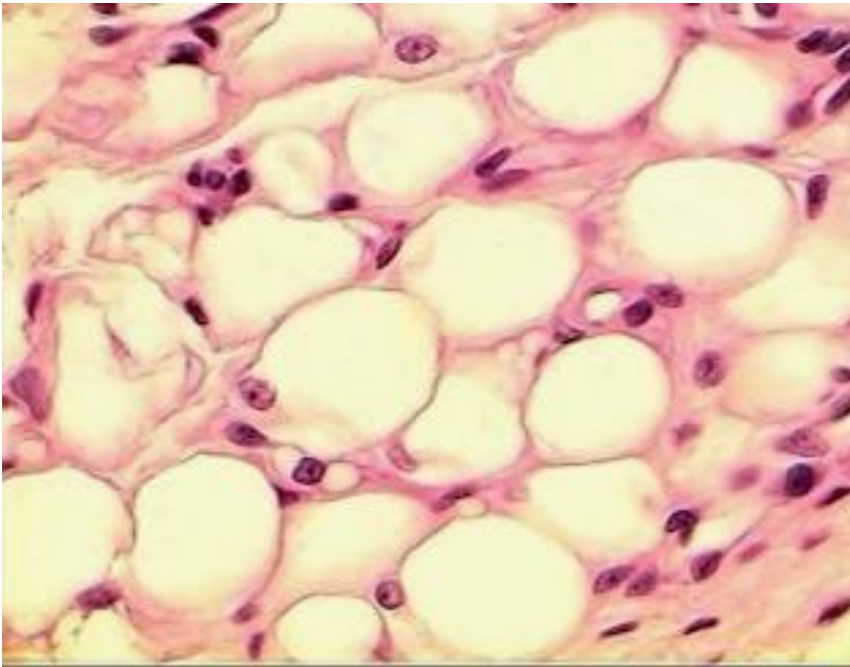


- They have a stellate body and long extensions that wrap the reticular fibers.
- In the cytoplasm, there is a well-expressed system of grER cisterns and the Golgi apparatus, which participate in the synthesis of collagen (reticular fibers).
- Part of the reticular cell population resembles fibrocytes, and the other part resembles macrophages.
- Adventitial cells in the bone marrow and littoral cells of the lymph node are considered a special variant of reticular cells.

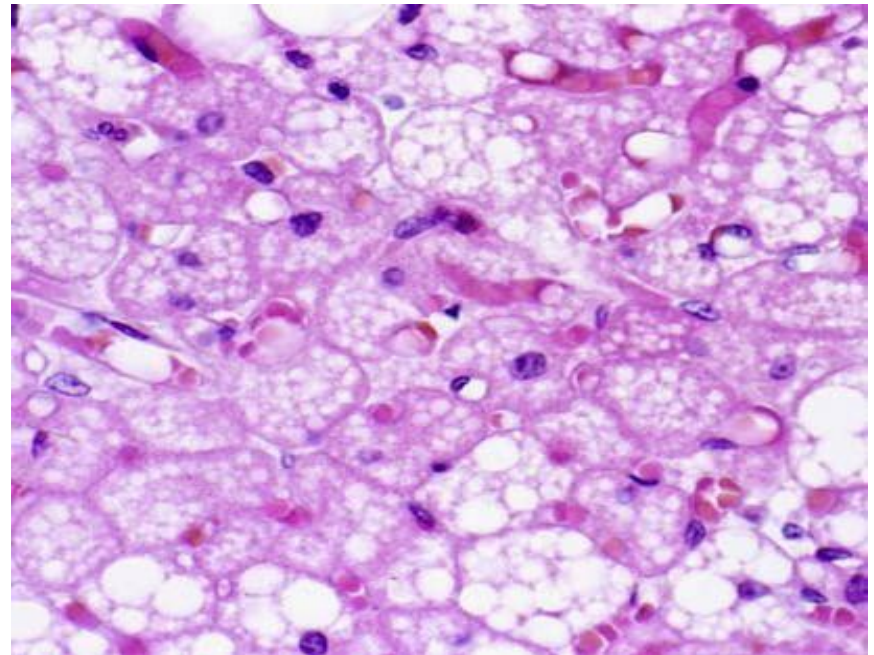


# Fat tissue

- \*Adipose tissue is a highly specialized cellular connective tissue dominated by cells specialized for lipid accumulation.
- \*It is built mainly from cells, while the ECM is less represented.
- \*Fat tissue accounts for about 12-15% of body mass in an adult, and 20-25% in a woman.
- \*It is divided into yellow and brown adipose tissue.

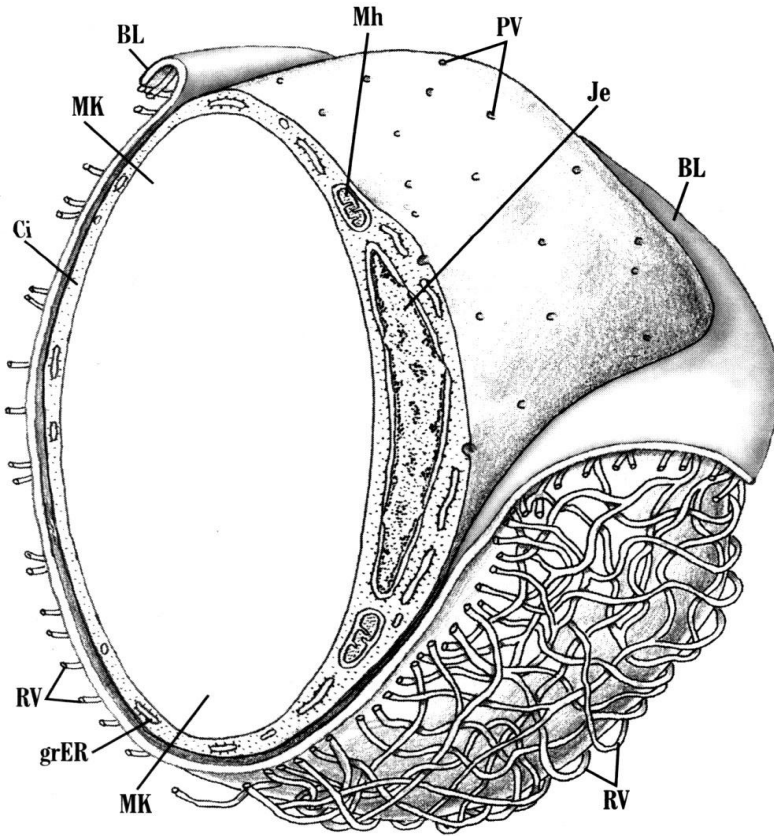


XE бојење -журо масно ткиво



XE бојење - мрко масно ткиво

# Adipocyte

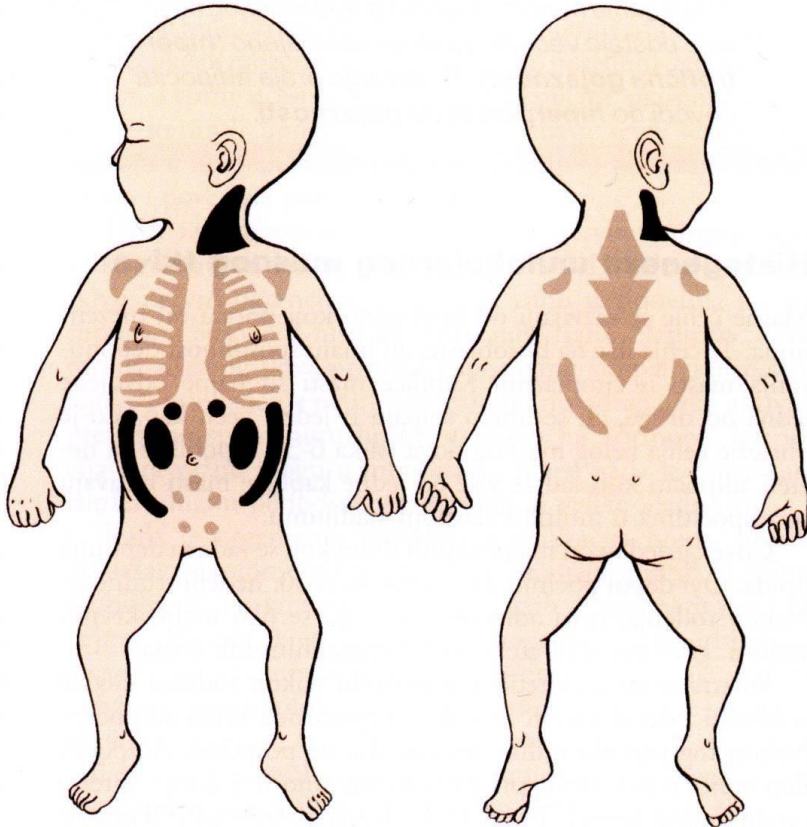


- \* Cells of yellow adipose tissue are called
- \* adipocytes or lipocytes.
- \* An adipocyte is a round cell, diam
- \* 50-150  $\mu\text{m}$ , surrounded by an external lamina.
- \* Organelles are weakly expressed, and the largest part of the cell is occupied by a fat drop. The nucleus is pushed to the periphery of the cell.
- \* Yellow adipose tissue is also called unilocous, because in adipocytes there is only one fat drop in which they are deposited
- \* triglycerides.
- \* Adipocytes secrete the hormones leptin, adiponectin, angiotensinogen and resistin, as well as cytokines called
- \* adipokines.

Roles of adipose tissue:

- energy depot
- mechanical role (shock adsorbent)
- thermal insulator
- thermoregulator
- endocrine role

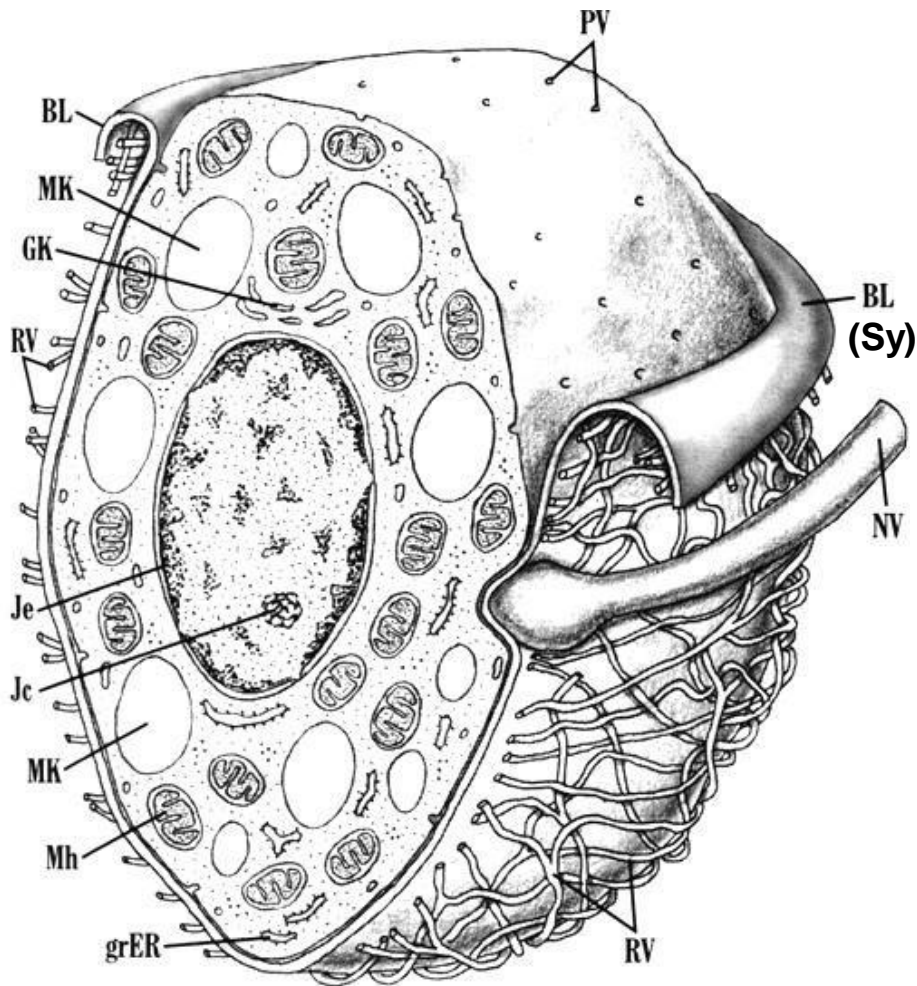
# Dark adipose tissue



- It makes up 2-5% of the newborn's body mass, later it disappears.
- It is located in the neck, mediastinum, abdomen.
- It is specialized in energy production ("chemical heater").
- The dark color of the tissue comes from the high concentration
- cytochromes and a rich network of capillaries.



