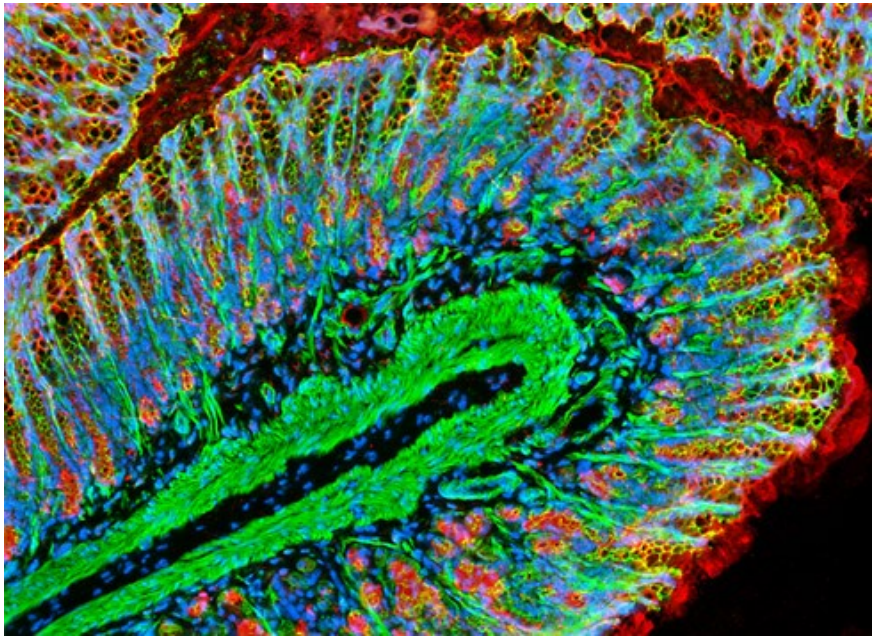

# CONNECTIVE TISSUE

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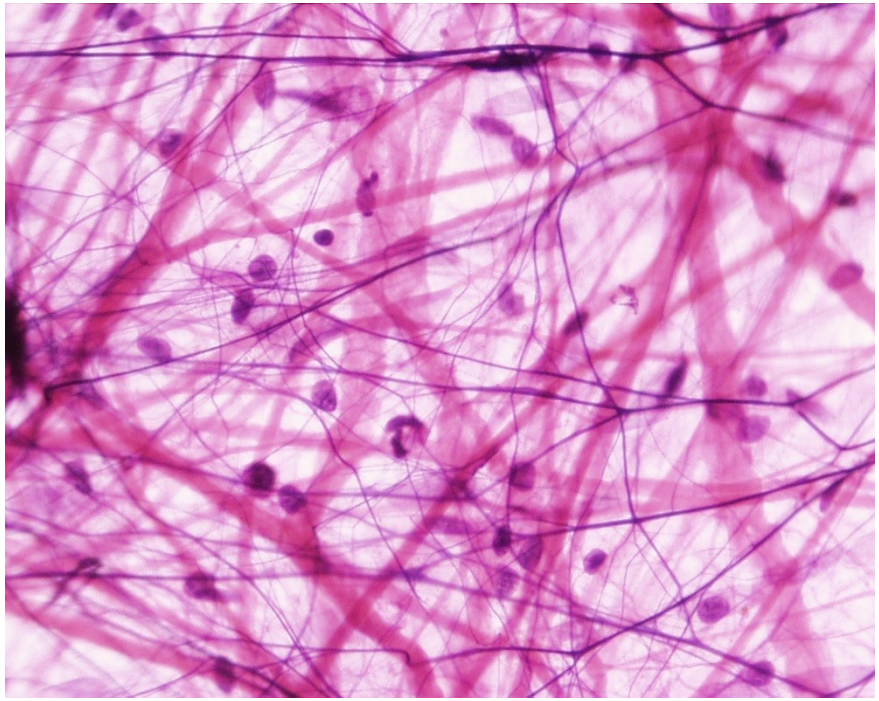
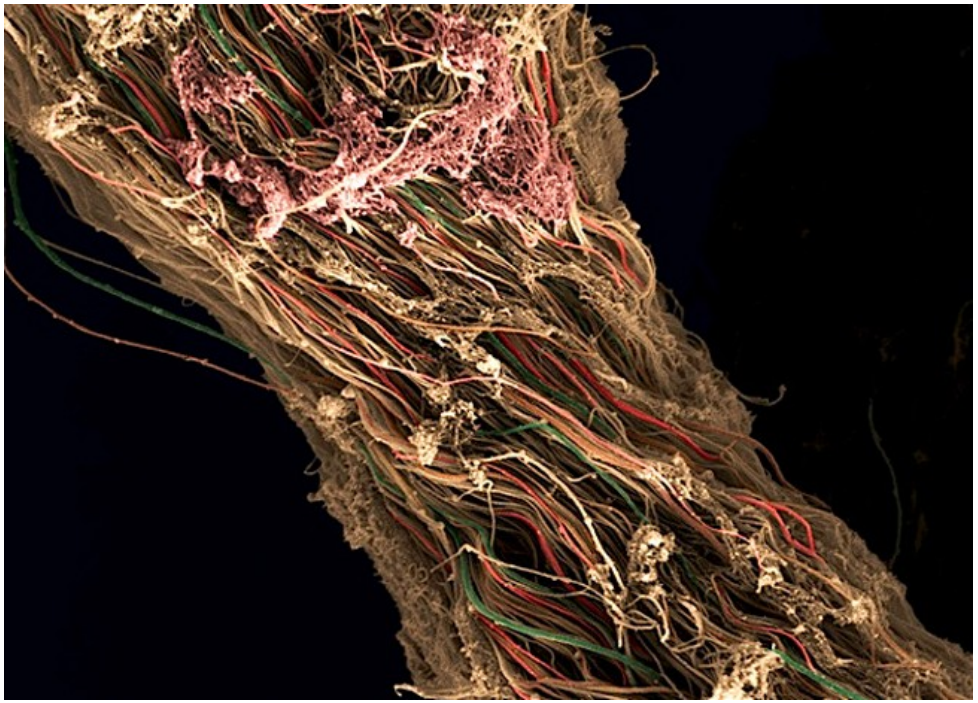
Faculty of Medicine MU

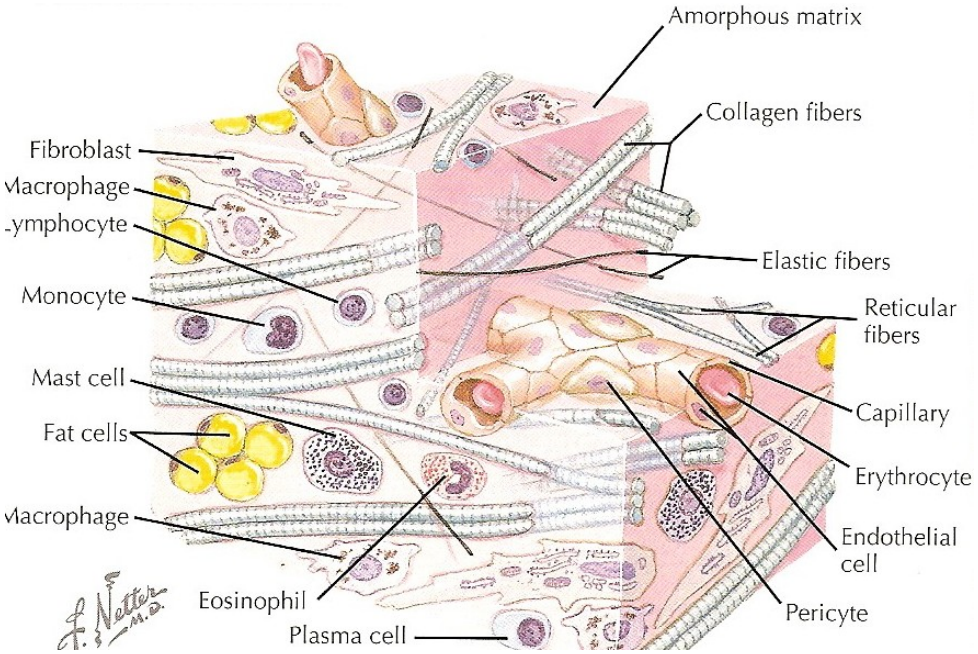
pvanhara@med.muni.cz





# Mechanical and biological properties

⟶ surrounds other tissues, allows compartmentalization, provides support, defines physico-chemical environment, brings immunological support, provides storage of energy, ...

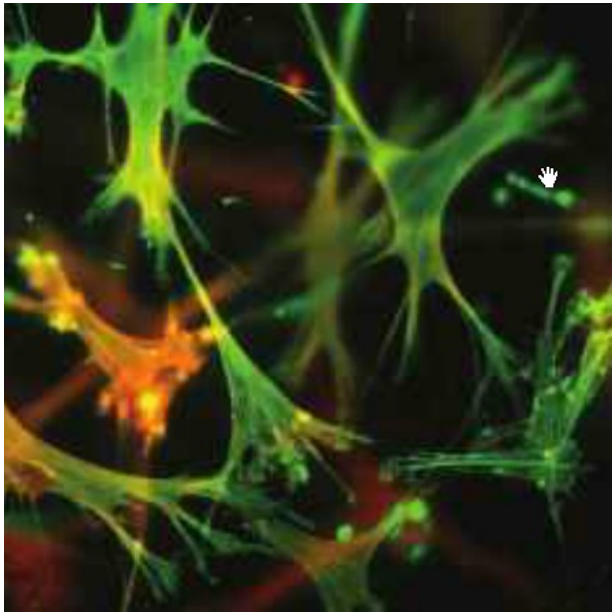


# GENERAL COMPOSITION OF CONNECTIVE TISSUE

## Cells and extracellular matrix (ECM)

- **Cells**

- **Connective tissue** – permanent and transient cell populations (e.g. fibroblasts/myofibroblasts, immune cells, adipocytes, adult stem cells)
- **Cartilage** – chondroblasts/chondrocytes
- **Bone** – osteoblasts/osteocytes/osteoclasts



- **Matrix** – fibrous and amorphous

- **Fibrous component**
  - collagen
  - reticular
  - elastic

- **Amorphous component** (amorphous ground substance)

Complex matrix consisting of
- glycosaminoglycans
- glycoproteins
- proteoglycans

composition dependent on tissue type (connective × ligament × cartilage × bone)

# CLASSSIFICATION OF CONNECTIVE TISSUE

- **Embryonic CT**

- Mesenchyme
- Jelly-like CT (Wharton jelly, dental pulp, stroma of iris)

- **Adult CT**

- Areolar (loose, interstitial) CT
- Dense collagen irregular CT

} CT

- Dense collagen regular CT
- Fat (adipose tissue)
- Cartilage
- Bone

} Specialized CT

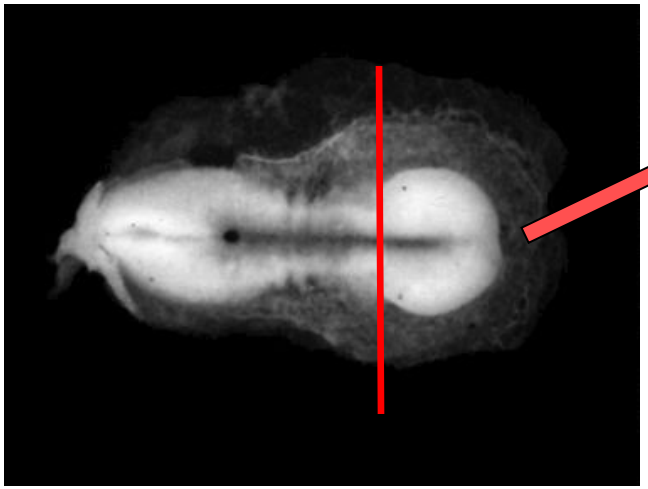
- Blood and hematopoietic tissue
- Lymphatic tissue

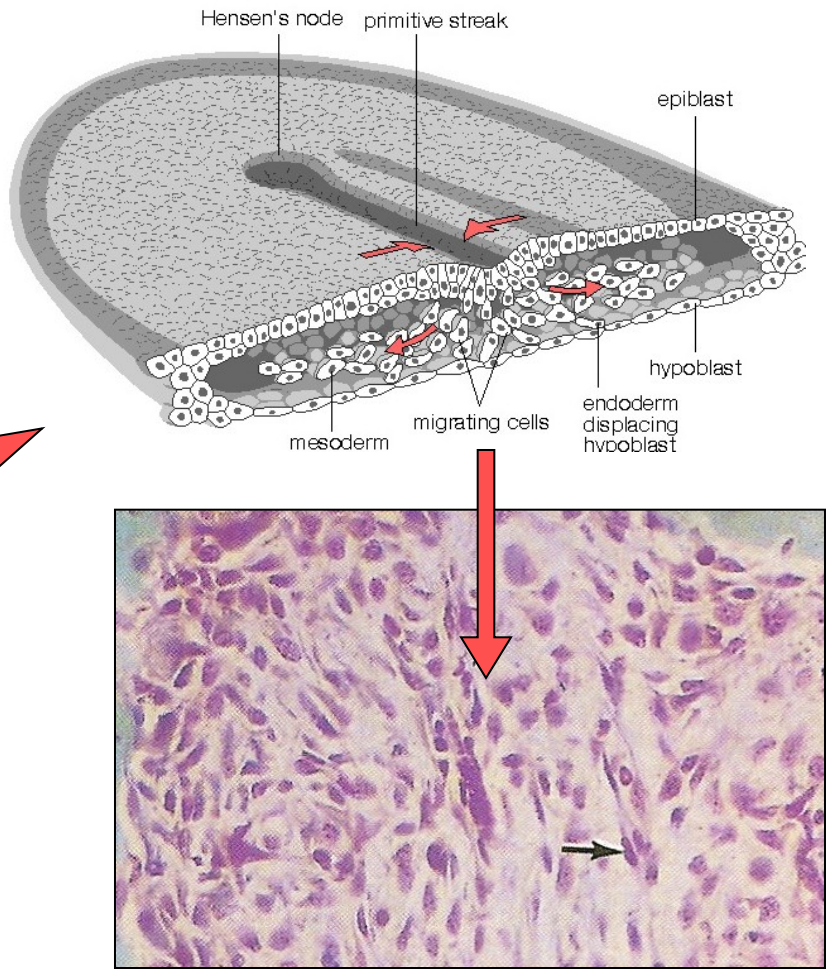
} Trophic CT (body liquids)

# EMBRYONIC ORIGIN OF CONNECTIVE TISSUE

- Mesenchyme = loose tissue between germ layers
- Complex network of star- or spindle-shaped cells
- Jelly-like amorphous ground substance

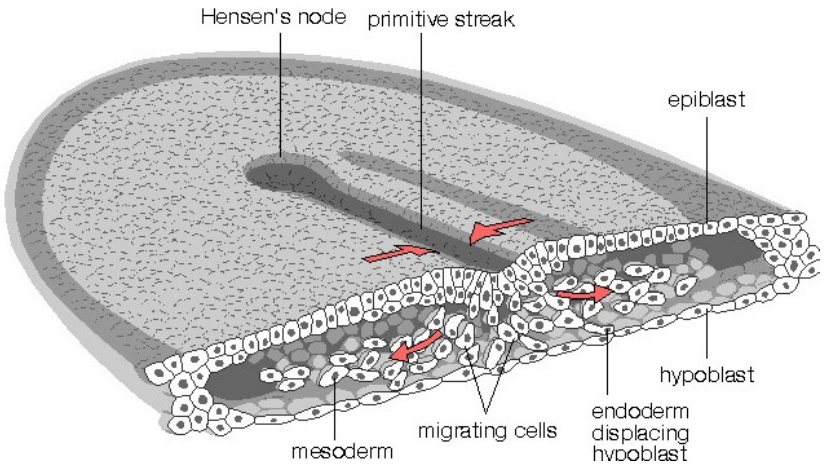
DAY 12 of embryonic development

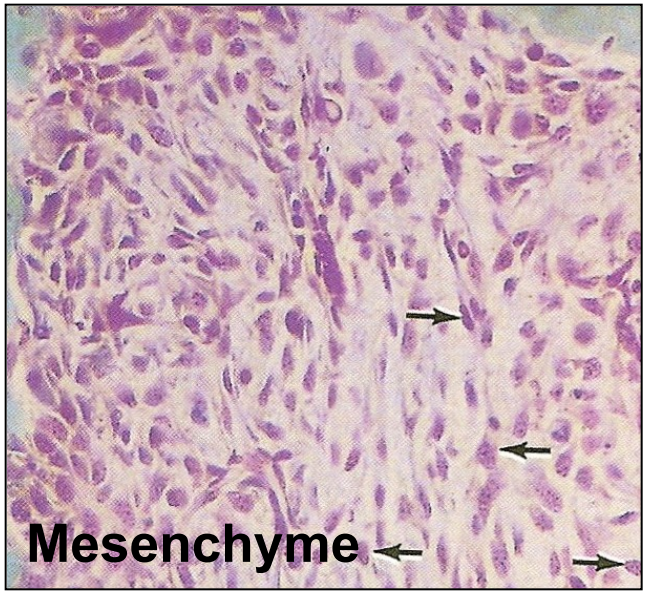


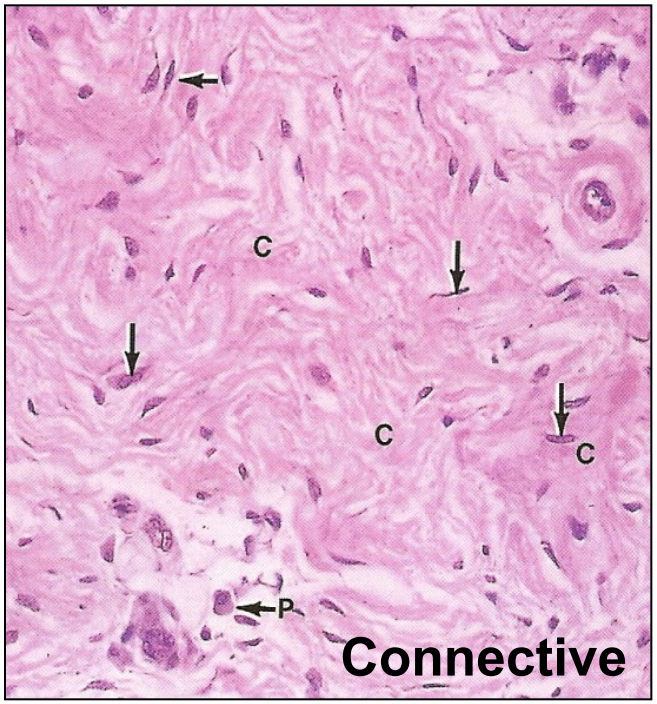



http://www.mun.ca/biology/desmid/brian/BIOL3530/DB_Ch02/DBNModel.html

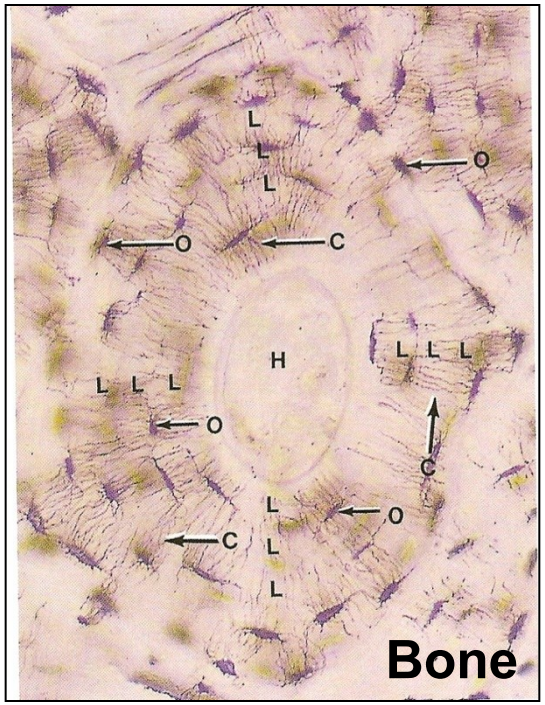
# DERIVATIVES OF CONNECTIVE TISSUE



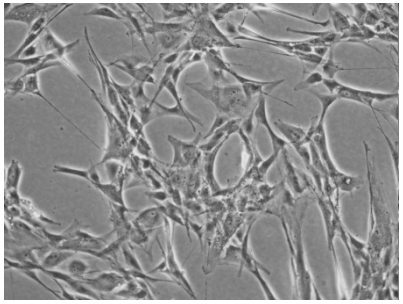


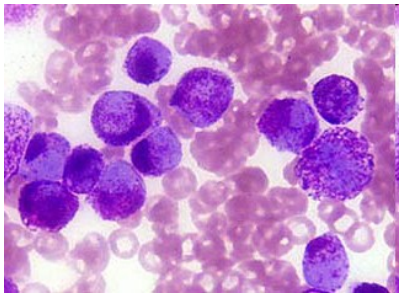


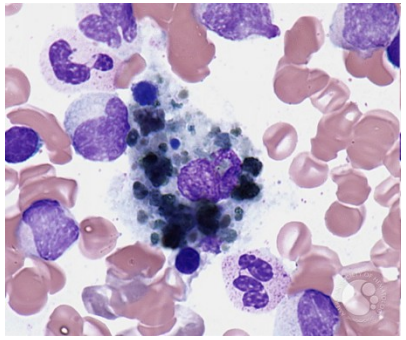
# LOOSE COLLAGEN CONNECTIVE TISSUE

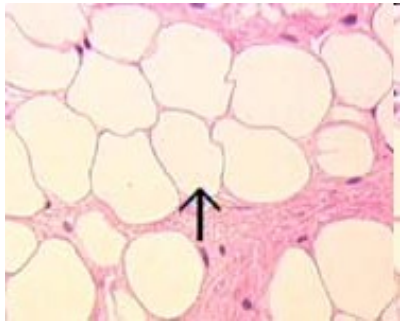
## Cells

- Fibroblasts/fibrocytes/myofibroblasts
- Heparinocytes
- Macrophages of CT = histiocytes
- Plasma cells
- Lymphocytes
- Adipocytes
- Adult stem cells



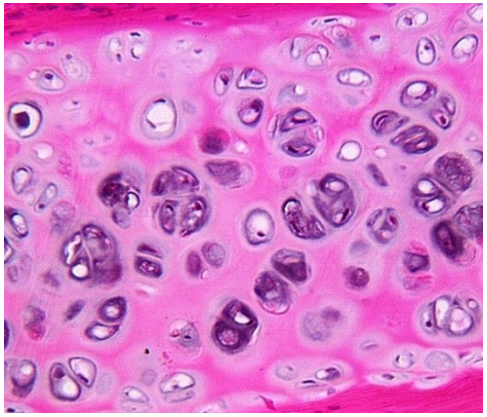


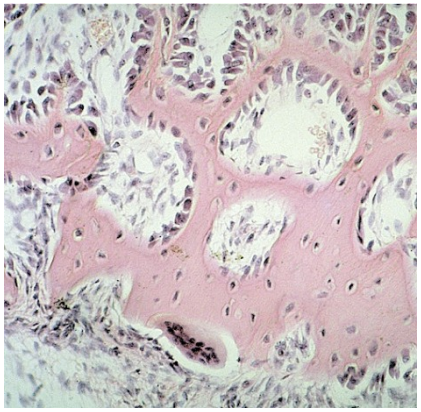


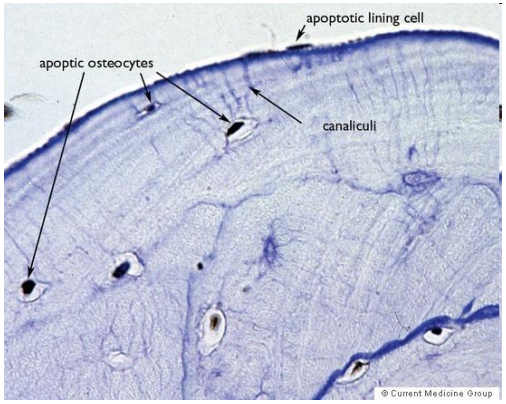


## Extracellular matrix

- Fibrous compound
- Amorphous ground substance

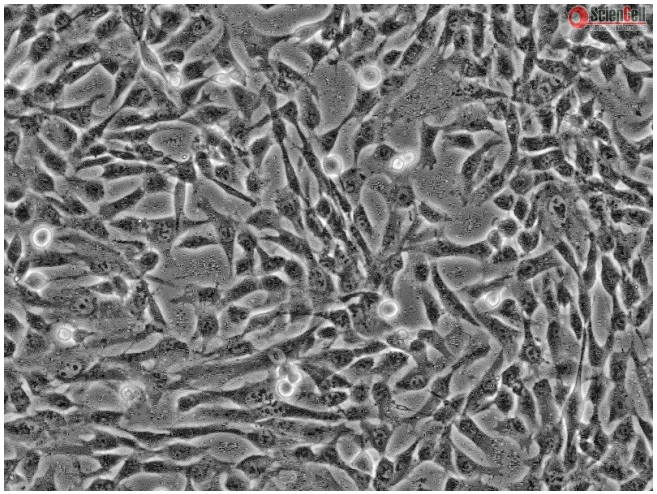


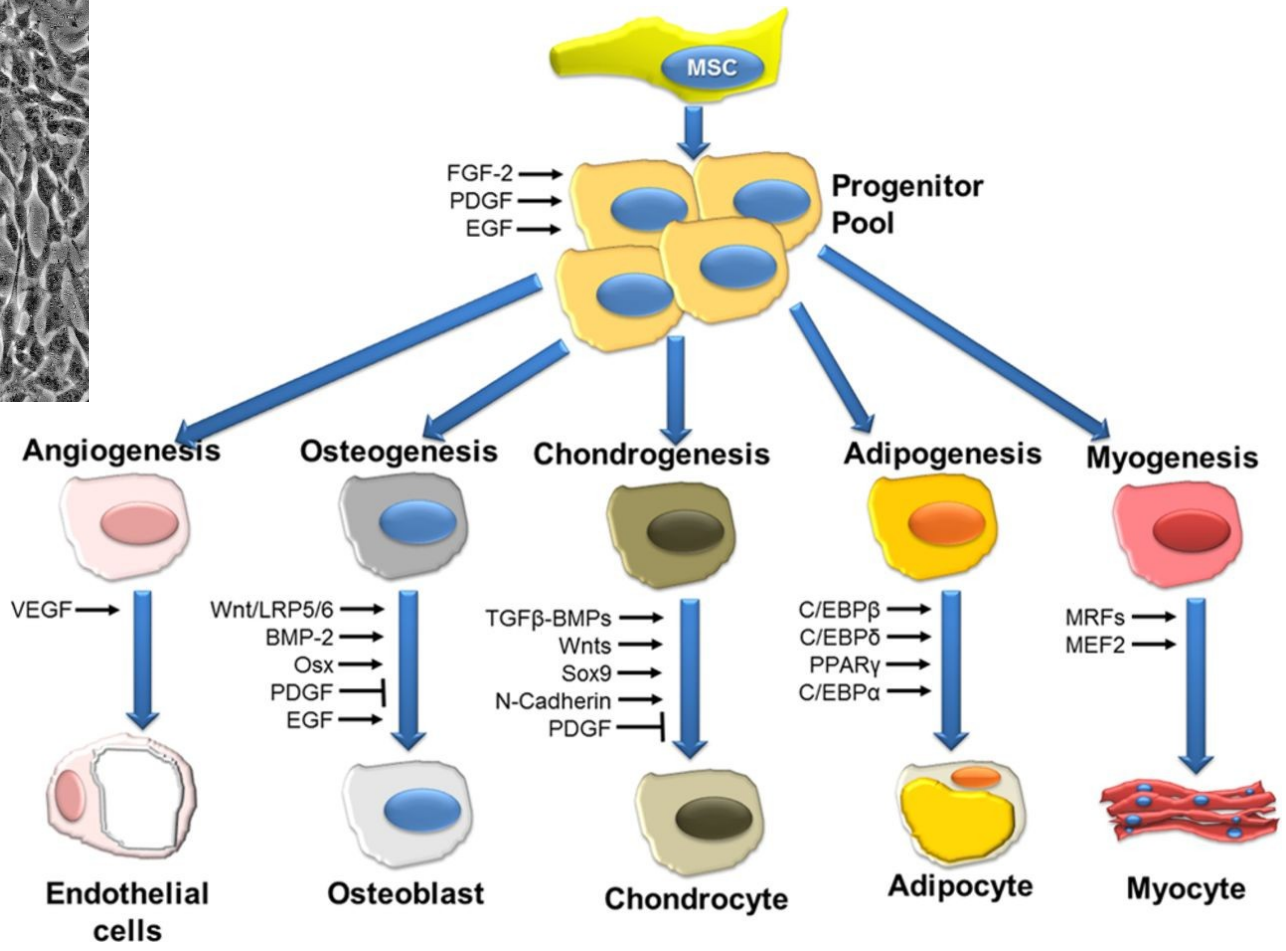




# CELLS OF LOOSE COLLAGEN CONNECTIVE TISSUE

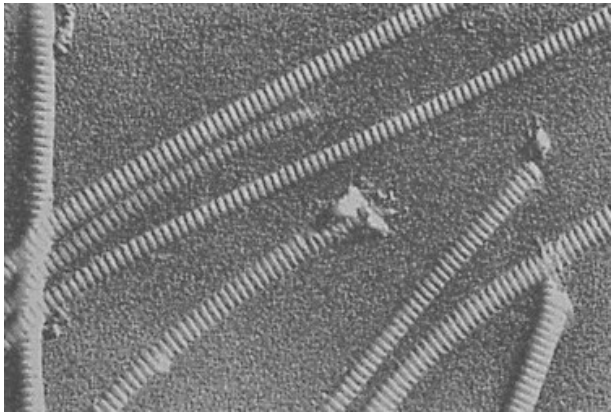
## Mesenchymal (adult) stem cells

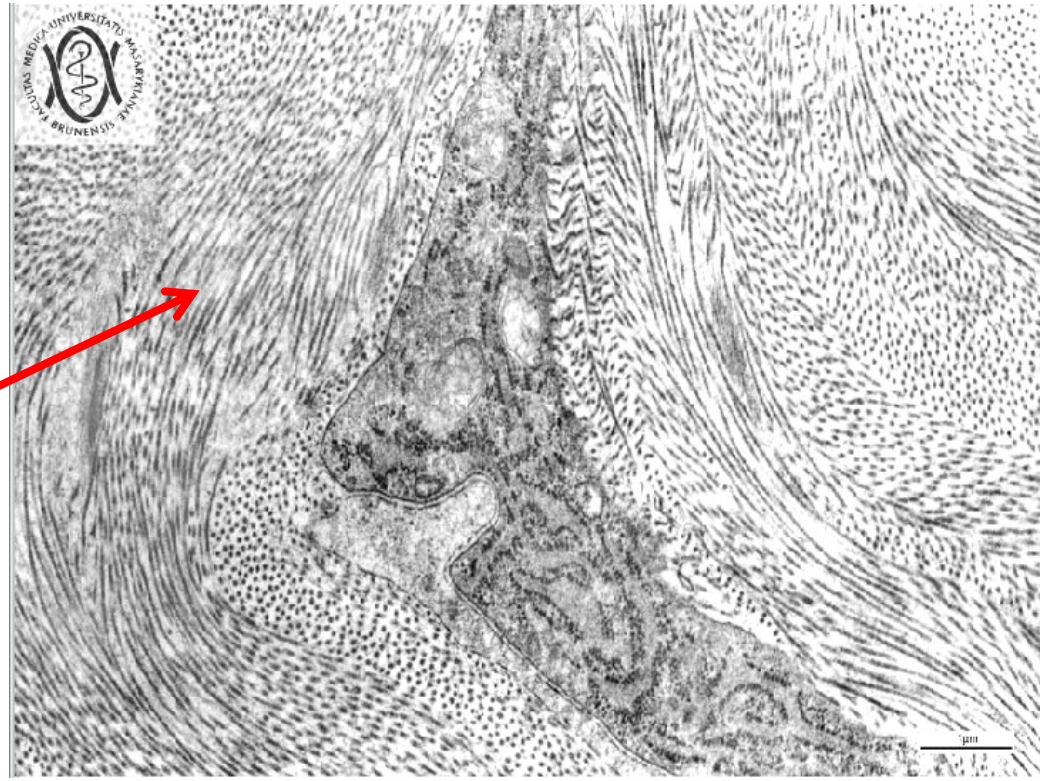




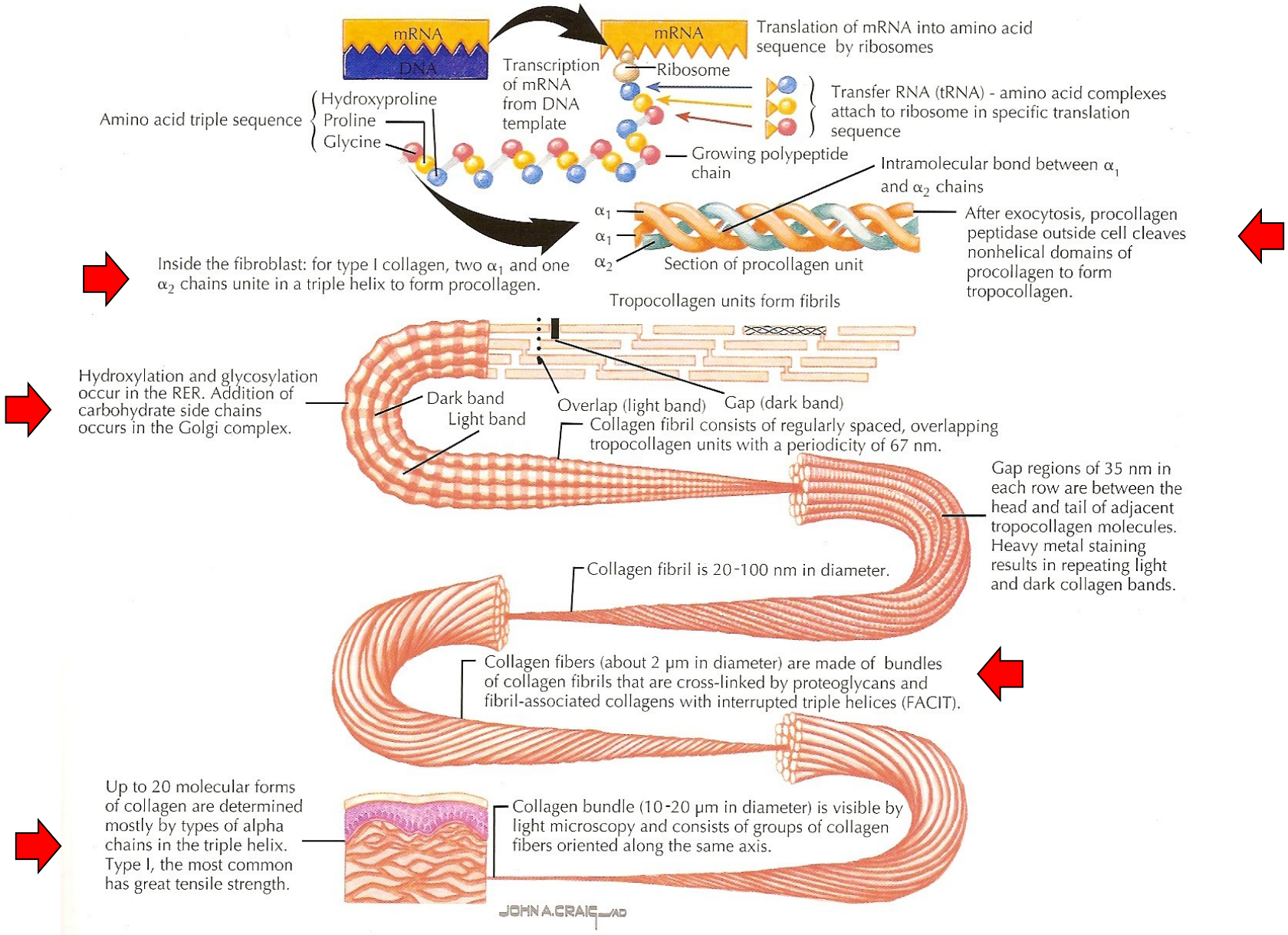
# Collagen fibers

- family of fibrous proteins encoded by >35 genes (2013)
- polymer – subunit = tropocollagen; triple helix
- different structural and mechanical properties (strength, elasticity, pliability…)
- most abundant protein in human body ( 30% dry weight)





