Cartilage

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- Cartilage is a flexible connective tissue found in various parts of the body.
- It provides support and cushioning in joints, structures, and organs.
- There are three main types of cartilage:
  - hyaline cartilage,
  - elastic cartilage,
  - fibrocartilage,
- each with distinct properties and functions.

Bone Composition Component (% by wt)

Composition Organic (30%) :

- **Cells (2%)**
- **Type I collagen (93%)**
- **Ground substance (5%)**

Inorganic (70%) :

- Ca2 and PO4 3 crystals

Functions of Cartilage

•**Support and Flexibility**: Provides structure and shape to various body parts like the ear, nose, and respiratory tract.

•**Cushioning, Shock Absorption:** : Acts as a shock absorber in joints, reducing friction and distributing load. Reduces the impact of mechanical forces in joints, aiding in the distribution of load and minimizing damage.

•**Growth**: Forms the growth plates in long bones, contributing to lengthening during development. Forms the initial skeleton in fetuses, which later ossifies into bone; essential in the growth of long bones through the epiphyseal plates.

•**Smooth Articulation: Provides a smooth, low-friction surface at joints, facilitating easy and pain-free movement.**

•**Repair**: While cartilage has limited repair capabilities due to lack of blood supply, it plays a role in the initial stages of healing in damaged tissues.

Structure of Cartilage

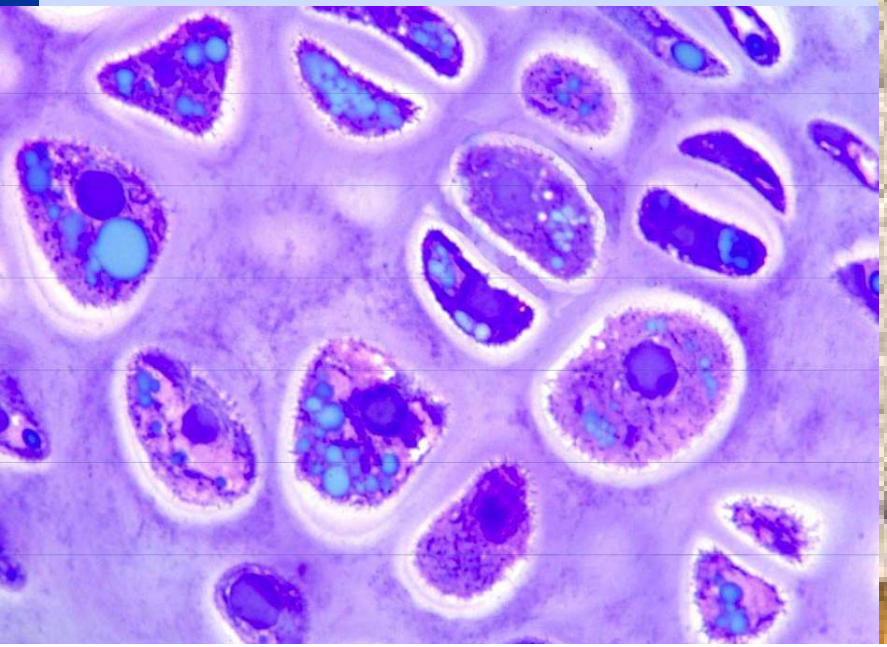
- **Chondrocytes**: The primary cells responsible for maintaining the cartilage matrix.
  - They originate from mesenchymal stem cells and are found within lacunae in the cartilage matrix.

- **Extracellular Matrix**:
  - Composed of
    - water,
    - collagen fibers (types I and II),
    - proteoglycans (such as aggrecan),
    - and glycosaminoglycans (GAGs) like hyaluronic acid and chondroitin sulfate.
- This matrix provides mechanical support and elasticity.

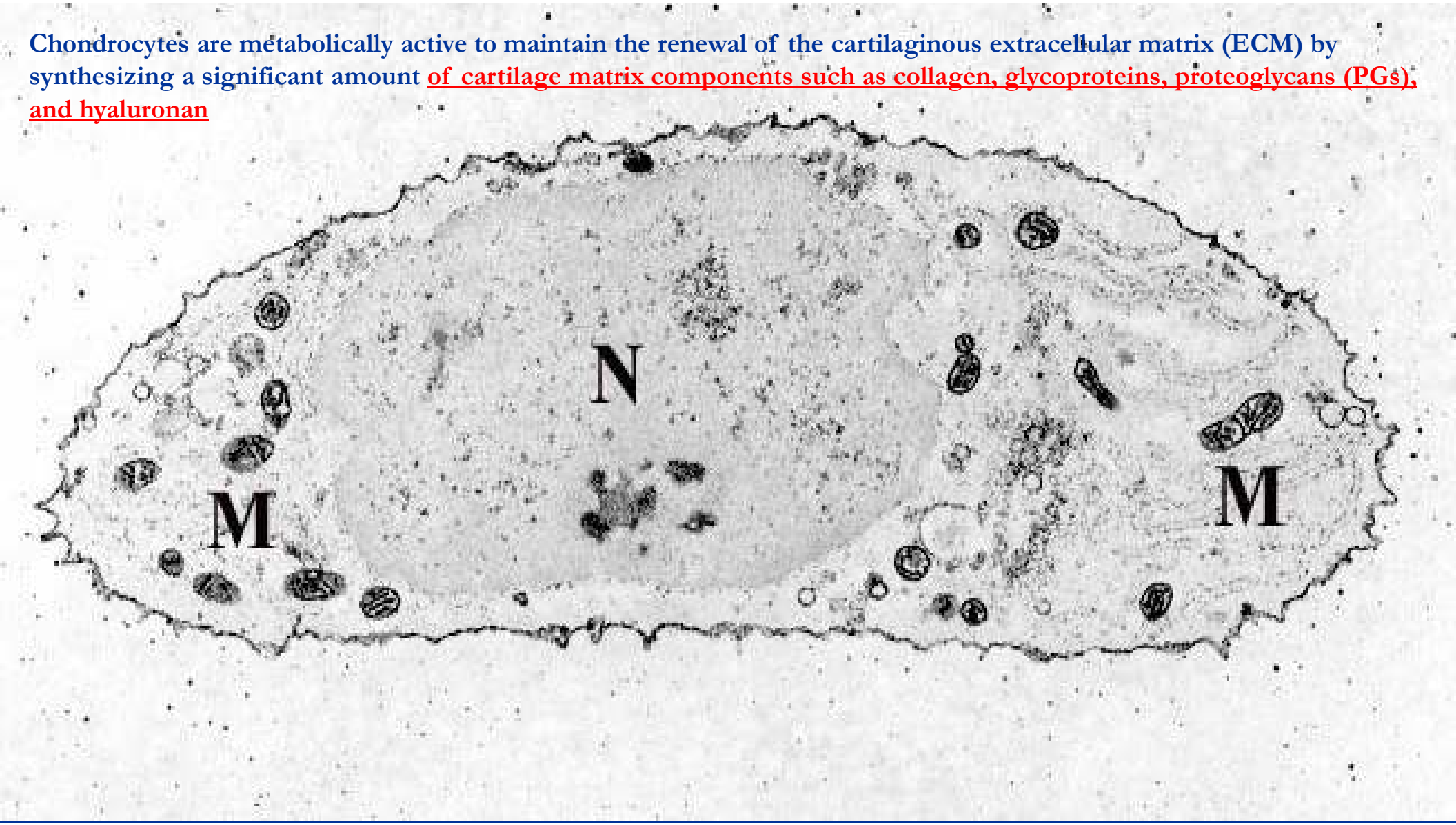
- **Perichondrium**: A layer of **dense irregular connective tissue** that surrounds most types of cartilage (except fibrocartilage and articular cartilage).
  - **It contains fibroblasts that differentiate into chondroblasts and is essential for cartilage growth and repair**.