# Xanthoadipocyte



- The cells of brown adipose tissue are called xanthoadipocytes.
- Xanthoadipocytes are
- polygonal in shape and are much smaller than adipocytes.
- The cell has a round, centrally placed nucleus and a large number of fat droplets (hence the name multilocular tissue).
- Unmyelinated sympathetic fibers directly innervate the cell.



# Cartilage

- Specialized connective tissue whose main role is to provide support to soft tissues
- It is made up of cells - chondrocytes and a tough but flexible extracellular matrix
- matrix
- Chondrocytes tend to group into smaller or larger groups
- They are located in small cavities called lacunae
- Around the cartilage there is an envelope made of dense connective tissue - the perichondrium
- Neither blood vessels nor nerves penetrate the cartilaginous tissue
- Cartilage cells are nourished by diffusion of substances from blood vessels
- perichondrium

# Perichondrium

- \*Cartilage is surrounded by the perichondrium, a sheath of dense connective tissue permeated with blood vessels and nerves. In mature cartilage, the perichondrium is
- \*compact, and two layers can be observed in the growing cartilage:
- \*Outer fibrous
- \*Internal cellular
- \*The outer layer of the perichondrium contains fibroblasts and collagen fibers,
- \*and the inner layer contains stem cells of cartilage tissue - chondrogenic cells
- \*Cartilaginous cells are nourished by diffusion of metabolites from the capillaries of the perichondrium.



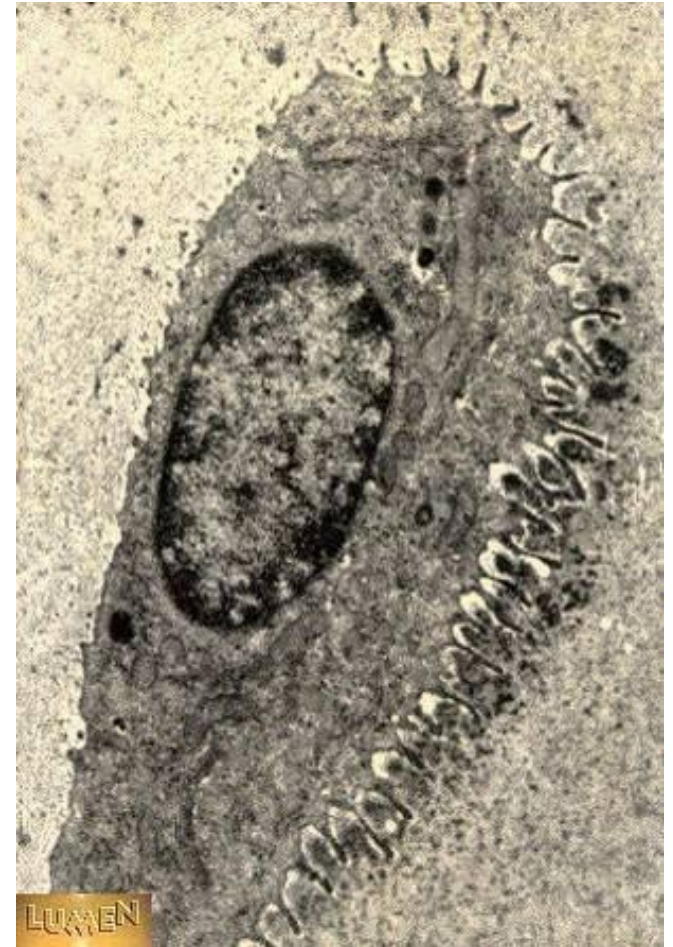
# Cartilage cells

- Cartilage contains three types of cells that belong to the same cell line:
- Chondrogenic cells - the inner layer of the perichondrium
- Chondroblasts - on the surface of the cartilage
- Chondrocytes - in the depth of the cartilage
- The main morphological characteristics of chondrogenic cells are a flattened shape, a dark oblong nucleus and weakly expressed organelles, which indicates their inactivity



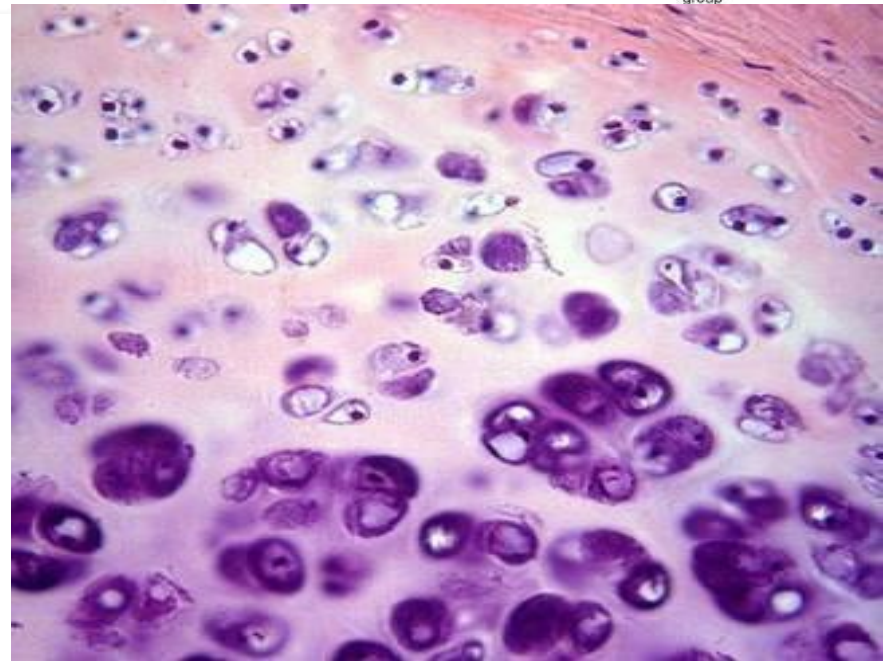
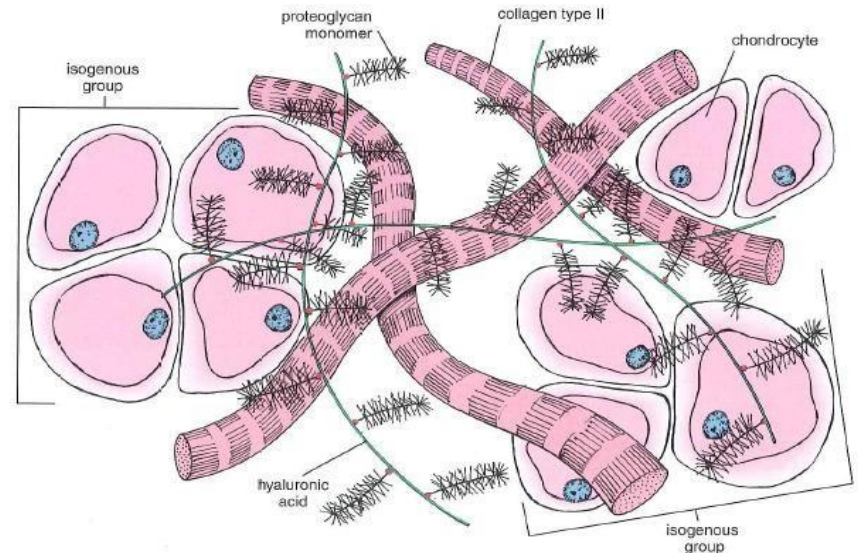


- In growing cartilage, chondrogenic cells are activated and differentiate into immature cartilage cells called chondroblasts
- The nucleus of the chondroblast is oval and bright, and the cytoplasm is filled with secretory organelles
- Chondroblasts synthesize and secrete extracellular matrix around themselves. When they are completely surrounded by cartilage
- cells can be considered matrix
- mature and are called chondrocytes



# Cartilage cells - chondrocytes

- \*Weakly expressed organelles and a lower level of activity than chondroblasts.
- \*The cavities in which the mature cartilage cells are located are called lacunae.
- \*Within the lacuna, chondrocytes can divide and form groups in which the cells are arranged in a row or in the form of a cluster.
- \*A cluster of chondrocytes in one lacuna
- \*is designated as an isogenic group
- \*The narrow band of the extracellular matrix that surrounds the isogenic groups is slightly darker
- \*colored and called territory, while the rest of the matrix is lighter in color and called
- \*interterritory
- \*Isogenic group and territory together
- \*they form a chondron



# Types of cartilage

There are three types of cartilage in the human body:

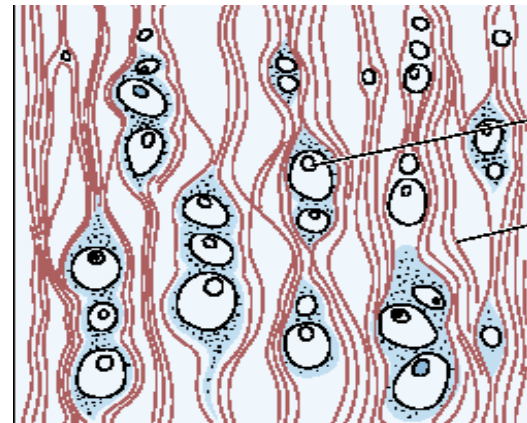
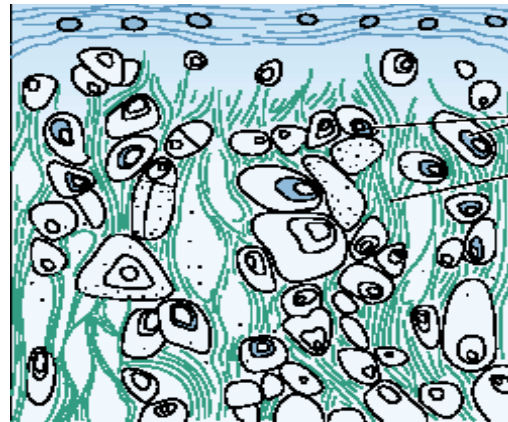
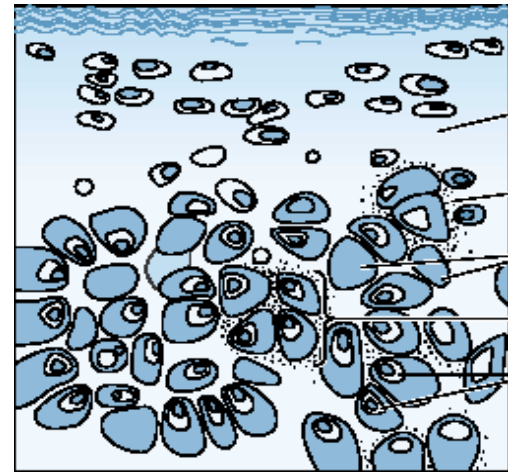
Hyaline

Elastic

Fibrous

\* The differences between them are related primarily to the type and amount of fiber contained in ECM

\* Hyaline cartilage contains fibers made of collagen type II, elastic, in addition to collagen, it also contains a network of elastic fibers, while the fibrous type is dominated by collagen type I fibers





# Hyaline cartilage

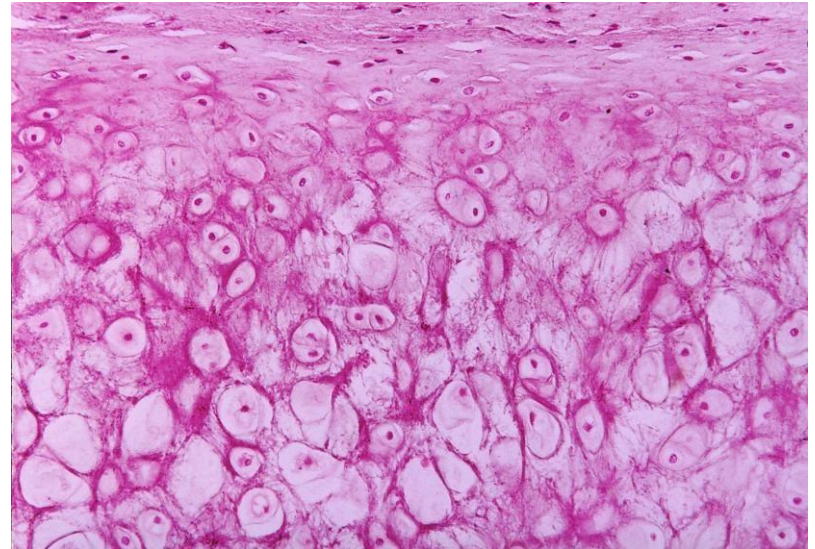
- \* The most common type of cartilage in the human body.
- \* In the embryonic period, it builds the temporary skeleton of the fetus, which is gradually replaced by bone tissue in the fetus
- \* In adults, hyaline cartilage is present on the articular surfaces of movable joints, in the airways and on the edges of the ribs
- \* On a fresh section, the extracellular matrix is transparent like glass, hence the name hyaline (Greek: hyalos - glass) cartilage. In hyaline cartilage
- \* as a rule, isogenic groups are circular in shape and contain 2, 4, 8 or more cells

# Hyaline cartilage

- The basic substance contains proteoglycans, glycoproteins and water
- Cartilage proteoglycans join together to form giant supramolecules
- - proteoglycan aggregates that have the greatest influence on the physical properties of cartilage (strength, flexibility, resistance to pressure)
- The most important proteoglycan is aggrecan
- Glycoproteins include: ancorin, tenascin and fibronectin
- 60-80% of hyaline cartilage is water, which is mostly, but not all, bound to aggrecan-hyaluronan aggregates, which enables the transport of substances through
- tissue matrix

# Elastic cartilage

- It is found in the auricle, external ear canal, auditory tube and larynx
- Chondrocytes in elastic cartilage are more numerous, larger and usually form small isogenic groups with two cells each in the lacuna
- In addition to collagen fibers, the extracellular matrix also contains a rich network of elastic fibers
- Elastin makes up this cartilage
- pliable and gives it a yellow color





# Fibrous cartilage

- \*It is found in the intervertebral discs, the symphysis of the groin, the menisci of the knee joint and at the point of attachment of tendons and ligaments to the bone.