# COLLAGEN




further study: https://www.ncbi.nlm.nih.gov/books/NBK507709/

# COLLAGEN

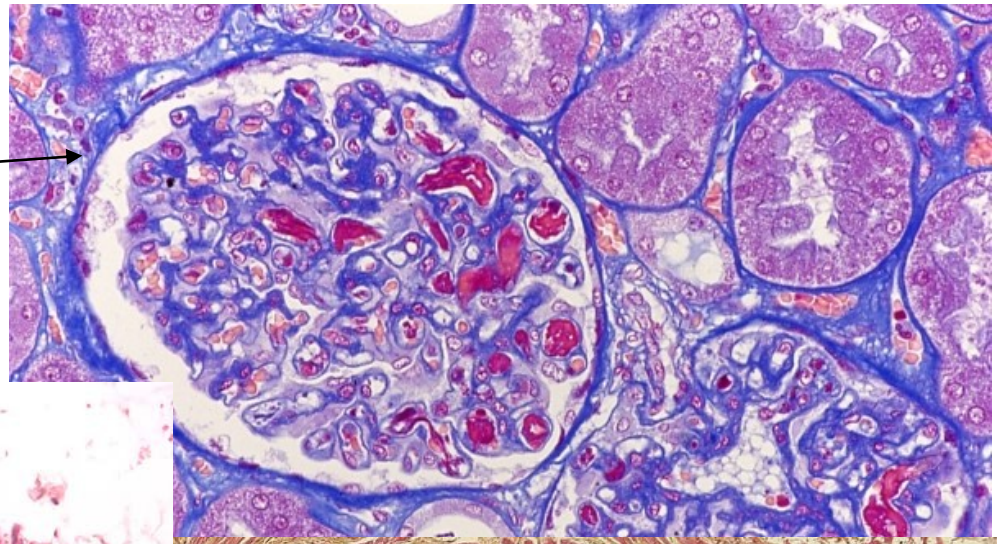
| Type | Localization | Structure | Main function |
|---|---|---|---|
| I | Bone, tendons, meniscus, dentin, dermis, capsules of organs, loose CT 90% of type I | Fibrils (75nm) – fibers (1-20μm) | Resilience in pull |
| II | Hyaline and elastic cartilage | Fibrils (20nm) | Resilience in pressure |
| III | Skin, veins, smooth muscles, uterus, liver, spleen, kidney, lung | Like I, high content of proteoglycans and glycoprotiens, reticular network | Shape formation |
| IV | Basal lamina of epithelium and endtohelium, basal membranes | No fibrils or fibers | Mechanical support |
| V | Lamina of muscle cells and adipocytes, fetal membranes | Like IV | |
| VI | Interstitial tissue, chondrocytes – adhesion | | Connecting dermis and epidermis |
| VII | Basal membrane of epithelium | | |
| VIII | Some endothelia (Cornea) | | |
| IX, X | Growth plate, hypertrophic and mineralized cartilage | | Growth of bones, mineralization |

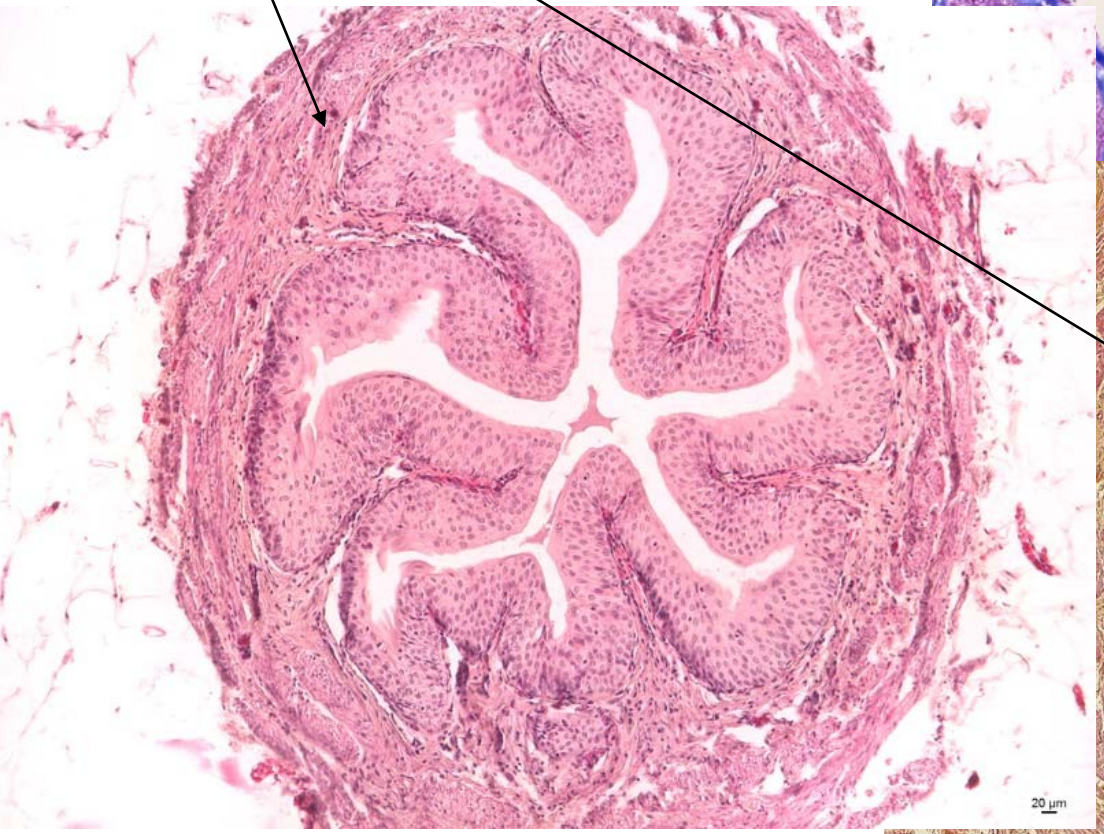
# COLLAGEN IN LIGHT MICROSCOPE

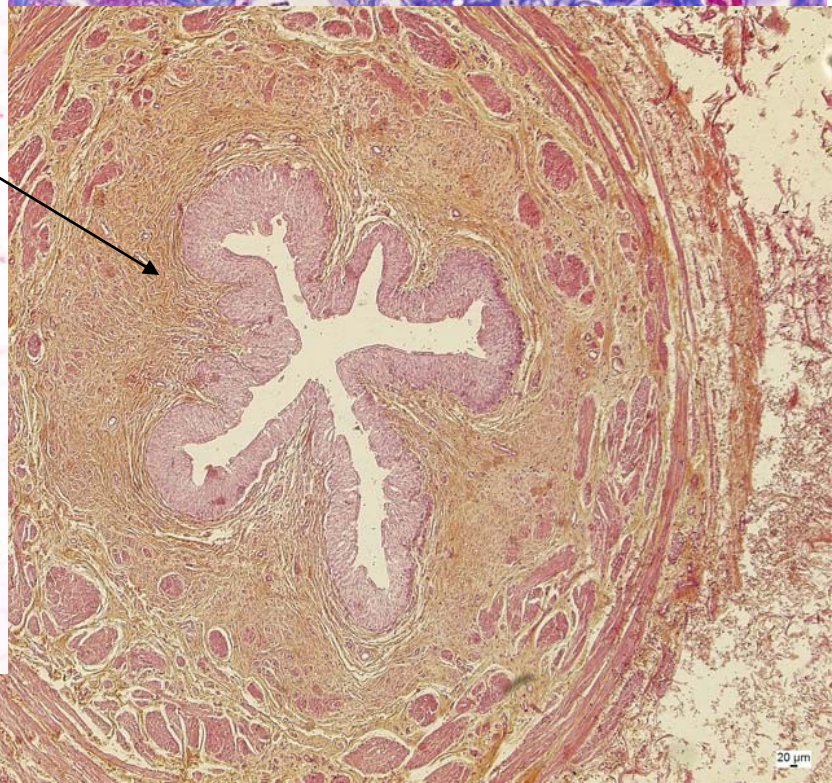
AZAN

HE

HES





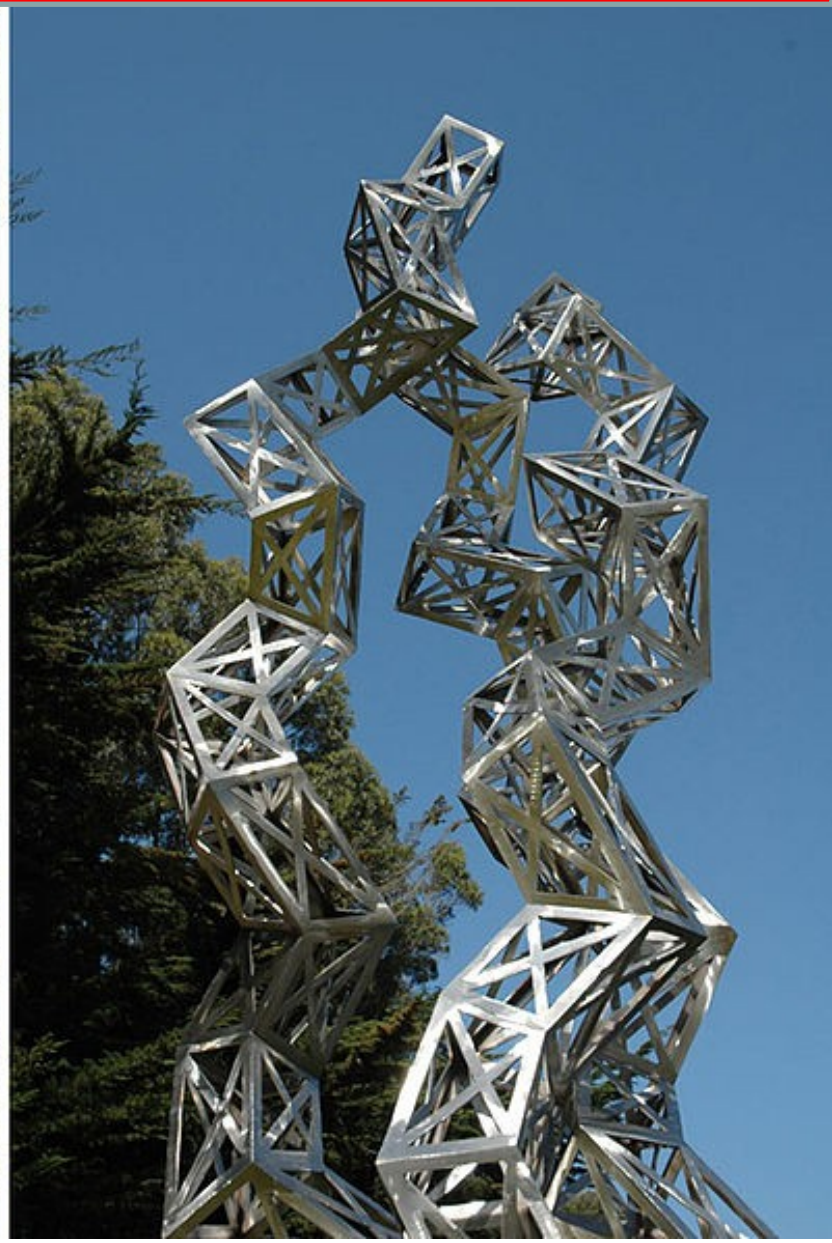



# COLLAGEN IN ART

**Julian Voss-Andreae**
**"Unraveling Collagen"**

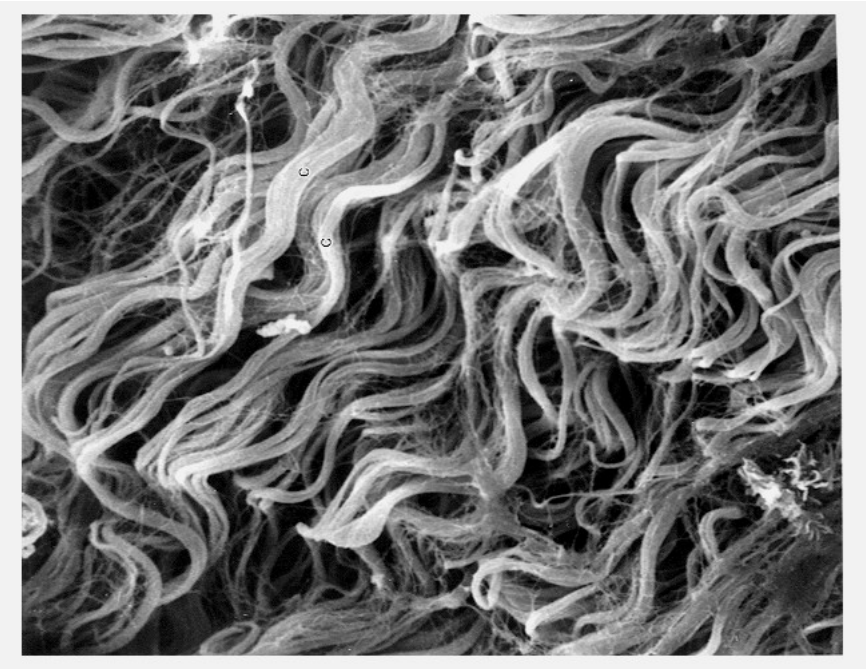
**2005**

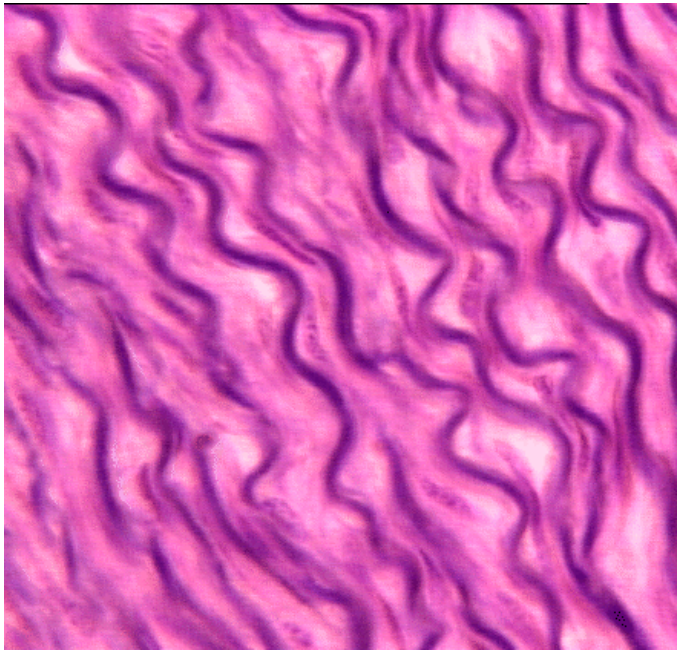
Orange Memorial Park
Sculpture Garden, City of
South San Francisco, CA



# ELASTIC FIBERS

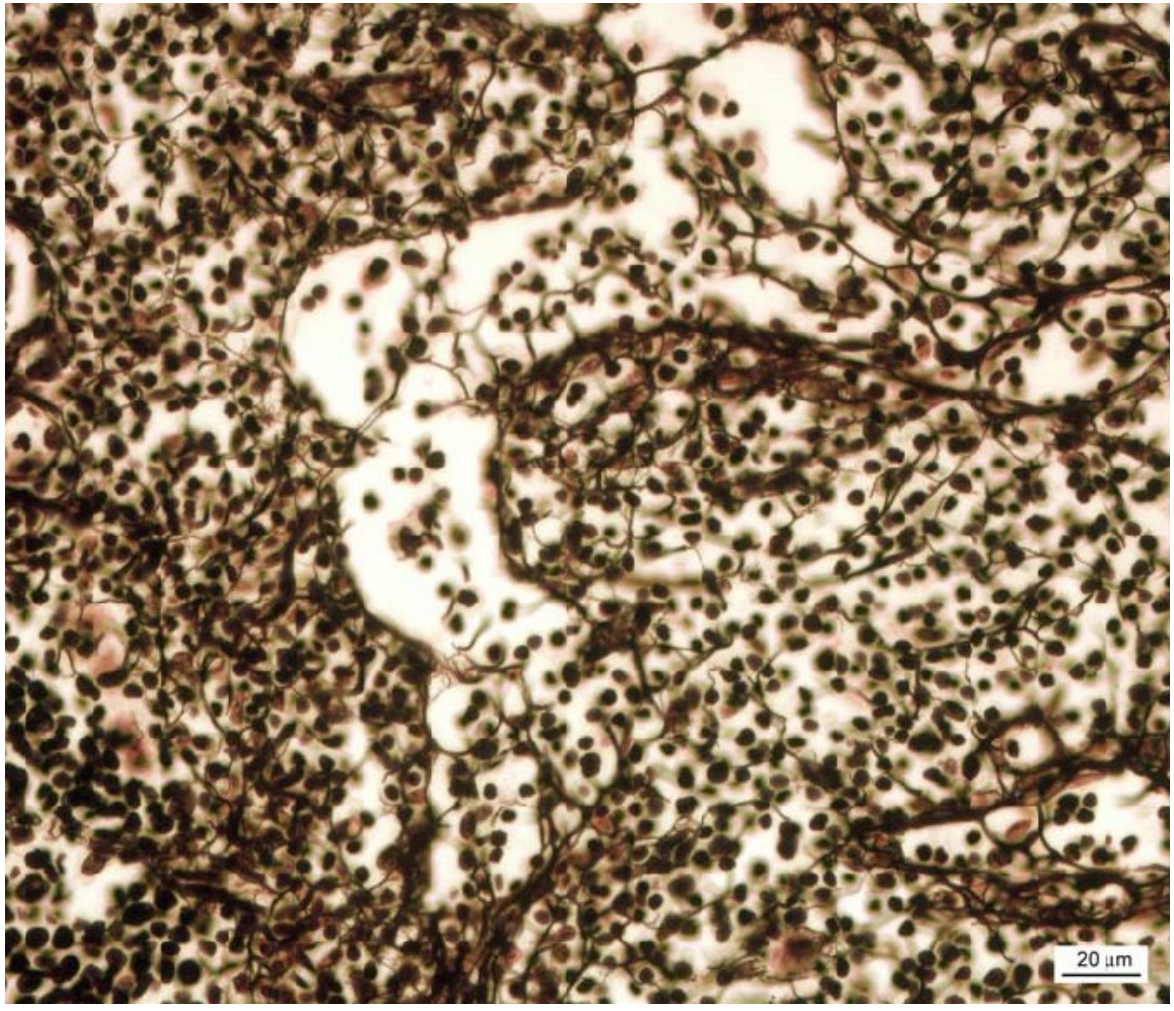
- less abundant than collagen
- polymer – tropoelastin
- minimal tensile resistance, loss of elasticity if overstretched
- reduction of hysteresis = allow return back to original state after mechanic change





# RETICULAR FIBERS

- collagen 3D meshwork
- bone marrow, spleen, lymphatic nodules
- microenvironment for e.g. hematopoietic stem cells and progenitors

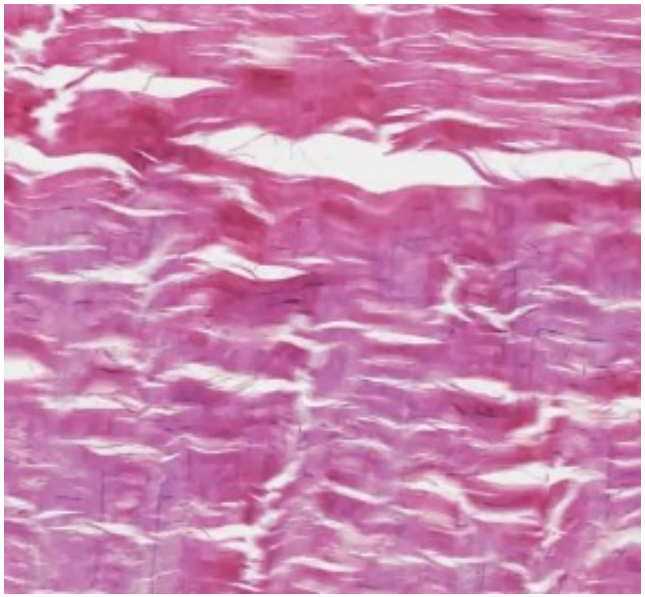


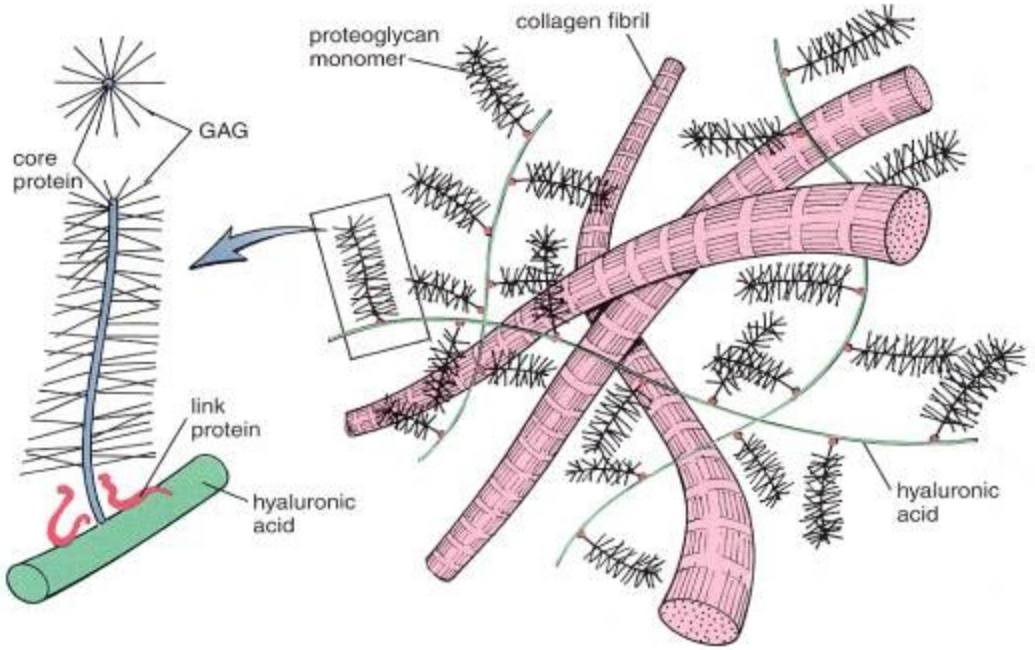
# RETICULAR CONNECTIVE TISSUE

# EXTRACELLULAR MATRIX – GROUND SUBSTANCE

Amorphous extracellular matrix

Colorless, transparent, homogenous substance consisting of glycosaminglycans, proteoglycans and structural glycoproteins



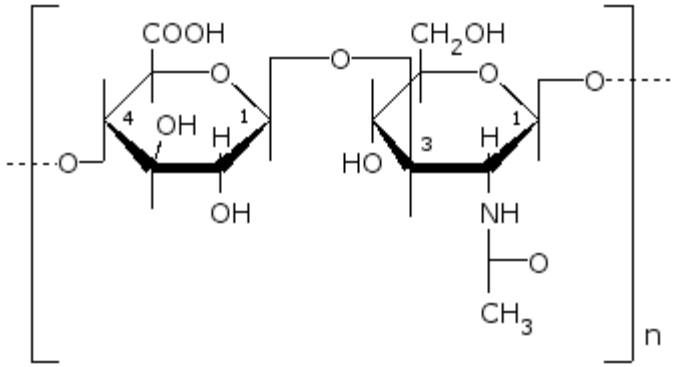


# GLYCOSAMINOGLYCANS

linear polysaccharides composed of two disaccharide subunits
– uronic acid and hexosamine

polysaccharides rich in hexosamines = acid mukopolysaccharides

glucuronic  or iduronic acid




glucosamin or galactosamin

# GLYCOSAMINOGLYCANS

They bind to protein structures (except for hyaluronic acid)

**Glyc**

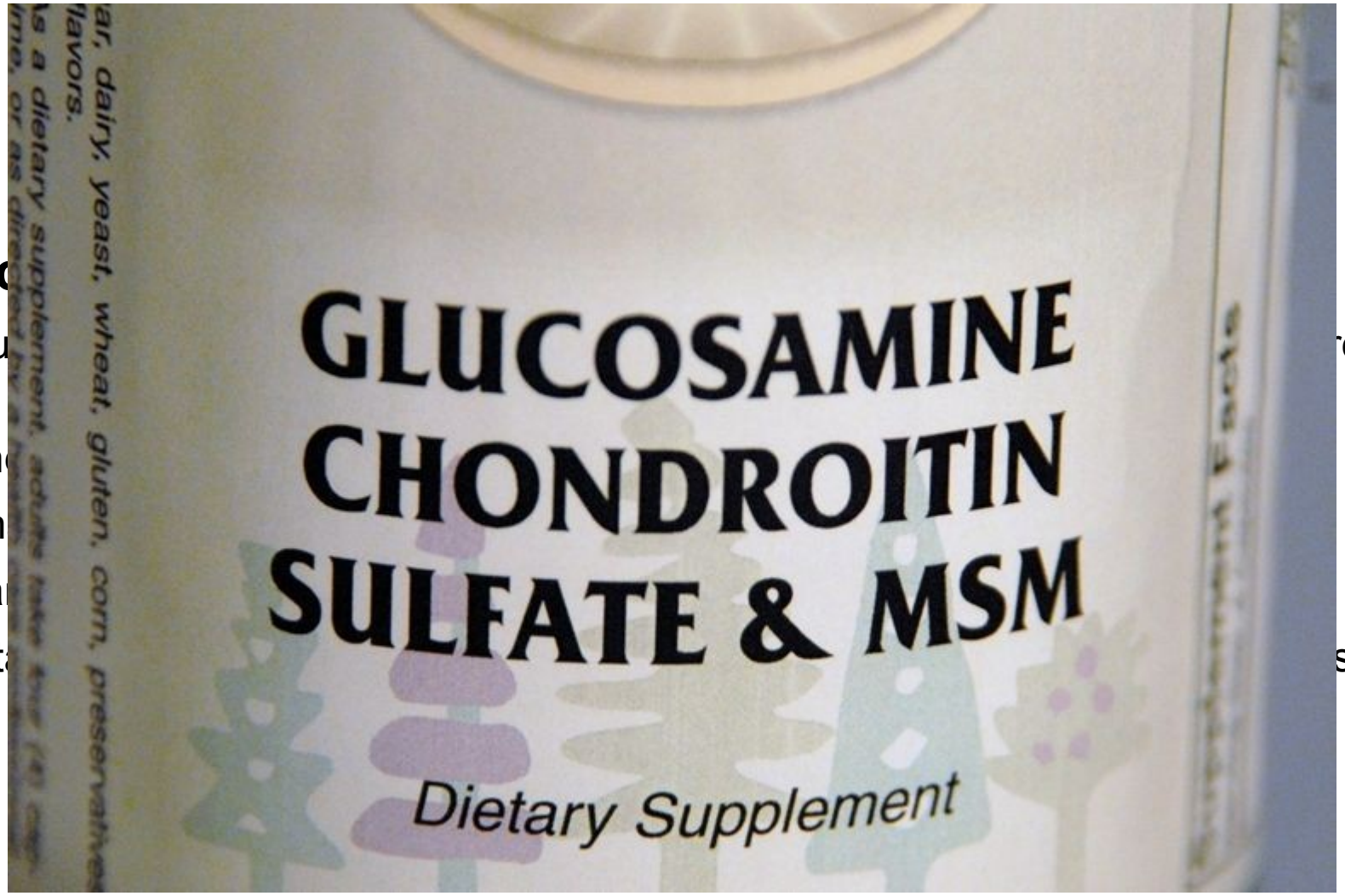
Hyalu reum,

Chon

Derm

Hepa

Kerat s



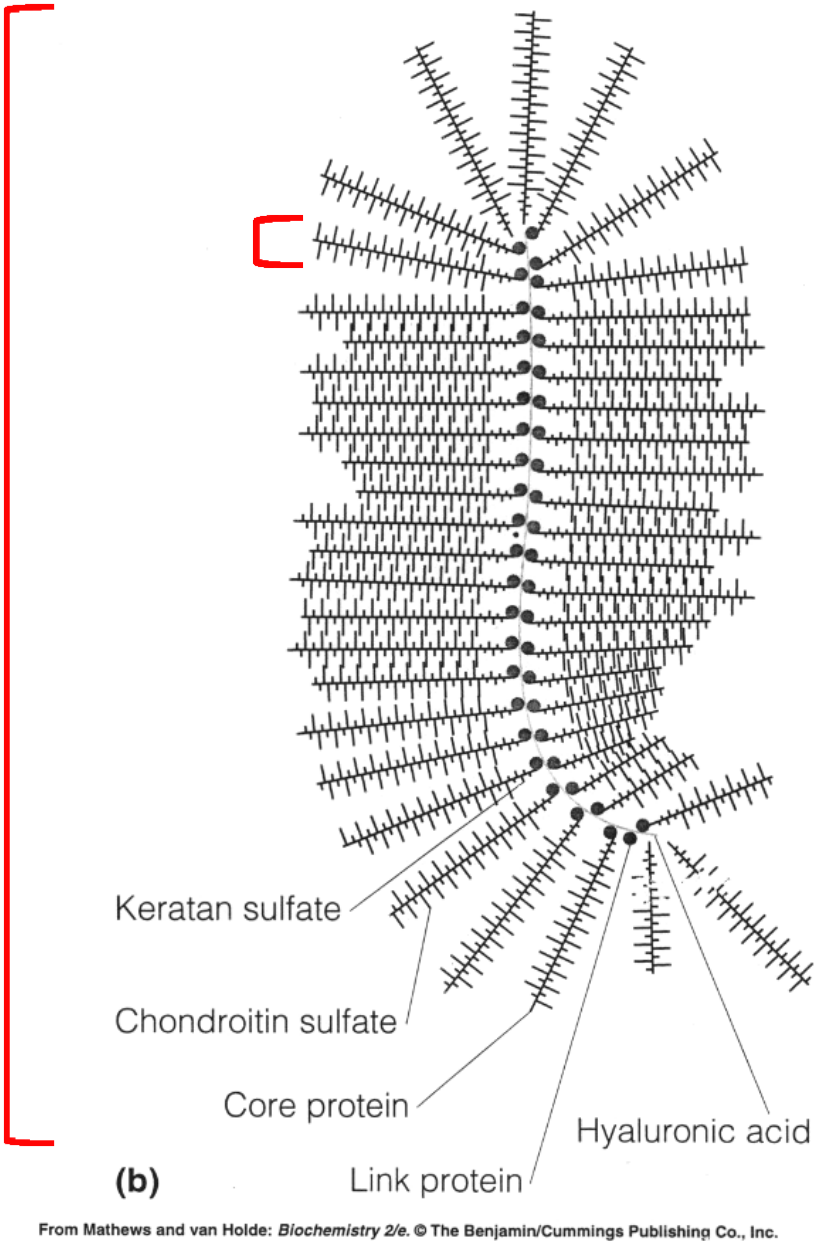
# PROTEOGLYCANS

— protein + dominant linear saccharide component

— proteoglycan aggregates

— water-binding, volume dependent of hydratation

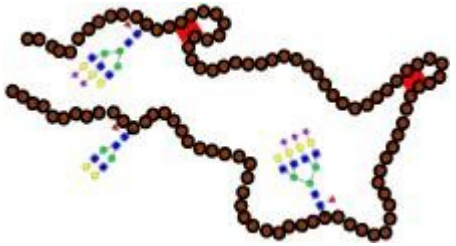
— aggrecan (cartilage)
— syndecan
— fibroglycan




From Mathews and van Holde: *Biochemistry 2/e.* © The Benjamin/Cummings Publishing Co., Inc.