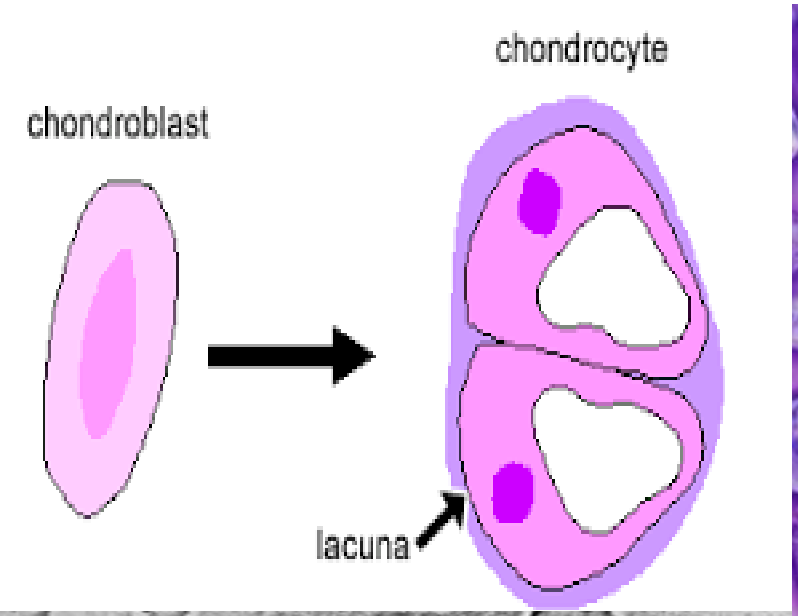
Chrondrocyte

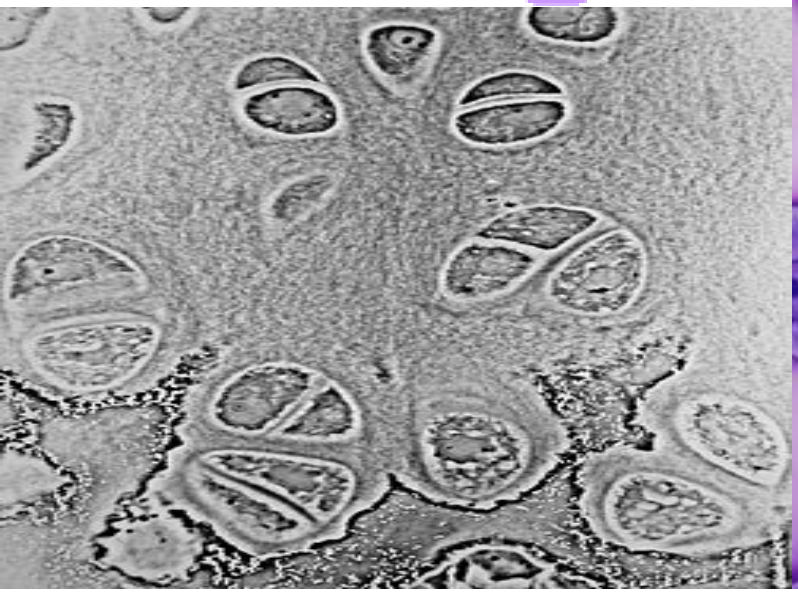
- **are the only cells found in healthy cartilage. 1%–5% of the total cartilage volume**
- They produce and maintain the cartilaginous matrix, which consists **mainly of collagen and proteoglycans.**

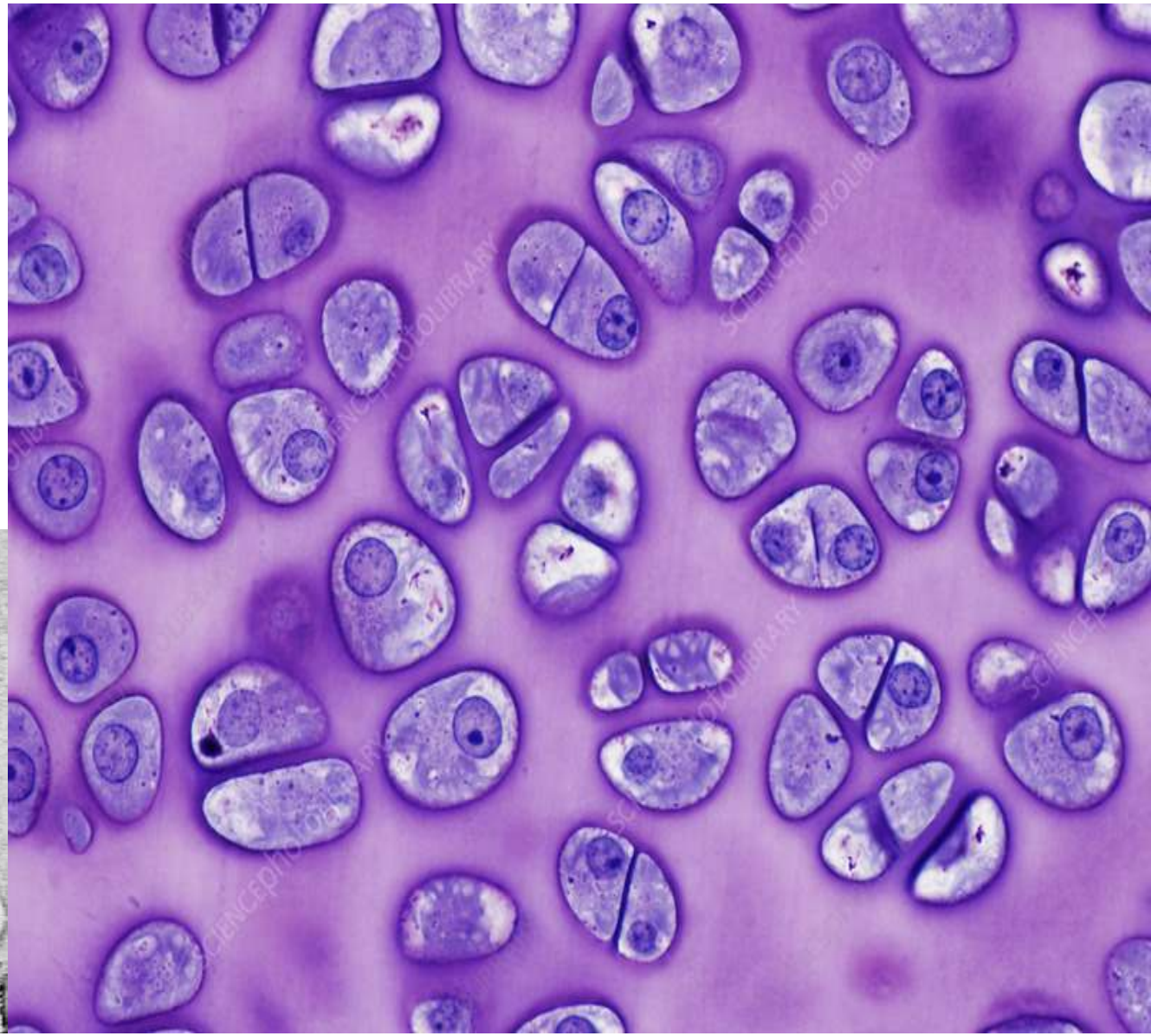


Chondrocytes are metabolically active to maintain the renewal of the cartilaginous extracellular matrix (ECM) by synthesizing a significant amount of cartilage matrix components such as collagen, glycoproteins, proteoglycans (PGs), and hyaluronan