- \*The only type of cartilage it does not possess

- \*perichondrium

- \*It contains a little basic substance and a big one

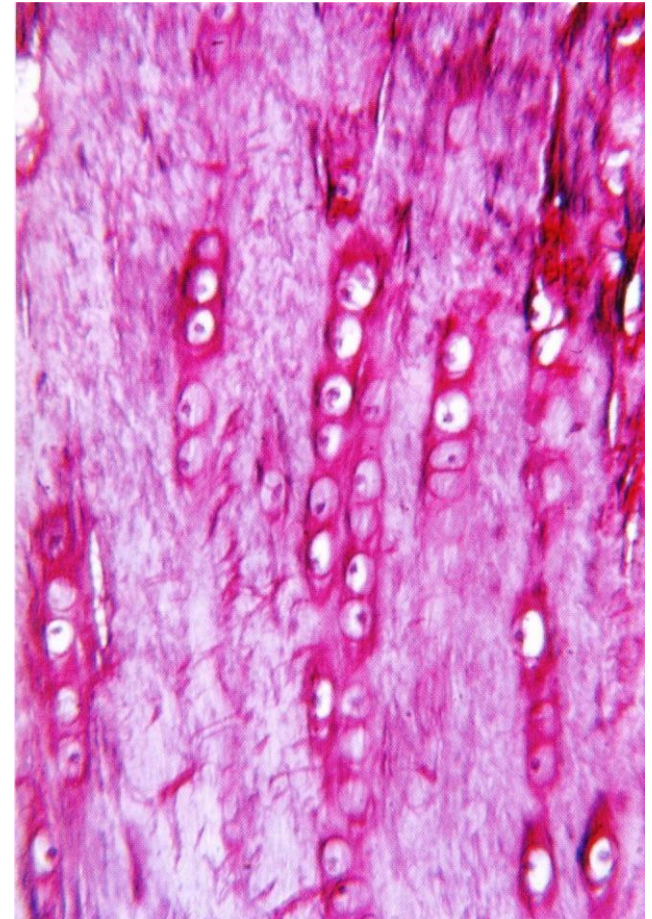
- \*amount of type I collagen fibers

- \*Collagen fibers are organized into bundles that give the cartilage its whitish color

- \*Chondrocytes are placed between bundles of collagen fibers as single cells or

- \*grouped in the form of a string

- \*Chondrocytes resemble fibrocytes, from which they differ in their oval shape



# Histogenesis and cartilage growth

At the site of cartilage tissue formation, the cells proliferate and create a cell cluster within the mesenchyme, which is called a chondrogenic blast, and the space it occupies is called a chondrification center.

Cells in the blastema begin to form a cartilaginous matrix and become  
Chondroblasts

Cartilage grows in two ways:

Appositional growth - new cartilage tissue is created from the surface of existing cartilage

Interstitial growth - new tissue is created inside the existing one

Cartilage regeneration is a limited regenerative power that is better pronounced in children, while in adults it is slow and incomplete - regeneration is carried out through the perichondrium

# Bone tissue

- Bone tissue is a supportive connective tissue with a mineralized intercellular matrix and numerous roles:
- Providing support and enabling movement
- Protection of vital organs in the cranial and thoracic cavity
- Storage of minerals, primarily calcium and phosphorus
- It is made of organic and inorganic material
- Its hardness is given by calcium phosphate precipitated in the form of hydroxyapatite crystals
- Its strength is given by the collagen fibers in which these crystals are incorporated



# Bone tissue

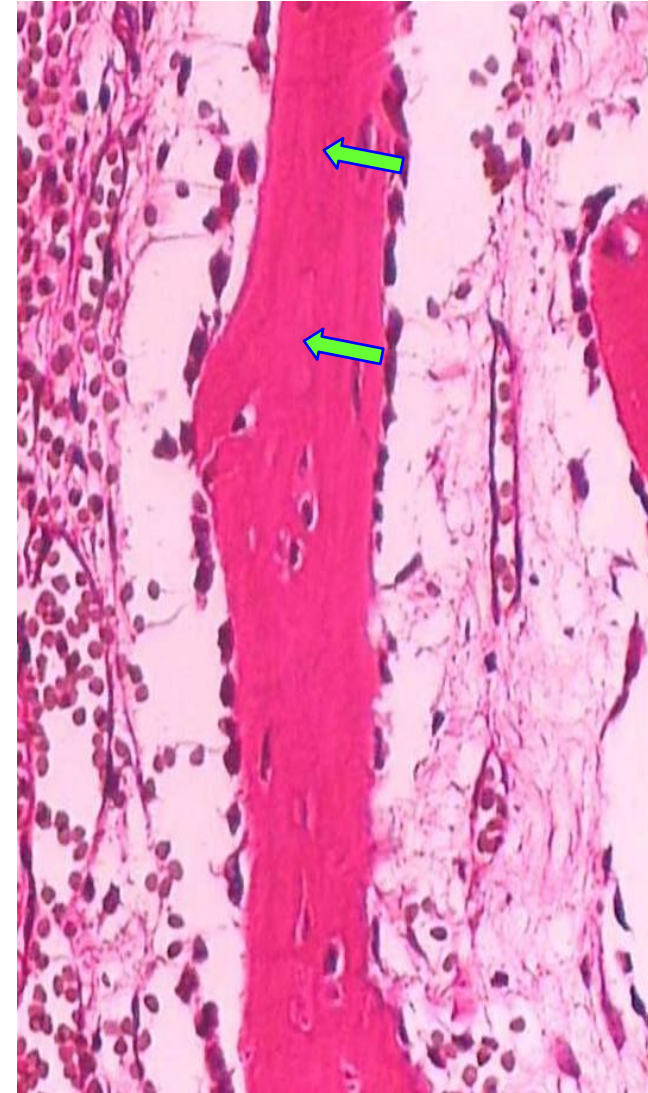
- In the case of demineralization, the bone becomes flexible like a tendon, and with the removal of the organic substrate, the bone becomes brittle and easily broken.
- In the human body, only enamel and dentin are harder than bone, and only cartilage better withstands mechanical stress
- The outer surface of the bone is covered by a layer of dense connective tissue (periosteum), and the inner endosteum
- Osteogenic cells are found in these bone sheaths
- Inside the bone tissue there are cavities (lacunae) in which they are located
- mature bone cells - osteocytes

# Bone tissue cells

- In the functional sense, four types of cells belong to the bone tissue:
- Osteoprogenitor cells
- Osteoblasts
- Osteocytes
- Osteoclasts
- Osteoprogenitor cells, osteoblasts and osteocytes represent the same
- a type of cell that is in different stages of maturity and activity
- Osteoclasts belong to a special cell line

# Bone tissue cells - osteoblasts

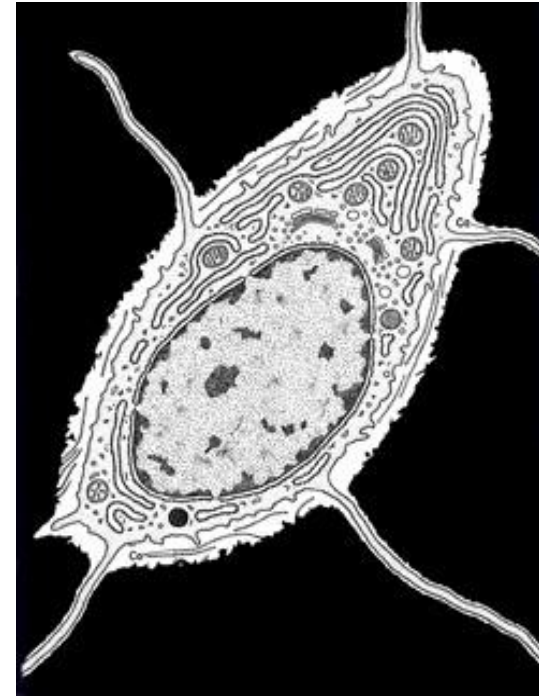
- Young bone cells located on the surface of bone tissue
- They differ from osteoprogenitor cells by their larger dimensions, oval shape, and numerous numbers
- micro pinches, light round stain and well
- developed organelles, especially those responsible for protein synthesis
- (granulated ER, Golgi complex)
- They secrete osteoid - an organic part outside the cell matrix, and help in its mineralization. Some osteoblasts remain during the secretion.
- "trapped" in the matrix they create around themselves and
- they become osteocytes





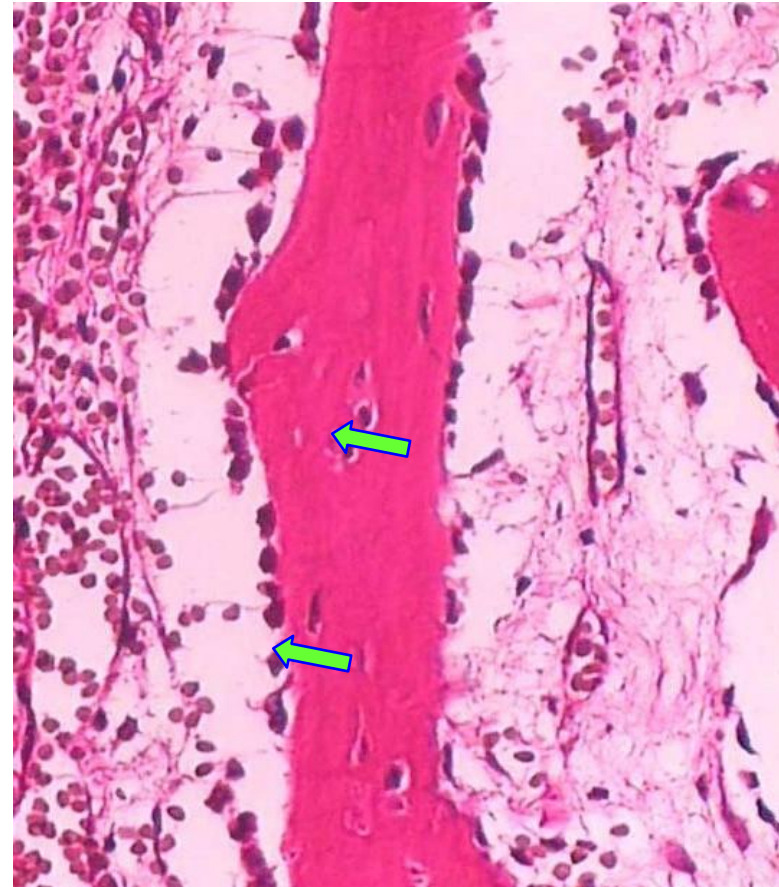
# Bone tissue cells - osteocytes

- Mature bone cells "trapped" in the mineralized bone matrix
  - They are located in small cavities called lacunae
  - There is one osteocyte in each lacuna
  - Adjacent lacunae are interconnected
  - narrow bone canals (canaliculi ossei)
  - Osteocytes are smaller than osteoblasts and have the shape of a plum stone
- 
- During their life, they go through phases of activity and rest  
Osteocytes have a long lifespan and do not have the ability to divide.  
Compared to osteoblasts, they have weaker organelles



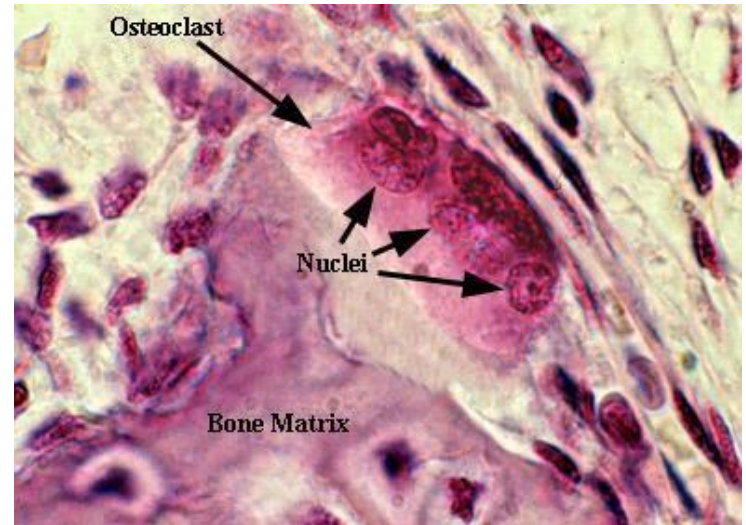
# Bone tissue cells - osteocytes

- Numerous thin and long extensions (filopodia) start from their surface and fill the bone canals
  - Filopodia of neighboring osteocytes touch, and at the point of contact nexuses are formed
  - Through the nexus, nutrients and gases are exchanged between nearby osteocytes (in this way, osteocytes are supplied with necessary substances through each other)
- \* Their role is to maintain the bone matrix.