# STRUCTURAL GLYCOPROTEINS

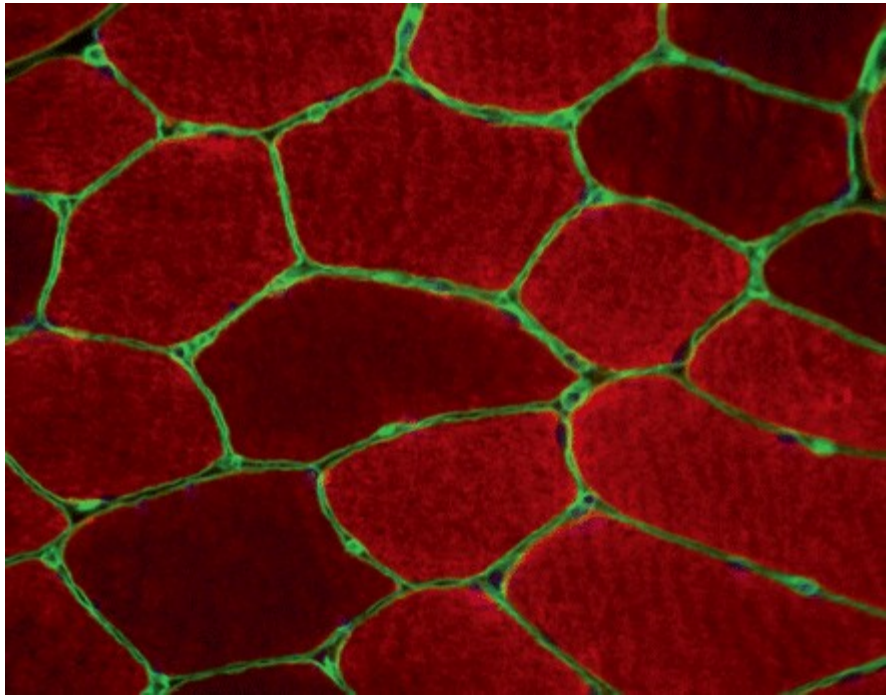
- dominant protein + branched saccharide component
- interaction between cells and ECM



— **fibronectin** – connects collagen fibers and glykosaminoglycans, cell adhesion and migration

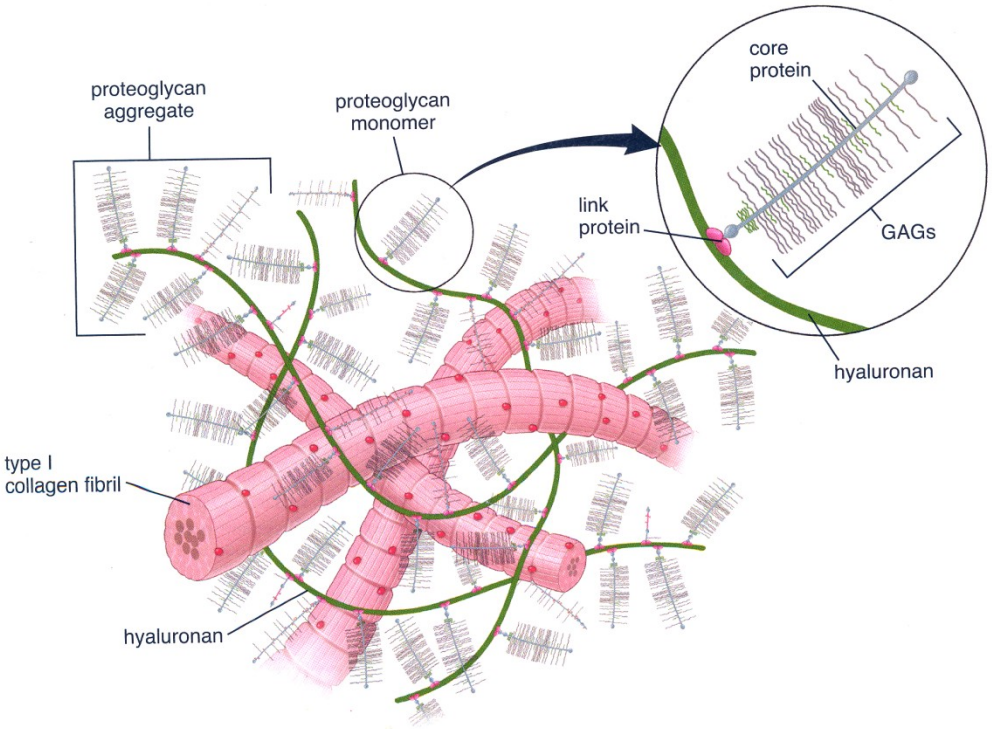
— **laminin** – basal lamina – epithelial integrity

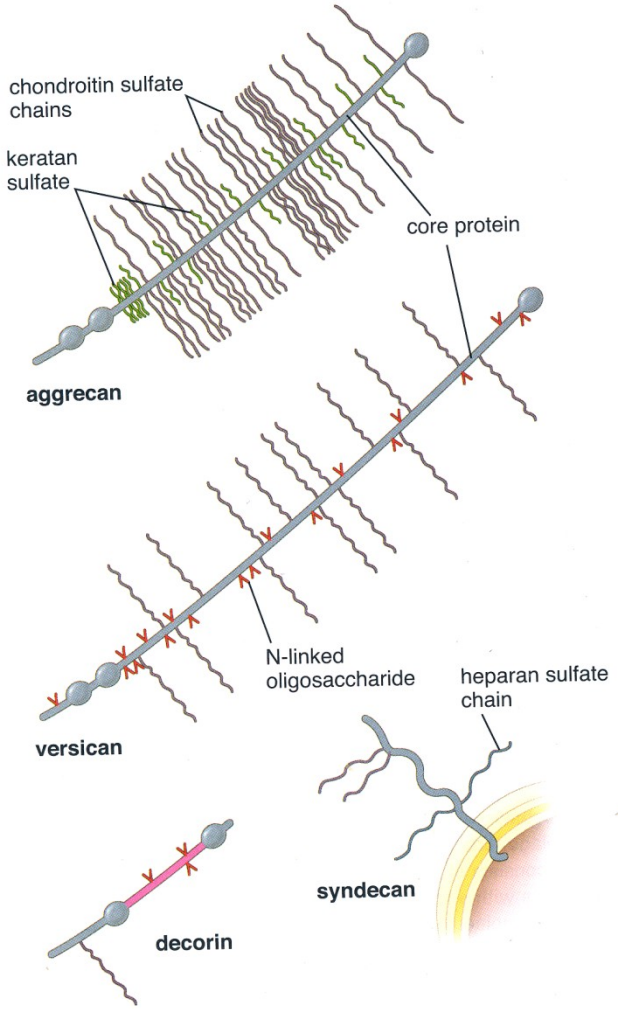
— **chondronectin** – cartilage – adhesion of chondrocytes to collagen



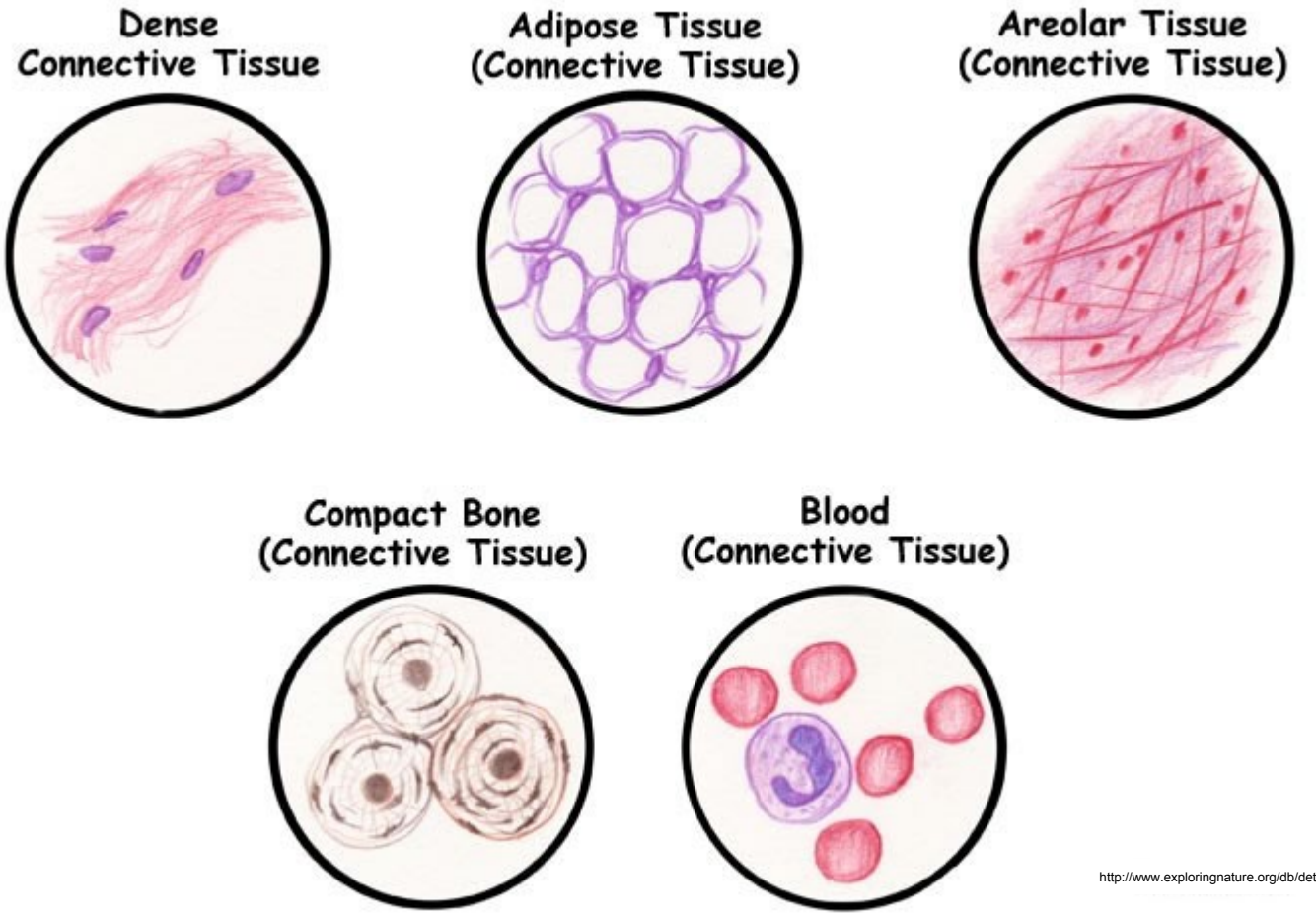
(J. Nutr. 136:2123-2126, 2006)

# COMPOSITION OF ECM



# CLASSIFICATION OF SPECIALIZED CONNECTIVE TISSUE

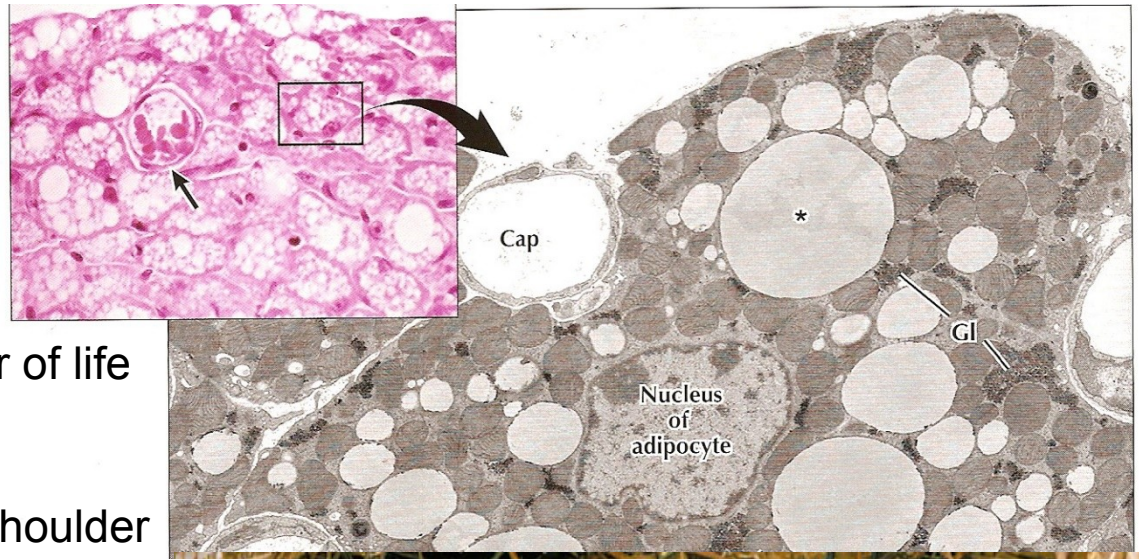



http://www.exploringnature.org/db/detail.php?dbID=21&detID=691

# ADIPOSE TISSUE

- Adipocytes, fibroblasts, reticular, collagen and elastic fibers, capillaries
- White and brown adipose tissue

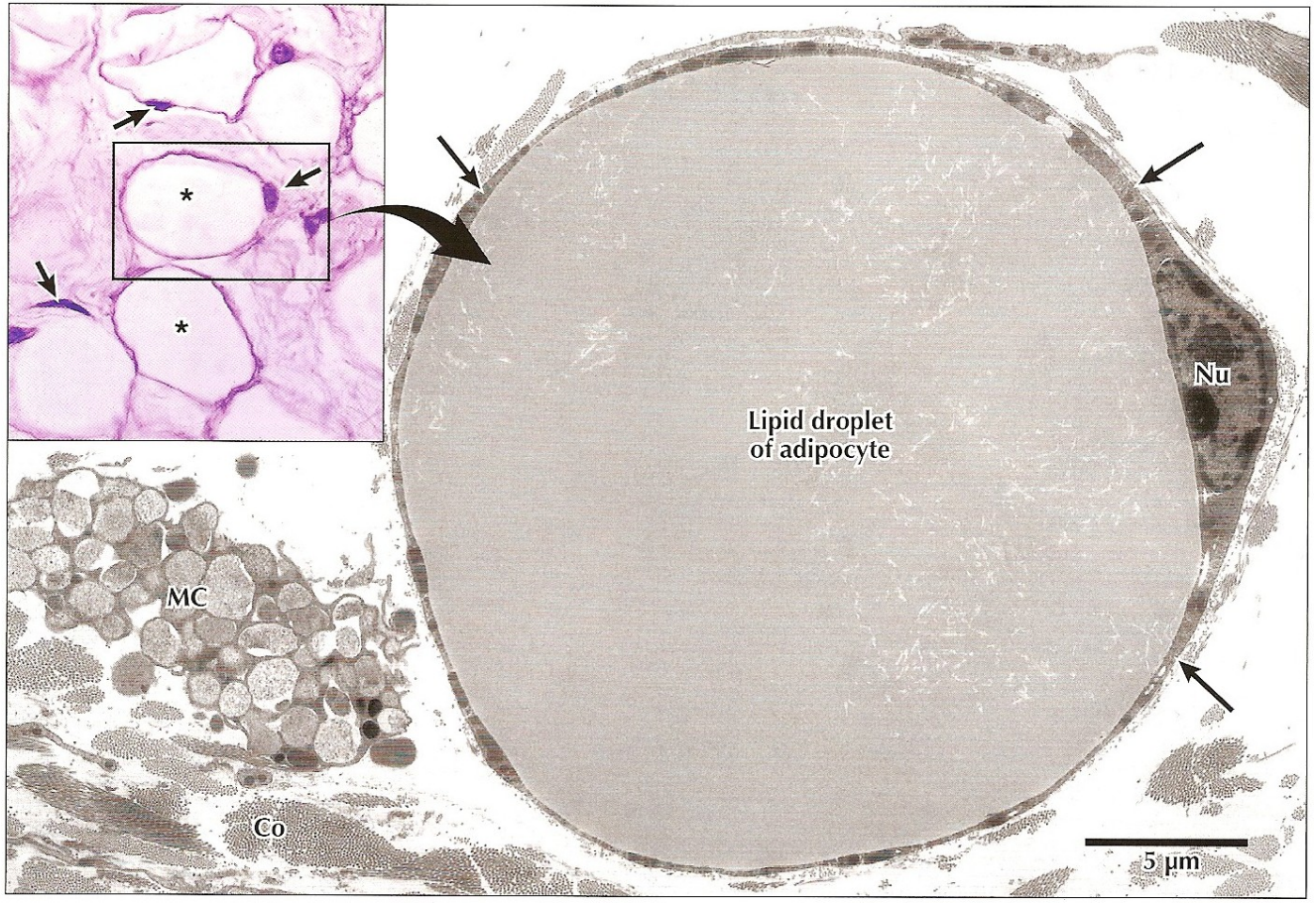
# BROWN ADIPOSE TISSUE



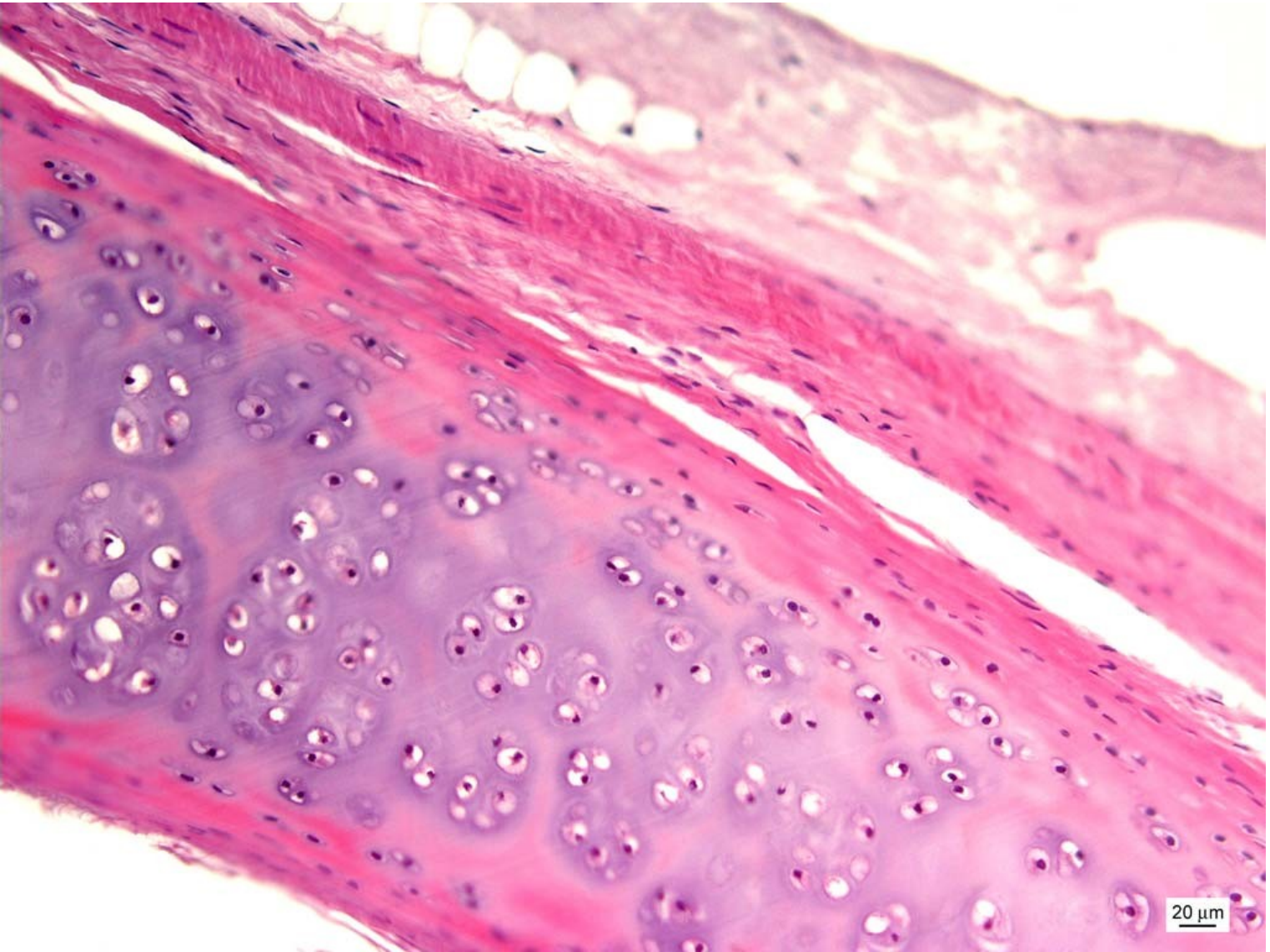

- fetus and children up to 1st year of life
- fast source of energy
- typical localization – between shoulder blades, axilla, mediastinum, around kidneys, pancreas, small intestine
- small cells with numerous fat droplets

# WHITE ADIPOSE TISSUE

- adipocytes are actively formed until 2nd year of life
- no innervations, but rich vascularisation
- adipocytes with only one lipid droplet
- leptin (adipokinins)



# ▪ CARTILAGE



# CARTILAGE

**General features:**

- **specialized connective tissue** with continuous ECM
- flexible, mechanically resistant
- avascular, non-innervated
- support of soft tissues - trachea, larynx
- skeletal support - costal cartilages
- diarthrosis - joints
- bone growth

1. **cells**
2. **fibrils**
3. **amorphous ground substance**

# CARTILAGE – COMPOSITION AND STRUCTURE

- Perichondrium – connective tissue around cartilage (except joints)

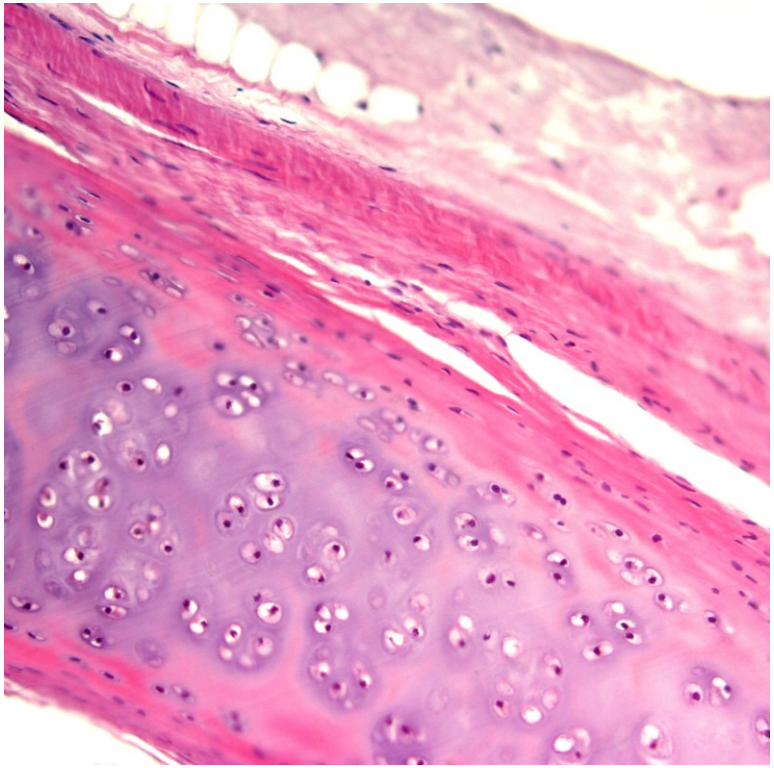
→ Nutrition
Growth

- Extracellular matrix – water, proteoglycans and collagen fibrils

→ Solid consistence
Pressure elasticity

- Cells of cartilage - chondroblasts, chondrocytes

→ Growth
ECM production



# DISTRIBUTION

Hyaline

Elastic

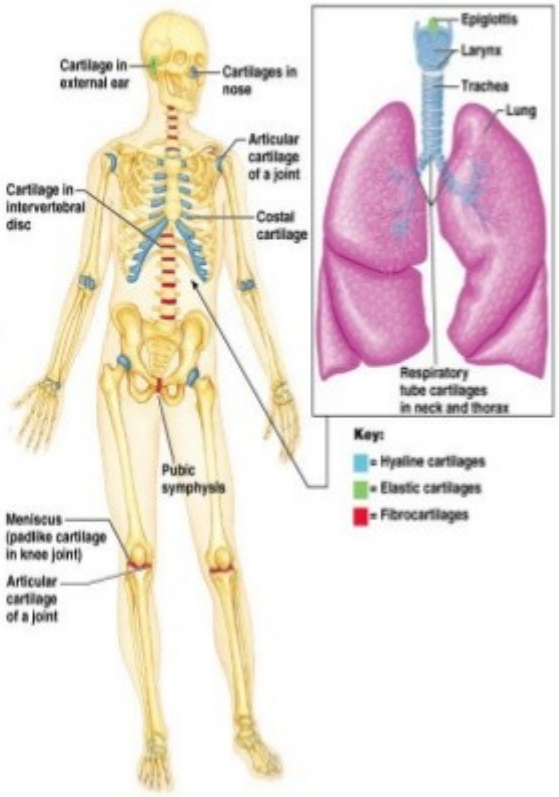
Fibrous

## cartilage in adults

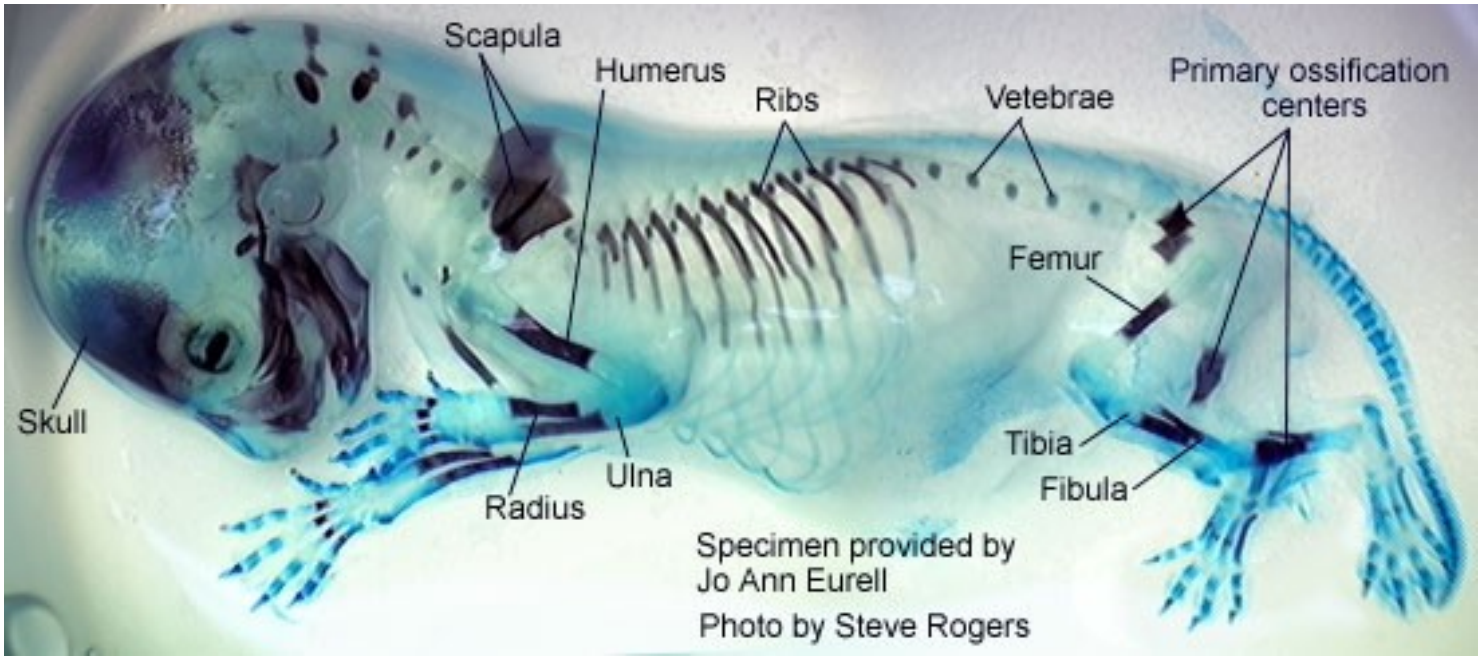
- Nose
- Joint surfaces
- Costal
- Larynx - voice box
- rings of trachea & bronch

- External ear
- Epiglottis
- Eustachian tube

- IVDs
- Pubic symphysis
- meniscus in knee joint



# Hyaline




Alcian Blue&Alizarin Red

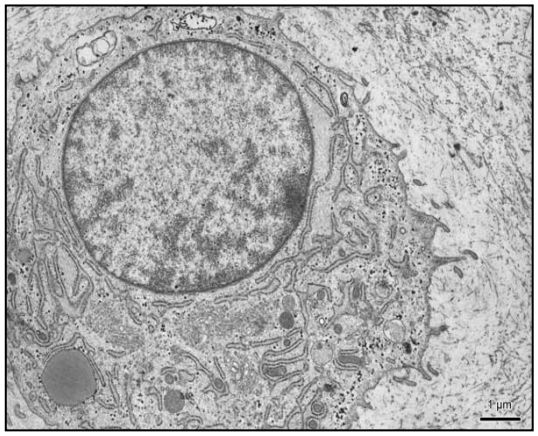
- most abundant
- temporary embryonal/fetal skeleton
- epiphyseal growth plate
- articulation (joints) respiratory passages

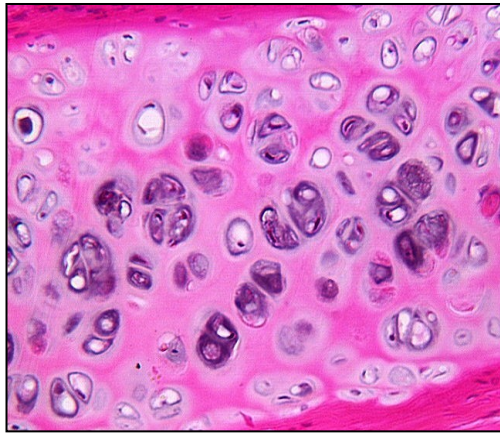
http://chickscope.beckman.uiuc.edu/explore/embryology/day14/dev2.html

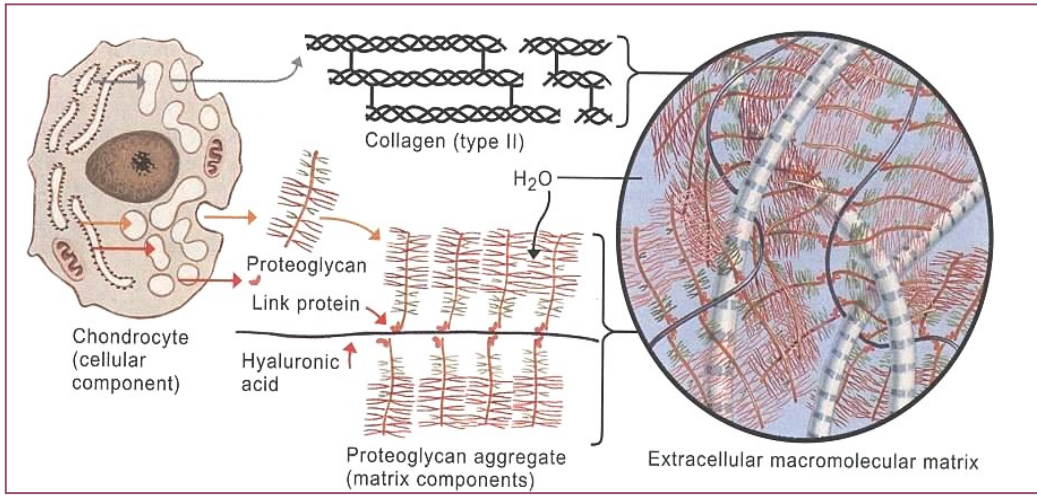
# CELLS OF CARTILAGE

- **Chondroblasts and chondrocytes**

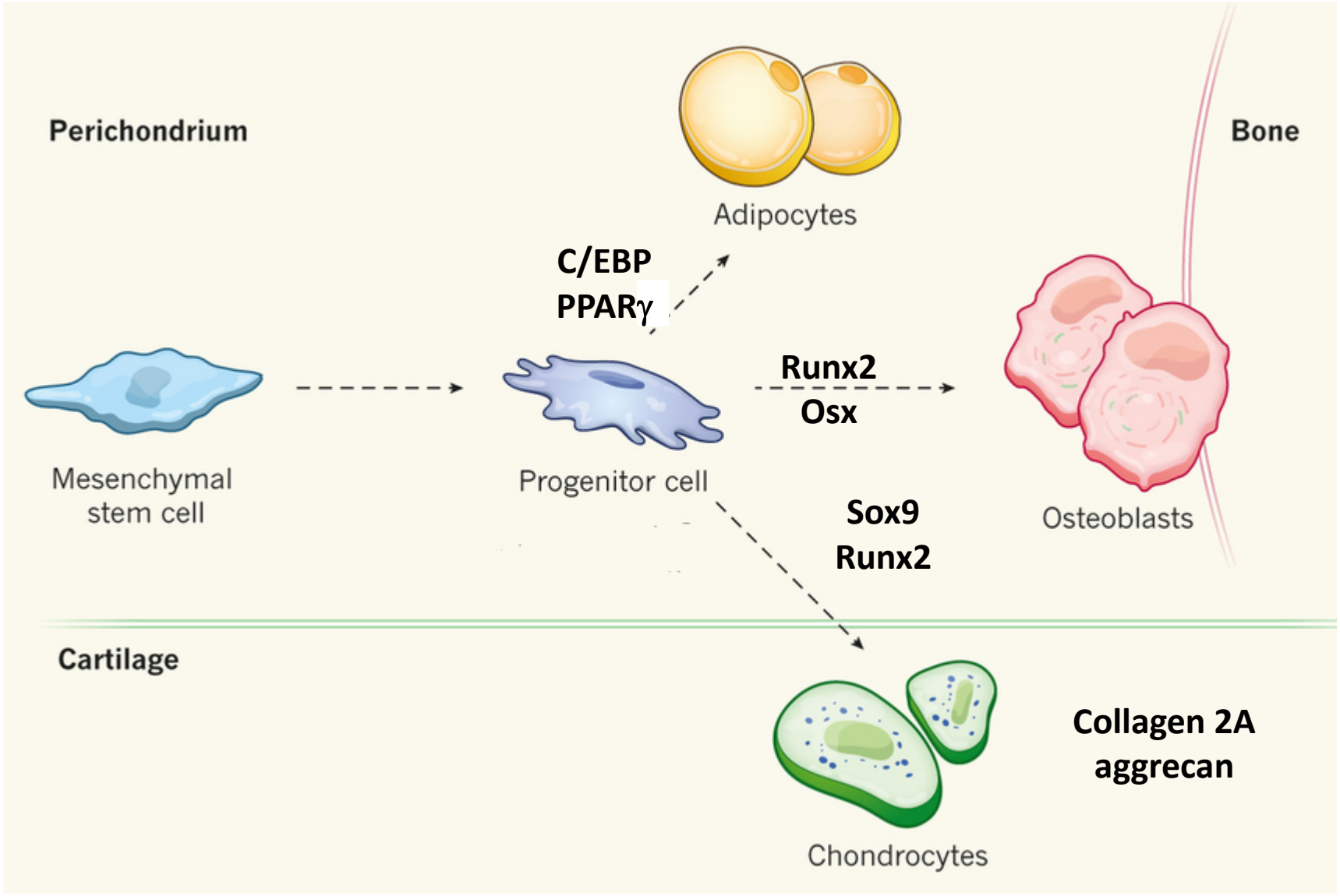
- mesenchymal origin
- typical ultrastructure of proteosynthetically active cells
- production of extracellular matrix
- interstitial proliferation
- isogenetic groups, lacunae