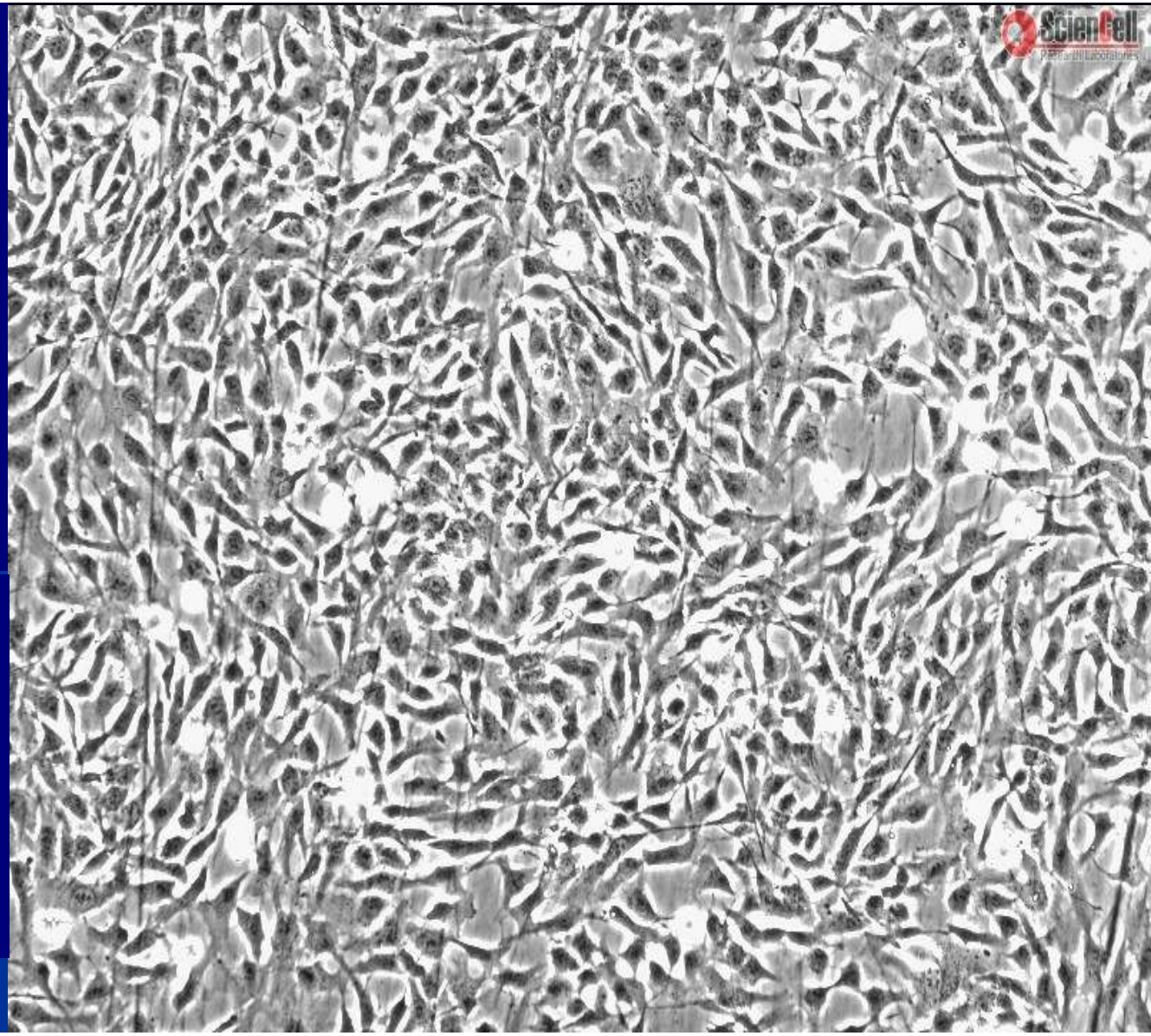

chondrocyte
chondroblast
lacuna

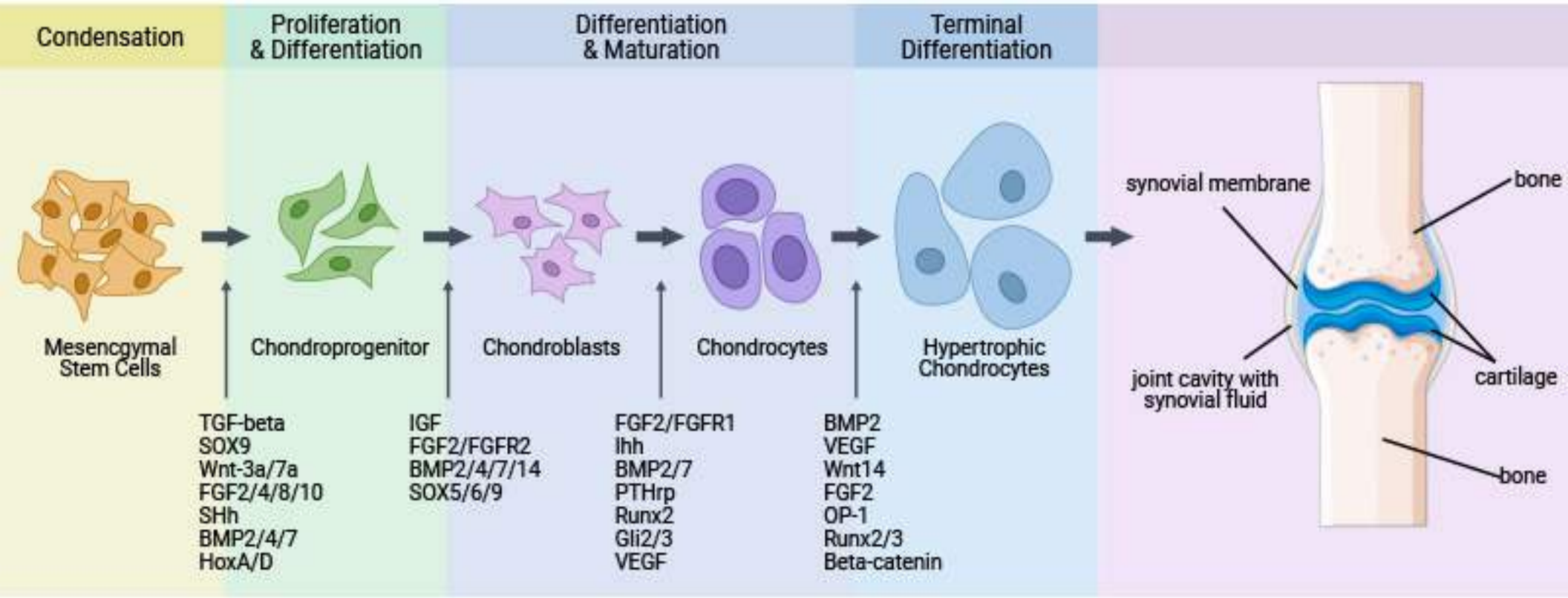


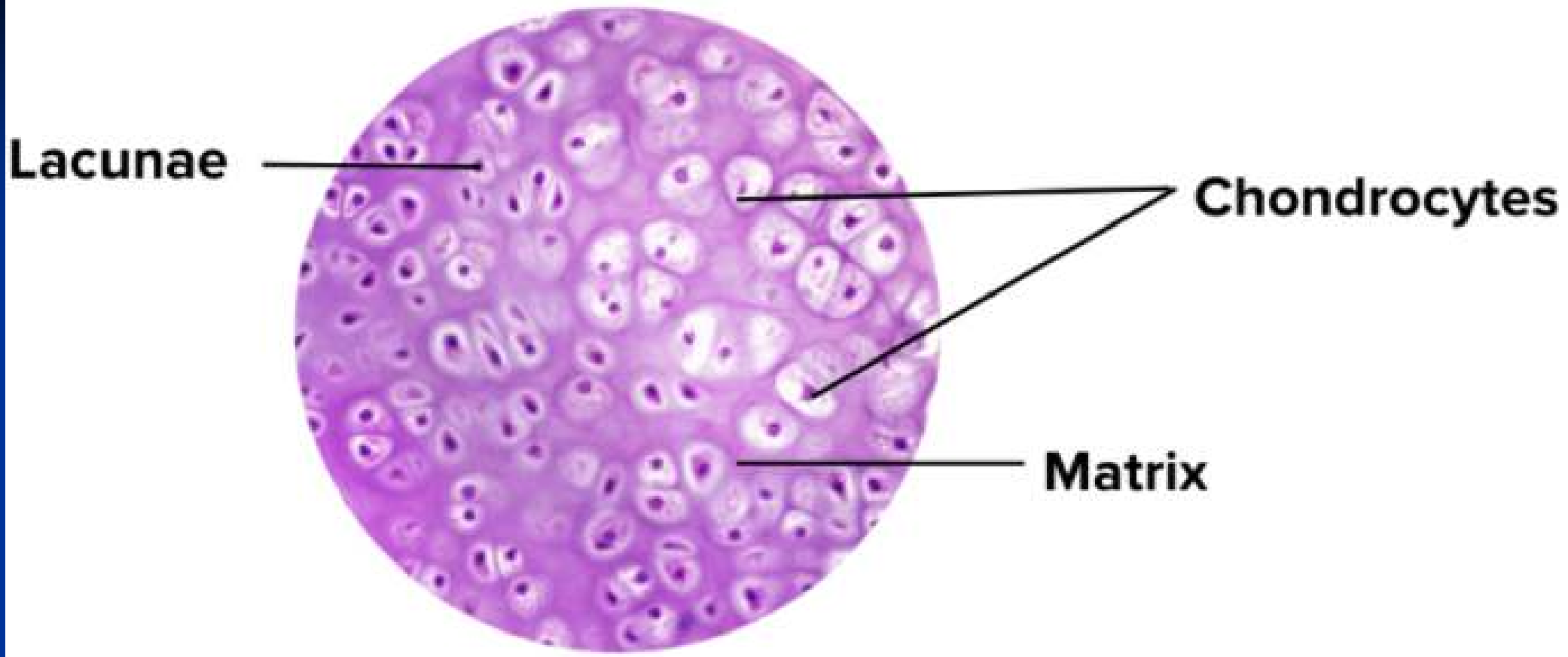


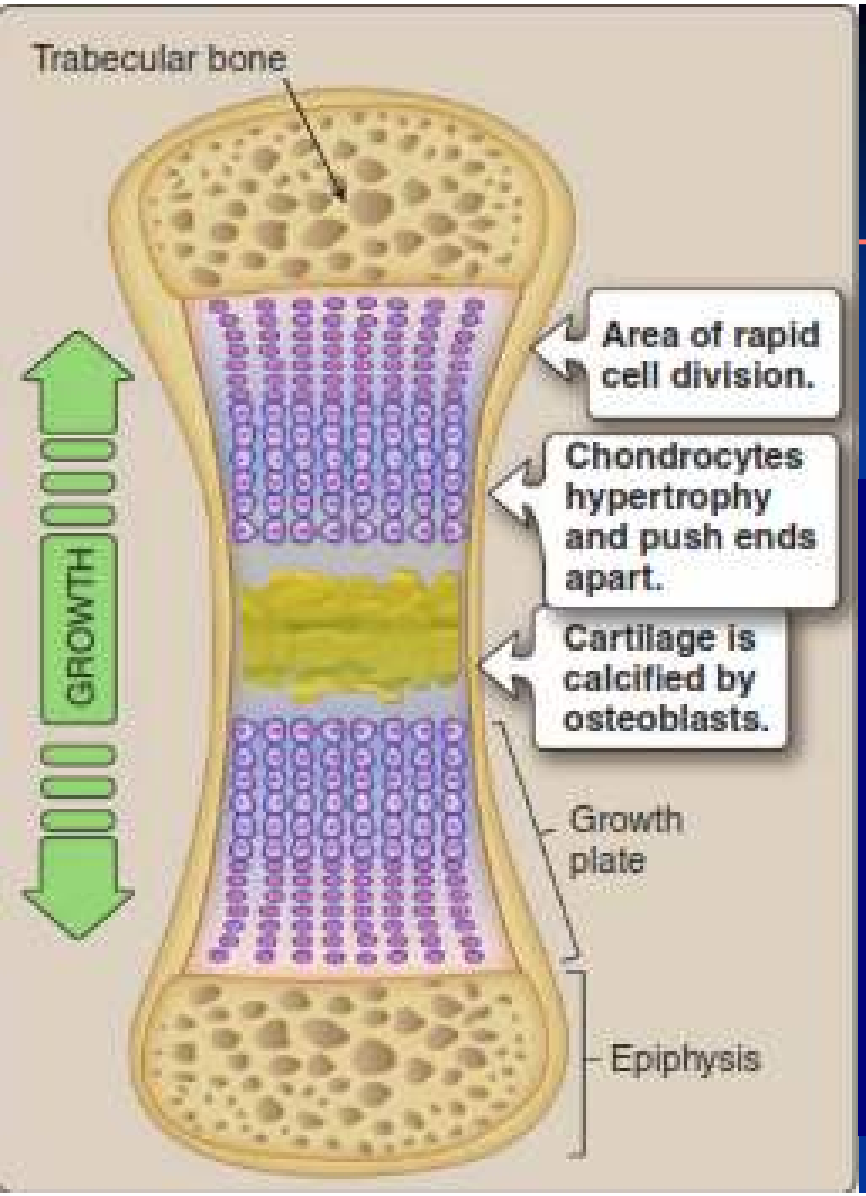
- Chondrocytes originate from bone marrow mesenchymal stem cells (MSCs) during embryonic development through chondrogenesis.
- MSCs condense and proliferate into **chondroprogenitor**s, which further differentiate into chondroblasts.
- Chondroblasts differentiate and mature into chondrocytes