# Bone tissue cells - osteoclasts

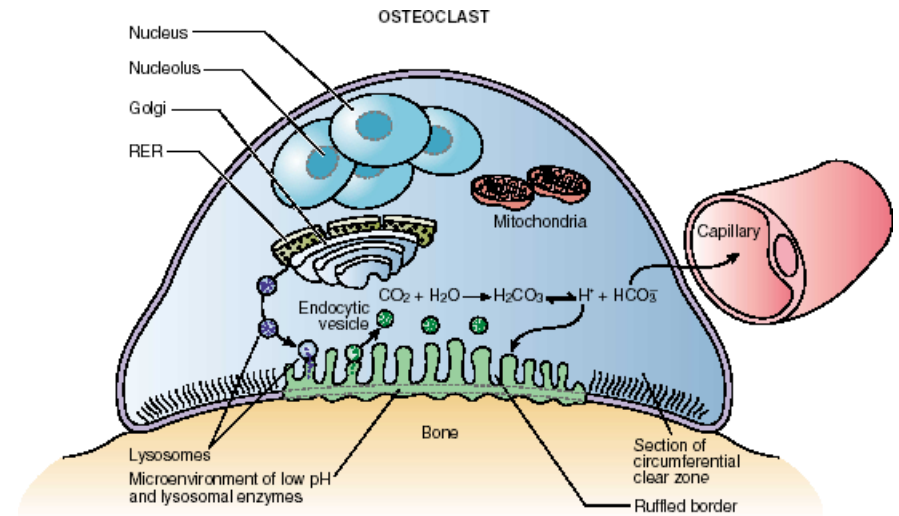
- Large motile cells that break down bone tissue
- They are formed by the fusion of a large number of monocytes
- They belong to the mononuclear phagocytic system
- They have 2-50 nuclei and well-defined organelles
- They act from the surface of the bone tissue where they make shallow depressions called Howship's lacunae





# Bone tissue cells - osteoclasts

- On the surface facing the bone tissue, osteoclasts have numerous fingers
- grows out. That part of the cell is called the ruffled border.
- The rest part
- of osteoclast surface is
- relatively smooth.
- Between the wrinkled edge and the bone there is a narrow subosteoclast space (it is created in it
- specific acidic microenvironment
- - catabolic pot)



# Bone tissue cells - osteoclasts

At the border between the smooth and wrinkled part of the osteoclast surface is located

the so-called bright zone (does not contain organelles and is used by the osteoclast to adhere to the bone)

Bone resorption takes place over the wrinkled edge (matrix demineralization and collagen breakdown) by expelling enzymes into the extracellular space

Cathepsin K participates in the breakdown of collagen and basic substances  
matrix metalloproteinases

HCl secreted by the osteoclast participates in matrix demineralization

\* Local and systemic humoral factors regulate osteoclast formation and activity

Systemic factors: parathormone (stimulates), calcitonin (inhibits), corticosteroids, estrogens and androgens

Local factors: RANKL (stimulates), osteoprotegerin (inhibits), interleukins, growth factor

# Osteoprogenitor cells

- Resting cells of bone tissue located in periosteum and endosteum
- They have a spindle shape, a flattened core and poorly developed organelles
- They have the ability to divide and differentiate into active bone cells -
- osteoblasts
- They are important for bone growth and fracture healing
- The factor for the activation of these cells is CBFA1 (core binding protein alpha1).

# Bone matrix

Organic content:

The largest part of the organic content (about 90%) is collagen type I, and much smaller

part basic substance

The main substance consists of:

Glycoproteins (osteonection, osteopontin, sialoprotein 1 and 2)

Proteoglycans, which are significantly less in bone than in cartilage (hyaluronan, chondroitin sulfate and keratan sulfate)

Inorganic content:

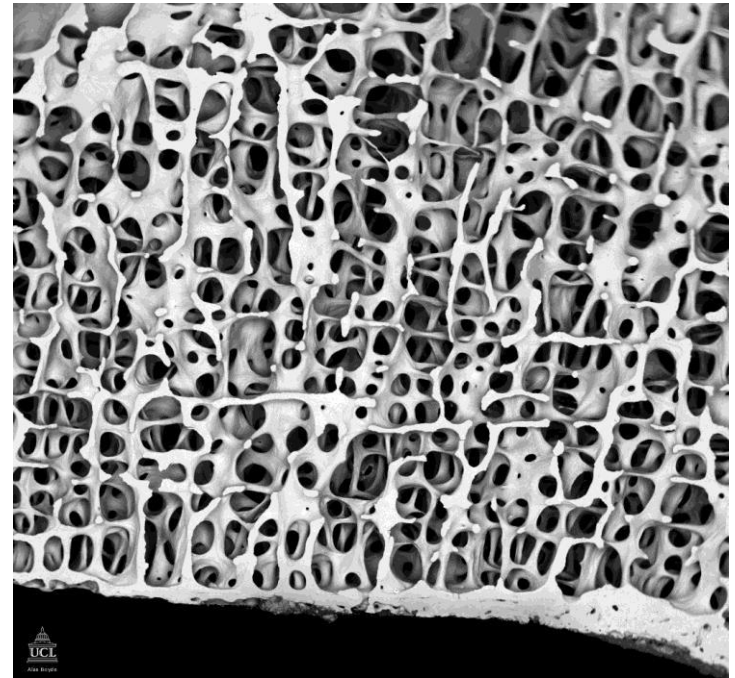
It consists mainly of calcium and phosphorus ions that build hydroxyapatite crystals (they look like needles that dig into collagen fibers).

In addition to calcium and phosphorus, ions are also present in the bone matrix magnesium, sodium, potassium, bicarbonate, citrate, etc.



# Bone structure

- According to the order of occurrence and histological
- bone structure can be:
- Primary or immature (formed during embryonic development)
- Secondary or mature (makes the largest part of adult skeleton)



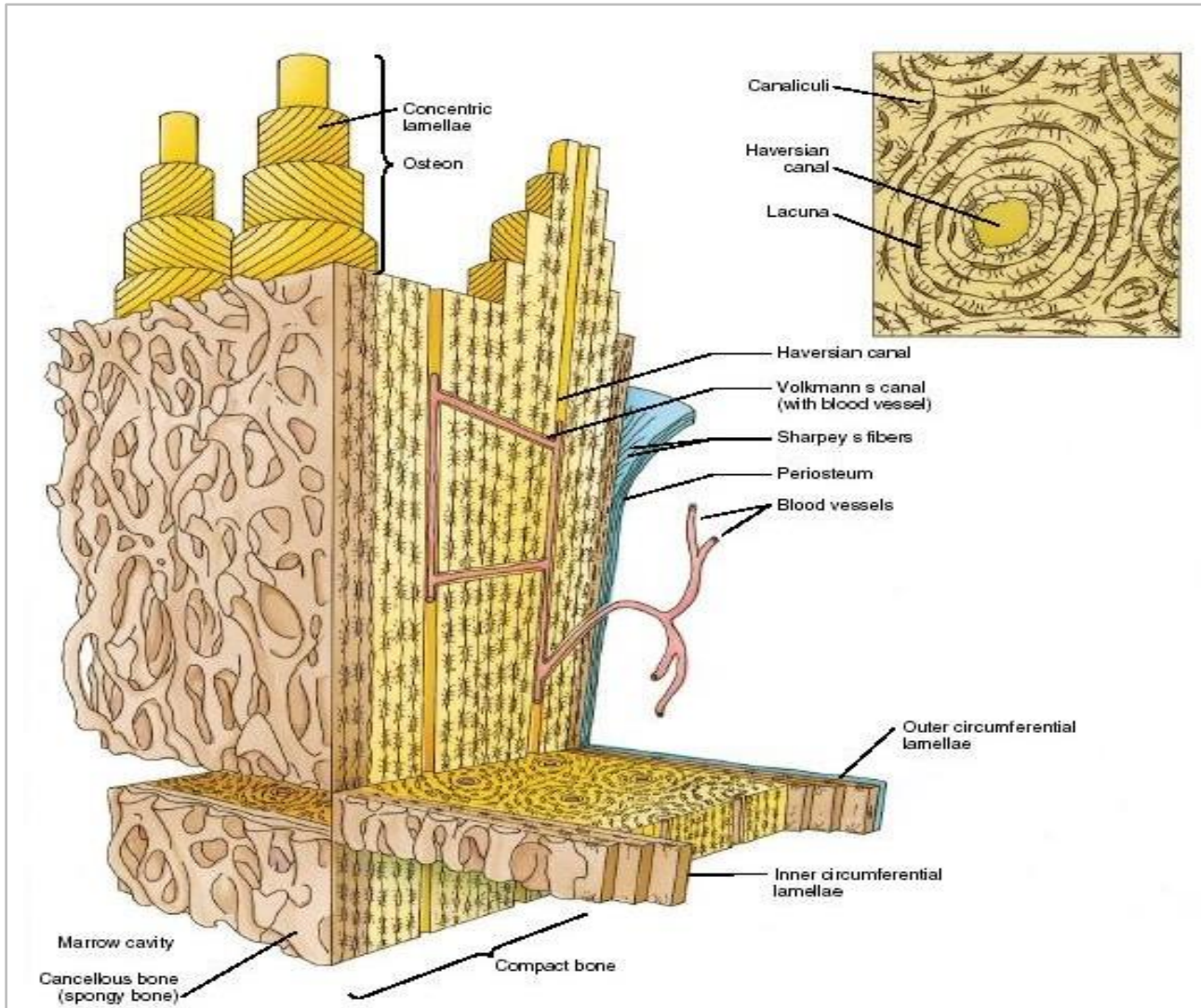
# Primary or immature bone

- It is formed during embryonic development or during bone healing
- fracture
- It is temporary in nature and is gradually replaced by mature bone
- It remains permanently only in dental alveoli, auditory ossicles and in
- near the sutures of the flat bones of the skull
- It contains more cells and basic substances and less minerals than mature bone
- Collagen fibers and osteocytes are distributed randomly, without any order or rule

# Secondary or mature bone

- It makes up the largest part of the skeleton in adults
- It can be compact and spongy
- Compact bone - bone tissue dominates, and the tiny canals that cut it lengthwise and crosswise are hard to see with the naked eye.
- Cancellous bone - basically has a spongy appearance because it contains narrow bone beds separated by wide cavities in which the bone marrow is located
- A layer of collagen fibers and a part of the mineralized matrix in which they are embedded form one bone lamella (sheet) - lamellar bone
- Mature bone cells are usually located between adjacent lamellae