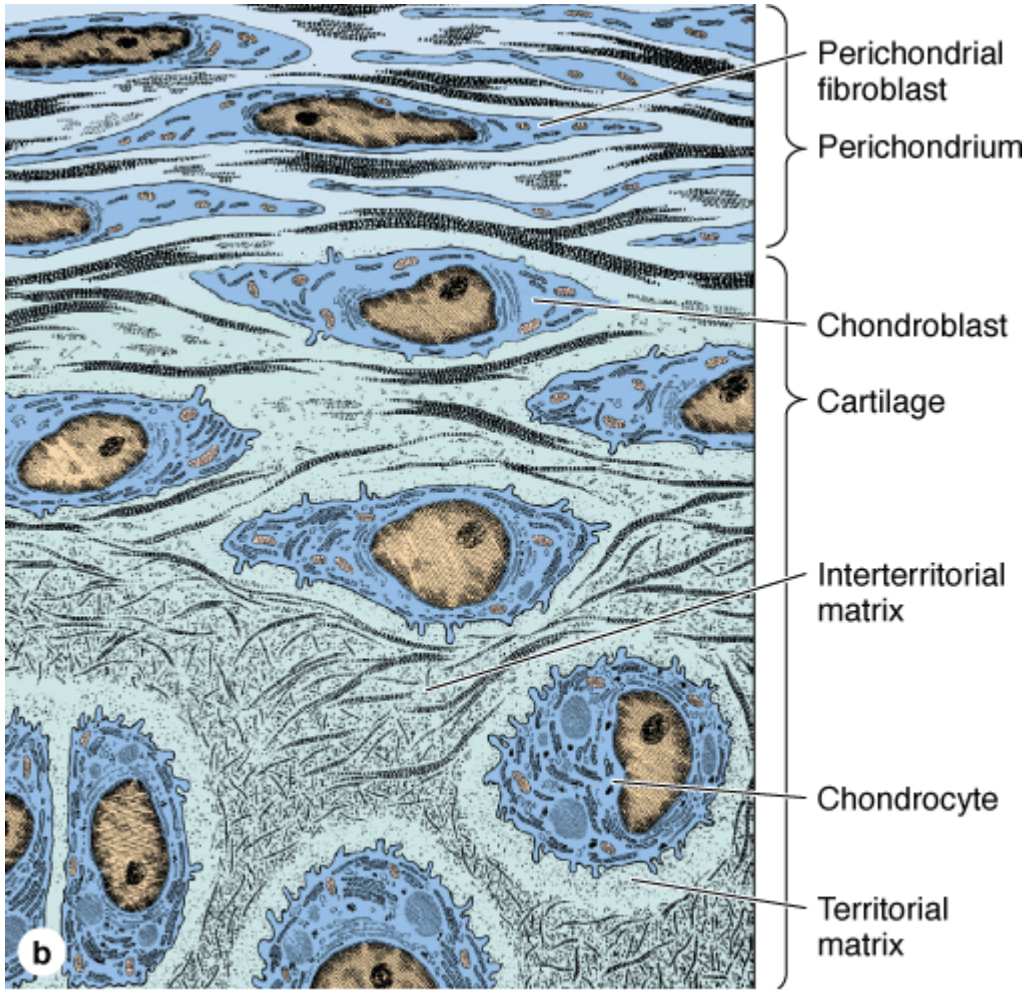


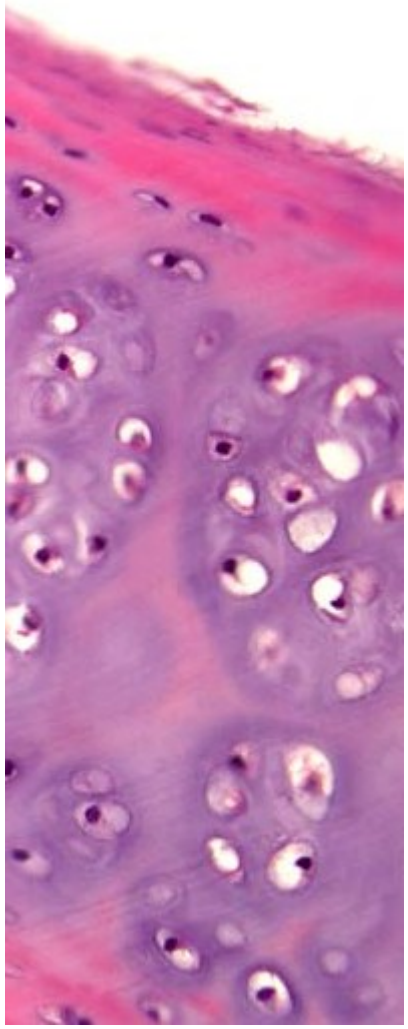


# DIFFERENTIATION OF CHONDROBLASTS



# DIFFERENTIATION OF CHONDROBLASTS

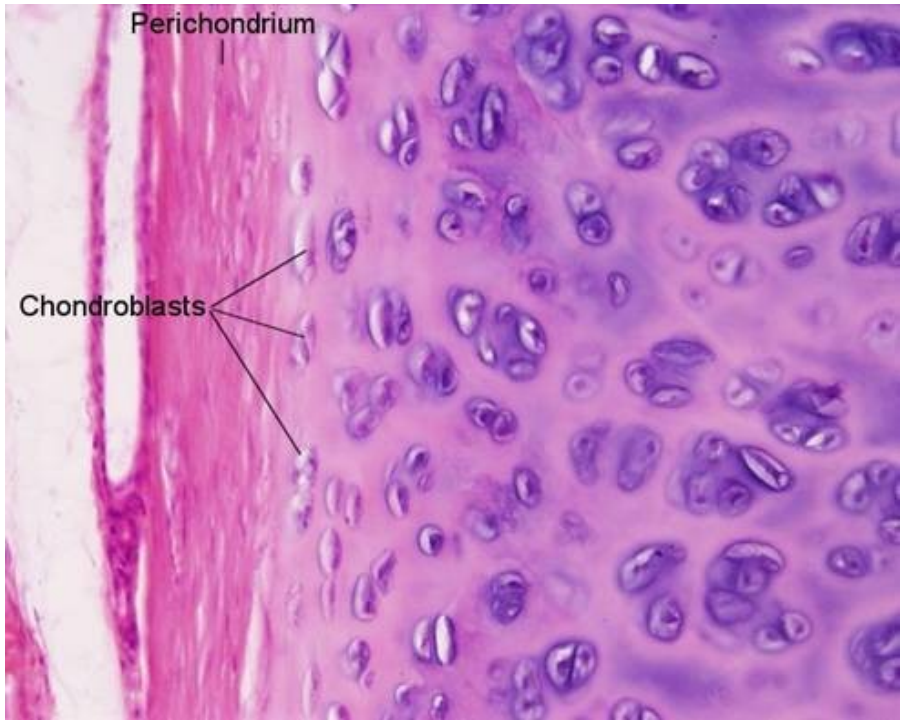


Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

# ULTRASTRUCTURE OF CHONDROBLASTS

- oval → round cells
- rich in organelles, especially rER and GA
- glycogen granules (anaerobic metabolism)
- occasionally lipid droplets



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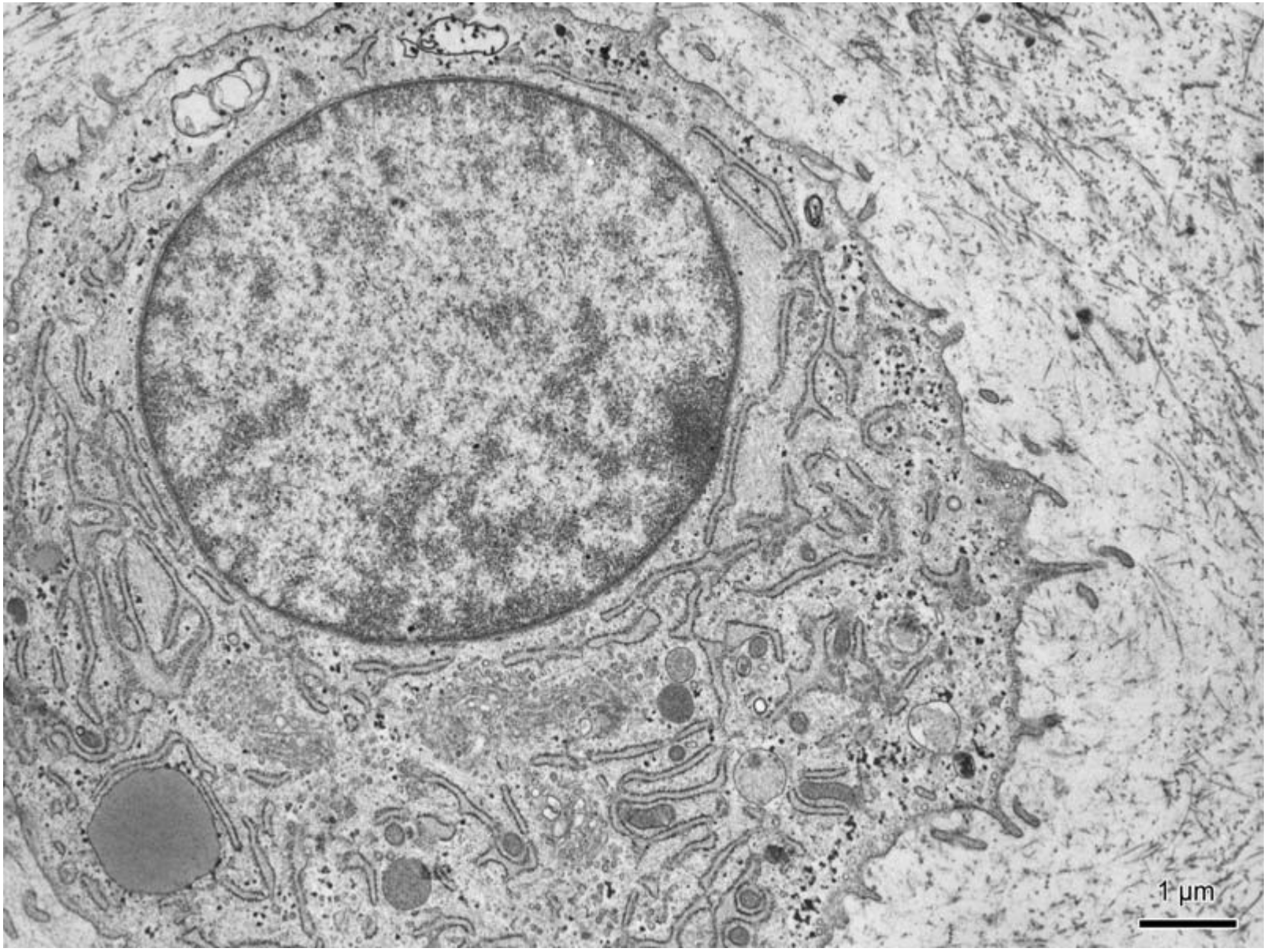
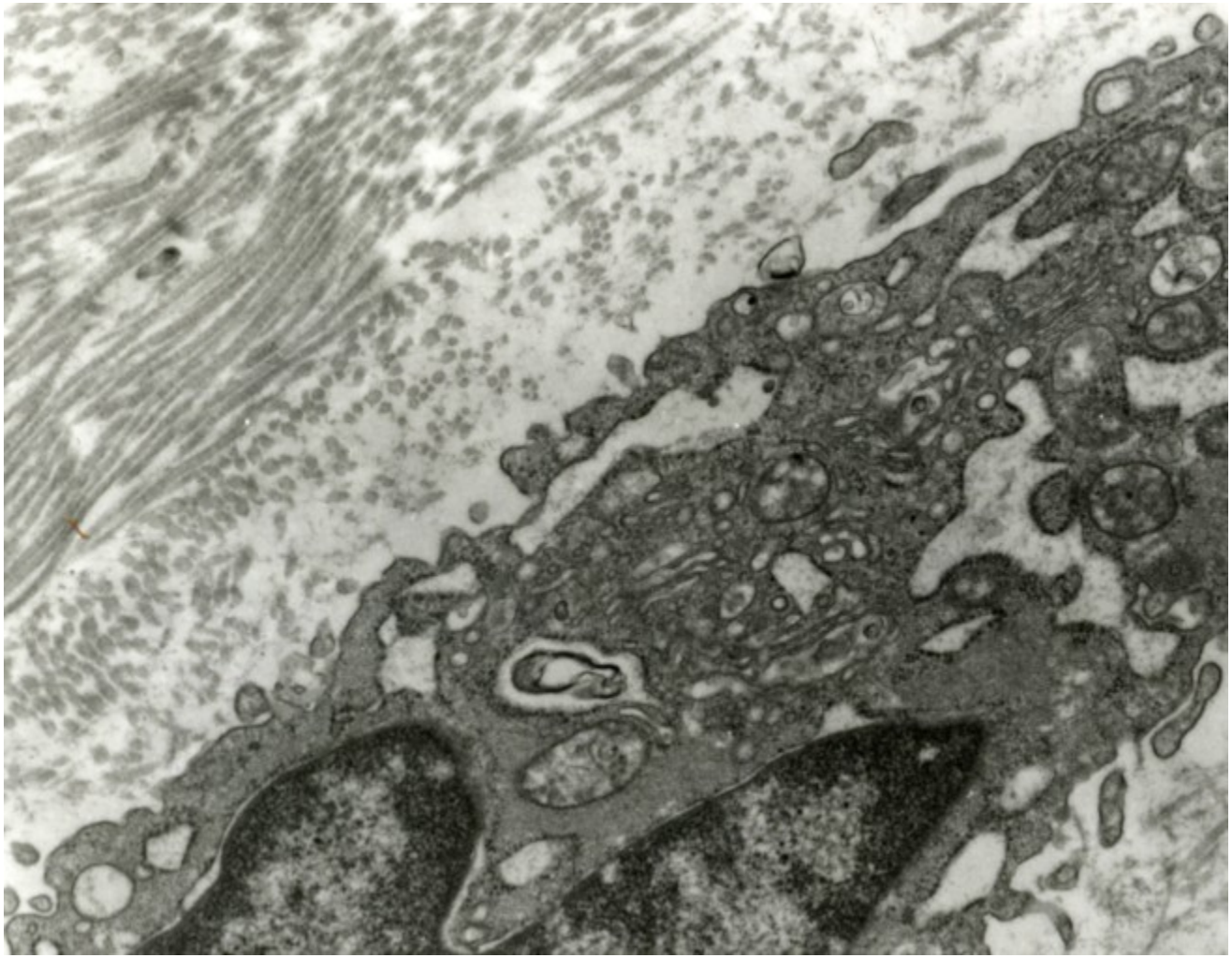
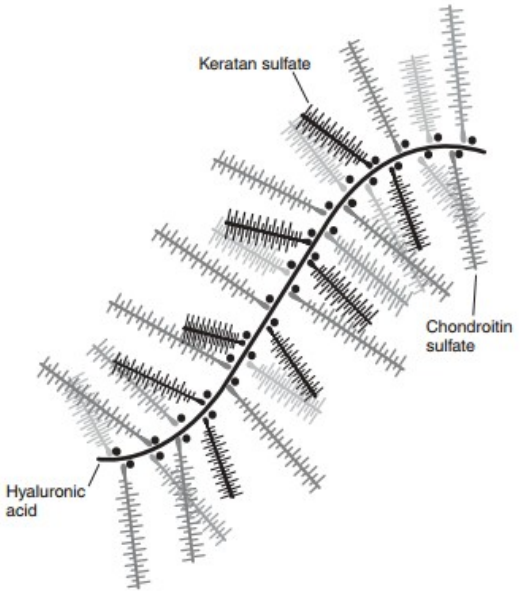


# ULTRASTRUCTURE OF CHONDROBLASTS



- Extracelullar matrix




glycosaminoglycans

proteoglycans

fibers

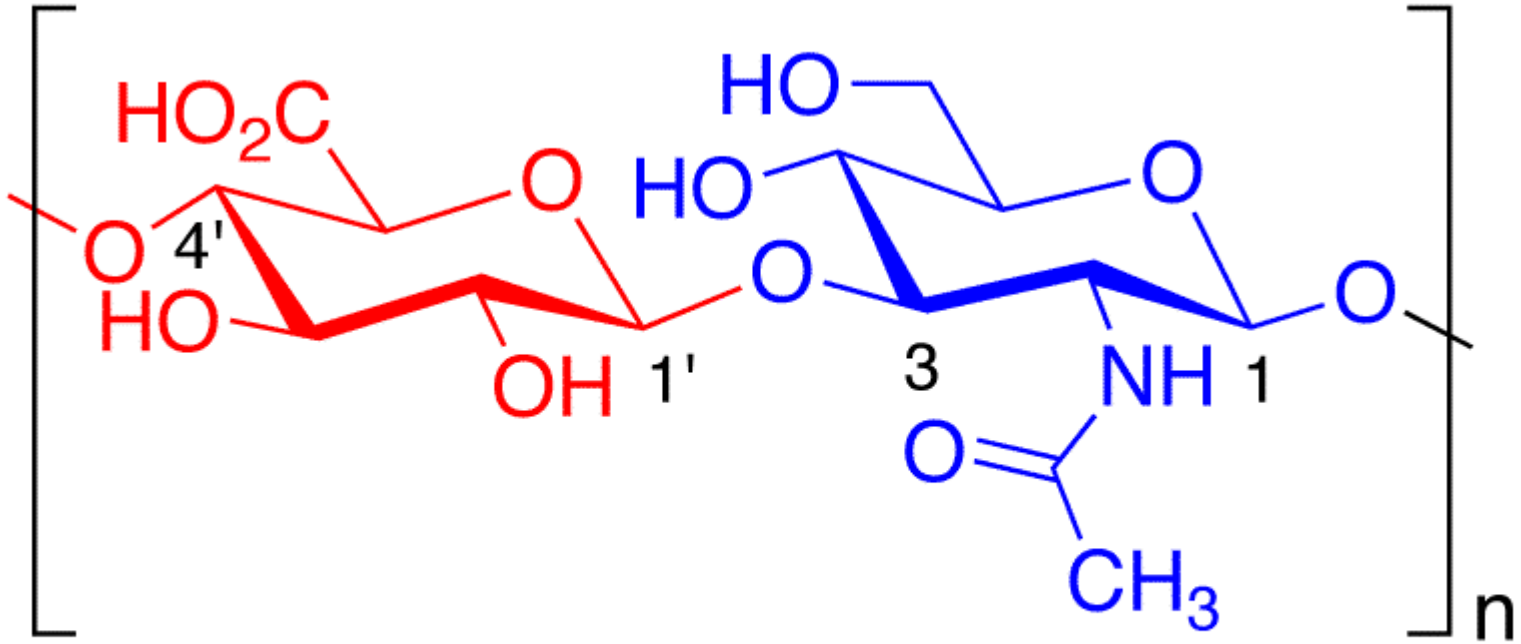
water

biomechanical properties

# GLYCOSAMINOGLYCANS IN CARTILAGE

linear unbranched polysaccharides containing a repeating disaccharide unit:
*1. N*-acetylgalactosamine (GalNAc) or *N*-acetylglucosamine (GlcNAc)
2. uronic acid (glucuronate (GlcA)) or iduronate.

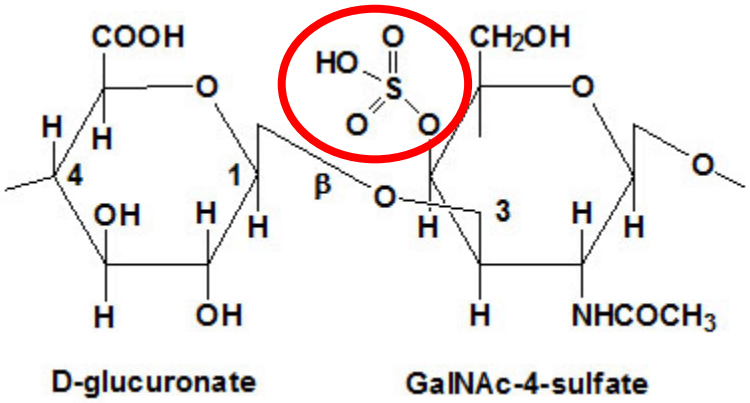
hyaluronic acid



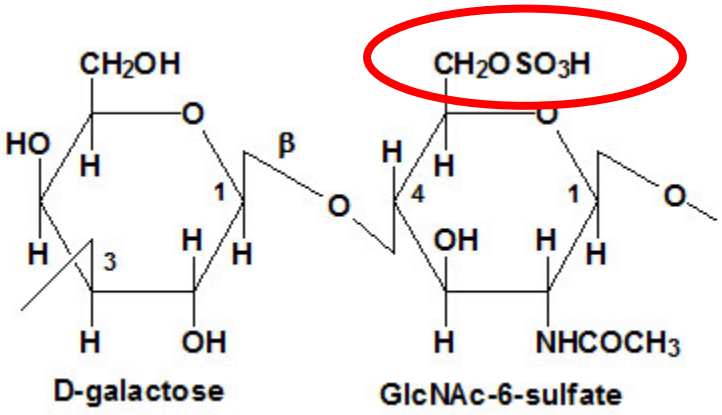

*Glucuronic Acid* *N-Acetyl-D-glucosamine*

# GLYCOSAMINOGLYCANS IN CARTILAGE

| Glycosaminoglycan | Localization |
|---|---|
| Hyaluronic acid | Umbilical cord, synovial fluid, fluid of corpus vitreum, cartilage |
| Chondroitinsulphate | Cartilage, bone, cornea, skin, notochord, aorta |
| Dermatansulphate | Skin, ligaments, adventitia of aorta |
| Heparansulphate | Aorta, lungs, liver, basal membranes |
| Keratansulphate | Iris, cartilage, nucleus pulposus, anulus fibrosus |



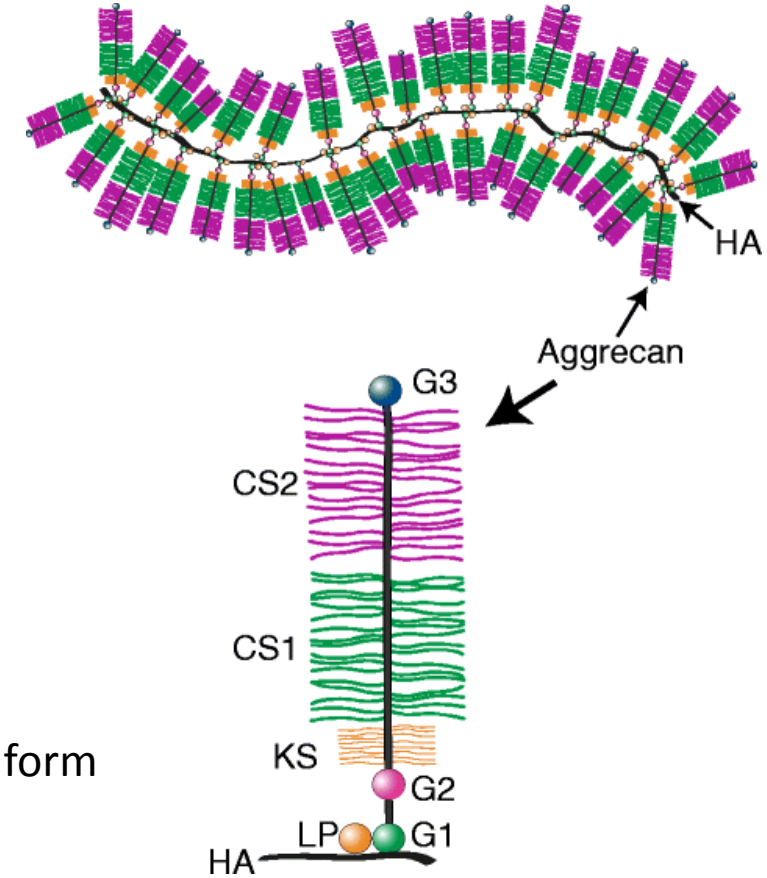

**Chondroitinsulphate**




**Keratansulphate**

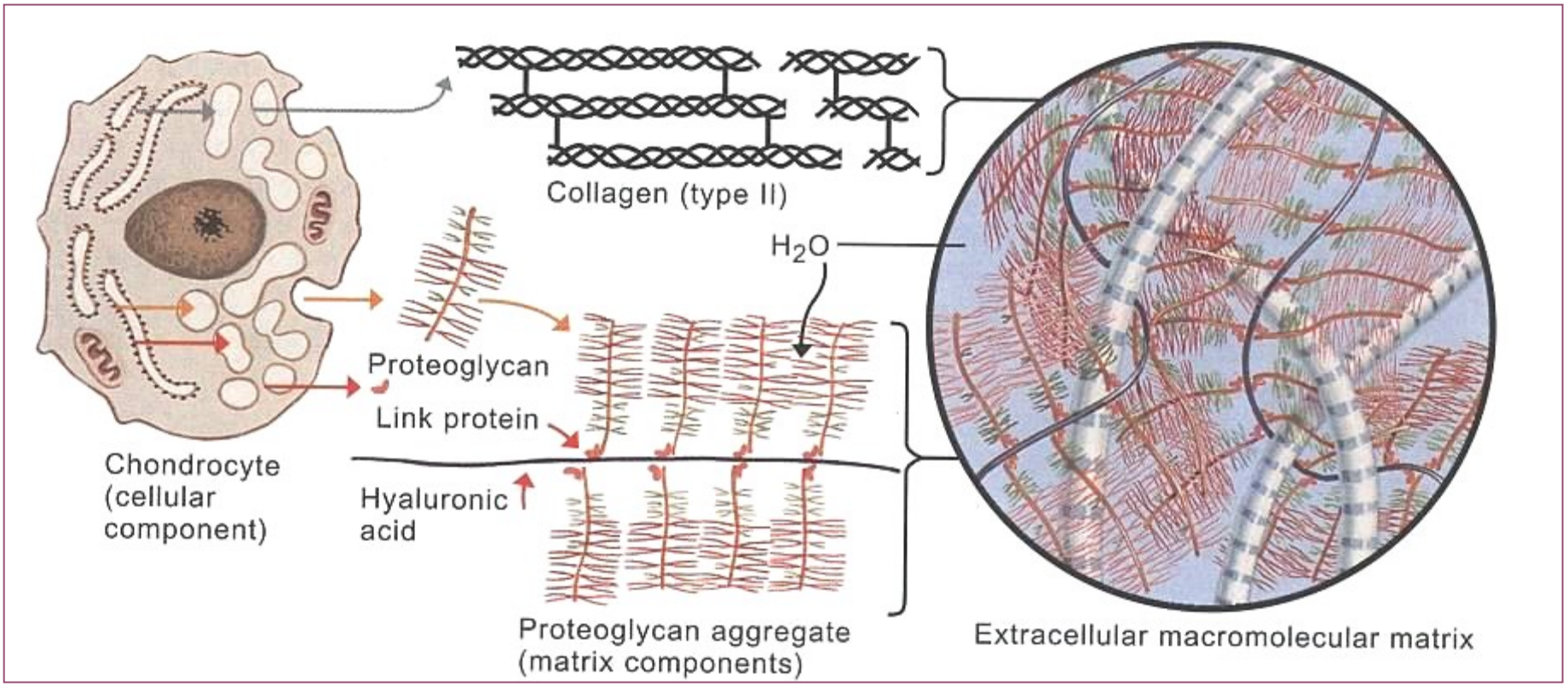
# PROTEOGLYCANS AND FIBERS

- **proteoglycans**
- protein + dominant linear saccharide component
- proteoglycan aggregates
- water-binding – 80%, volume dependent of hydratation
  - **aggrecan (cartilage)**
  - syndekan
  - fibroglykan




- **collagen fibrils**
- col II + col IX/XI
- thin fibrils (15-20 nm → no striation) that do not form fibers like col I
- interconnected with perichondrium
- elastic fibers

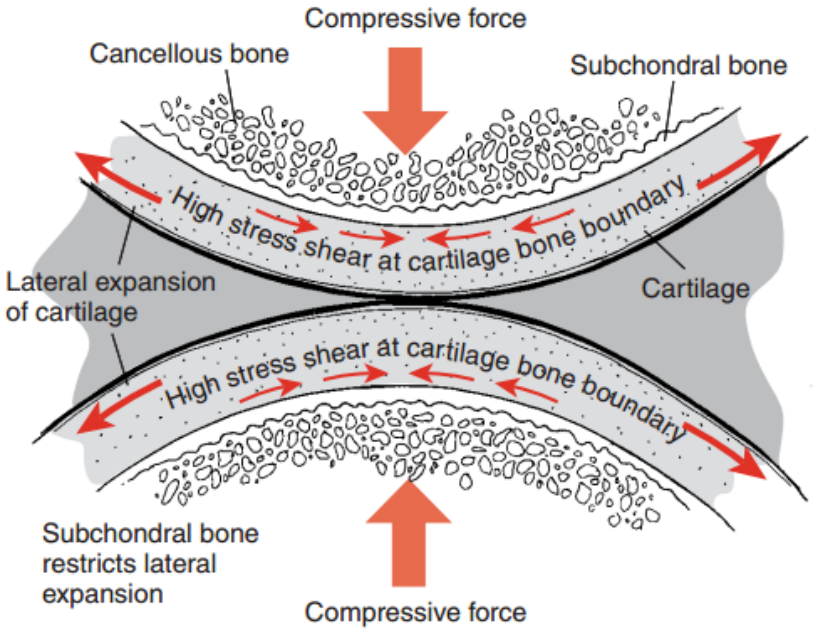
# TISSUE ARCHITECTURE OF CARTILAGE ECM




transduction of biochemical and biomechanical signals

# TISSUE ARCHITECTURE OF CARTILAGE ECM

- **pressure elasticity**
- proteoglycans – polyanionic ($COO^-$, $SO_4^{II-}$)
- expansion prevented by collagen fibrils
- repulsion forces




- **biphasic model of cartilage** conditioned by ECM composition
- proteoglycans, collagen, cells, and lipids constitute the solid phase of the mixture
- interstitial fluid that is free to move through the matrix fluid phase)
- under impact loads, fluid flows through the framework, until the cartilage start to behave as a single-phase, incompressible, elastic solid - the fluid does not flow
- after load release, fluid returns
- nutritive aspect