- Chondrocytes are the resident cells of cartilage and are responsible for synthesizing a range of collagenous and non-collagenous extracellular matrix macromolecules.
- **These include collagen type II, aggrecan, link protein, collagen type IX, and collagen type XI.**




Condensation
Proliferation & Differentiation
Differentiation & Maturation
Terminal Differentiation
Mesencgymal Stem Cells
Chondroprogenitor
Chondroblasts
Chondrocytes
Hypertrophic Chondrocytes
TGF-beta
SOX9
Wnt-3a/7a
FGF2/4/8/10
SHh
BMP2/4/7
HoxA/D
IGF
FGF2/FGFR2
BMP2/4/7/14
SOX5/6/9
FGF2/FGFR1
Ihh
BMP2/7
PTHrp
Runx2
Gli2/3
VEGF
BMP2
VEGF
Wnt14
FGF2
OP-1
Runx2/3
Beta-catenin
synovial membrane
bone
joint cavity with synovial fluid
cartilage
bone


Lacunae
Chondrocytes
Matrix

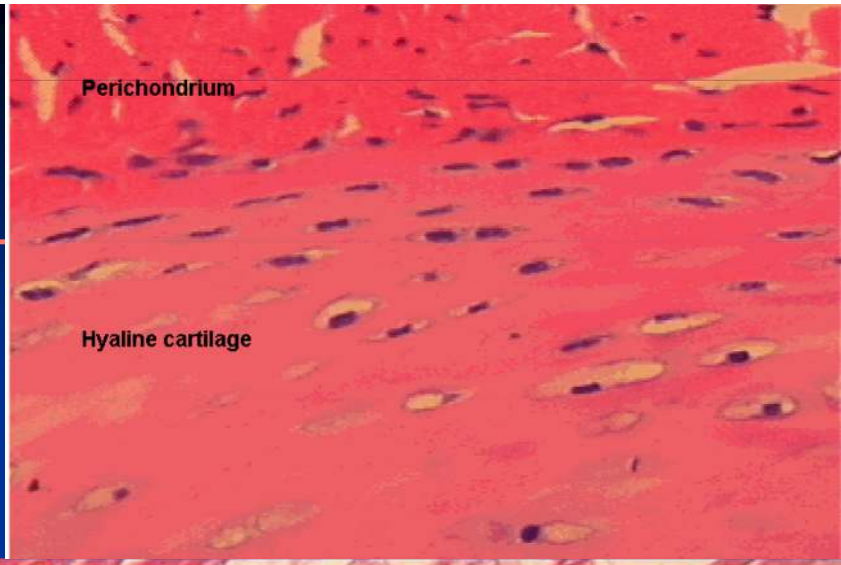


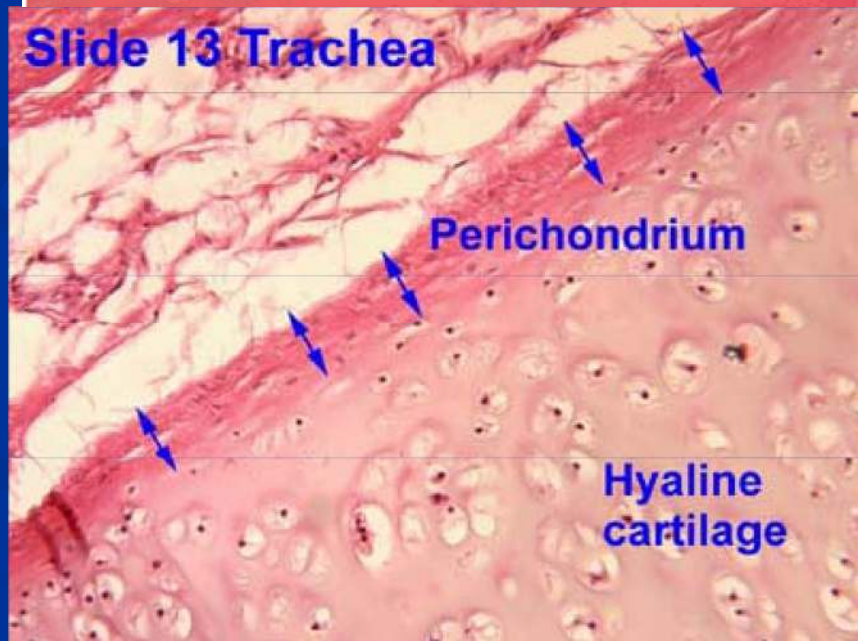
- **Chondrocytes are derived from the same mesenchymal stem cell line that gives rise to osteoblasts .**
- **Are arranged in 10–20 columns within a growth plate. Chondrocytes nearest the ends of the bone divide rapidly**

- Chondrocytes also secrete cartilage, which becomes mineralized by osteoblasts and forms a template for further ossification.
- Older chondrocytes eventually undergo apoptosis, leaving spaces within the matrix that are invaded by nerves, blood vessels, and additional osteoblasts, which complete the task of bone maturation.
- When skeletal growth is complete, the growth plate dwindles, and the two epiphyses are united with the shaft (epiphyseal closure).

Skeletal Cartilage

- Contains **no blood vessels or nerves**
- **The matrix is composed of an amorphous ground substance containing proteoglycan aggregates and chondronectin, in which type II collagen is embedded**
- **Surrounded by the perichondrium** (dense irregular connective tissue) that resists outward expansion
- chondrocytes embedded in matrix. Surrounding the cartilage is the perichondrium housing chondroblasts and chondrogenic cells.
- **Three types –**
  - **hyaline**
  - **elastic**
  - **fibrocartilage**





Types of Cartilage

- Hyaline
  - **Smooth** (but not totally flat!), bluish color
  - **Articular cartilage** and Cartilaginous Endplate
  - Larynx, trachea, bronchi, ribes, articular surface of bones
  - – Epiphyseal plate
- Elastic
  - More flexible than hyaline
  - Epiglottis, external ear
  - Elastic fibers for resiliency
- Fibrocartilage
  - Fibrous tissues
  - Annulus Fibrosus (intervertebral discs), Meniscus, pubic symphysis
  - Type I collagen fibers for tensile strength, frictional forces
  - Between cartilage and connective tissue –,