# Secondary or mature bone



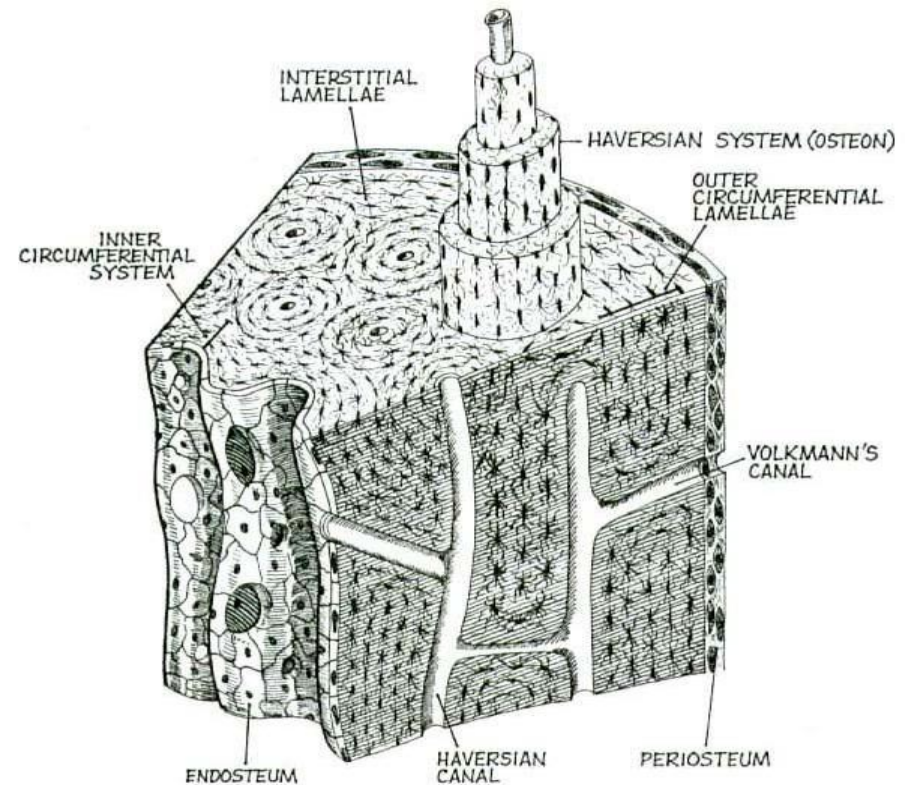


# Cancellous bone

- It makes up about 10% of the skeleton of an adult
- It consists of bone beds that limit the narrow spaces filled
- bone marrow
- Bone beds are usually thin and do not contain blood vessels, ie
- Haversian and Folkmanian canals
- Osteocytes from cancellous bone are fed by diffusion of substances from
- bone marrow

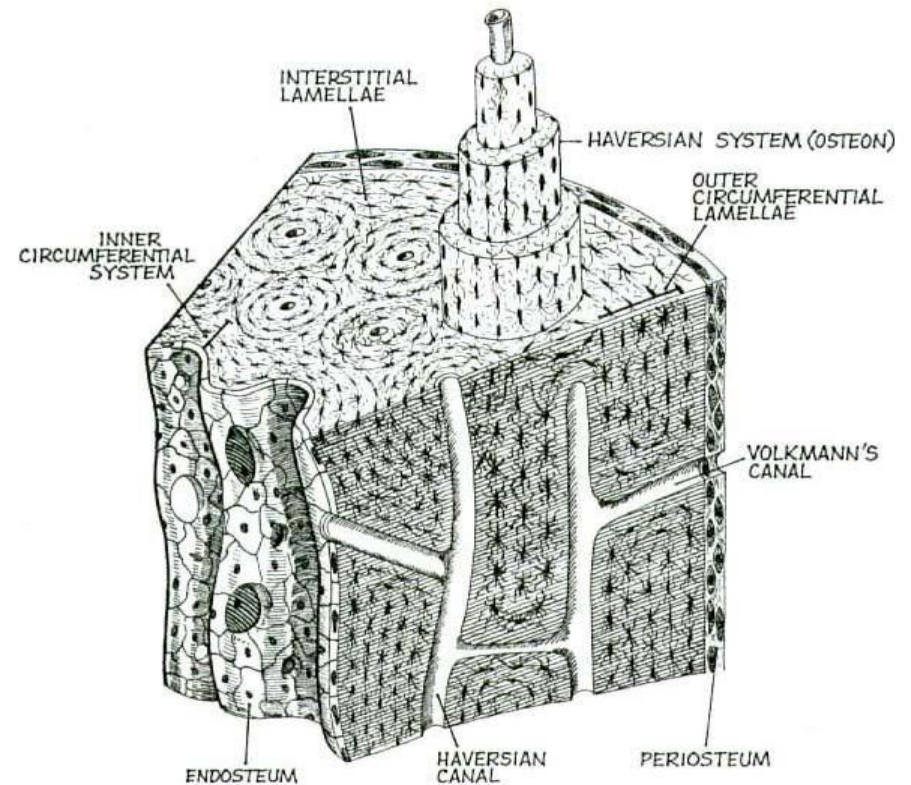
# Compact bone

- \*The basic morphological unit of compact bone is the osteon or Havers system.
- \*Compact bone contains four types of lamellae, most of which are stacked concentrically, like knots in a tree trunk
- \*Between the lamellae there are lacunae with osteocytes
- \*Adjacent lamellae are connected by narrow canals (canaliculi ossei) through which osteocytes provide filopodia and establish mutual communication.



# Compact bone

- \*Communication between osteons is carried out through Folkman's channels
- \*In addition to concentric (Haversian) lamellae, they are described in compact bone three more types of lamellae:
  - \*interstitial (transitional) lamellae between osteons
  - \*outer circular lamellae below the periosteum
  - \*internal circular lamellae around the bone marrow cavity



# Bone histogenesis

- A smaller part of the skeleton is formed by intramembranous ossification, and a larger part
- by the process of enchondral ossification
- This division indicates only the mechanism of initiation of the ossification process (with intramembranous ossification - directly from the mesenchyme, with enchondral - through the previous cartilaginous model)
- In both cases, primary (immature) bone is formed first, which it later replaces
- secondary (mature) bone
- Even after the cessation of growth in mature bone, two continuous processes take place
- the opposite process - creation of new and breakdown of existing bone tissue (reshaping or remodeling)



# Bone histogenesis

Intramembranous ossification (direct ossification)

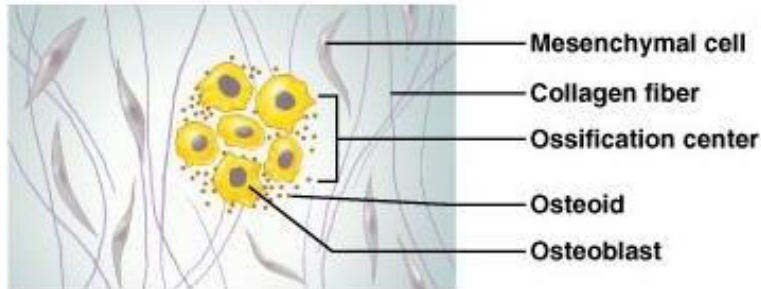
This is how most of the flat bones (bones of the roof of the skull, face, clavicle) are formed.

Mesenchymal cells cluster, differentiate into osteoblasts and form primary ossification center from which the osteoid bands spread radially in the form of beds (trabeculae)

The osteoid is gradually mineralized, and the cells within the trabeculae transform into osteocytes

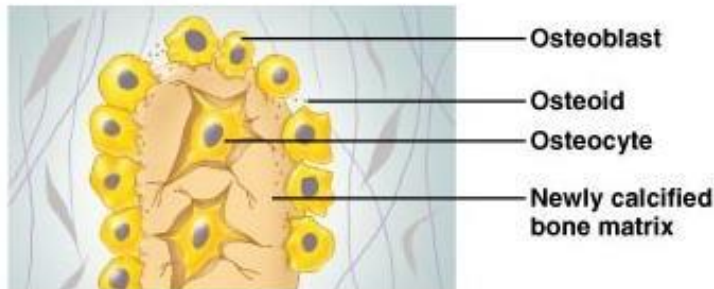
# Bone histogenesis

- Intramembranous ossification  
(direct ossification)**



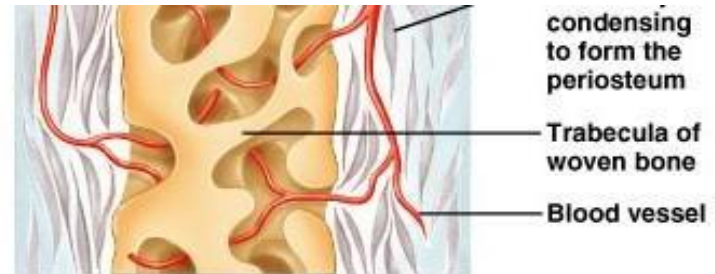
**① An ossification center appears in the fibrous connective tissue membrane.**

- Selected centrally located mesenchymal cells cluster and differentiate into osteoblasts, forming an ossification center.



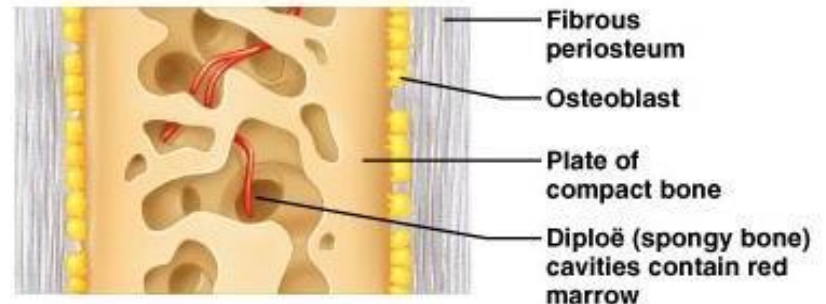
**② Bone matrix (osteoid) is secreted within the fibrous membrane.**

- Osteoblasts begin to secrete osteoid, which is mineralized within a few days.
- Trapped osteoblasts become osteocytes.



**③ Woven bone and periosteum form.**

- Accumulating osteoid is laid down between embryonic blood vessels, which form a random network. The result is a network (instead of lamellae) of trabeculae.
- Vascularized mesenchyme condenses on the external face of the woven bone and becomes the periosteum.



**④ Bone collar of compact bone forms and red marrow appears.**

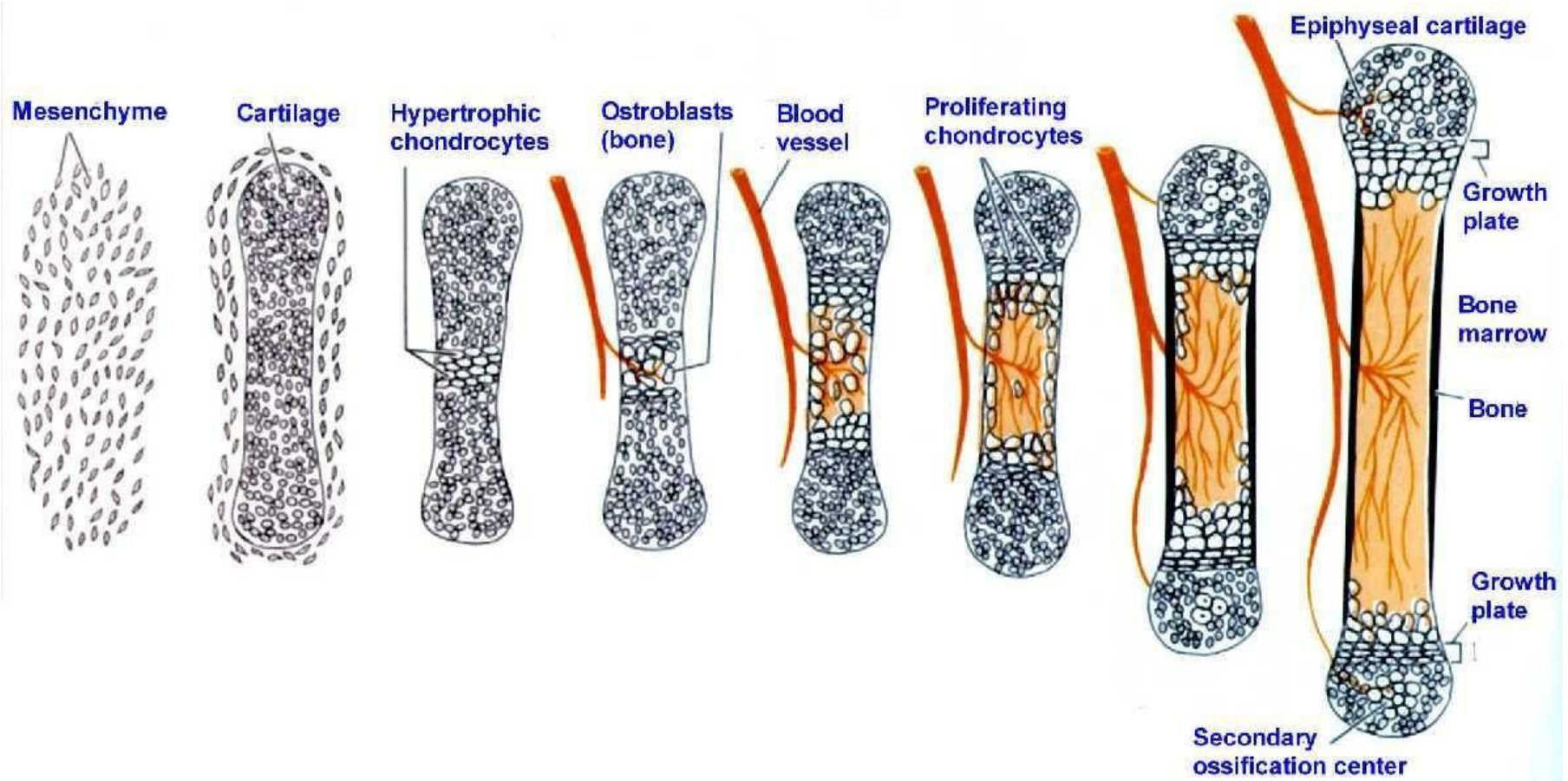
- Trabeculae just deep to the periosteum thicken, forming a woven bone collar that is later replaced with mature lamellar bone.
- Spongy bone (diploë), consisting of distinct trabeculae, persists internally and its vascular tissue becomes red marrow.