# TISSUE ARCHITECTURE OF CARTILAGE ECM

- **synovial cartilage**

I. tangential (superficial) zone

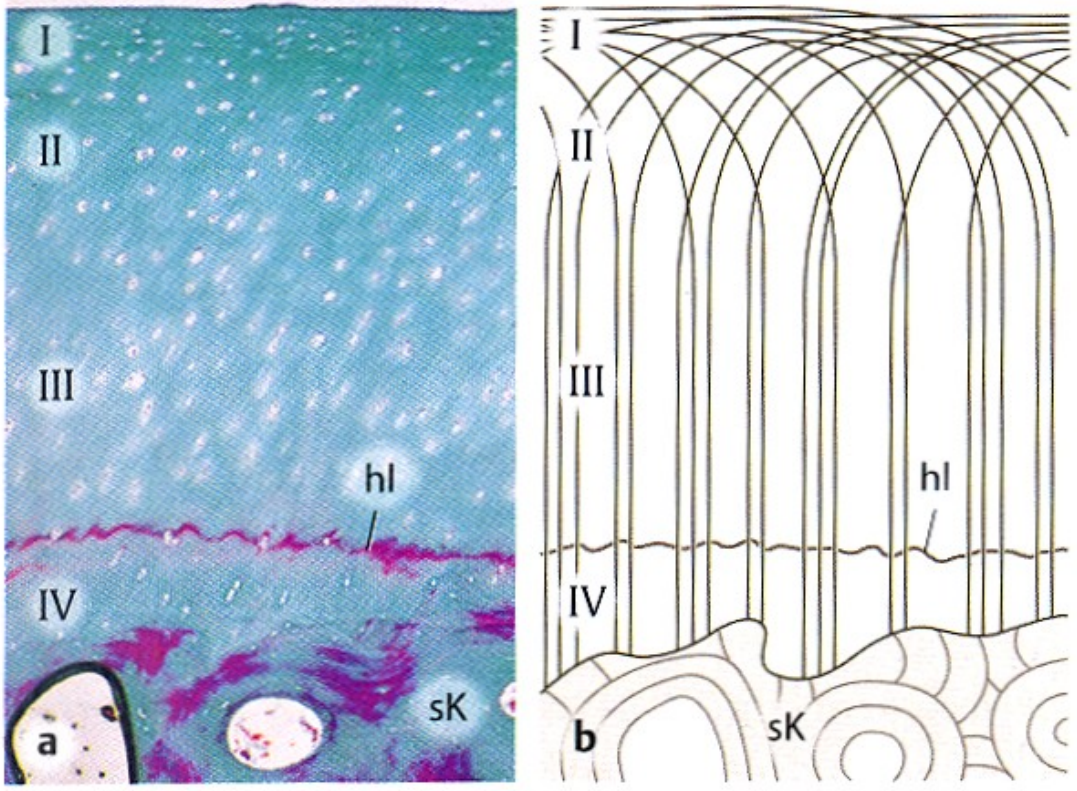
II. transitional zone

III. radial (deep) zone

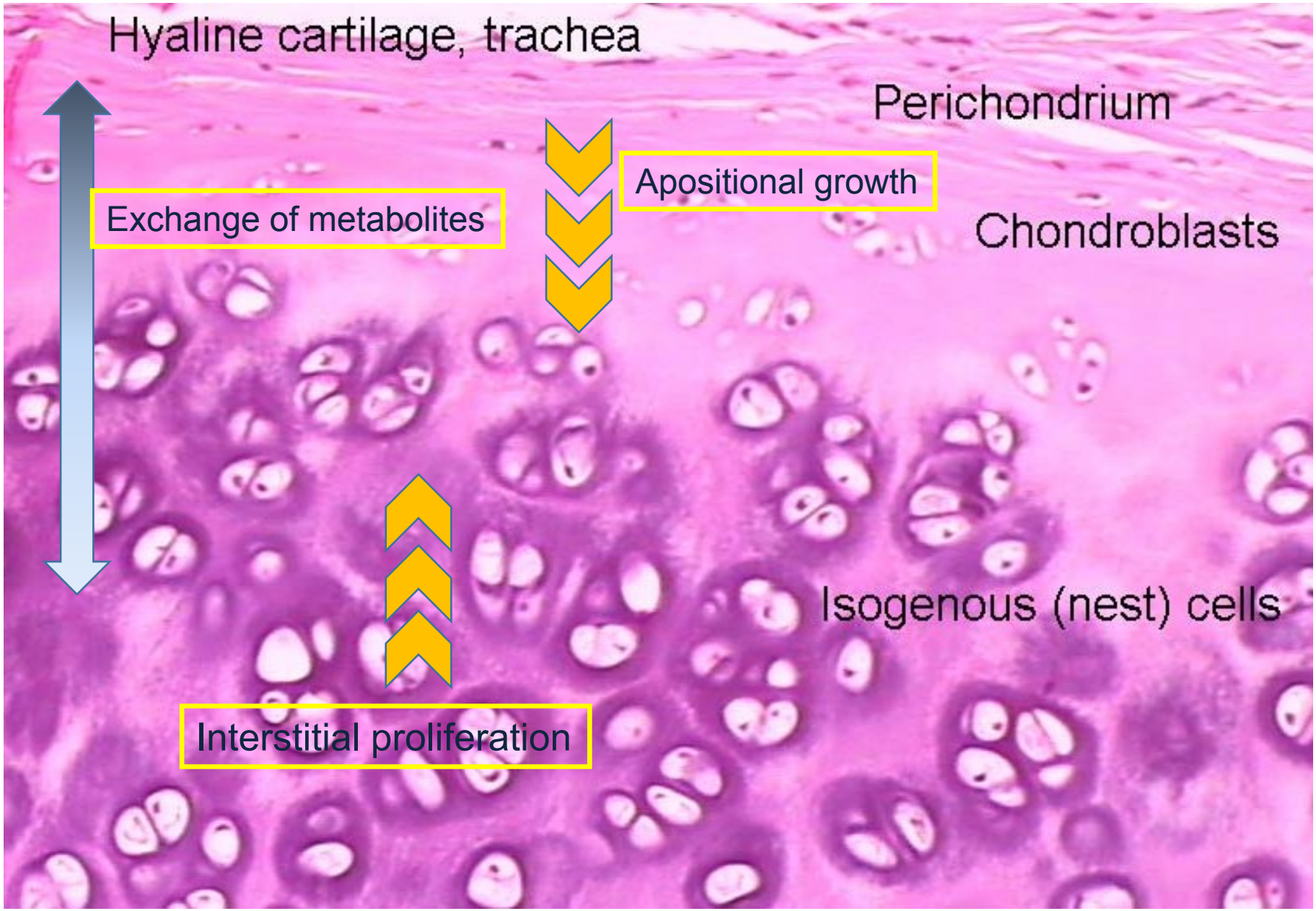
tide mark

I. mineralized cartilage zone

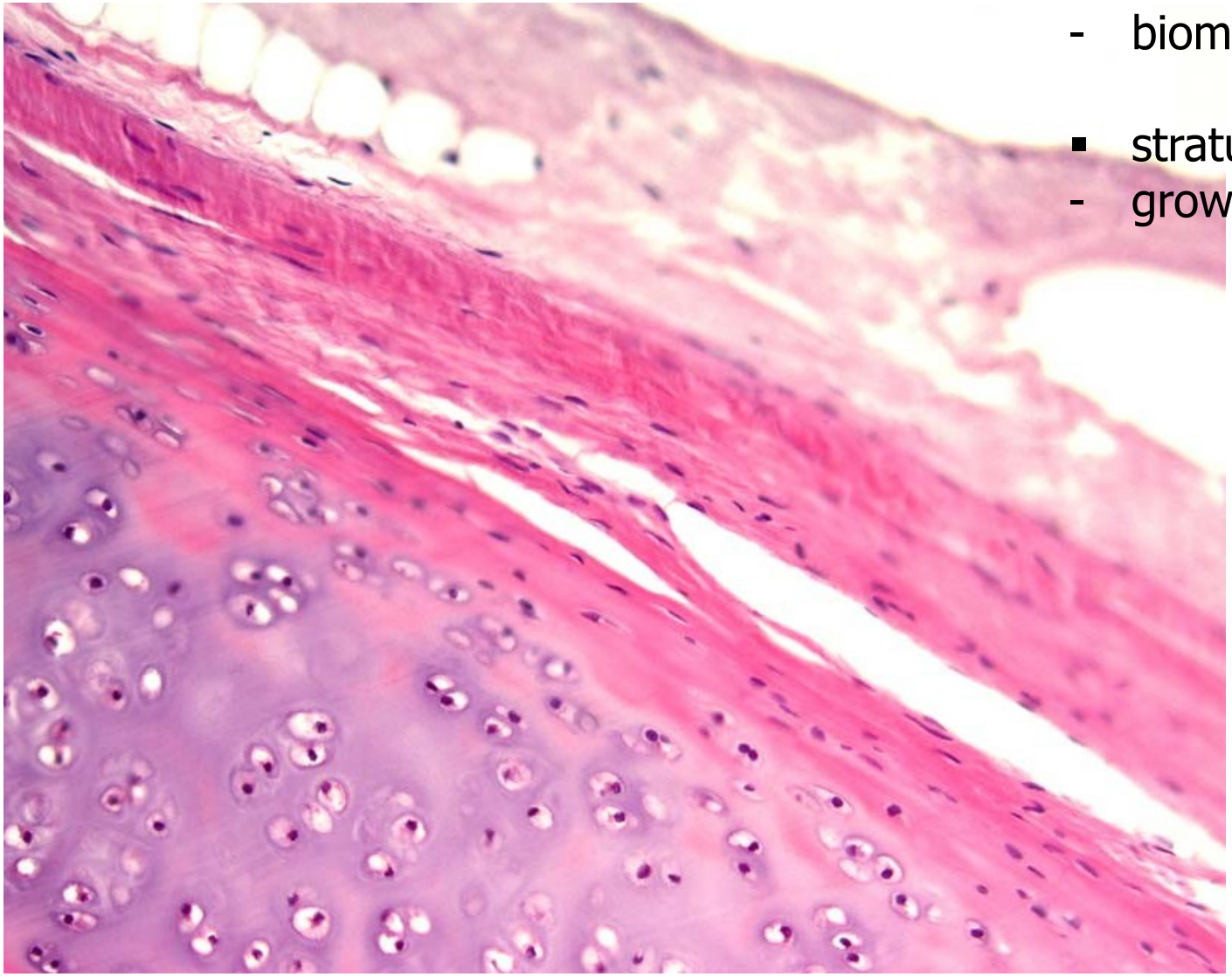
subchondral bone



# NUTRITION AND GROWTH



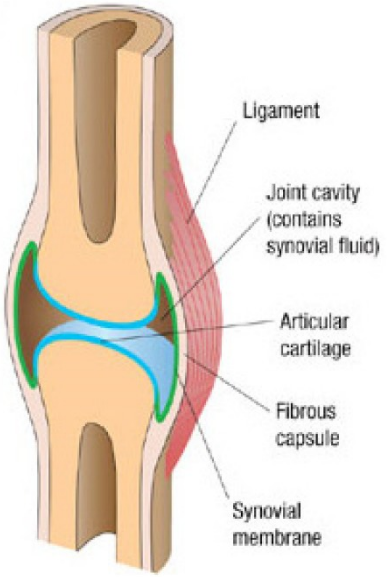
# PERICHONDRIUM

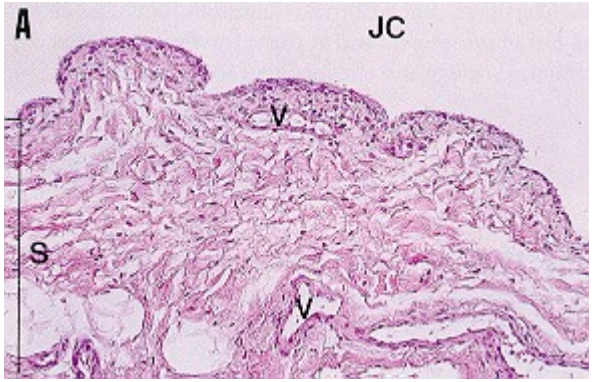


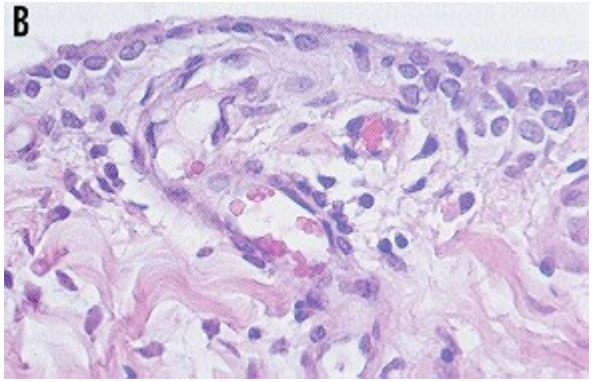
- stratum fibrosum
  - biomechanics
- stratum chondrogenicum
  - growth

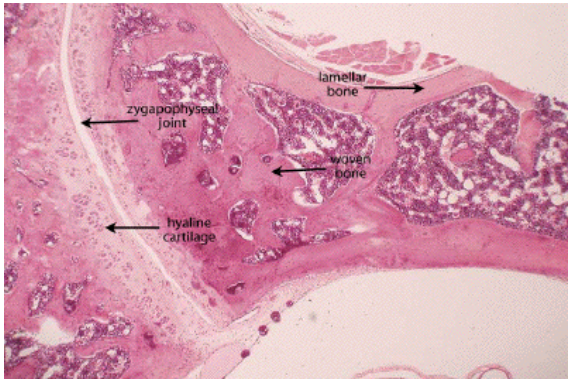
# SYNOVIUM

- *membrana fibrosa*
- dense collagen c.t.
- *membrana synovialis*
- intima, subintima
- folds extending to the joint cavity
- numerous blood and lymphatic vessels, nerves
- discontinuous cell layers (synovialocytes)
- basal membrane and intercellular junctions absent - **not an epithelium:** mesenchymal (c.t.) origin
- synovial fluid rich in hyaluronans
- *bursae synoviales, vaginae tendineum*




http://www2.indstate.edu/thcme/mmmoga/histology/slide35.html

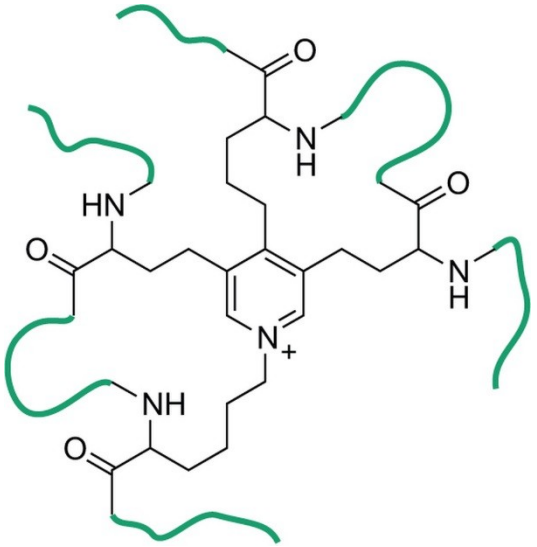
https://www.dartmouth.edu/~anatomy/Histo/lab_2/bone/DMS090/53.gif

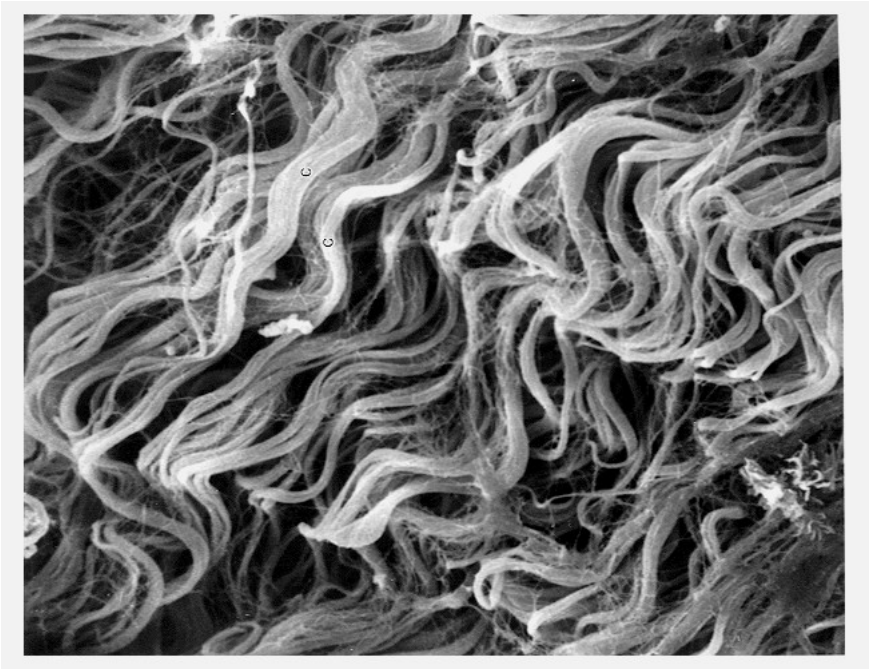
# ELASTIC CARTILAGE

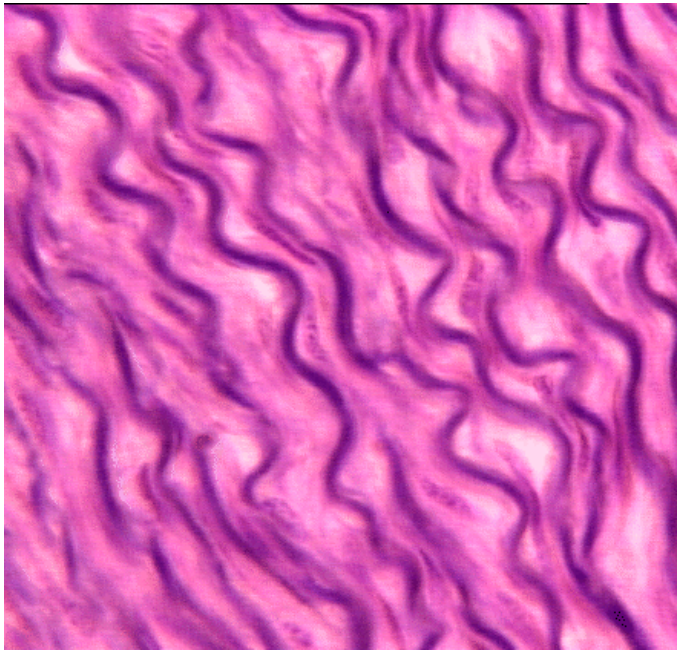
- acidophilic elastic fibers dispersed in matrix
- no isogenetic groups
- auricula, meatus, larynx, epiglottis

# ELASTIC FIBERS

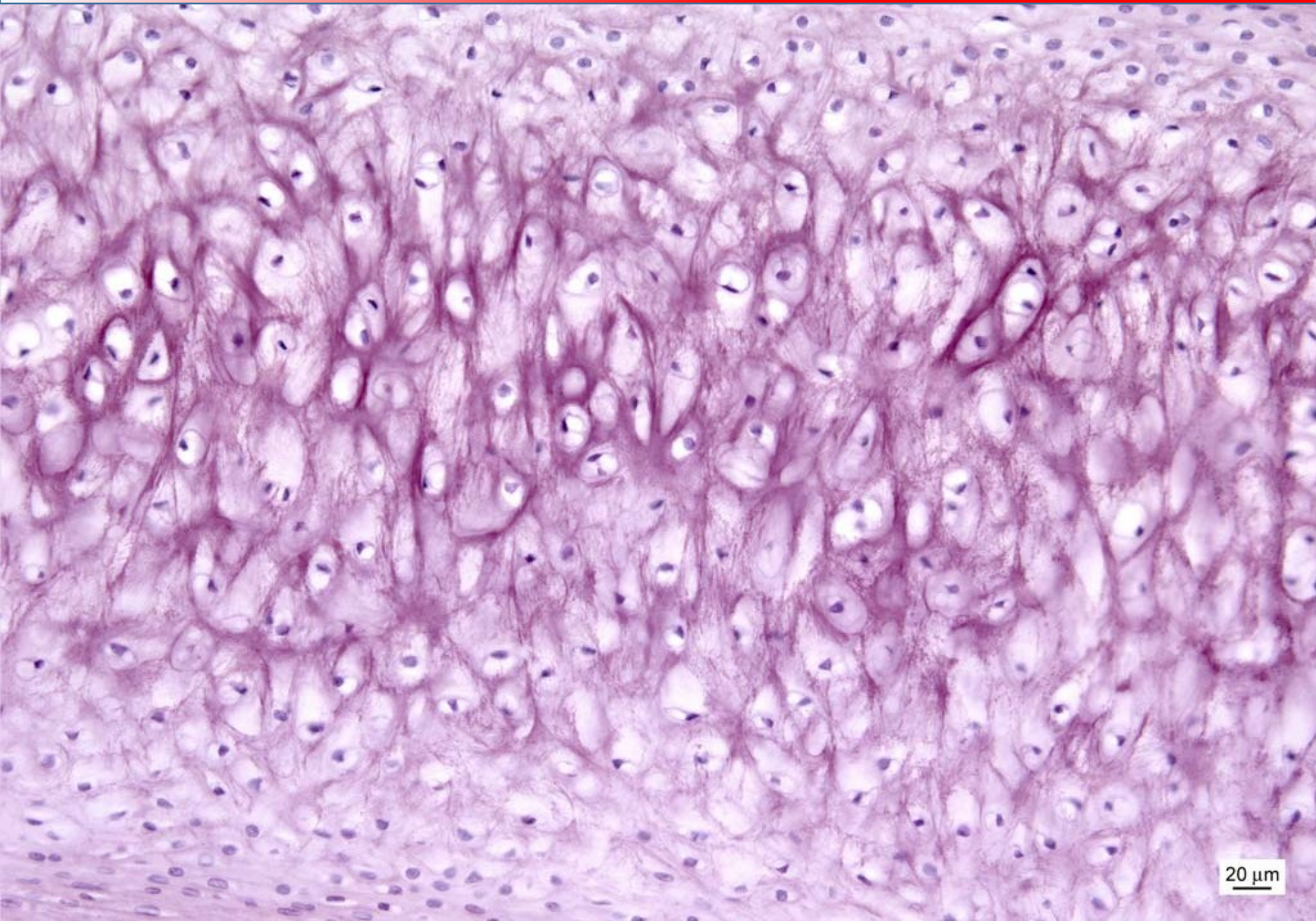
- less abundant than collagen
- polymer – tropoelastin
- minimal tensile resistance, loss of elasticity if overstretched
- reduction of hysteresis = allow return back to original state after mechanic change



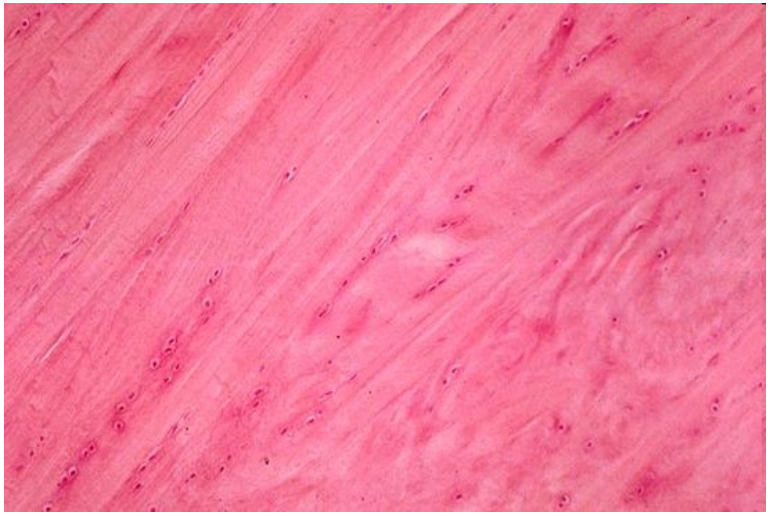


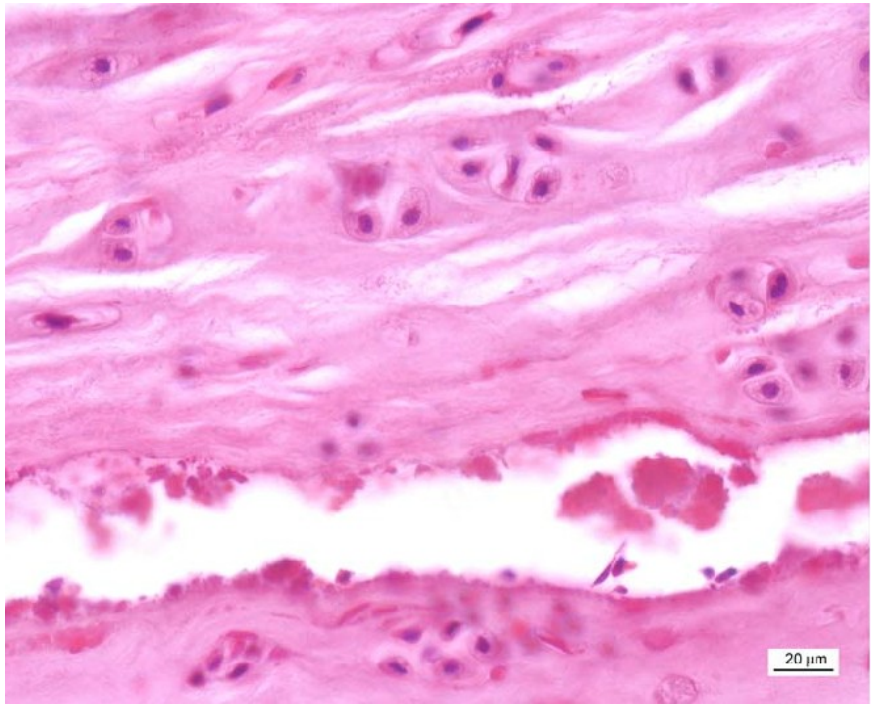
# ELASTIC CARTILAGE

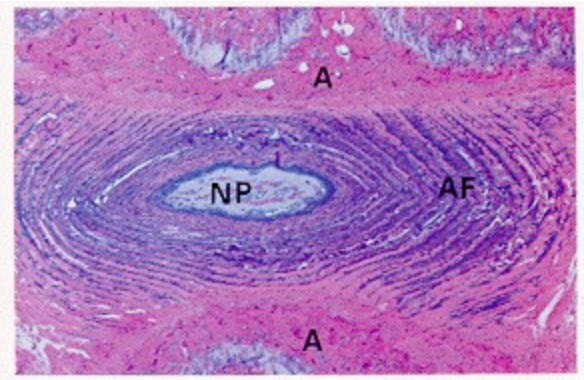


# FIBROCARTILAGE

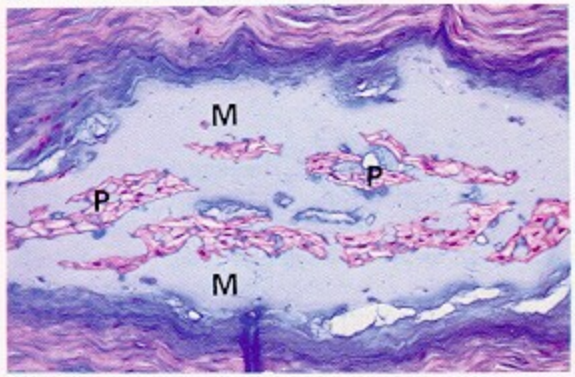
- fibrous compound dominant – collagen I and II – mechanical durability
- minimum of amorphous matrix-fibers visible
- intervertebral discs, symphysis pubis, articular discs, meniscus





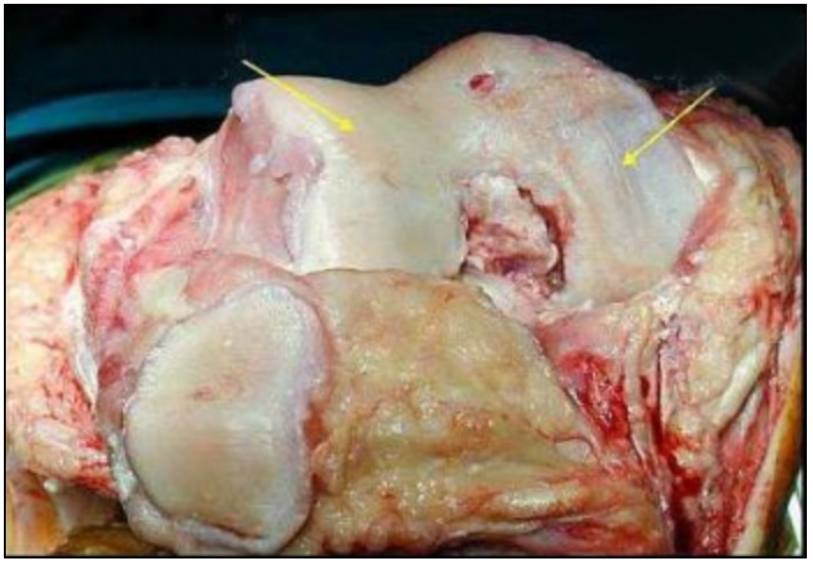
(a)



(b)

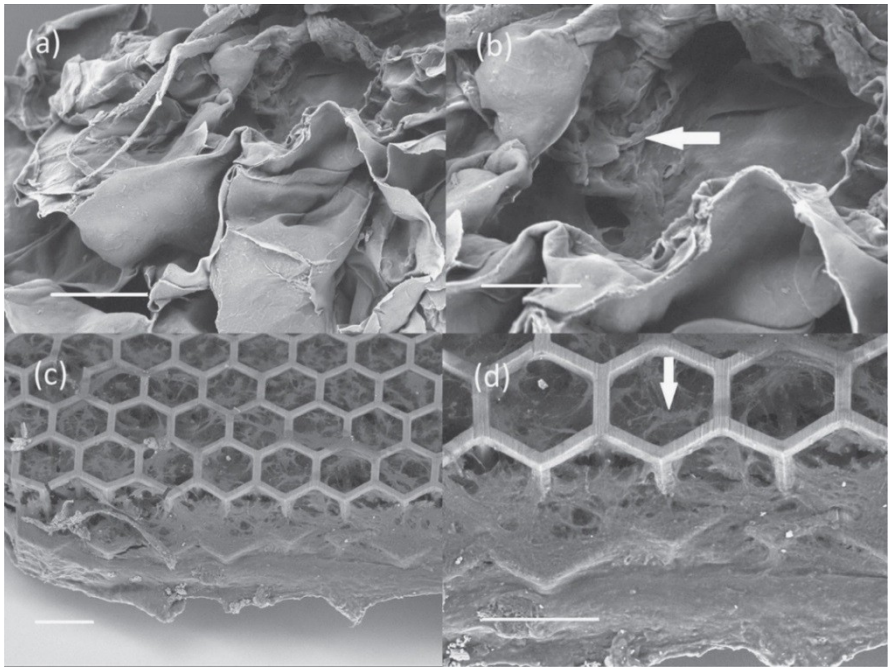
# CLINICAL CORRELATION

- Cartilage – no innervation, no vascularization – no spontaneous regeneration
- No migration of chondrocytes to site of damage
- Initiation of other degenerative events leading to cartilage erosion (arthritis)



Therapy:

- joint mobility
- restoration of biochemical and biophysical parameters of cartilage
- prevention of further damage
- removal of damaged tissue, autologous transplantation, MSCs on biocompatible scaffolds

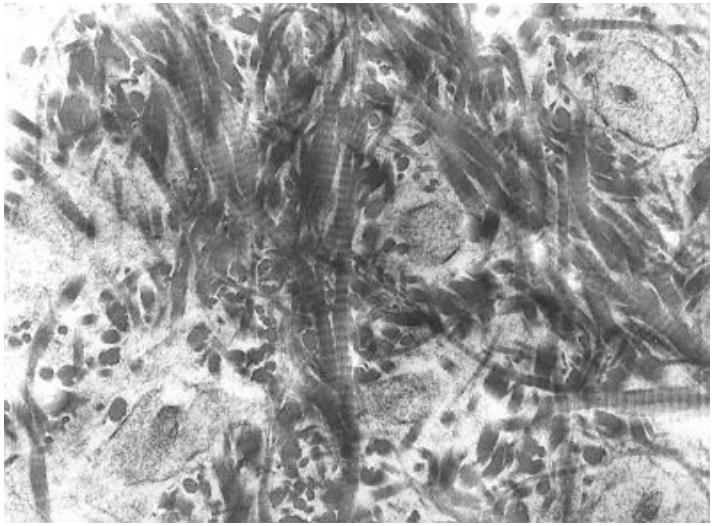



BONE
20 µm

# HISTOLOGICAL CLASSIFICATION OF BONE TISSUE

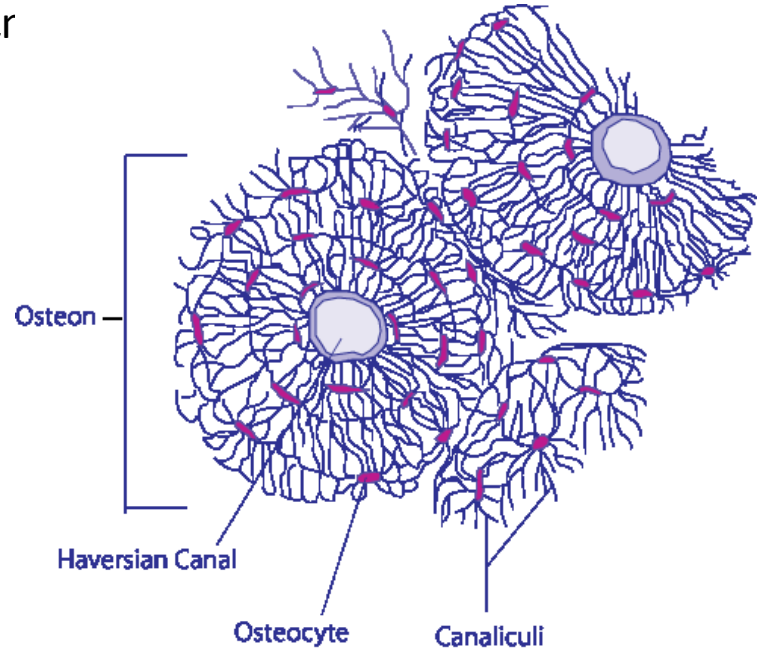
- **Primary (woven, fibrous)**

- Temporary, growth and regeneration of bones, collagen fibrils woven
- Replaced by secondary bone
- Remains only in some parts of body - sutures of skull, *tuberositas ossium*, tooth cement



- **Secondary (lamellar)**

- Lamellae – collagen fibers in concentric layers (3-7μr around a canal with capillaries = Haversian system (osteon)



# PRIMARY (WOVEN) BONE

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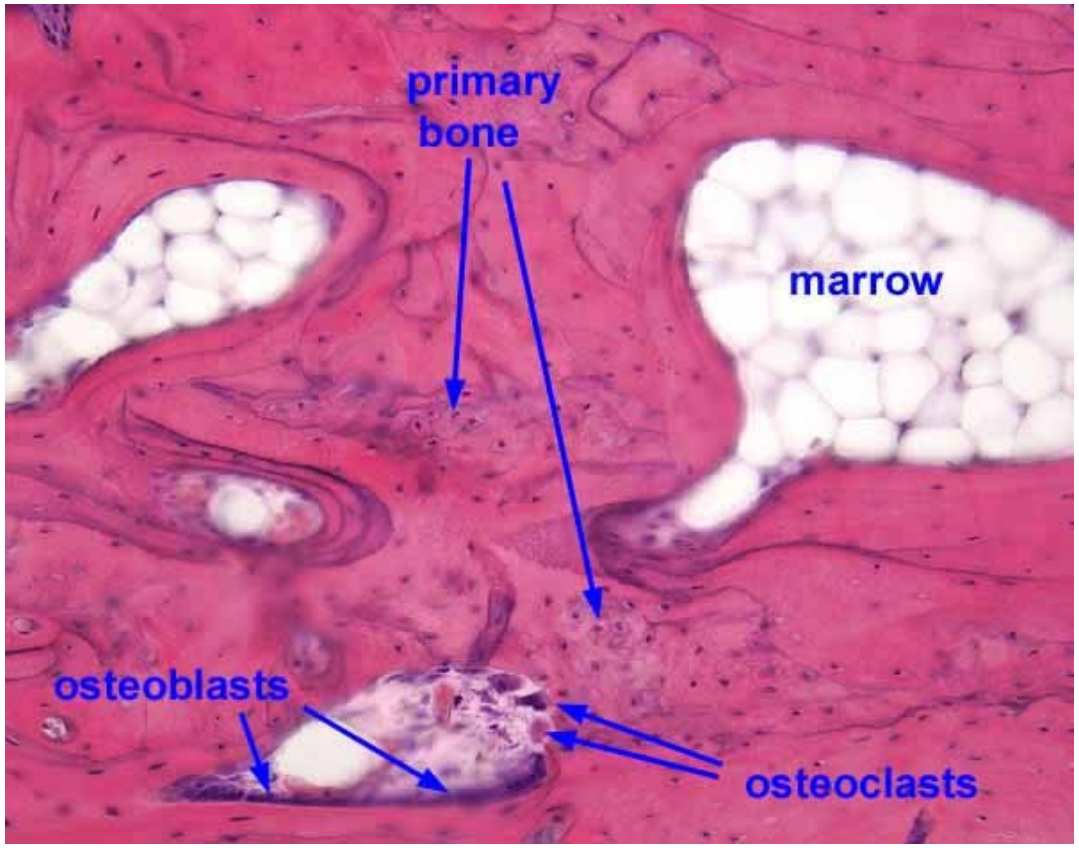
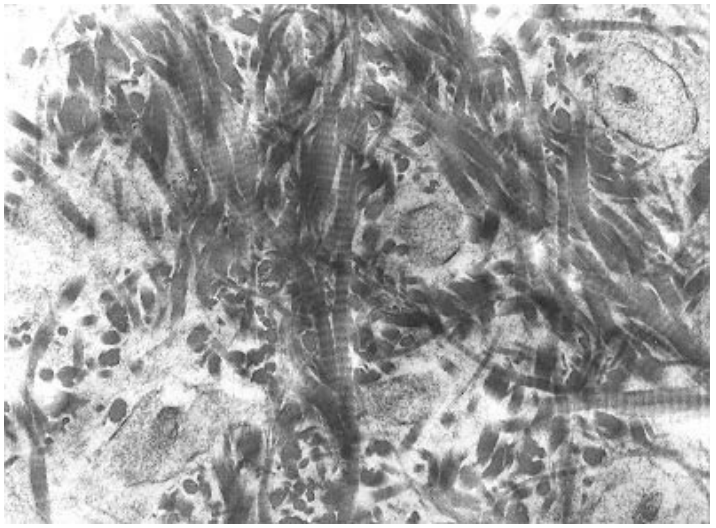
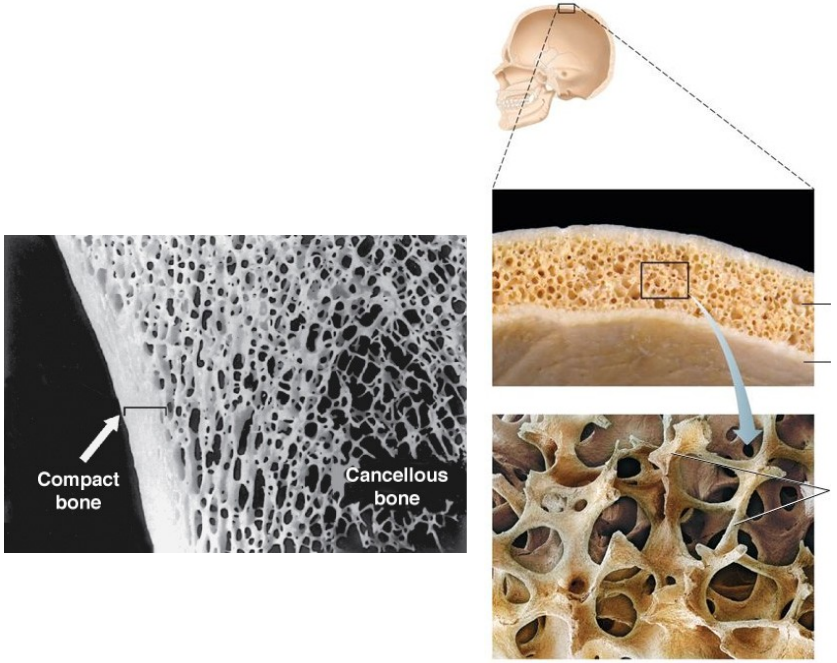
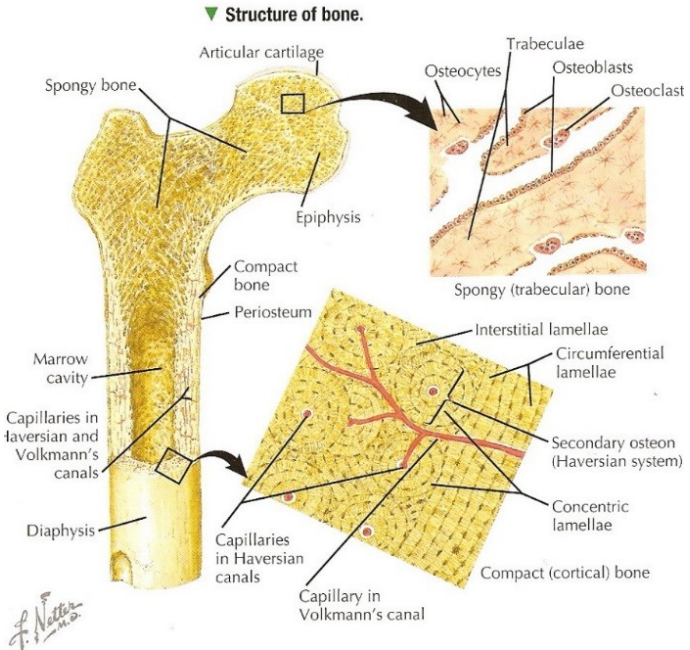