Bones and Cartilages of the Human Body

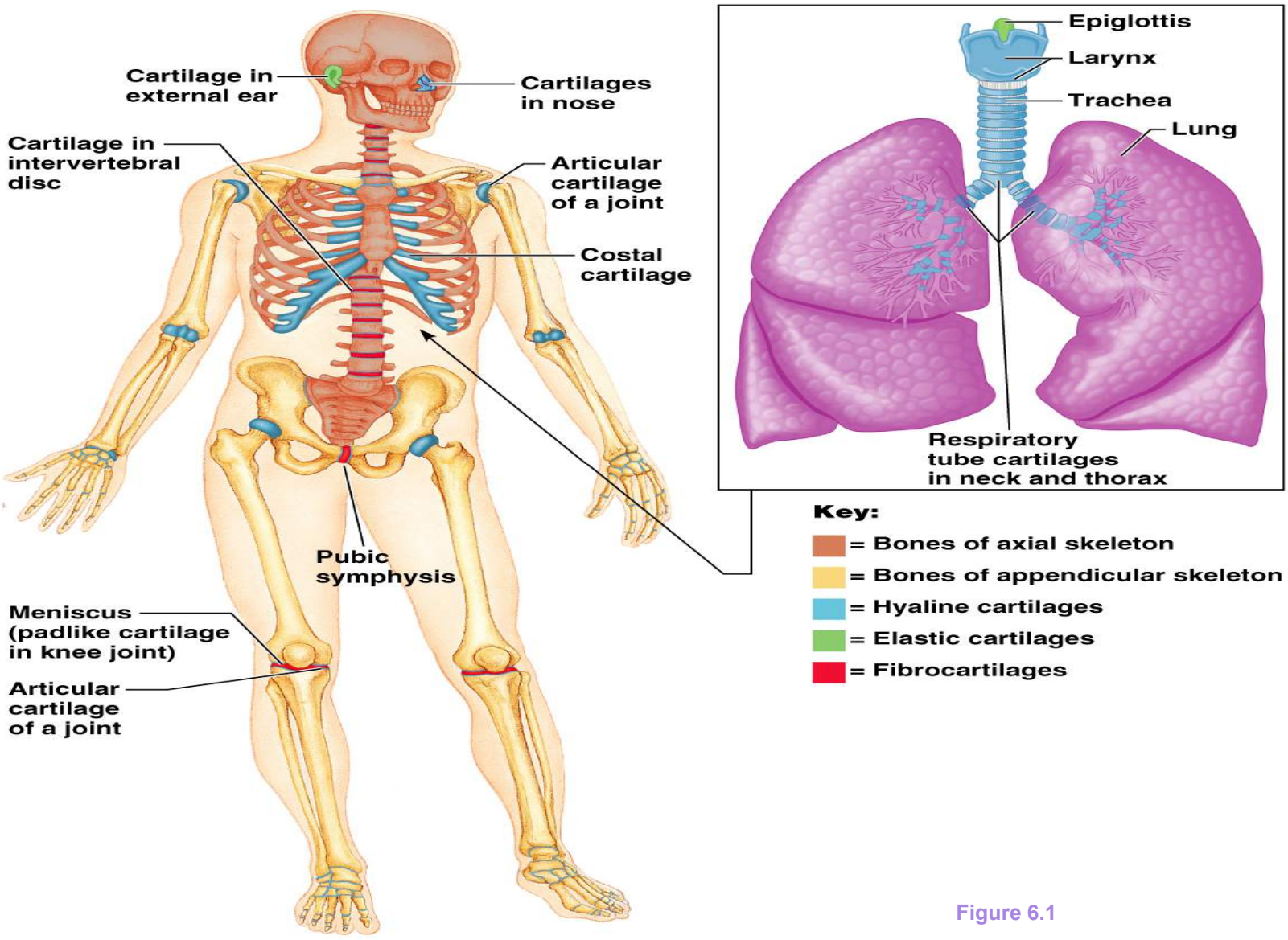


Figure 6.1

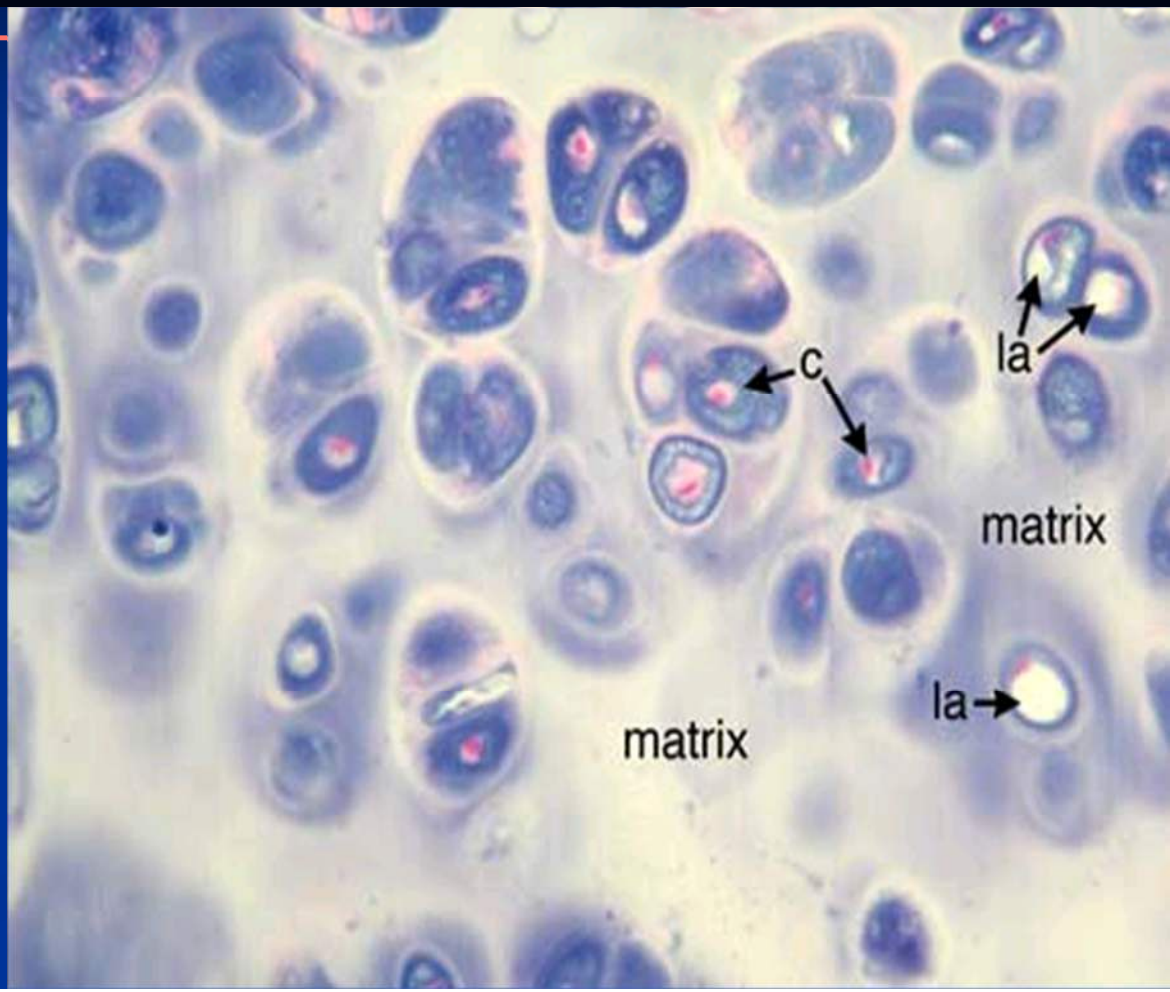
Type of Cartilage	Identifying Characteristics	Perichondrium	Location
Hyaline	Type II collagen, basophilic matrix, chondrocytes usually arranged in groups (isogenous groups)	Perichondrium usually present except on articular surfaces	Articular ends of long bones, nose, larynx, trachea, bronchi, ventral ends of ribs, template for endochondral bone formation
Elastic	Type II collagen; elastic fibers	Perichondrium present	Pinna of ear, auditory canal and tube, epiglottis, some laryngeal cartilages
Fibrocartilage	Type I collagen, acidophilic matrix, chondrocytes arranged in parallel rows between bundles of collagen, always associated with dense collagenous connective tissue and/or hyaline cartilage	Perichondrium absent	Intervertebral discs, articular discs, pubic symphysis, insertion of tendons, meniscus of knee

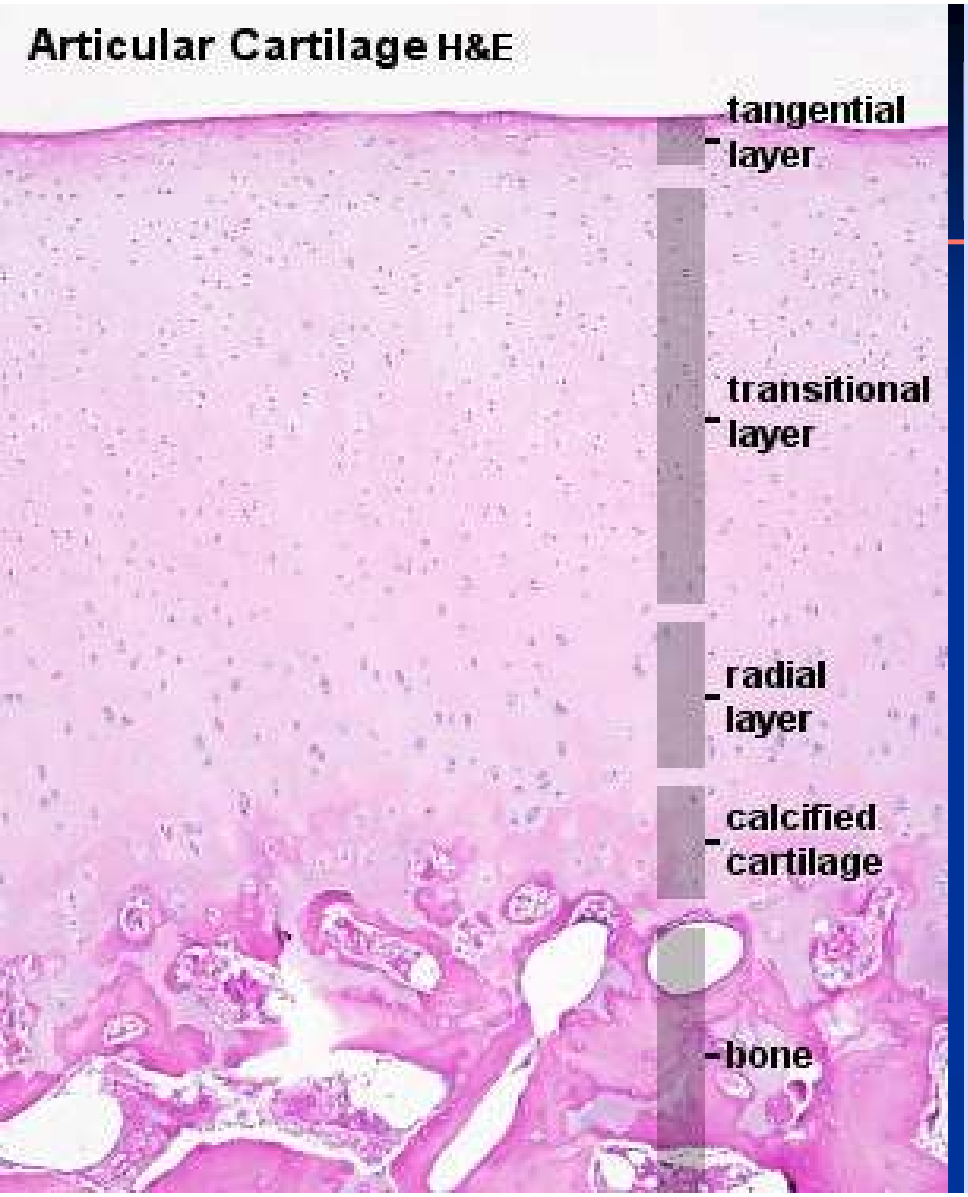
Adapted with permission from Gartner LP, Hiatt JL. *Color Textbook of Histology*. Philadelphia, PA: Saunders; 1997;133.