# Bone histogenesis

- **Enchondral ossification (indirect ossification)**
- **This is how most of the bones of the human body (the bones of the base of the skull, the spine, the pelvis and the bones of the limbs) are formed.**
- **The process has two stages, in the first a miniature skeleton is created from hyaline cartilage (cartilaginous model), and in the second bone tissue is deposited in its place**
- **The cartilaginous model is created by chondroblasts originating from mesenchymal cells and it grows by appositional and interstitial growth**
- **It begins in the twelfth week of development and lasts as long as a person's growth lasts**
- **The area in the diaphysis where ossification begins is called the primary (diaphyseal) center of ossification and from there ossification spreads towards both epiphyses**

# Bone histogenesis

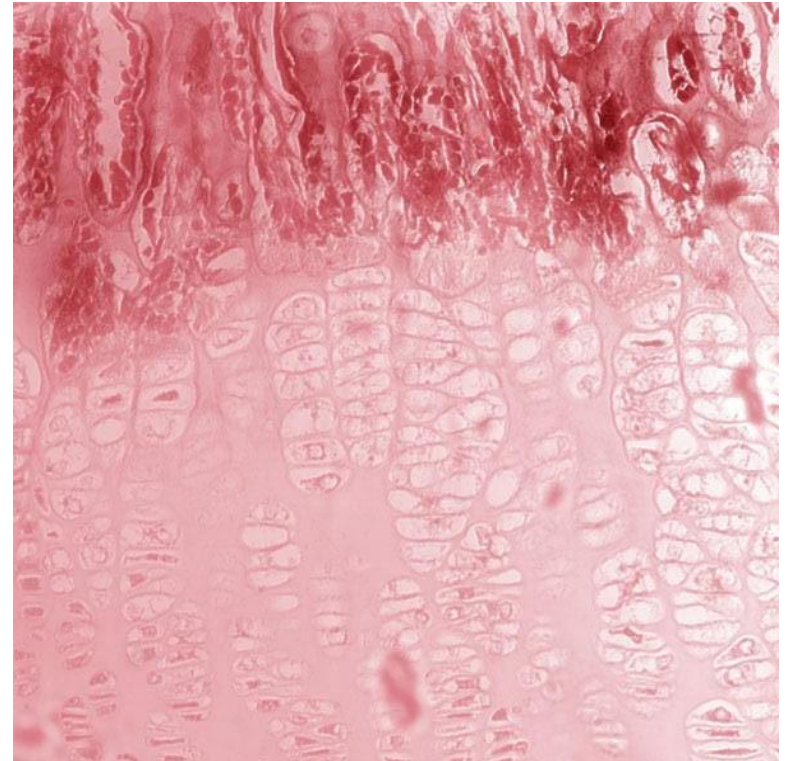
- **Enchondral ossification**  
(indirect ossification)





# Bone histogenesis

- At the border between the epiphysis and the diaphysis, a band of cartilaginous tissue remains, called the epiphyseal cartilage or epiphyseal plate.
- (growth plate)
- In the epiphyseal plate it can be separated
- five zones:
- resting zone
- proliferation zone
- zone of hypertrophy
- zone of calcification
- ossification zone



- Factors that regulate bone growth
- Vitamin D: increases the absorption of Ca from the intestine
- Parathyroid hormone (PTH): increases the level of calcium in the blood
- Calcitonin: reduces the level of calcium in the blood
- Growth hormone: causes bone growth through the growth of the epiphyseal plate
- Sex hormones: closure of the epiphyses of the bone
- IGF, TNF, TGF beta, BMP (bone morphogenic protein), IL1, IL6.....

# Blood

- Specialized connective tissue, which does not have fibers, and the cells do not have a fixed position.
- Basic roles of blood:
- Transport of oxygen and nutrients,
- Transport of carbon dioxide and metabolic products,
- Maintaining homeostasis, osmotic pressure and acid-base balance,
- Dissemination of hormones and regulators,
- Regulation of body temperature,
- Transport of immunoglobulins and lymphocytes.

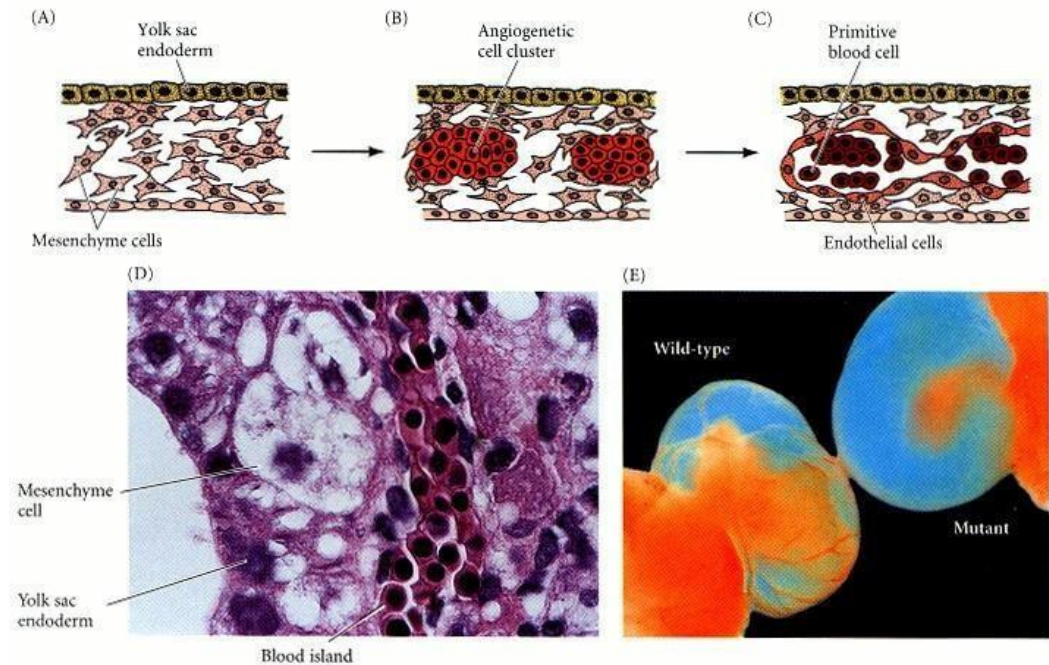
# Blood composition

- By centrifuging the blood, the precipitate is separated, which consists of 45% blood cells, and 55% liquid intercellular substance - blood plasma.
- Blood plasma consists in the largest percentage of water (91-92%) in which proteins, ions, glucose, vitamins, lipids, amino acids, hormones and enzymes are dissolved.
- Plasma proteins (7-8%) consist of albumins (responsible for osmotic pressure), globulins (immunoglobulins), and fibrinogen (responsible for blood clotting).
- The blood cells in the largest number are erythrocytes 45%, and the rest 1% are leukocytes and thrombocytes.



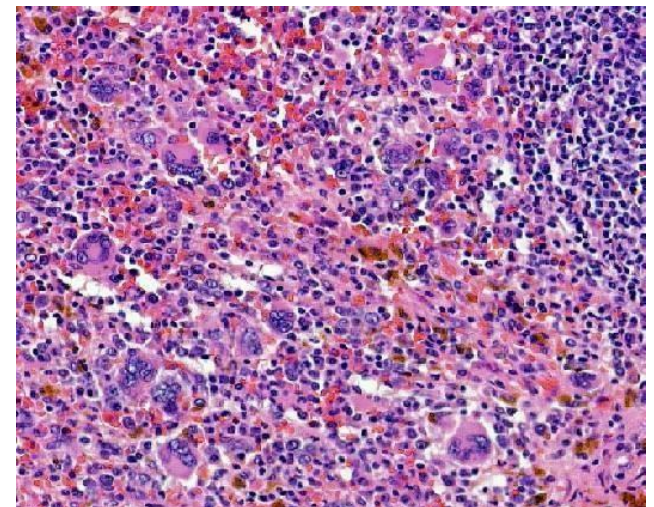
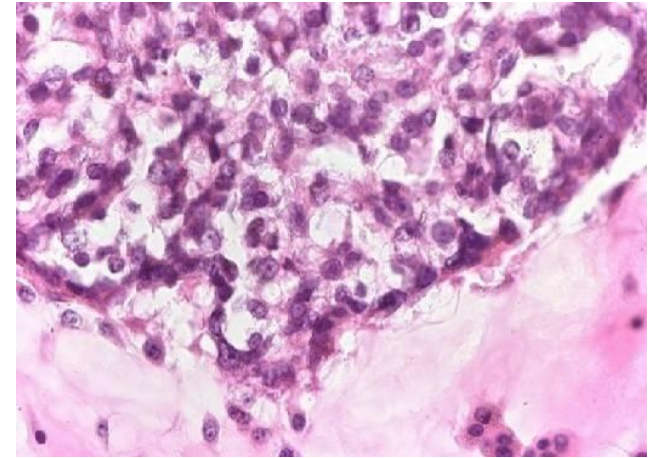
# Hematopoiesis

- It represents the process of creation and maturation of mature blood elements.
- It begins in the third week of embryonic development and lasts until the end of life.
- It is divided into prenatal and postnatal hematopoiesis



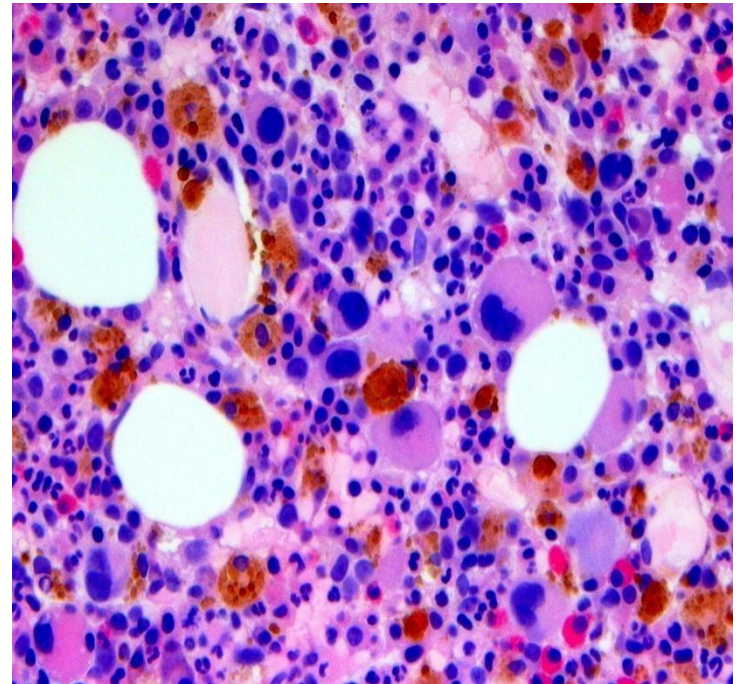
# Prenatal hematopoiesis

- It begins with the formation of large embryoblast (megaloblast) cells in the wall of the yolk sac in the third week of embryonic development.
- Megaloblasts then mature into primitive erythrocytes.
- In the sixth week of gestation, the focus of hematopoiesis is moved to the liver where the formation of leukocytes and trobocytes begins.
- In the seventh week, hematopoiesis takes place in the spleen.
- From the sixth month of intrauterine development
- the main hematopoietic organ becomes bone core



# Postnatal hematopoiesis

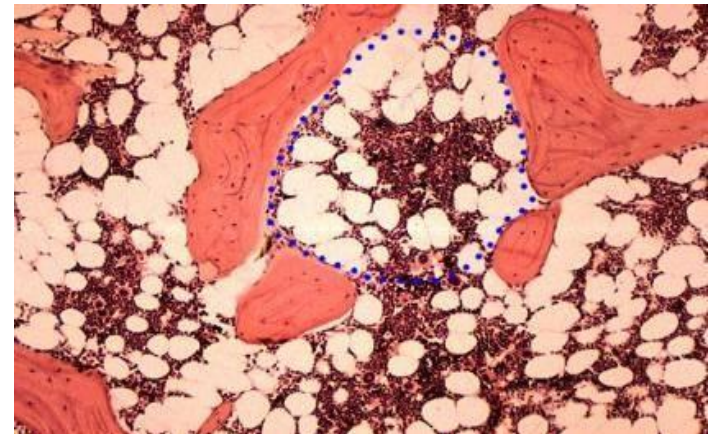
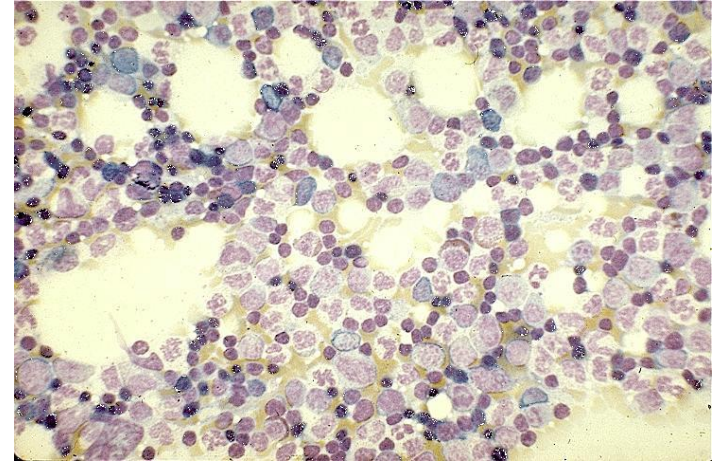
- It takes place in hematopoietic tissue
- red bone marrow.
- Liver and spleen in the postnatal period
- period, they do not participate in hematopoiesis, except in certain pathological conditions.
- In normal physiological conditions, only mature cellular elements go into the circulation, the exception being lymphocytes whose maturation and
- functional activation ends in
- lymphatic organs.