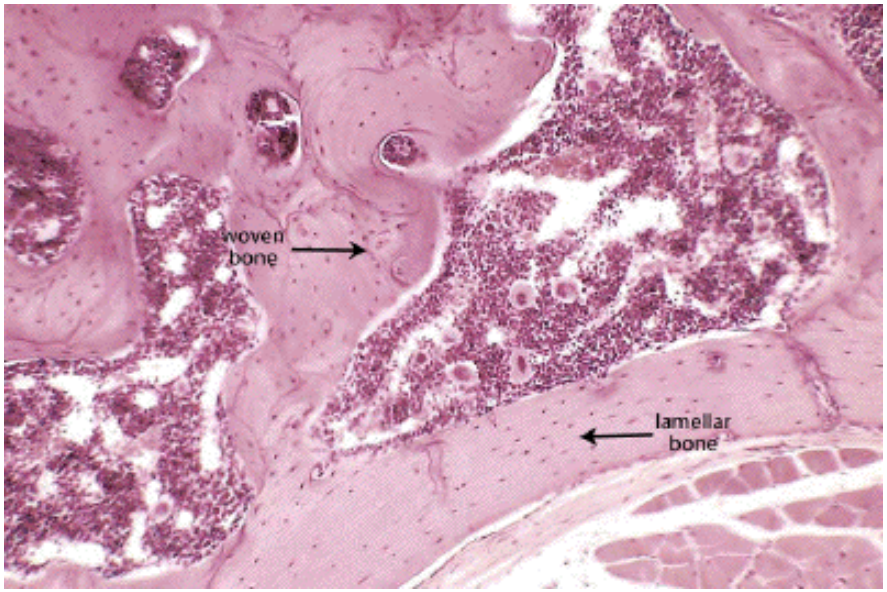



# SECONDARY (LAMELLAR) BONE

- Lamellae – collagen fibers in concentric layers (3-7μm) around a canal with capillaries = Haversian system (osteon)
- **Spongy (trabecular)**
  -Trabeculae, similar to compact
  -Epiphyses of long bones, short bones, middle layer of flat bones of the skull (*diploe*)
- **Compact**
  - Outer and inner coat lamellae typical Haversian systems
  - Volkmann's canals
  - Interstitial canals

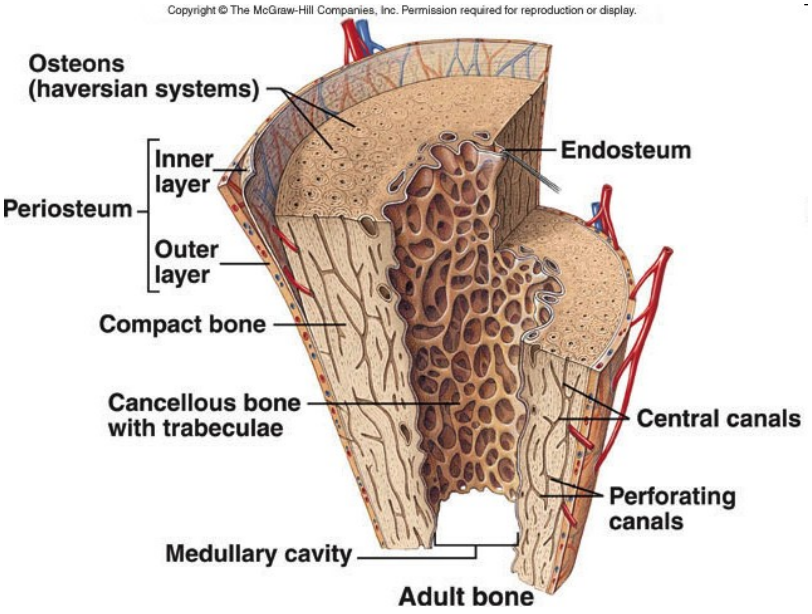


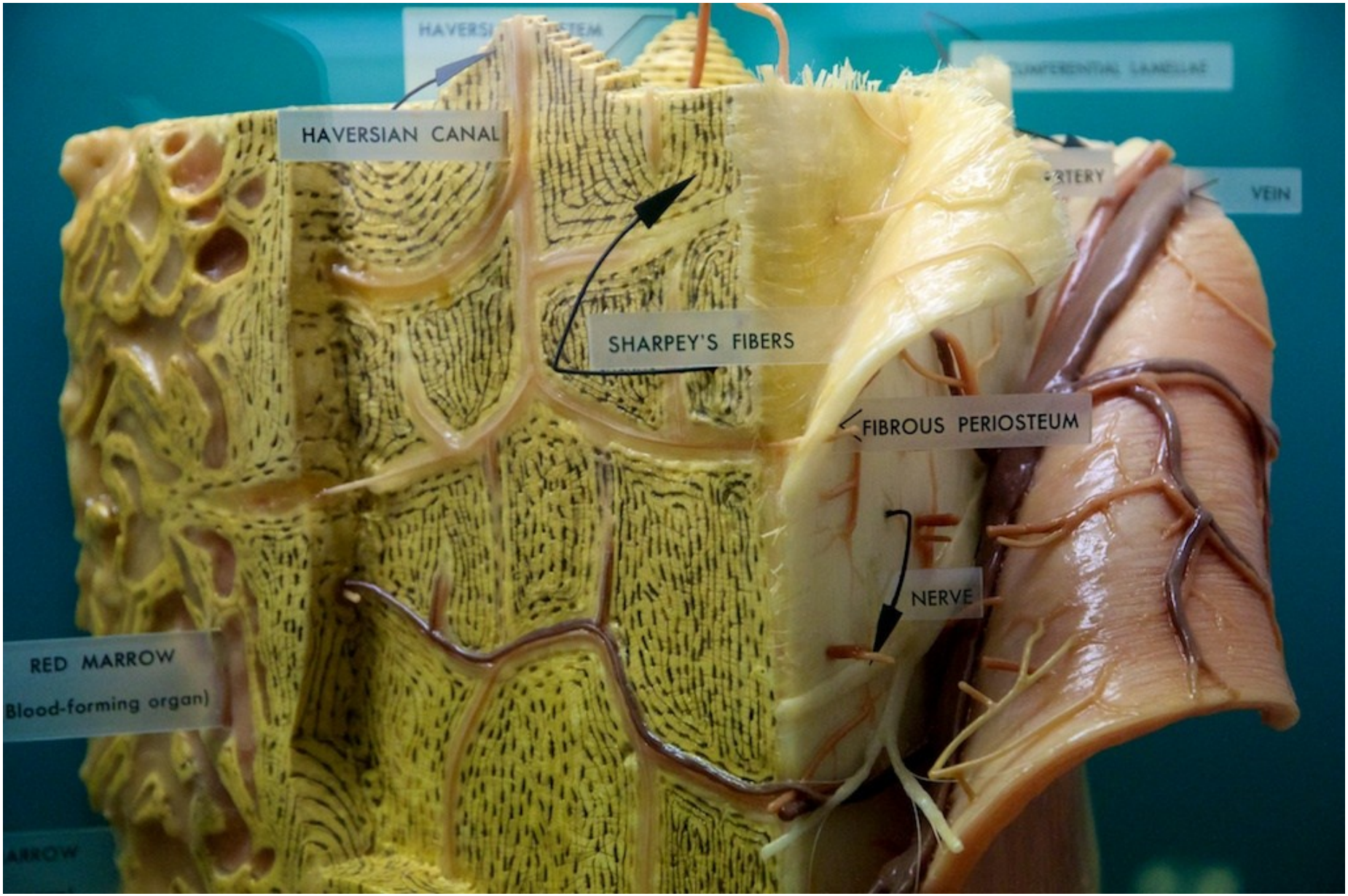



# BONE SURFACES

- **Outer surface**
- Synovial joint – hyaline cartilage
- **Periosteum (periost)** – membrane – dense CT, inner layer (osteoblasts) and outer layer (fibrous CT)
- Inactive bone - fibrous CT in periost dominant
- Collagen fibers – parallel to the bone surface
- Sharpey's fibers fix periost to the bone

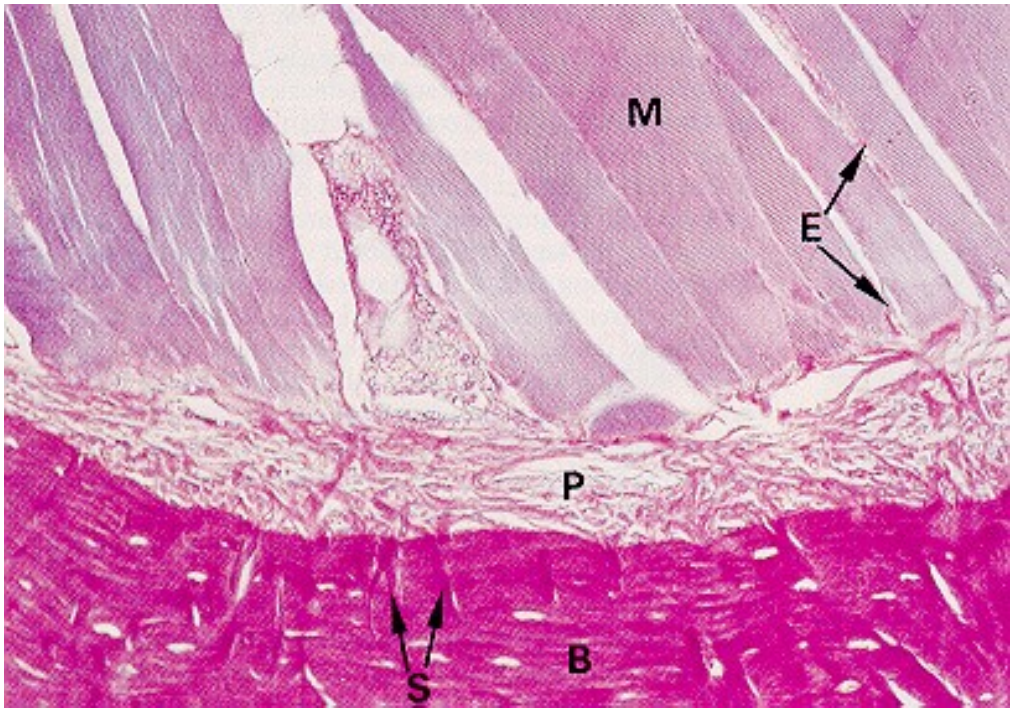


# BONE SURFACES

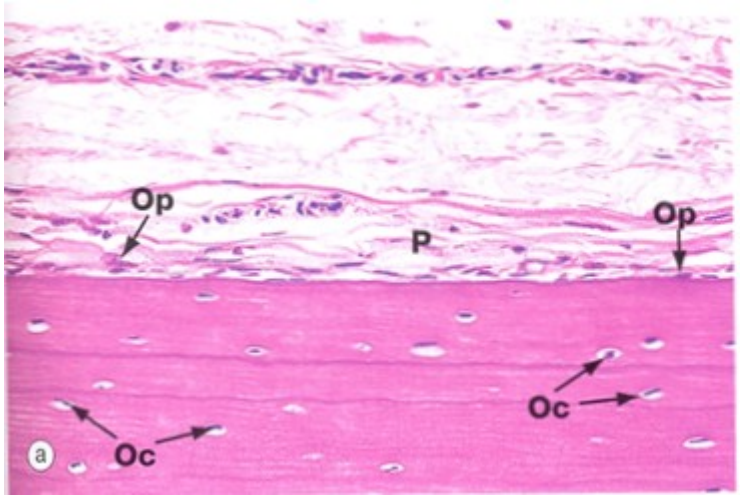



National Museum of Natural History NY, USA

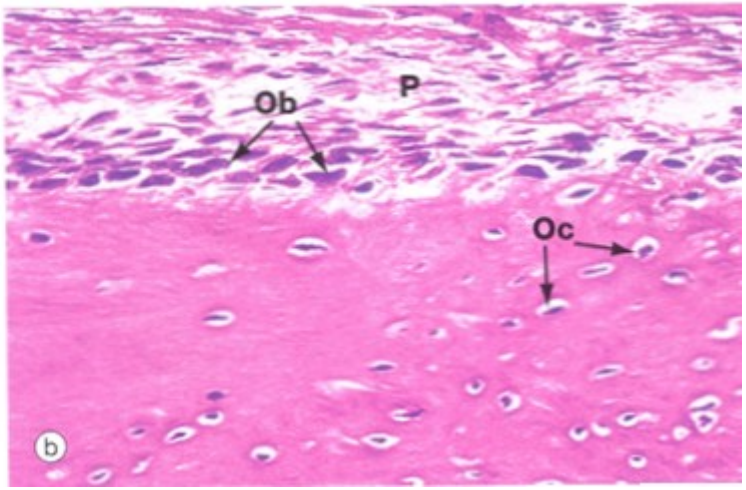
# BONE SURFACES




Inactive

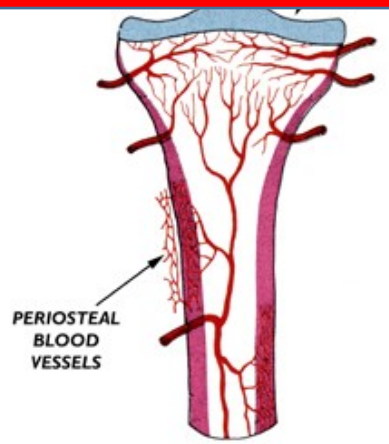


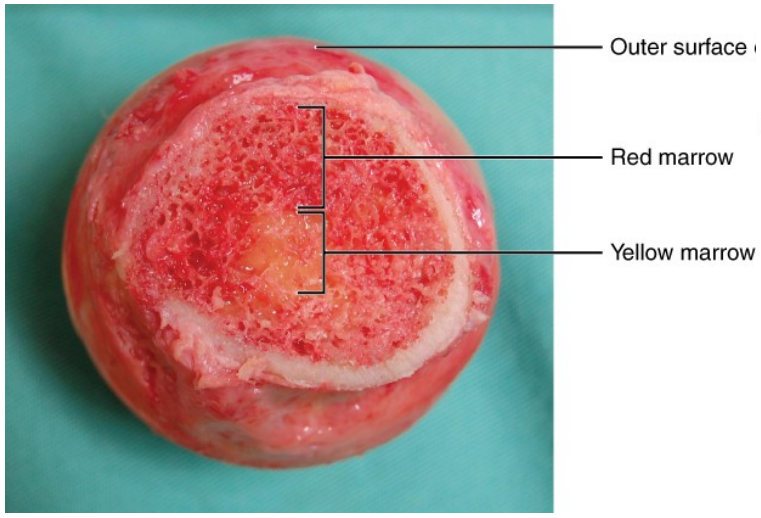

Active

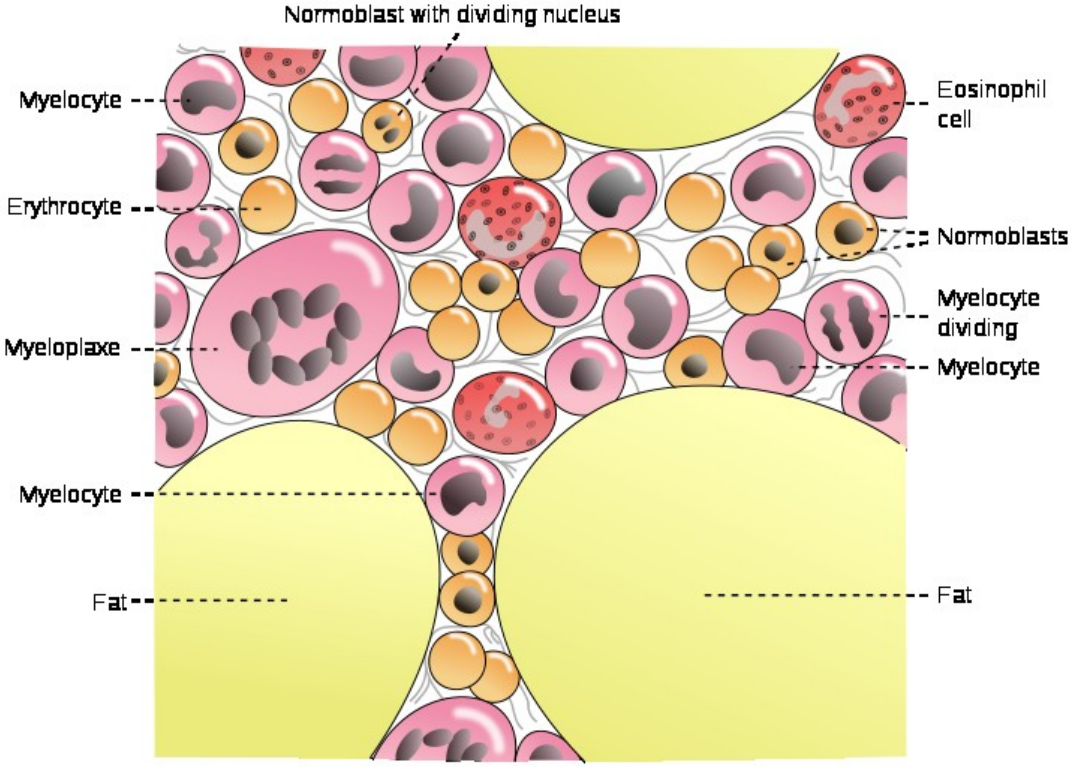


# BONE SURFACES

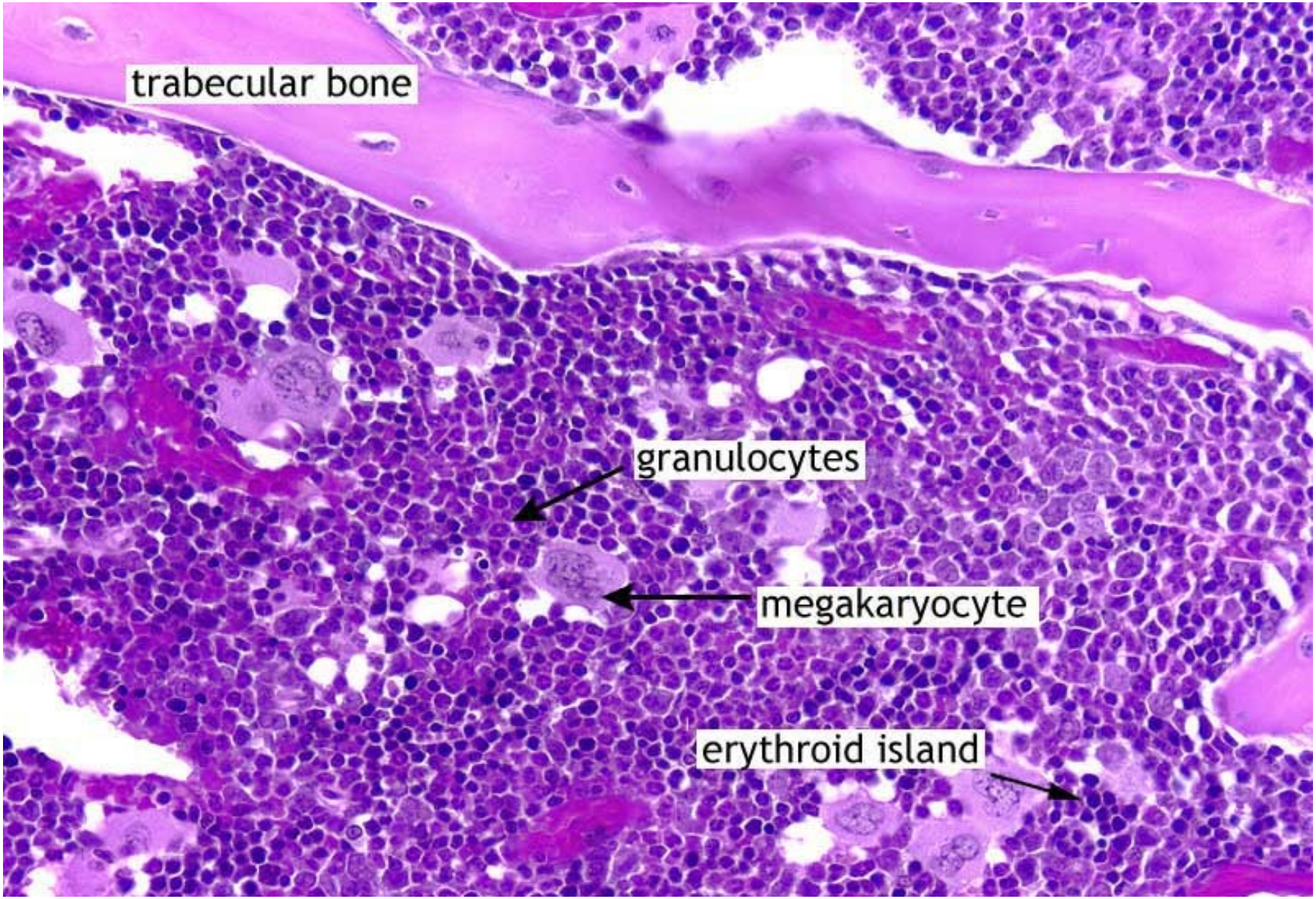
- **Inner surface** – lining of cavities
- medullar cavity
- endosteum (endost) – single cell lining – bone remodeling
- red bone marrow – hematopoiesis
- yellow and gray bone marrow – adipocytes or CT
- rich vascularization
- hematopoietic niche



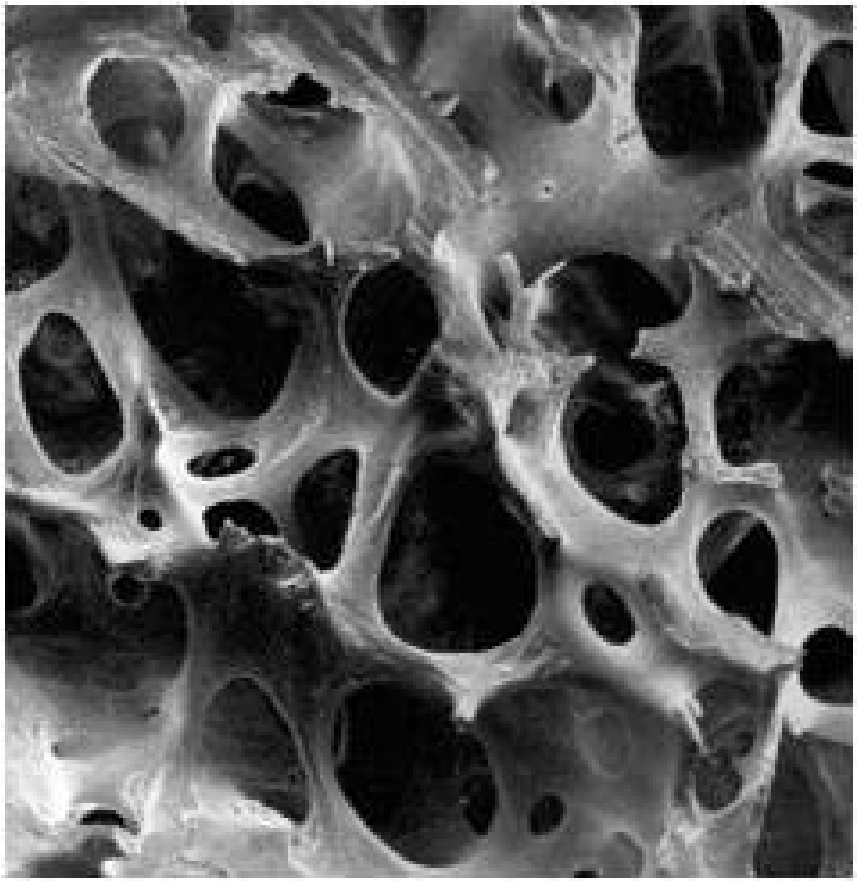



# ENDOSTEAL SURFACE OF COMPACT BONE

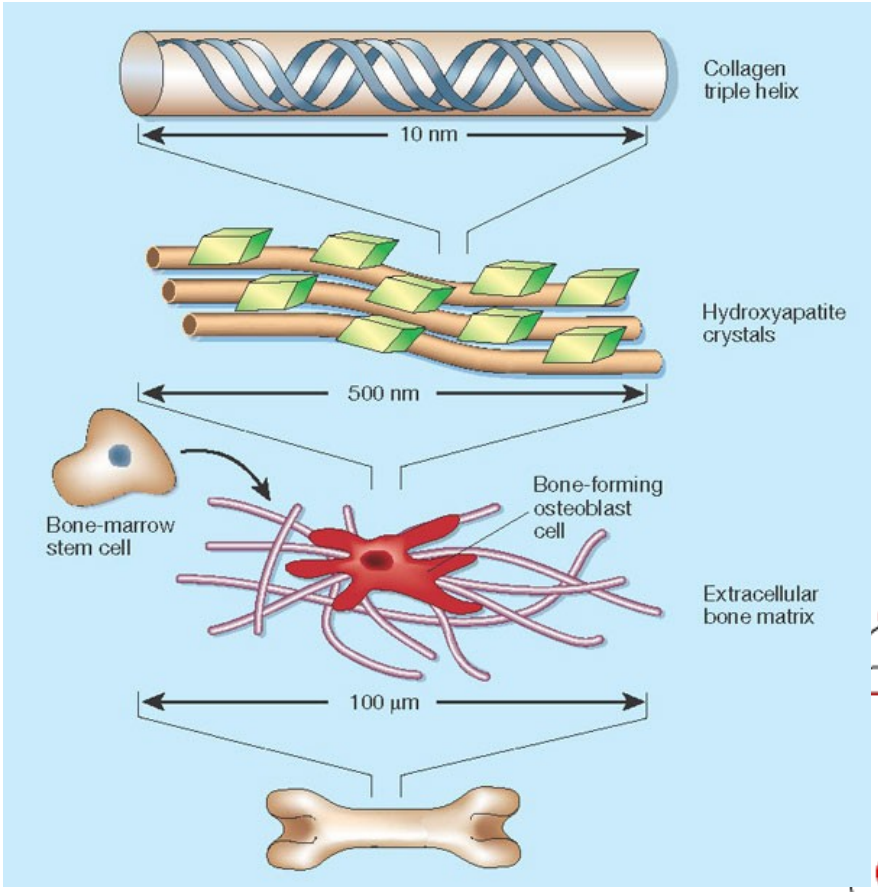


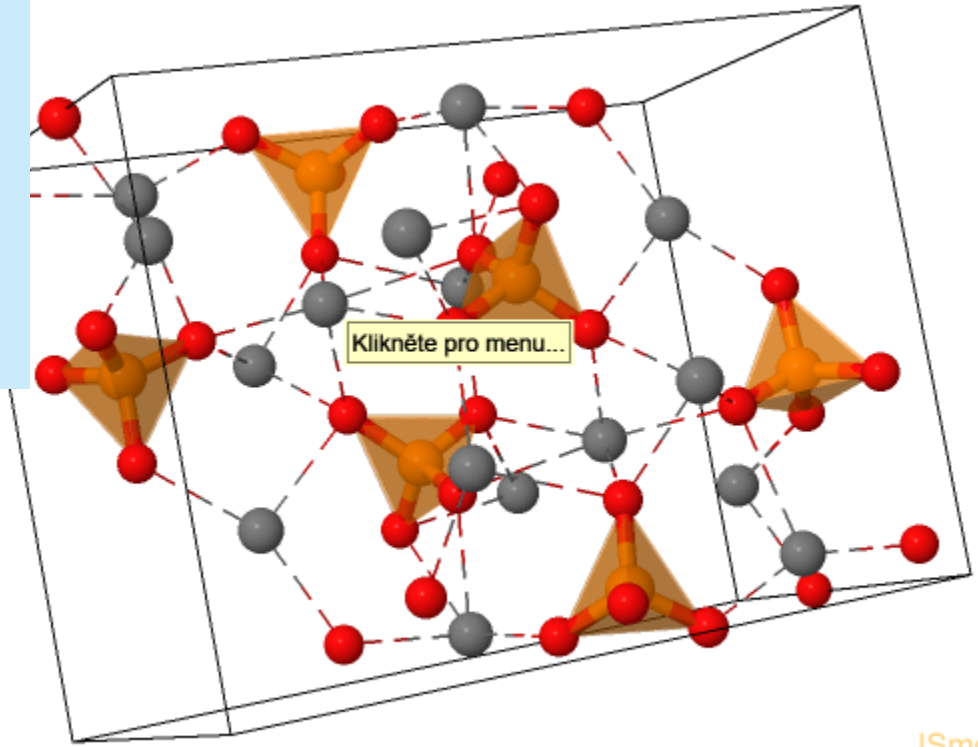
# BONE MATRIX

- 60% mineral compound, 24% organic compound 12% $H_20$, 4% fat
- crystals – calcium phosphate, hydroxyapatite



# BONE MATRIX

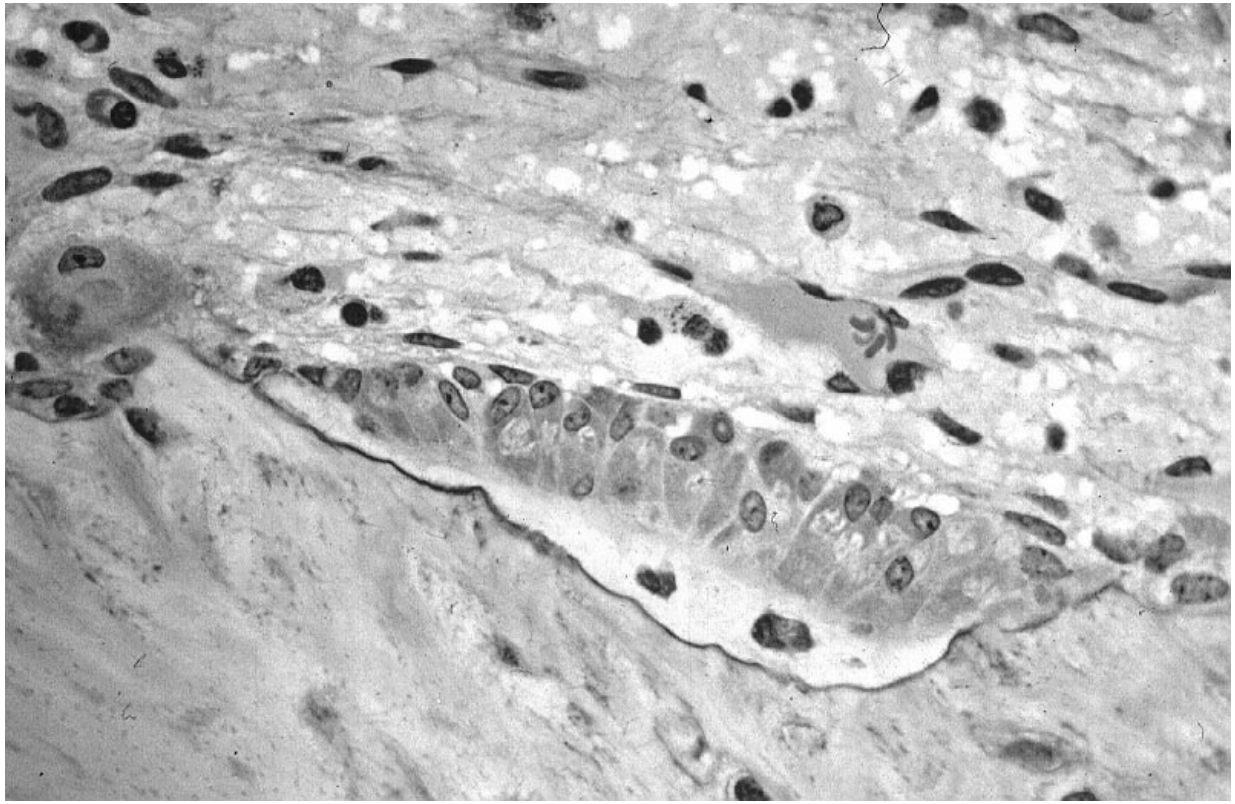

Collagen triple helix
10 nm
Hydroxyapatite crystals
500 nm
Bone-marrow stem cell
Bone-forming osteoblast cell
Extracellular bone matrix
100 µm