Hyaline Cartilage

- Provides support, flexibility, and resilience
- Is the most abundant skeletal cartilage
- Is present in these cartilages:
  - **Articular** – covers the ends of long bones
  - **Costal** – connects the ribs to the sternum
  - **Respiratory** – makes up larynx, reinforces air passages
  - **Nasal** – supports the nose

la = lacuna (chondrocytes shrunken or lost as artifact of slide preparation)
c = chondrocyte



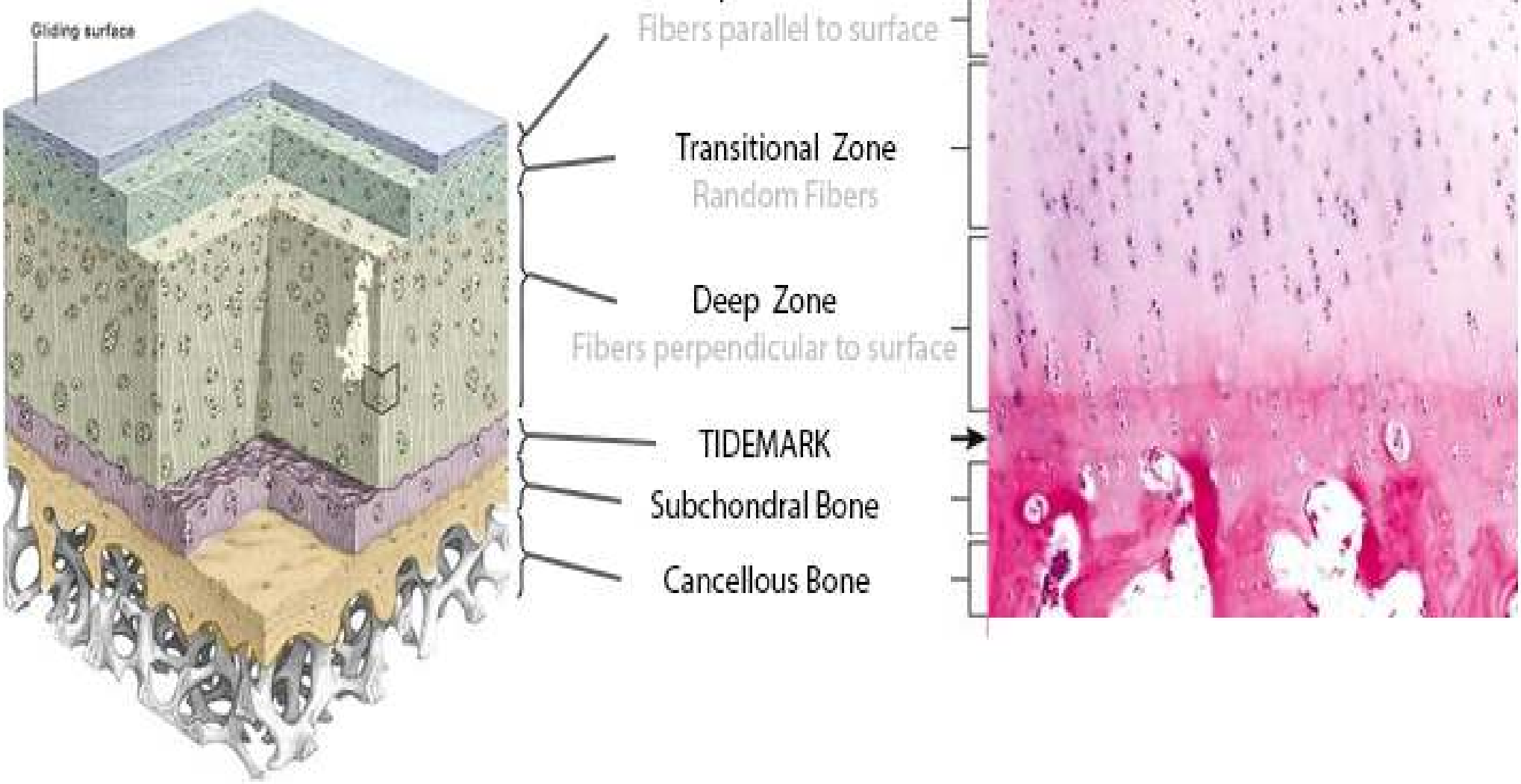


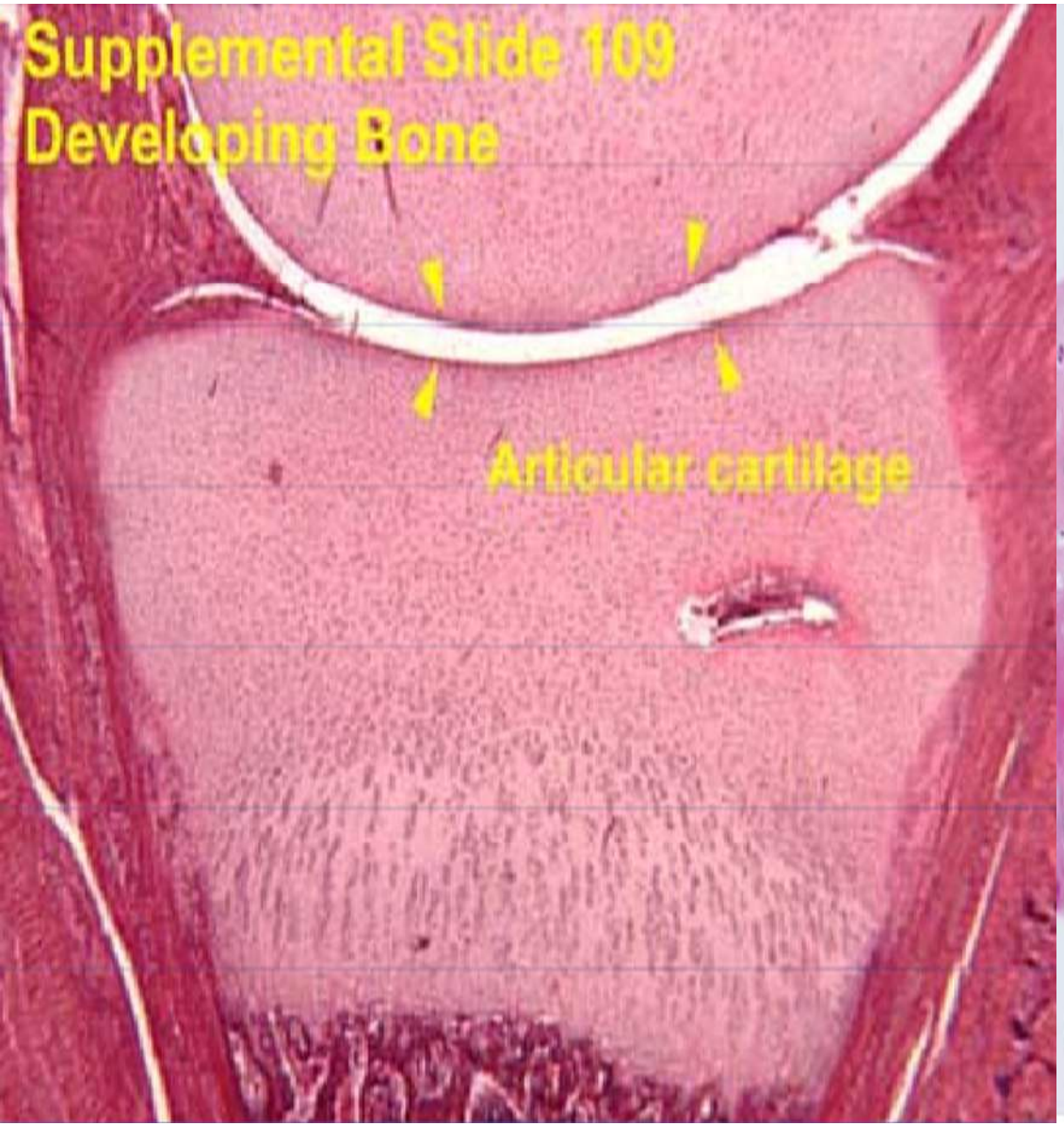