# Bone marrow

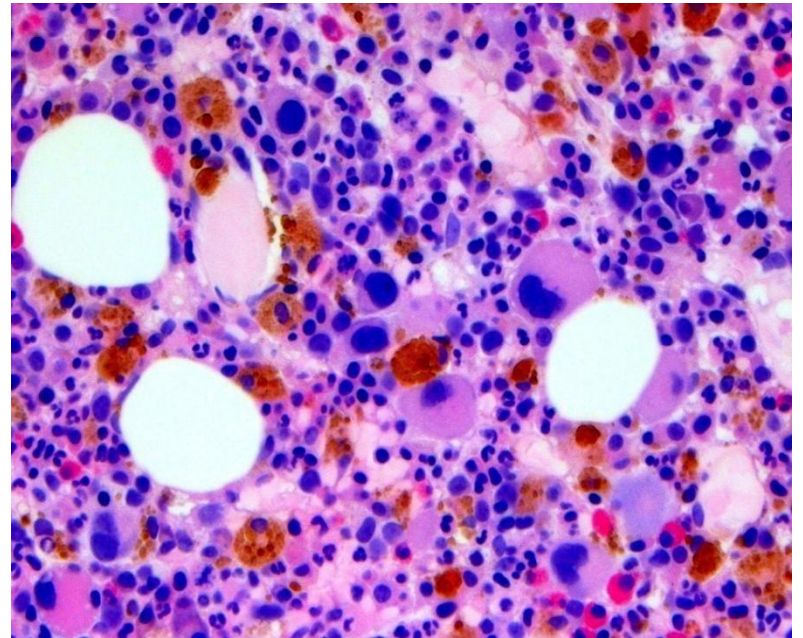
- It represents a specialized well-vascularized reticular connective tissue in which hematopoiesis takes place.
- In newborns, all bone cavities are filled with active bone marrow called red bone marrow.
- From the age of five, the process of infiltration by fat cells begins, so that in adults, the red bone marrow lags behind only in flat bones, while the rest are filled with yellow (fatty) bone marrow.
- One of the most important characteristics of bone marrow is cellularity.





# Bone marrow

- Stroma
  - Reticular connective tissue
  - Fat cells, macrophages and etc
- Vascular compartment
  - Sinusoidal capillaries
  - Hematopoietic strips



# Stem, progenitor and precursor cells

- Cells of all blood lineages arise from a common pluripotent stem cell in the bone marrow.
- The basic characteristics of the stem cell are the impossibility of morphological identification, self-renewal, orientation, determinism.
- The division of these cells results in two types of multipotent stem cells:
  - cells of the myeloid lineage
  - cells of the lymphocyte lineage

# Stem, progenitor and precursor cells

- \*The division of the multipotent stem cell for the formation of the myeloid lineage produces five types of progenitor cells for the formation of erythrocytes, eosinophilic granulocytes, basophilic granulocytes, trobocytes and a common progenitor cell for the formation of neutrophil granulocytes and monocytes.
- \*The division of the multipotent stem cell of the lymphocyte lineage results in two
- \*cell types of progenitor cells, one for the formation of T lymphocytes, a
- \*other B lymphocytes.
- \*Proliferation and differentiation of progenitor cells give rise to the first morphologically differentiated cells called precursor cells.
- \*Further differentiation of precursor cells leads to the formation of a mature cell.

# Erythropoiesis

The process of formation and maturation of erythrocytes.

Erythropoiesis is regulated by various factors, the most important of which is the hormone erythropoietin.

Stages of erythrocyte development:

- Proerythroblast

- Basophilic erythroblast

- Polychromatophilic erythroblast

- Acidophilic erythroblast - (nucleus expulsion)

- Reticulocyte (contains mitochondria, ribosomes, Golgi apparatus)

- Erythrocyte

The process of differentiation and maturation of erythrocytes is characterized by:

- Reduction in cell size,

- gradual loss of cytoplasmic basophilia,

- organelle reduction,

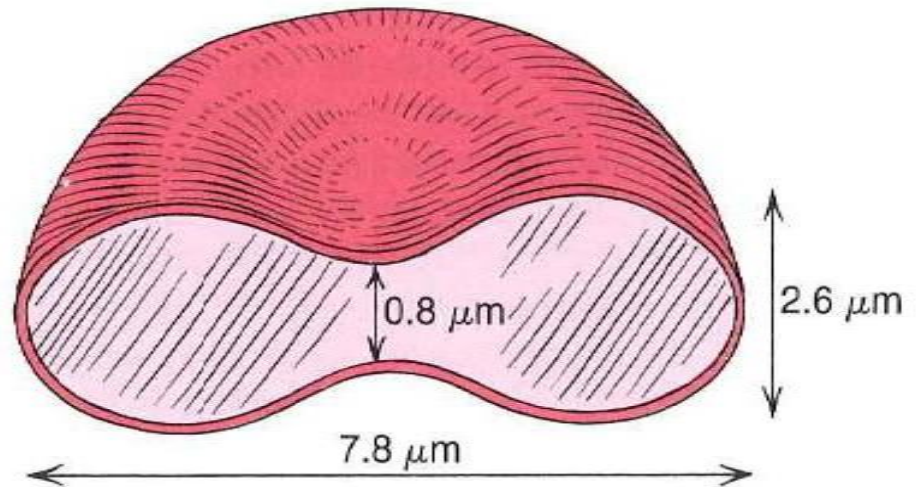
- increase in hemoglobin synthesis and

- reducing the size of the cell until its complete disappearance.



# Erythrocytes

- \* Erythrocytes are in charge of transporting oxygen and
- \* removal of carbon dioxide from all cells in the body.
- \* Mature erythrocytes have the appearance of a biconcave disk with a diameter of  $7.5 \times 2.6 \mu\text{m}$
- \* An erythrocyte is a cell without a nucleus and mitochondria
- \* whose shape and elasticity it enables
- \* spectrin membrane skeleton
- \* Normal number of erythrocytes
- \* for men it is 4.3-5.7 million, and for women
- \* 3.9-5.0 million.



- \* The lifespan is 120 days, after which the aged cells are broken down in the spleen, bone marrow and liver. The main component of erythrocytes is hemoglobin, which transports oxygen from the lungs to the tissues and carbon dioxide in the reverse direction
- \* It is synthesized during the development of the erythrocyte lineage and consists of a protein part - globin and a functional group - heme, which contains an iron ion in the central part.

# Leukocytes

\*Leukocytes are divided into granulocytes, which include neutrophils, eosinophils and basophilic granulocytes, and agranulocytes, which include lymphocytes and monocytes.

\*They have a role in defense and immune reactions.

\*Unlike erythrocytes, they have a nucleus, cell organelles and granules.

\*Normal values of leukocytes range from 5000 to 9000.

\*Leukocyte formula:

\*neutrophils 50-70%

\*basophils 0.5-1%

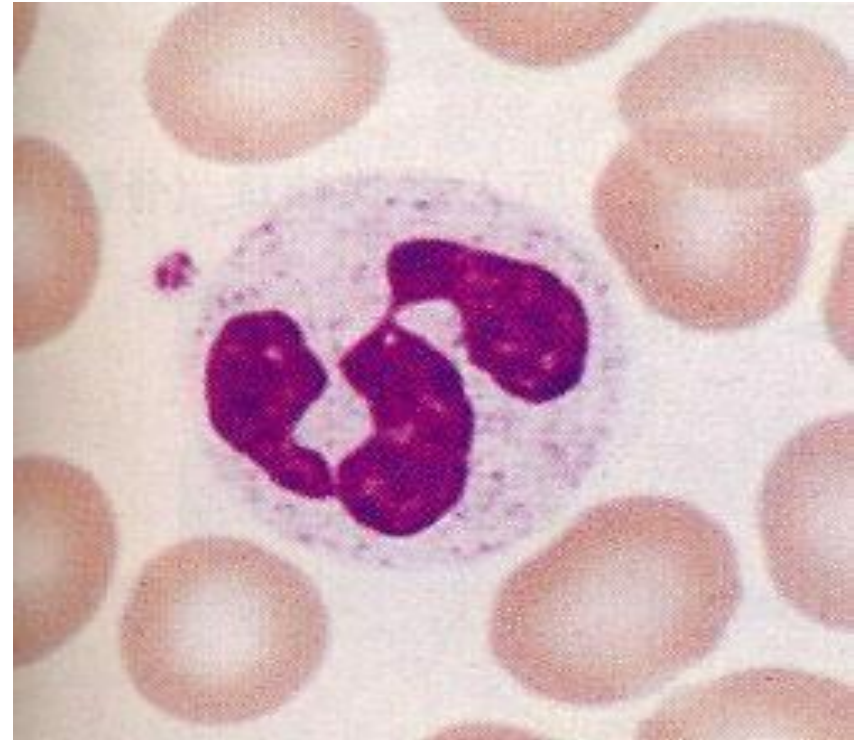
\*eosinophils 1-4%

\*lymphocytes 20-30%

\*monocytes 3-8%

# Neutrophils

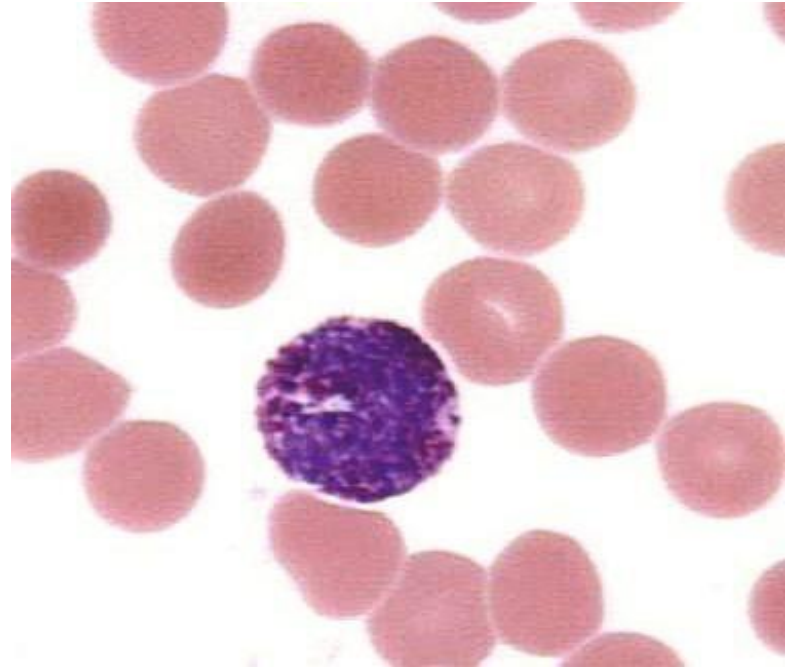
- \* Neutrophils make up 50% to 70%
- \* from the total population of leukocytes,
- \* They have dimensions of 10-12  $\mu\text{m}$ ,
- \* Lifetime 3-4 days,
- \* The sail has 3 to 5 segments,
- \* They are located in the cytoplasm
- \* specific and azurophilic granules.



- \*They have microvilli on the surface, and when they enter tissues, they move using pseudopodia, performing phagocytosis. This is why they are called microphages.
- \*They represent the body's first line of defense, mainly against bacterial infections.
- \*They produce mediators of inflammatory reactions.