Klikněte pro menu...
JSmol

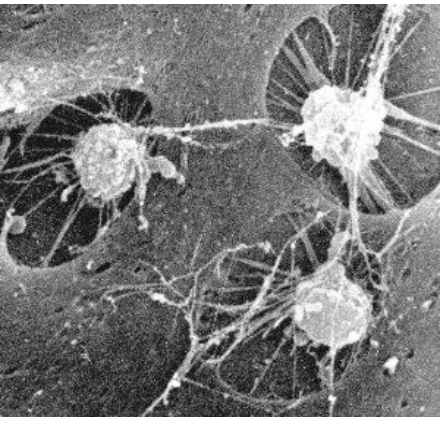
# CELLS OF BONE – OSTEOBLASTS

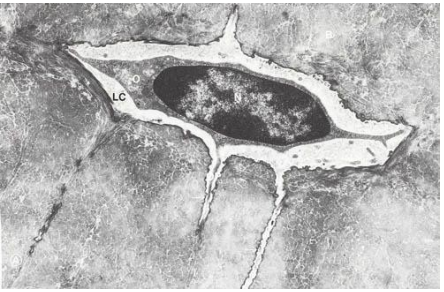
- lining bone surface
- produce ECM – collagen (I) and noncollagenous proteoglycans, glycoproteins
- basophilic cytoplasm, rER, well developer Golgi Apparatus
- euchromatin nucleus

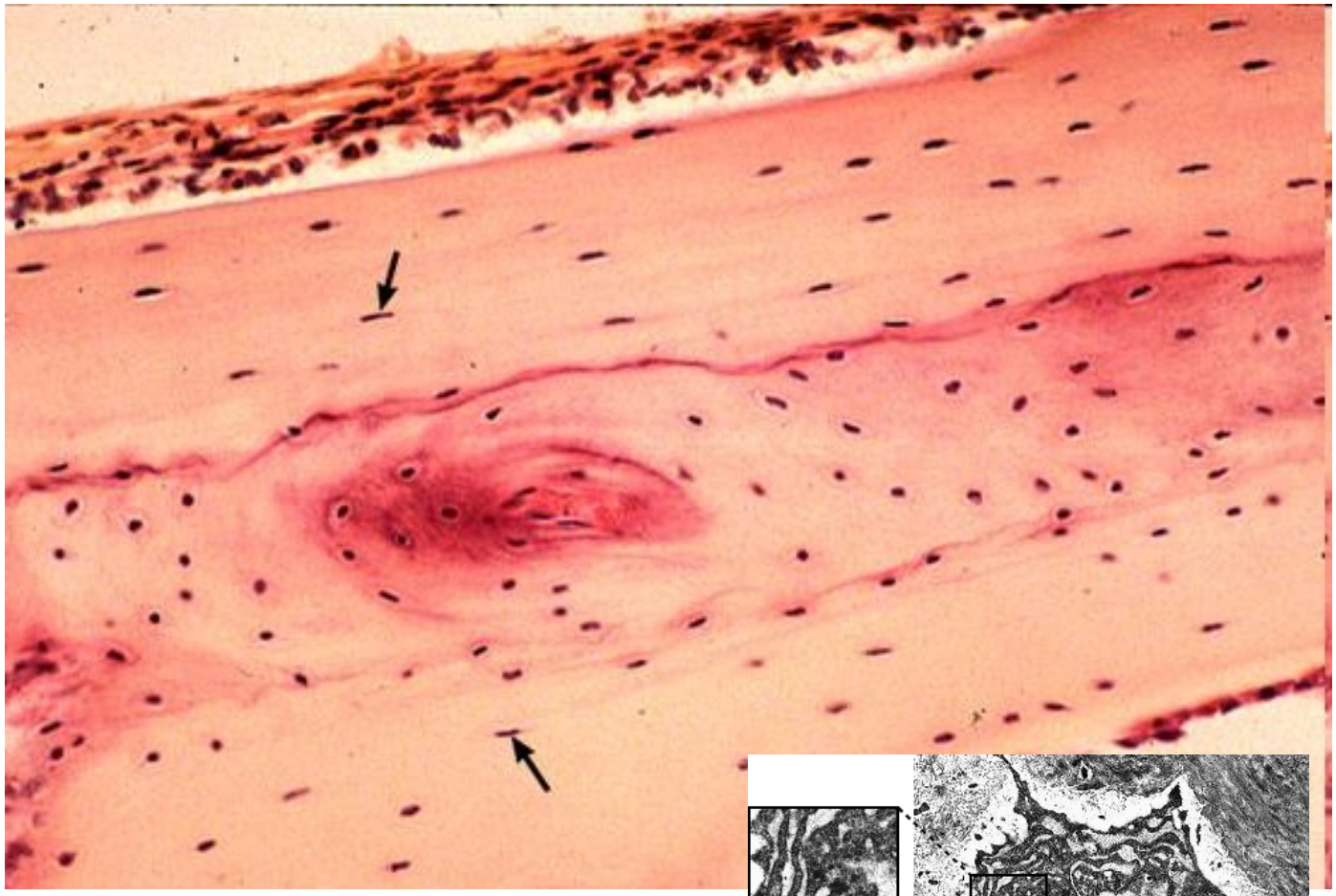
- **osteocytes** embedded in matrix
- *canalliculi ossium*



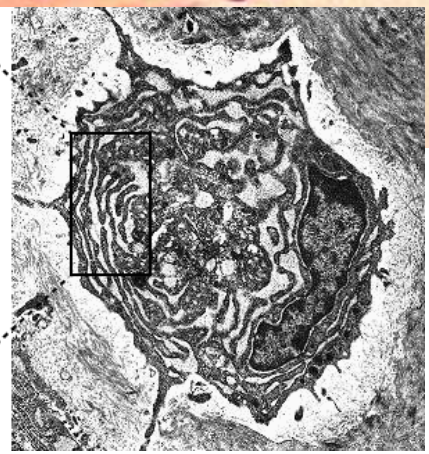
# CELLS OF BONE – OSTEOCYTES





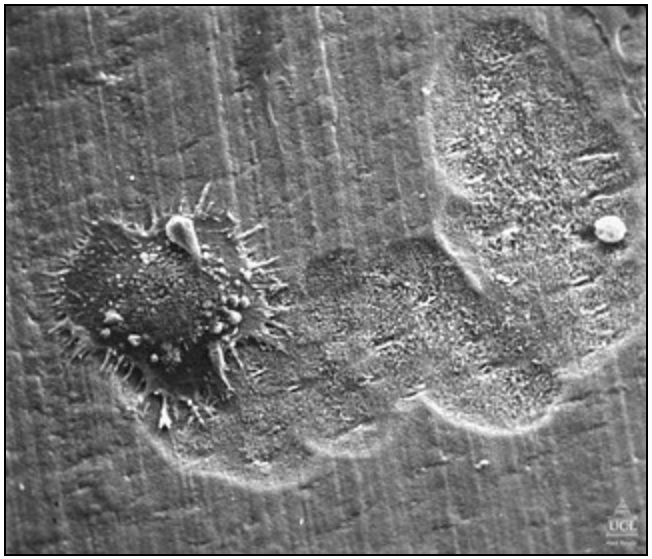



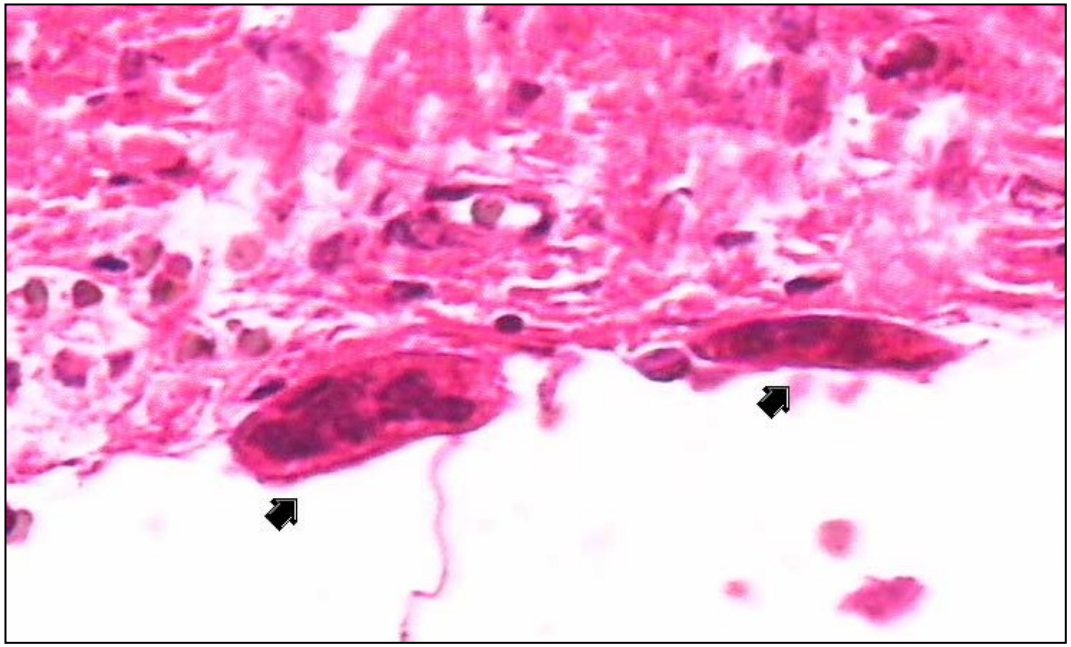
RER
-rough
endoplasmic
reticulum



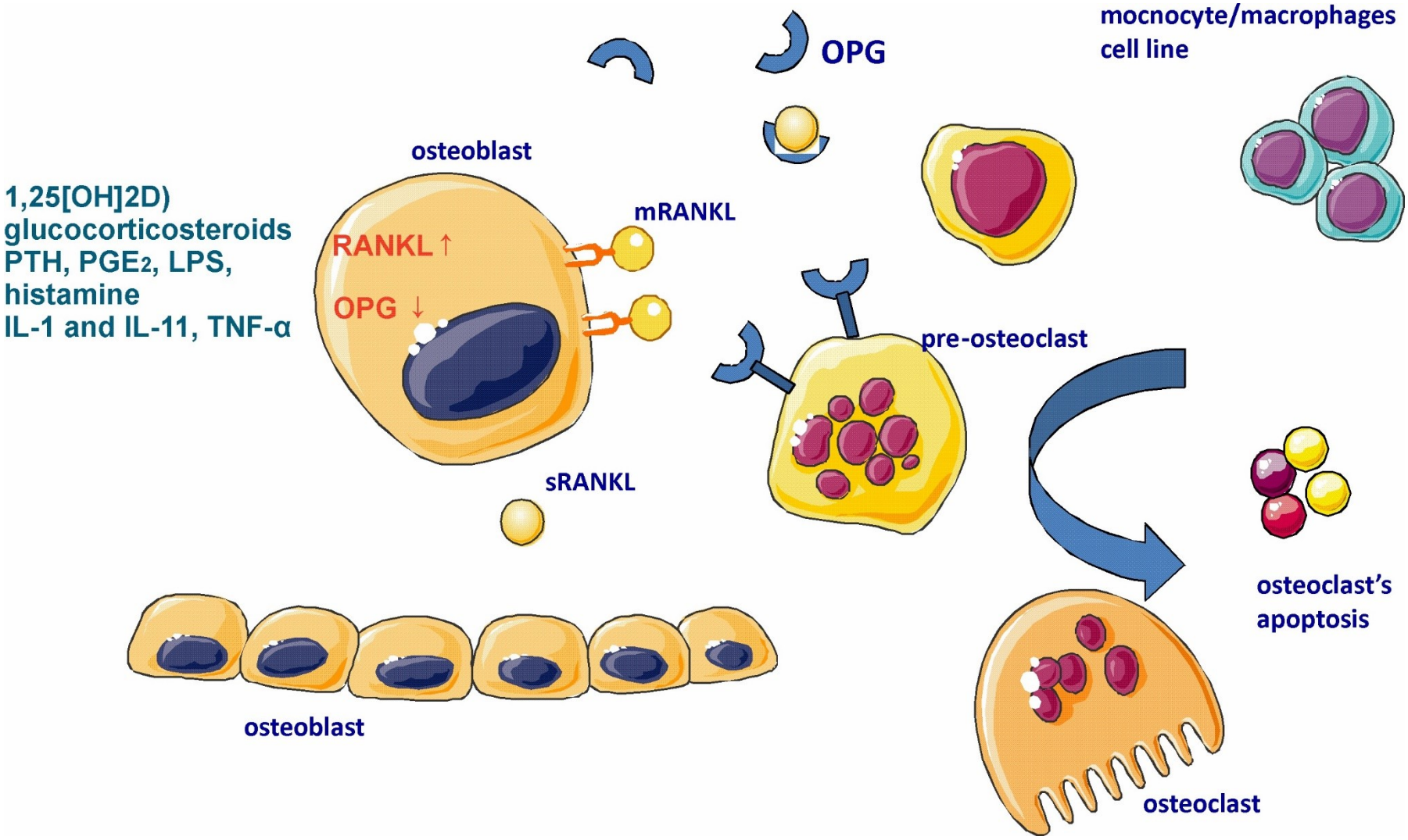
# CELLS OF BONE – OSTEOCLASTS

- multinuclear, formed by fusion of mononuclear macrophages
- bone matrix resorption



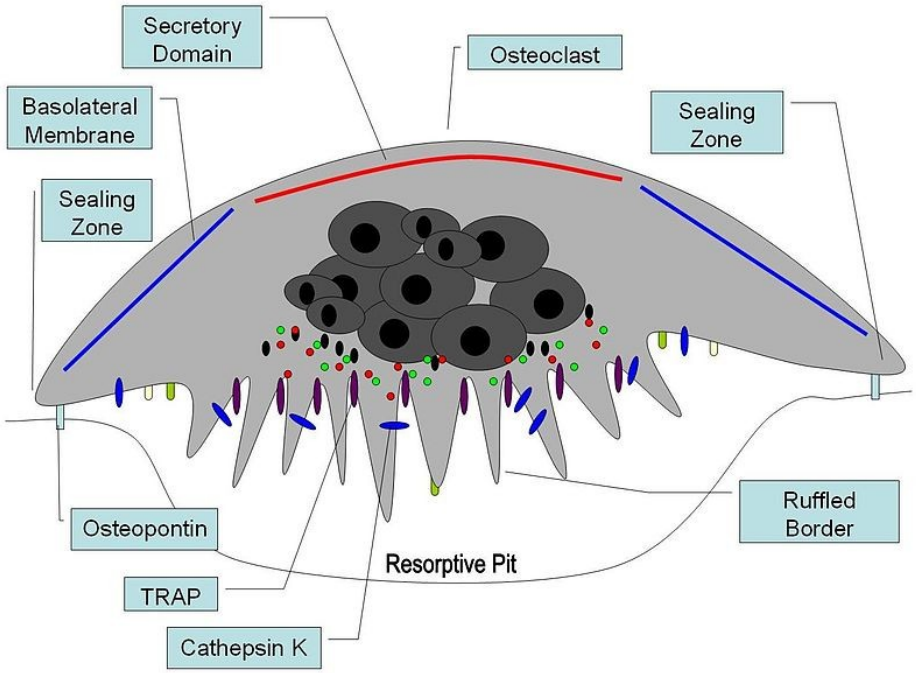


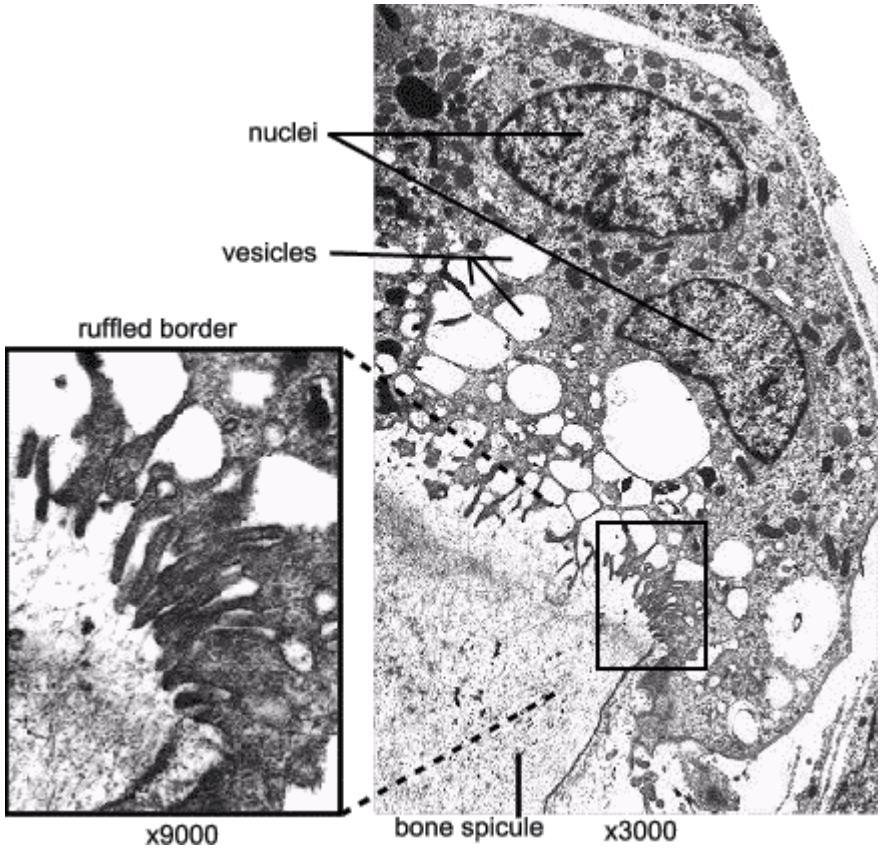
# CELLS OF BONE – OSTEOCLASTS



# CELLS OF BONE – OSTEOCLASTS

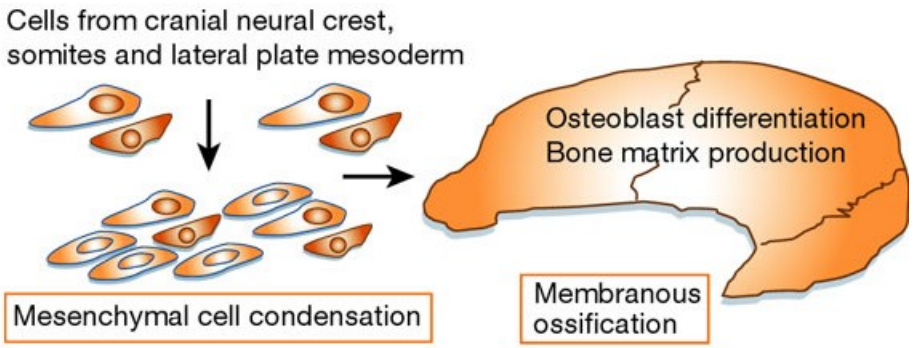
- complex architecture
- enzymes degrading organic matrix
- HCl



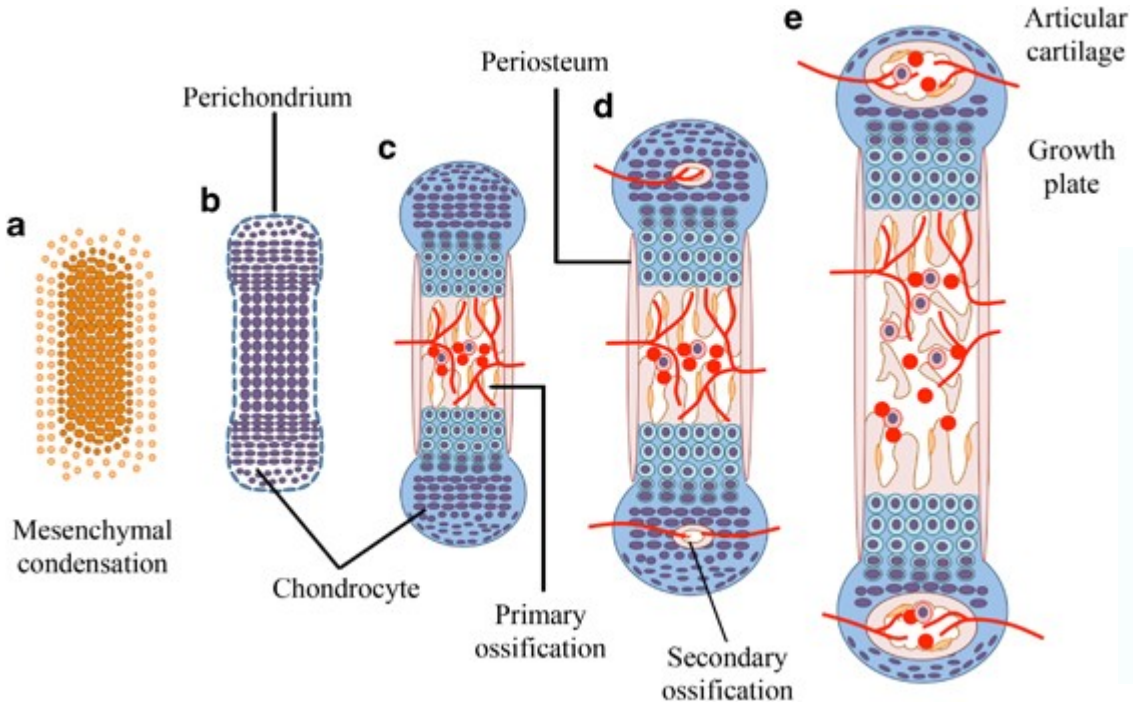



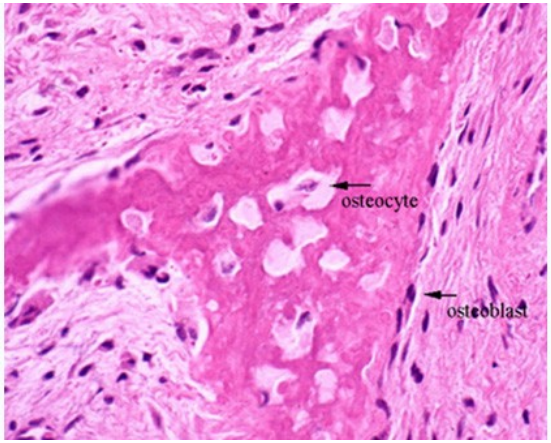
# BONE OSSIFICATION

- Intramembraneous

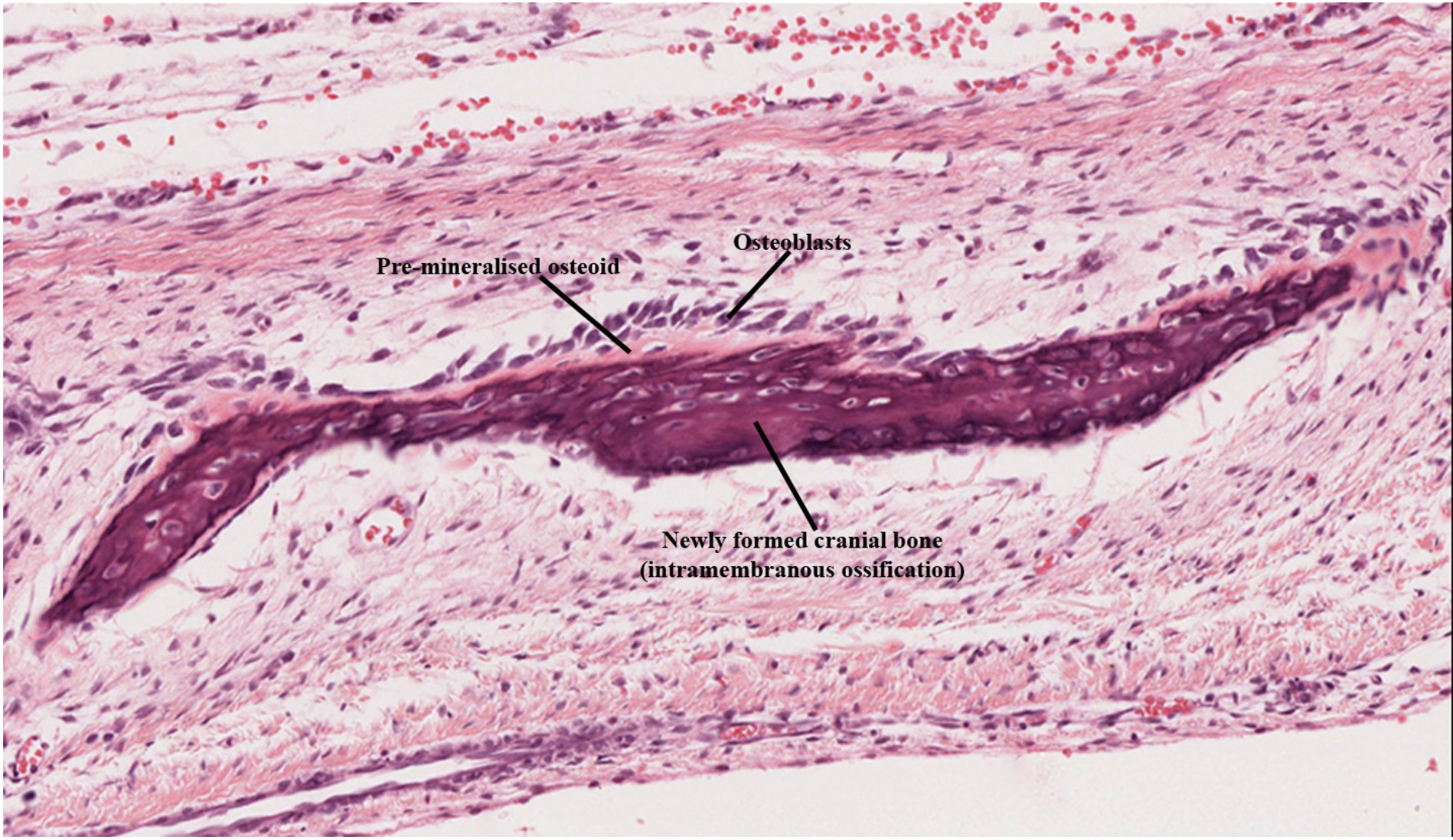



- Endochondral

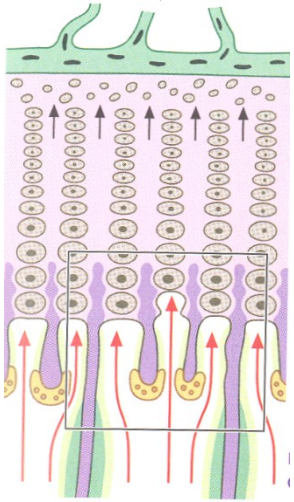


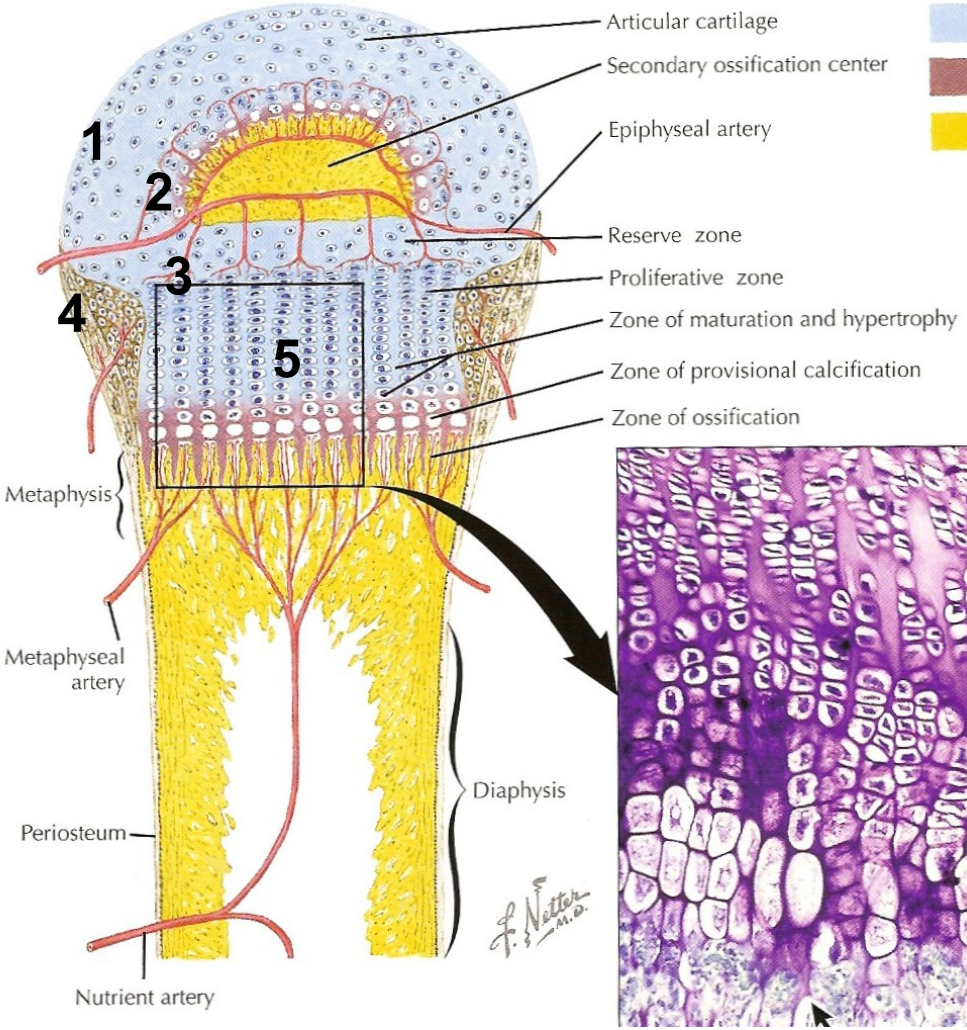



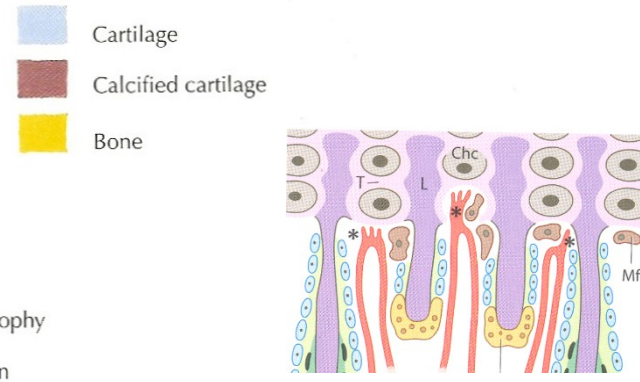
# INTRAMEMBRANEOUS OSSIFICATION



# ENDOCHONDRAL OSSIFICATION

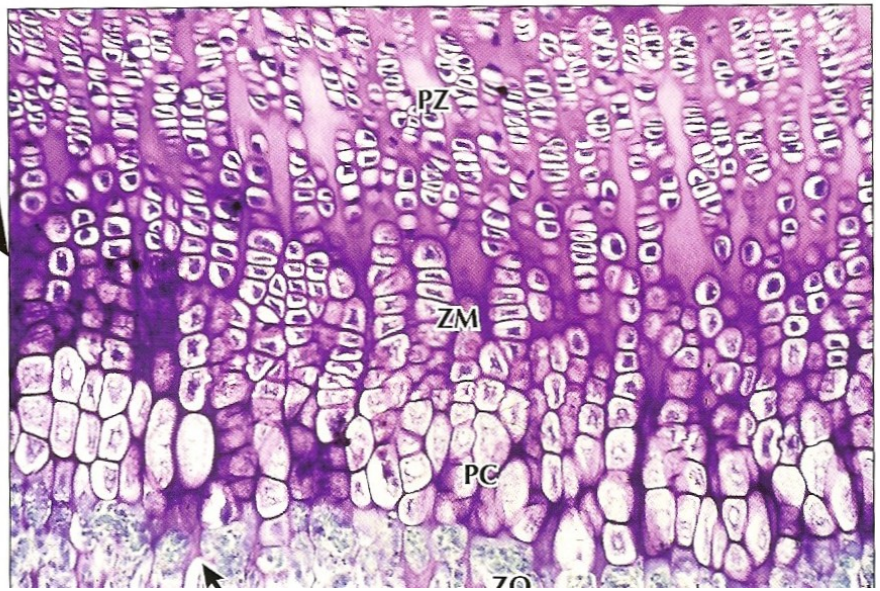










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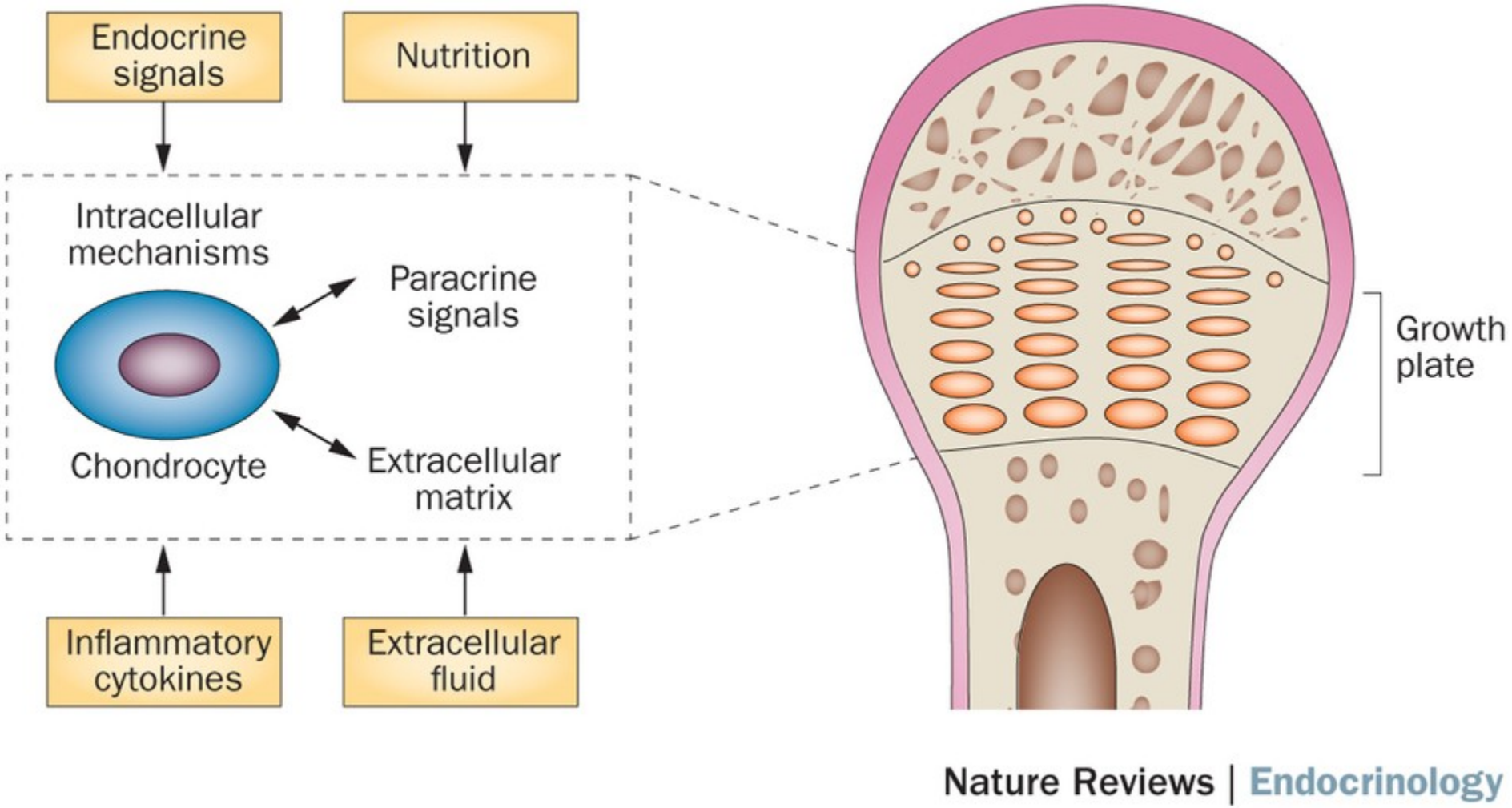