# Basophils

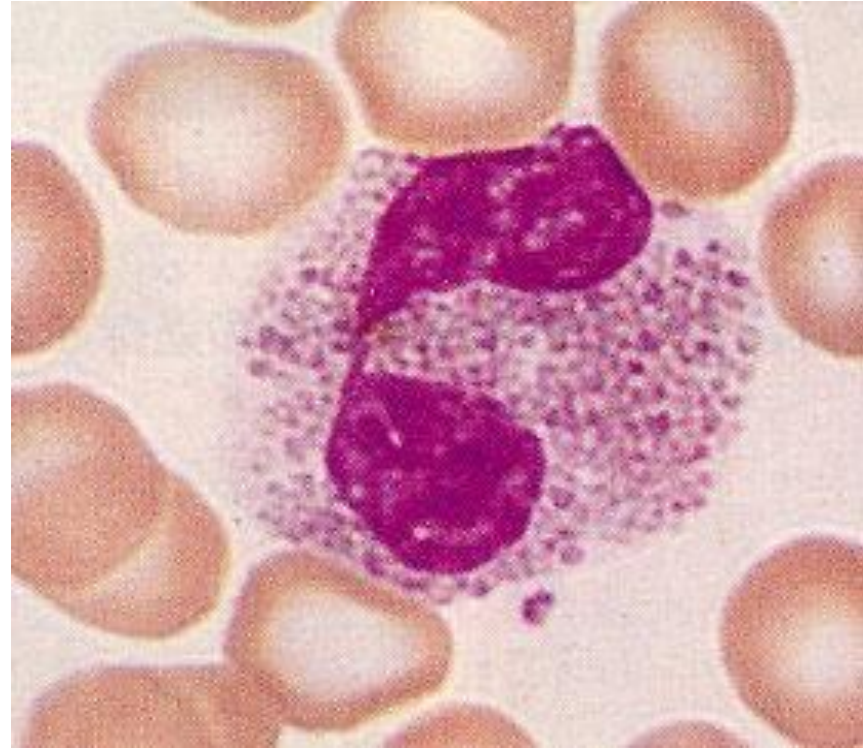
- \*Basophils have the smallest diameter of all granulocytes (9-11  $\mu\text{m}$ ),
- \*They make up 0.5% to 1% of total leukocytes,
- \*They have a bilobed core that is masked by a large number of granules:
- \*specific granules (heparin, histamine and leukotrienes)
- \*azurophilic granules (myeloperoxidase)
- \*\* Basophils are activated in allergic reactions.





# Eosinophils

- \* They have the same shape as neutrophils,
- \* but they are somewhat larger (up to 14  $\mu\text{m}$ ),
- \* They make up 1-4% of the total number of leukocytes,
- \* The sail consists of two segments
- \* There are two types of granules in the cytoplasm:
  - \* specific granules - which have a high affinity for acid dyes,
  - \* azurophilic granules



- \* In allergic and parasitic diseases, their number increases, and they destroy the parasites by pushing out the contents of the granules.

# Monocytes

- Monocytes are the largest blood cells with dimensions of 12-20  $\mu\text{m}$ , round shape and a large, oval, eccentric core.
- They are present in the cytoplasm
- mitochondria, ribosomes, Golgi apparatus and cisterns of the endoplasmic reticulum and azurophilic granules.
- By moving into the connective tissue
- monocytes are subject to phenotypic modifications and increased macrophages responsible for phagocytosis.



# Thrombocytopoiesis

- \*Thrombocyte development begins with a progenitor cell for megakaryocytes, which divides to form a megakaryoblast.

- \*Megakaryoblast, through nuclear division without cell division, first forms a diploid, then a tetraploid nucleus, and in the maturation phase it can reach

- \*polyploid form with 64 nuclei. With these divisions, the cell becomes

- \*lobed, and azurophilic granules appear in the cytoplasm, and the cell at that stage is called a promegakaryocyte.

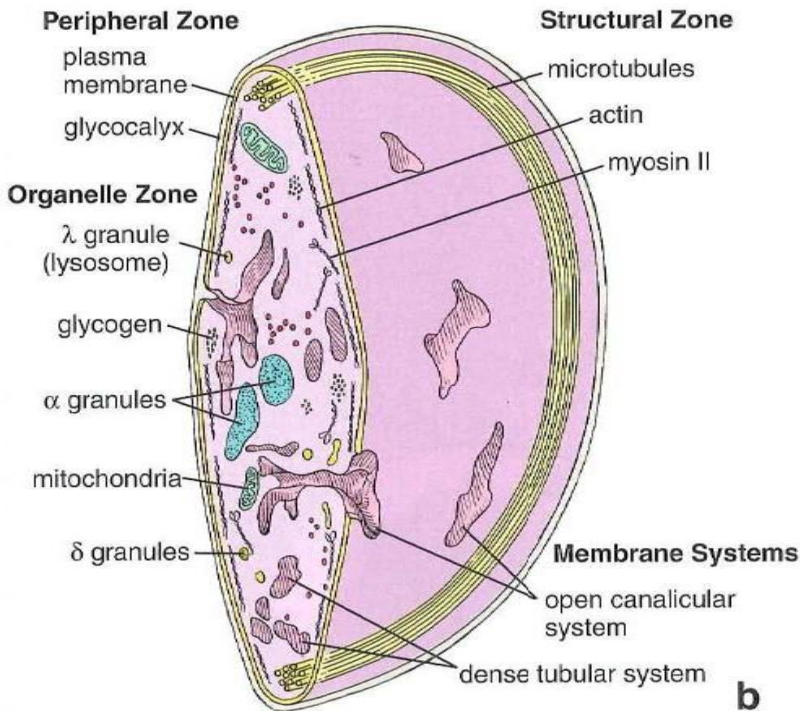
- \*Further differentiation of the promegakaryocyte results in a megakaryocyte.

- \*The megakaryocyte does not enter the circulation, but remains attached to the wall of the sinusoidal capillaries extending its extensions into the lumen.

- \*Platelets break off from the extensions under the pressure of the blood currents and enter the circulation.

- \*Thrombocytopoiesis is regulated by the glycoprotein thrombopoietin.

# Thrombocyte



\*Granulomer - the central part of the platelet in which there are:

\*alpha granules (von Willebrand's

\*factors, factor VIII, platelet factor IV),

\*delta granules (serotonin, pyrophosphate, ATP, ADP)

\*lambda granules (lysosomes with hydrolase enzymes)

\*Hyalomere - the peripheral part of platelets, does not contain organelles, but only elements of the cytoskeleton

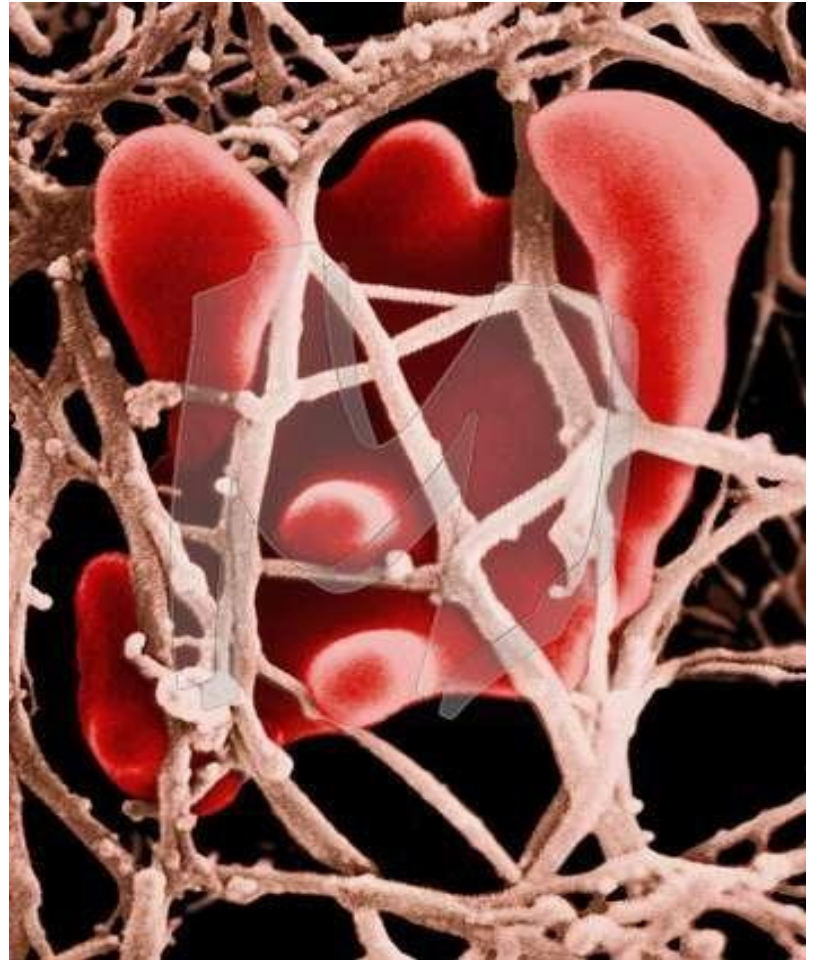
\*marginal bundle of microtubules (8- 24)

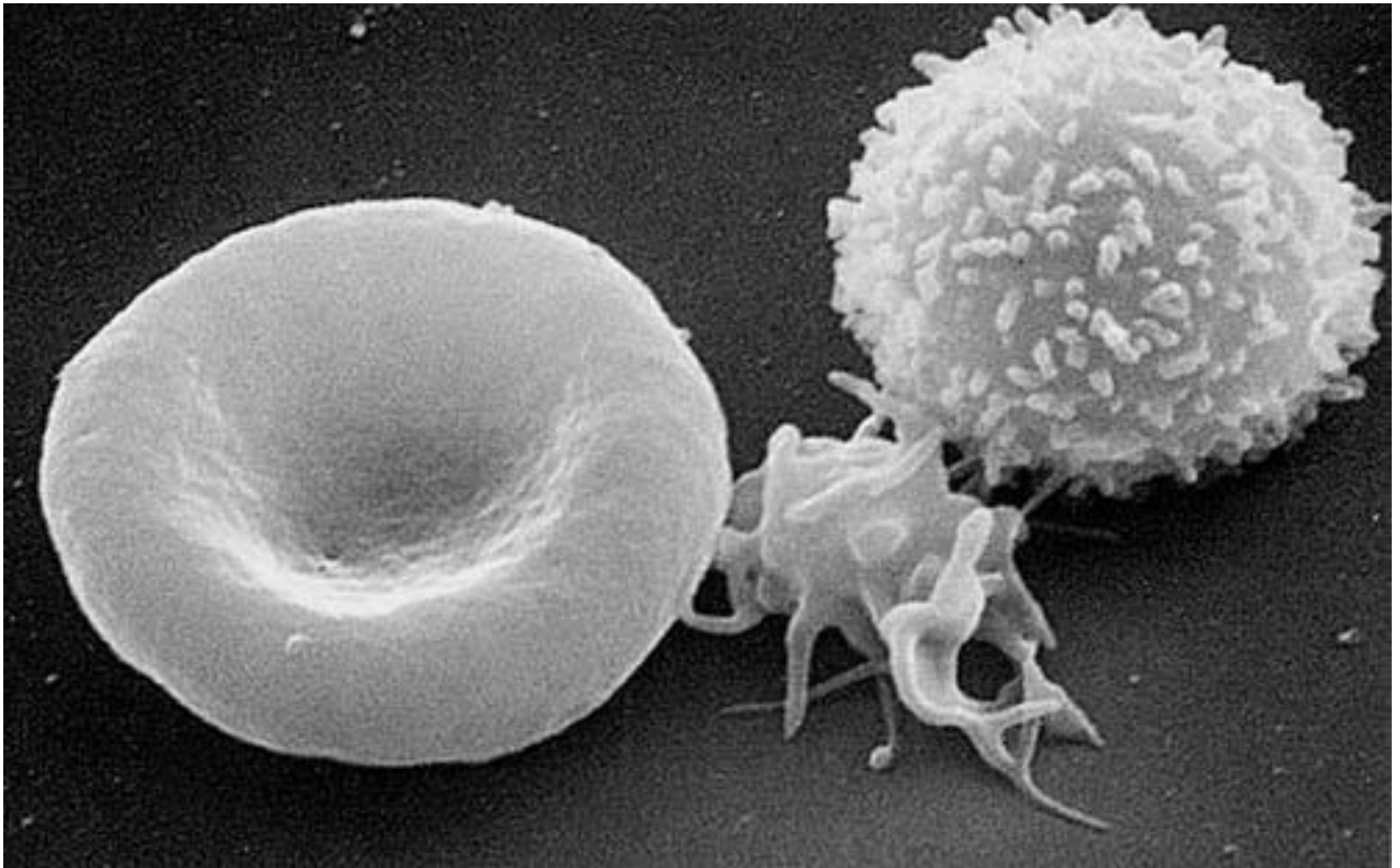
\*actin and myosin



# Thrombocyte

- Platelets play a key role in the processes of hemostasis and clot formation at the site of blood vessel damage.
- The normal number of platelets is 150,000-400,000 per cubic millimeter of blood.





erythrocyte, blood platelet and lymphocyte