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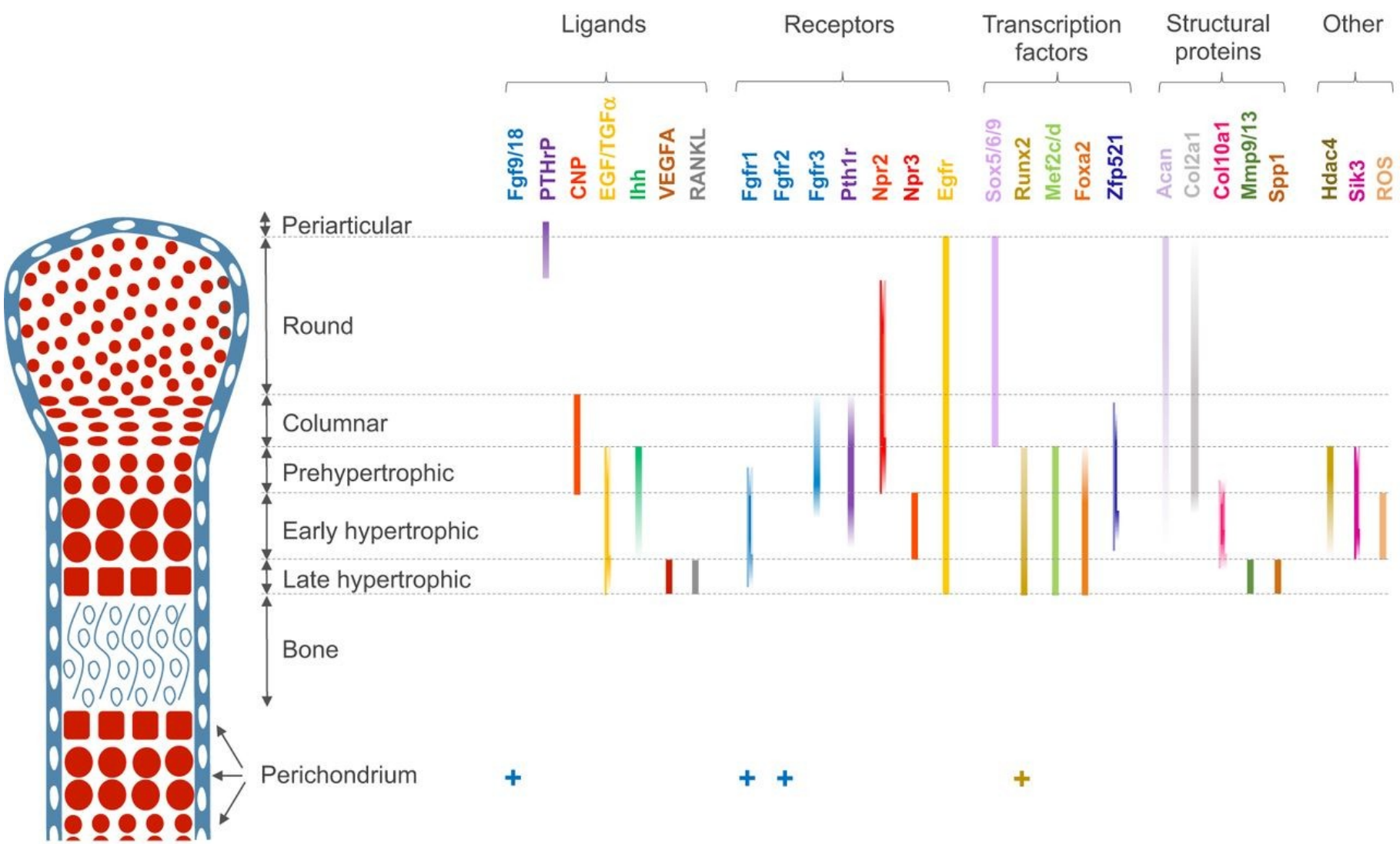
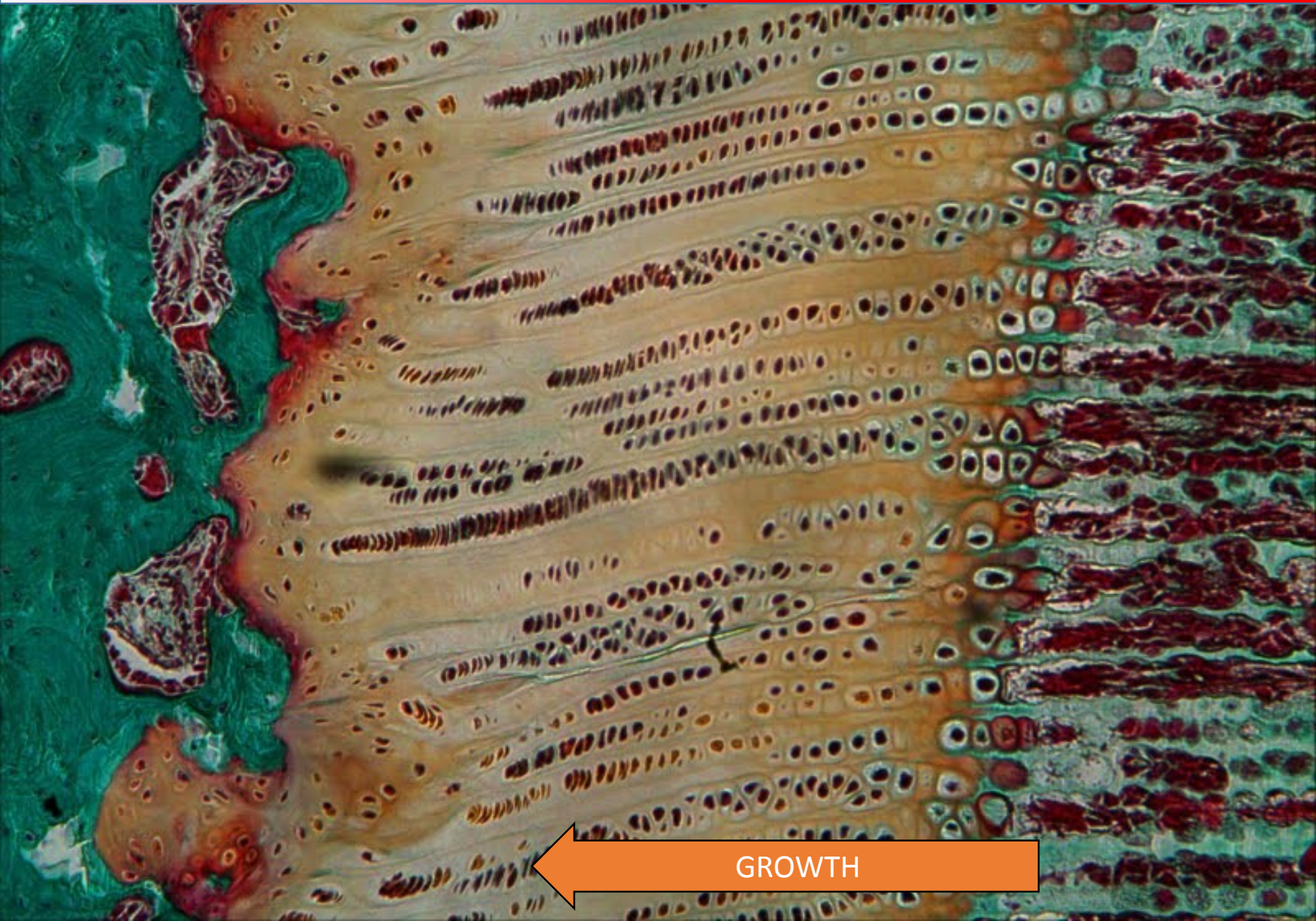
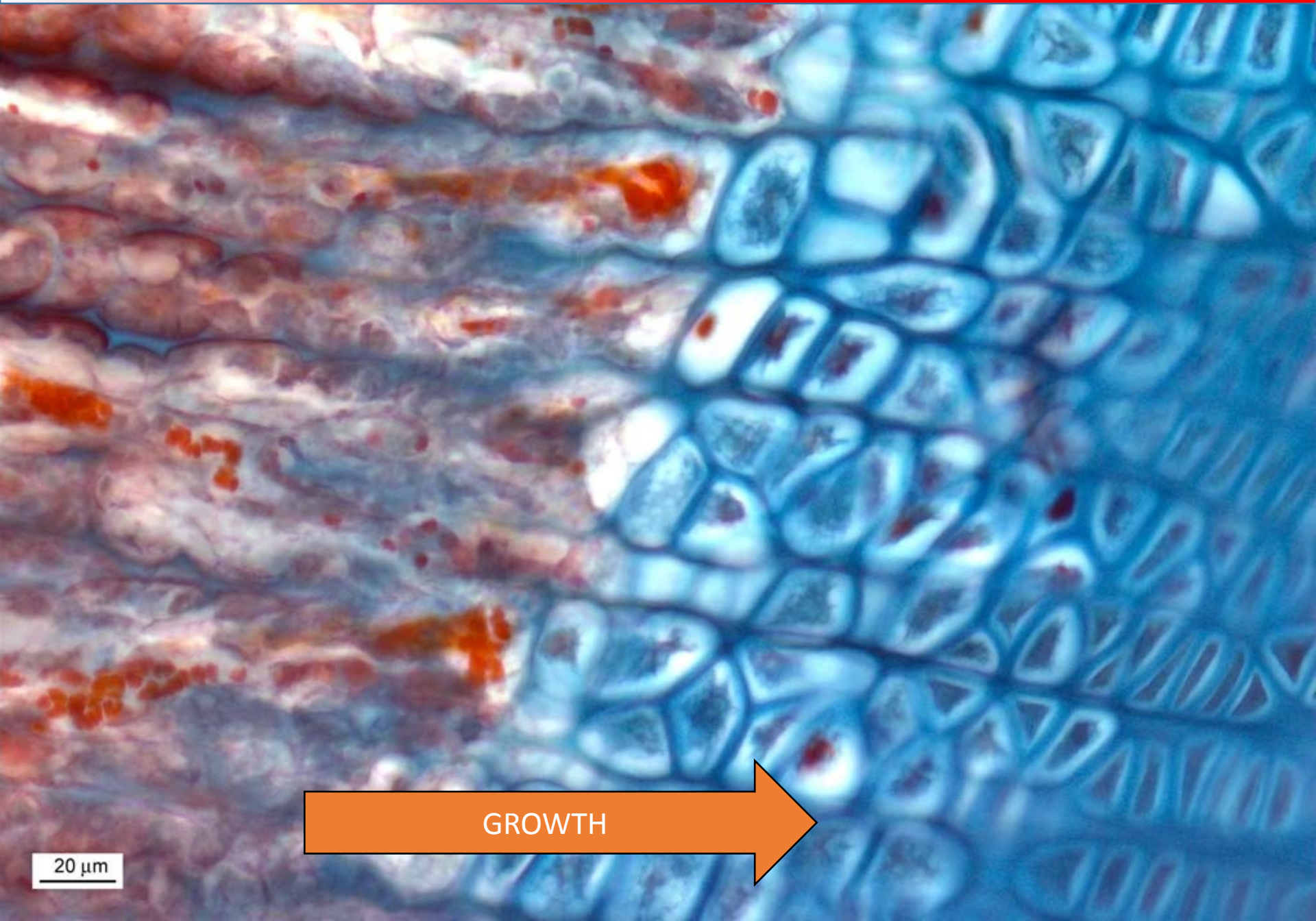


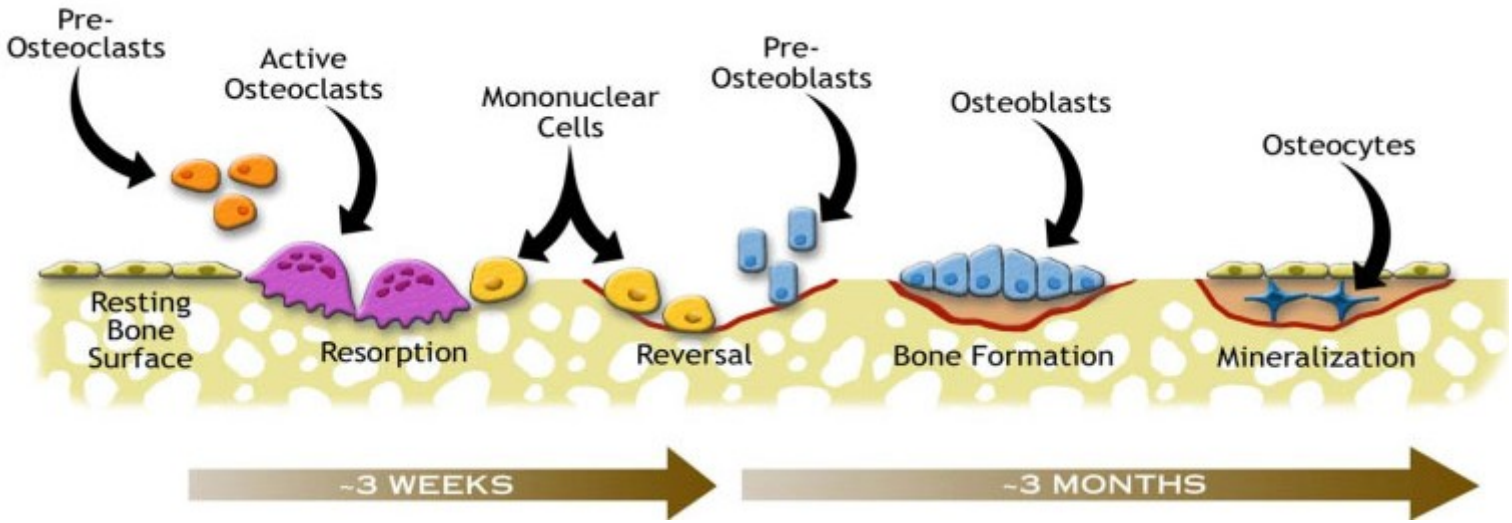
# GROWTH PLATE

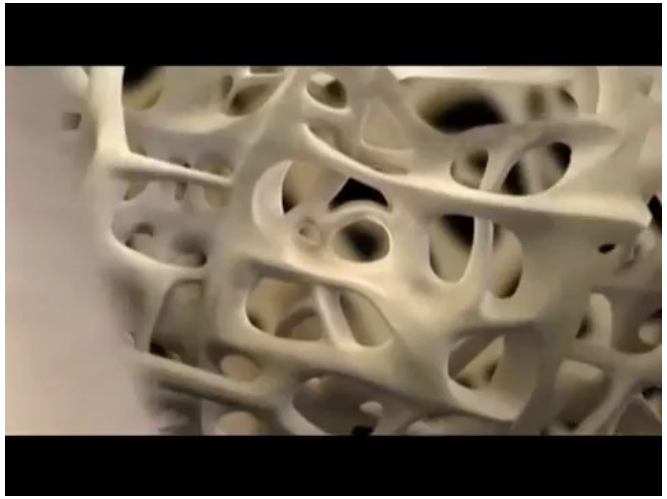


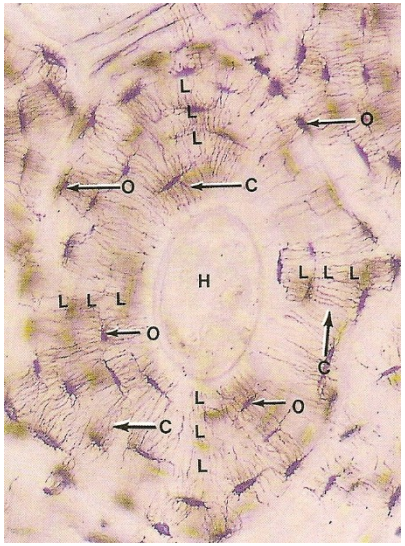
# GROWTH PLATE



# BONE REMODELLING

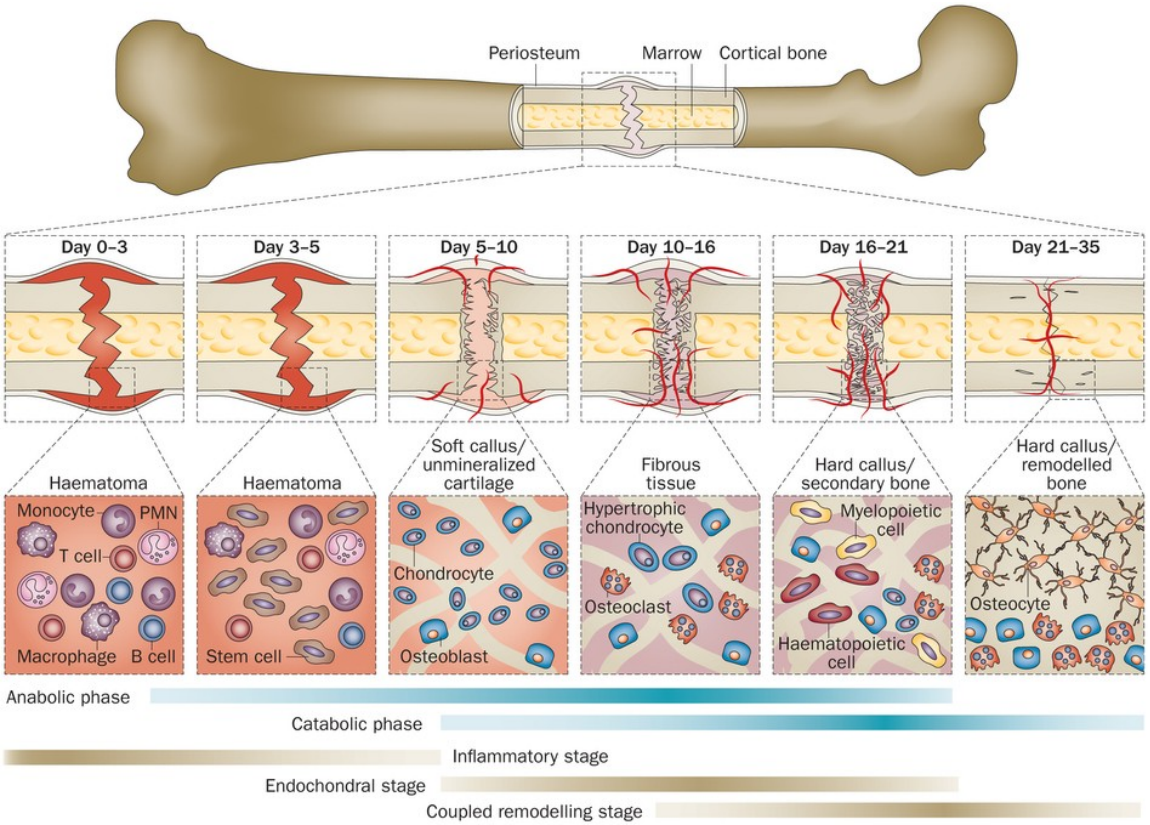





http://ns.umich.edu/Releases/2005/Feb05/img/bone.jpg

# CLINICAL CORRELATIONS – FRACTURE HEALING




**Reactive phase**

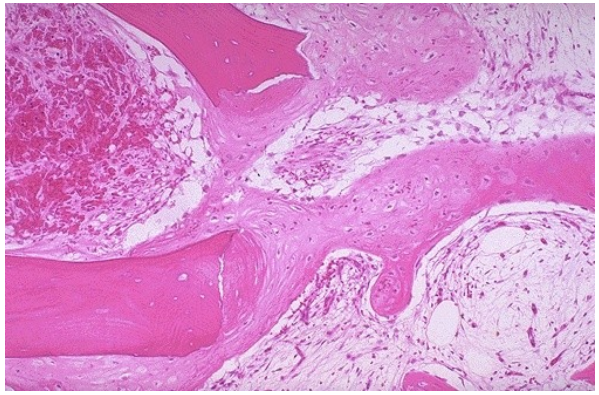
- fracture and inflammatory phase
- granulation tissue formation

**Reparative phase**

- cartilage *callus* formation
- lamellar bone deposition

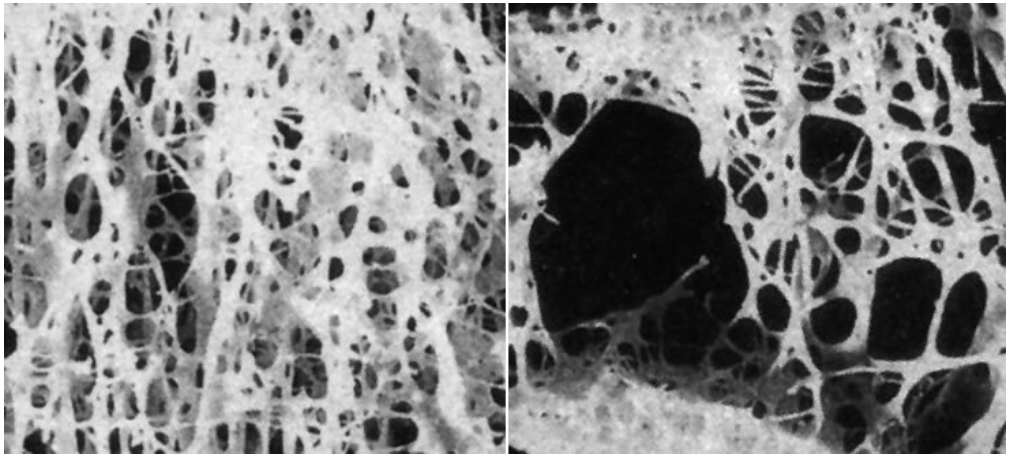
**Remodeling phase**

- remodeling to original bone shape



# CLINICAL CORRELATIONS – DISBALANCE OF BONE HOMEOSTASIS

- **OSTEOPOROSIS**



- **REVMATOID ARTHRITIS**

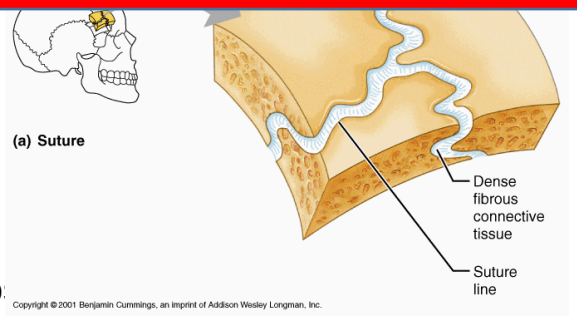

- **OSTEOPETROSIS**

- **PAGET DISEASE**

# JOINTS

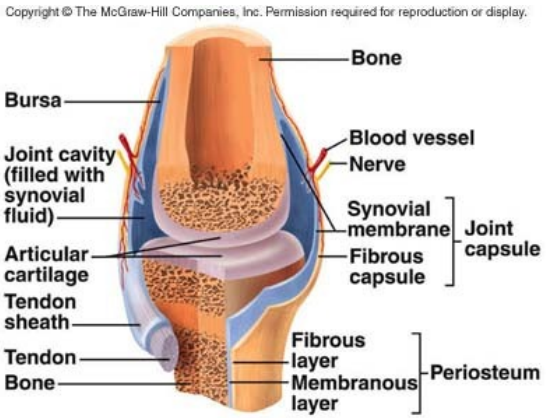
## Synarthrosis

- joint by intercalated tissue (catilage, bone or c.t.)
  - **Synostoses** – joint by bone tissue – os coxae, os sacrum
  - **Synchondrosis** – joint by hyaline cartialge – development of synosto
  - **Symphysis** – joint by fibrocartilage– os pubis, intervertebral discs
  - **Syndesmosis** – dense collage regular c.t. – sutures of skull, gomphosis



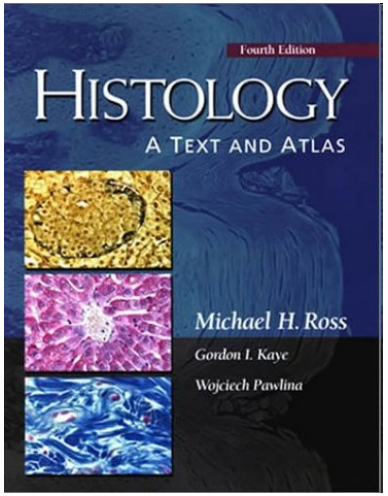

## Diarthrosis

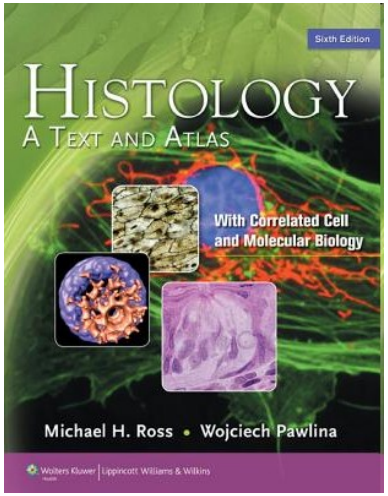
- synovial joint
  - hyaline cartilage without perichondrium
  - cartialge calcification in site of attachment to the bone
  - joint capsule
    - *Stratum fibrosum*
    - *Stratum synoviale*

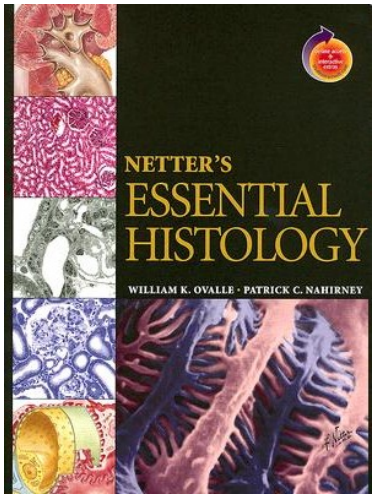


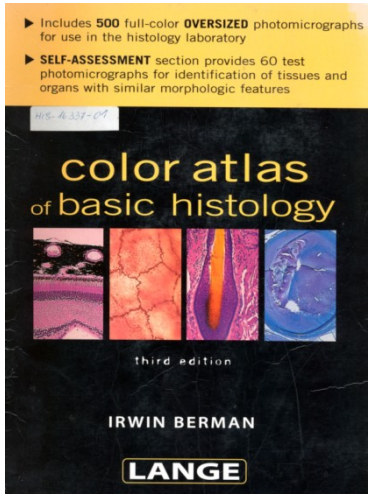

  - meniscus – fibrocartialge, avascular, without inervation
  - tendons – dense collagen regular c.t., elastic fibers
  - bursae – like joint capsule

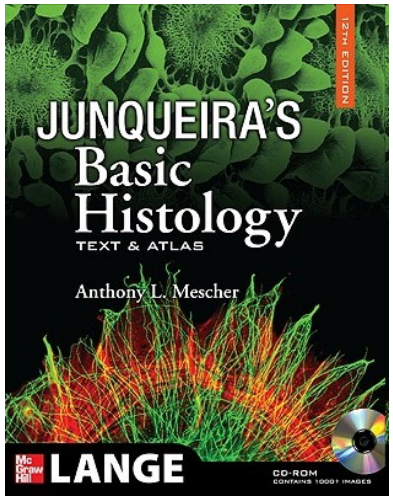
# FURTHER STUDY

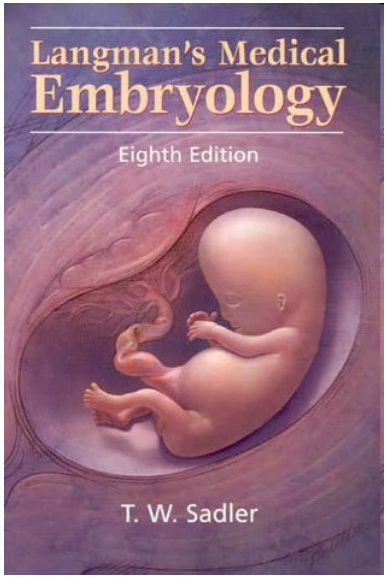


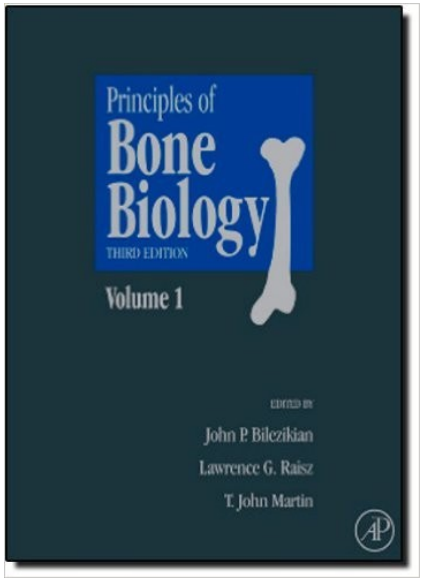



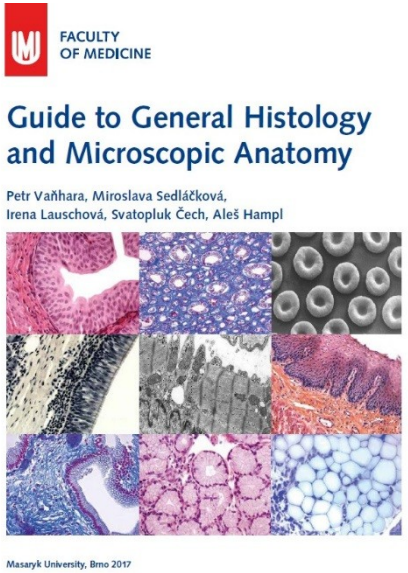



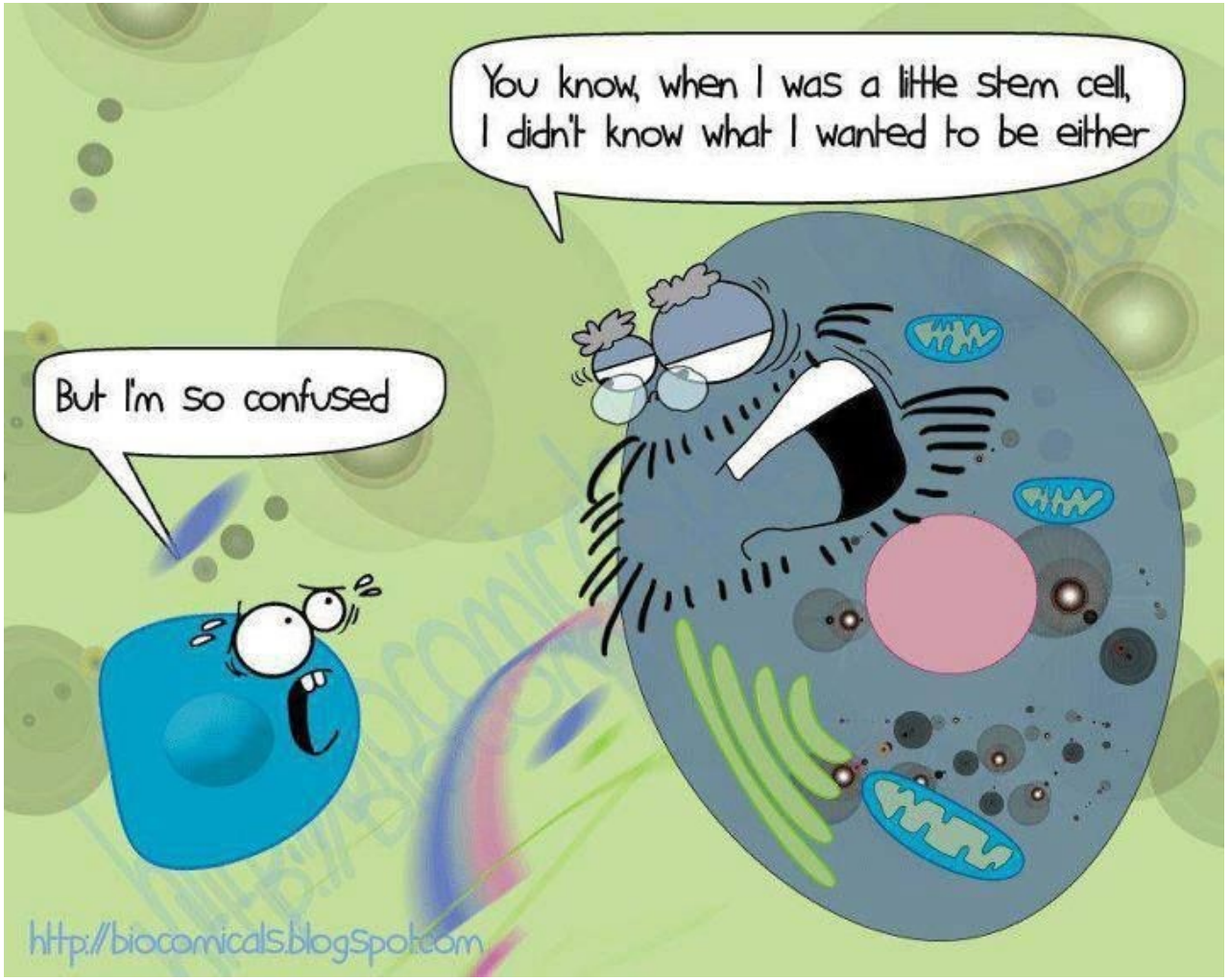




http://www.med.muni.cz/histology




# Thank you for attention