- **Articular Cartilage**

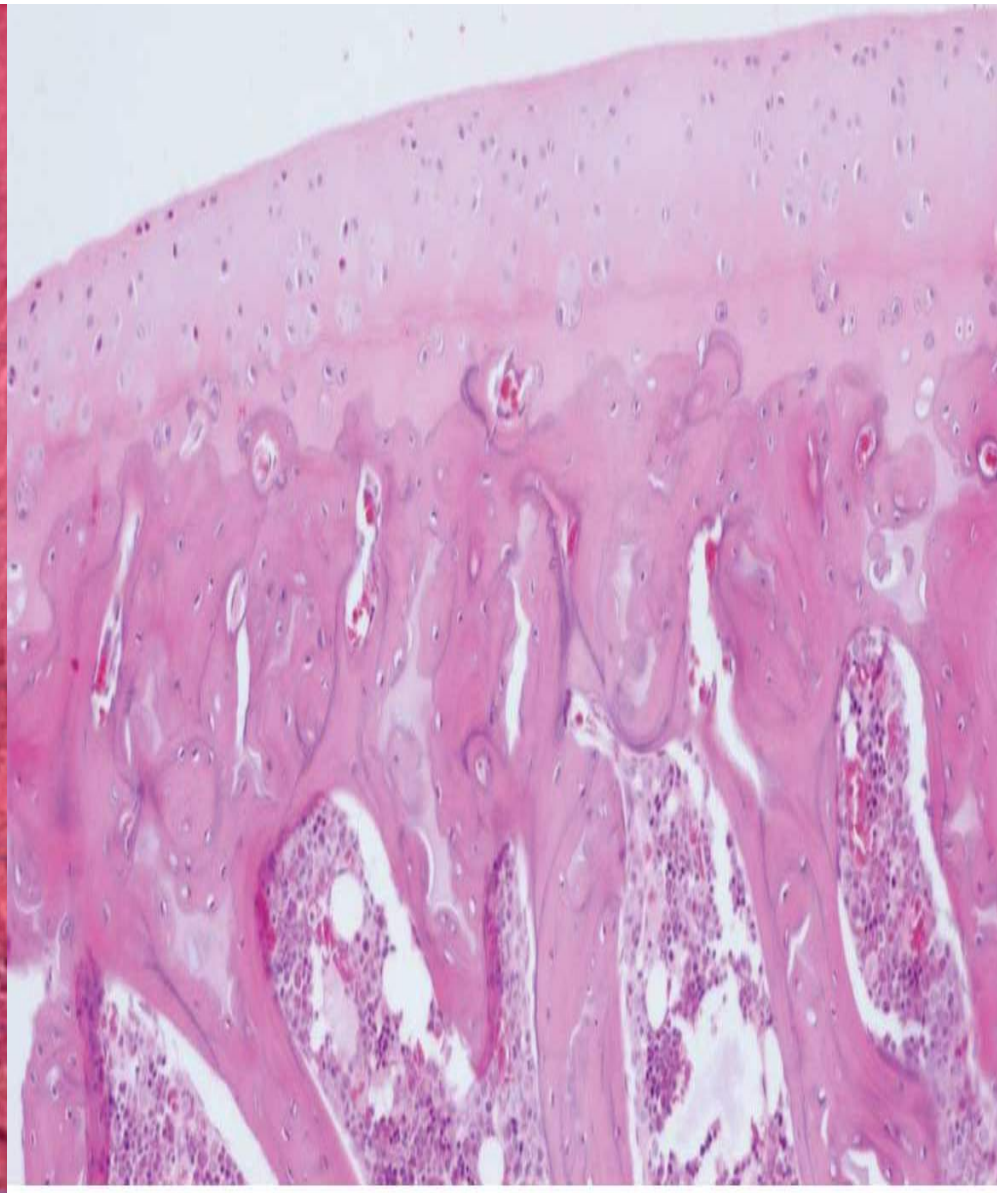
is a specialised form of hyaline cartilage.

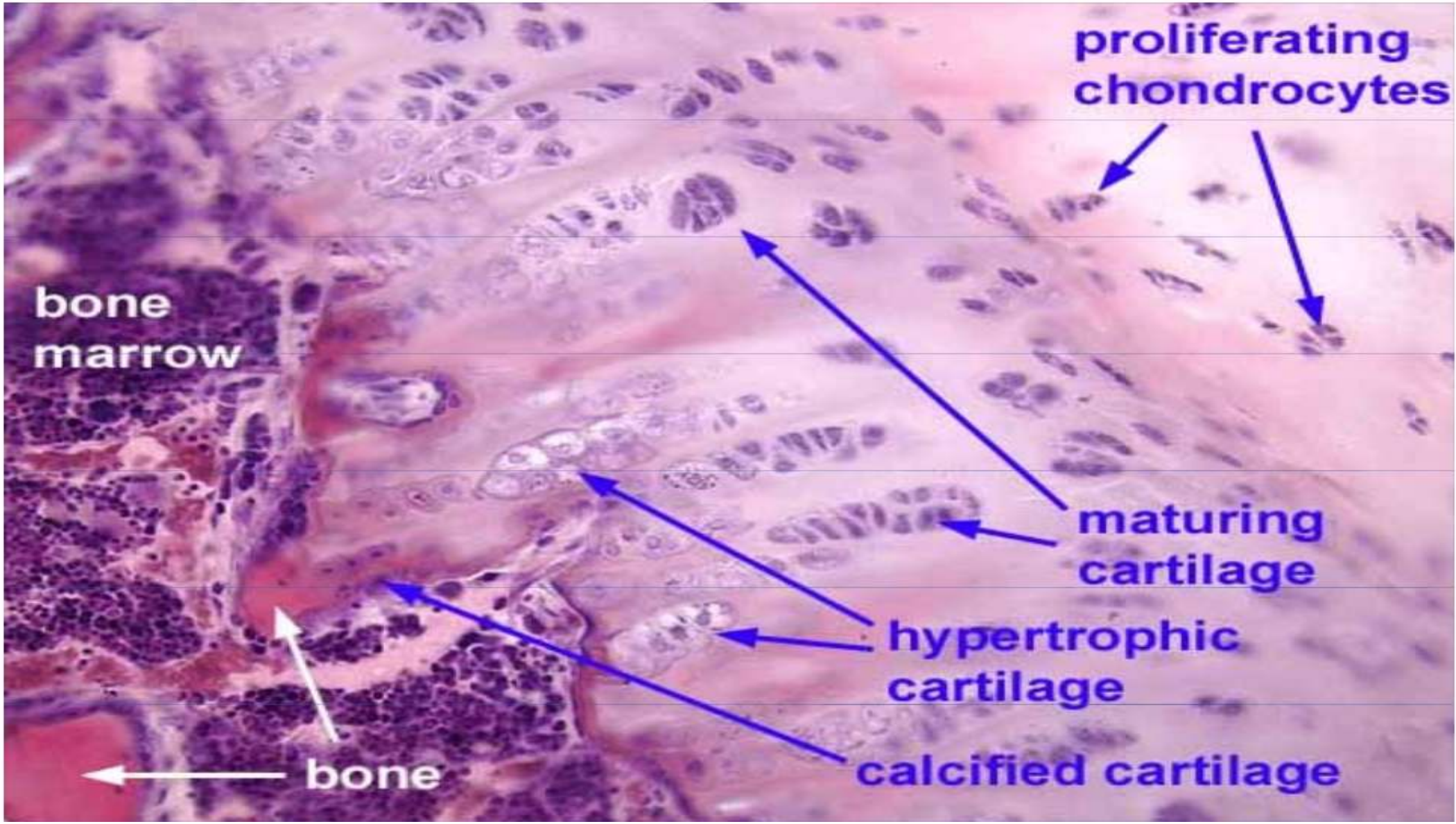
transforms the articulating ends of the bones into lubricated, wear-proof, slightly compressible surfaces, which exhibit very little friction.

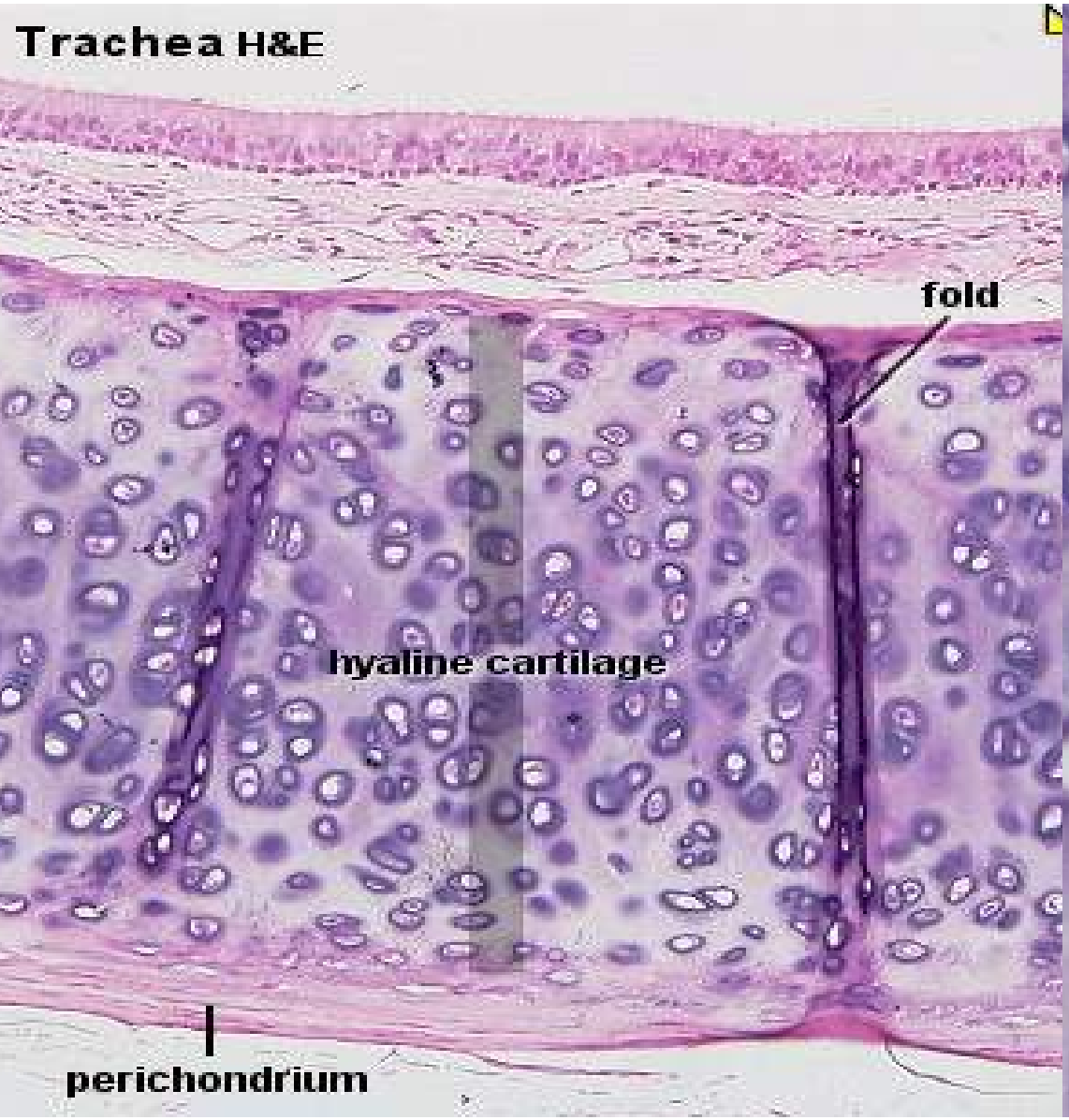
is not surrounded by a perichondrium and is partly vascularised.
is, depending on the arrangement of chondrocytes and collagenous fibres, divided into several zones:

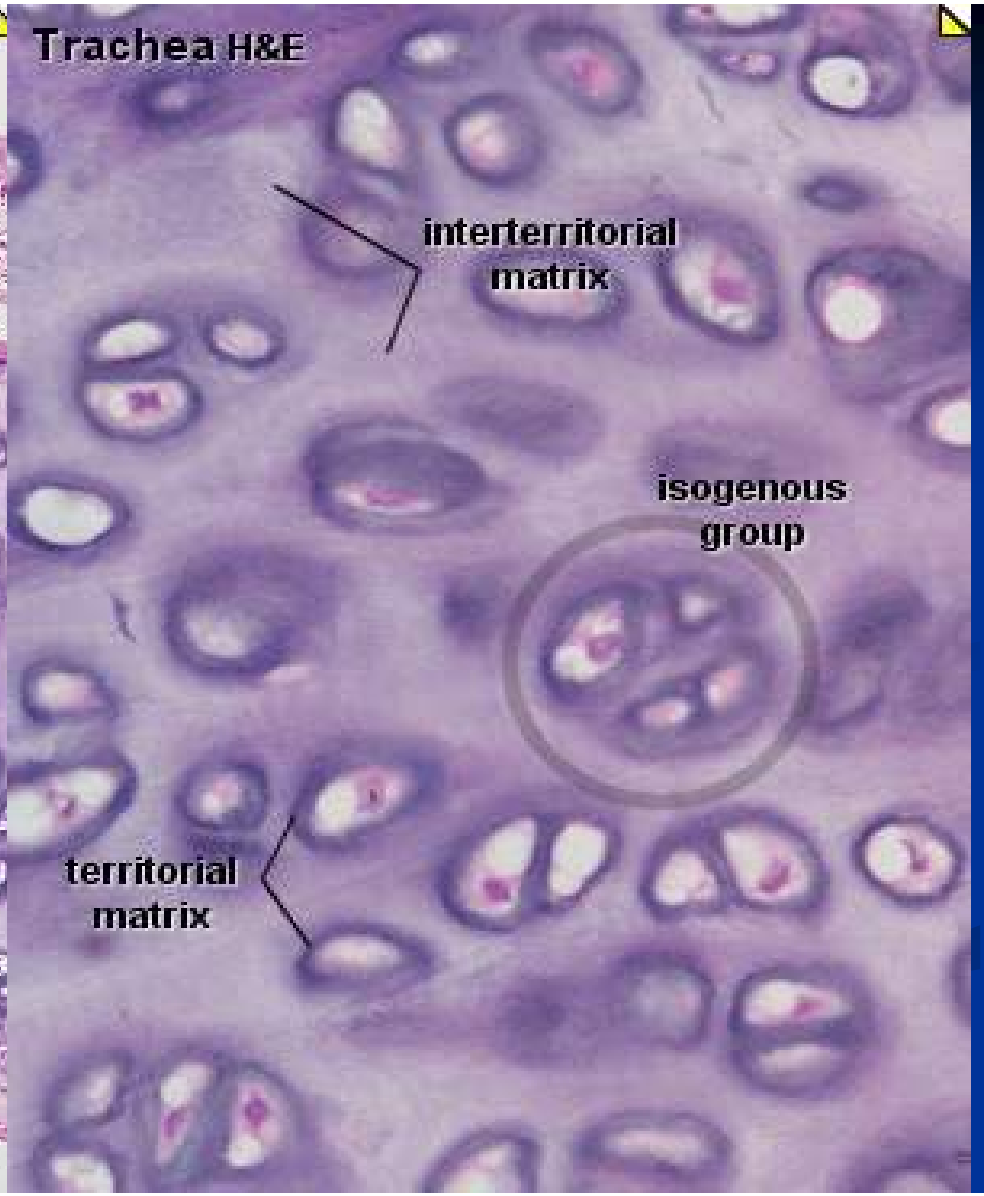

Gliding surface
Superficial Zone
Fibers parallel to surface
Transitional Zone
Random Fibers
Deep Zone
Fibers perpendicular to surface
TIDEMARK
Subchondral Bone
Cancellous Bone

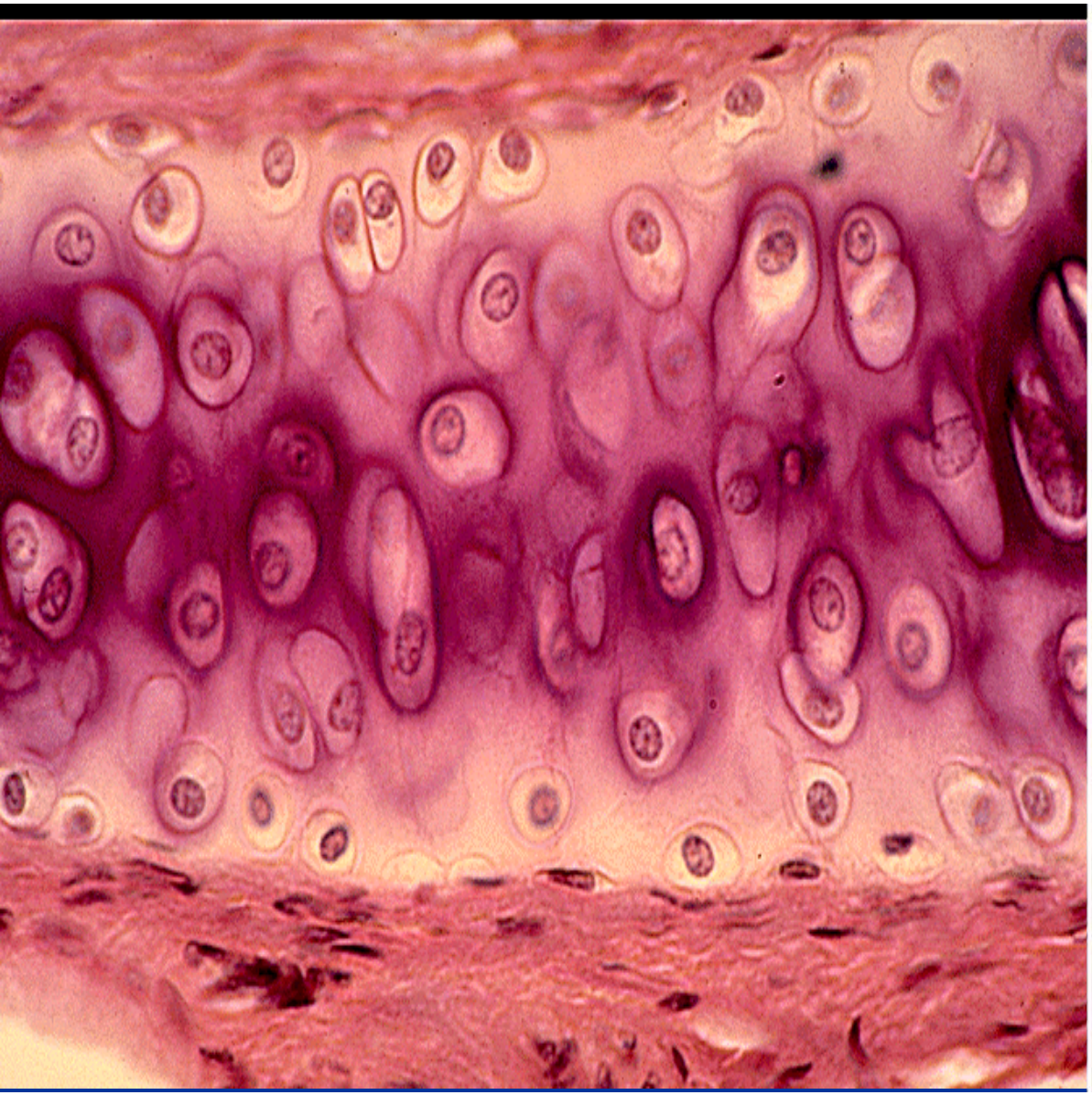

Supplemental Slide 109
Developing Bone
Articular cartilage

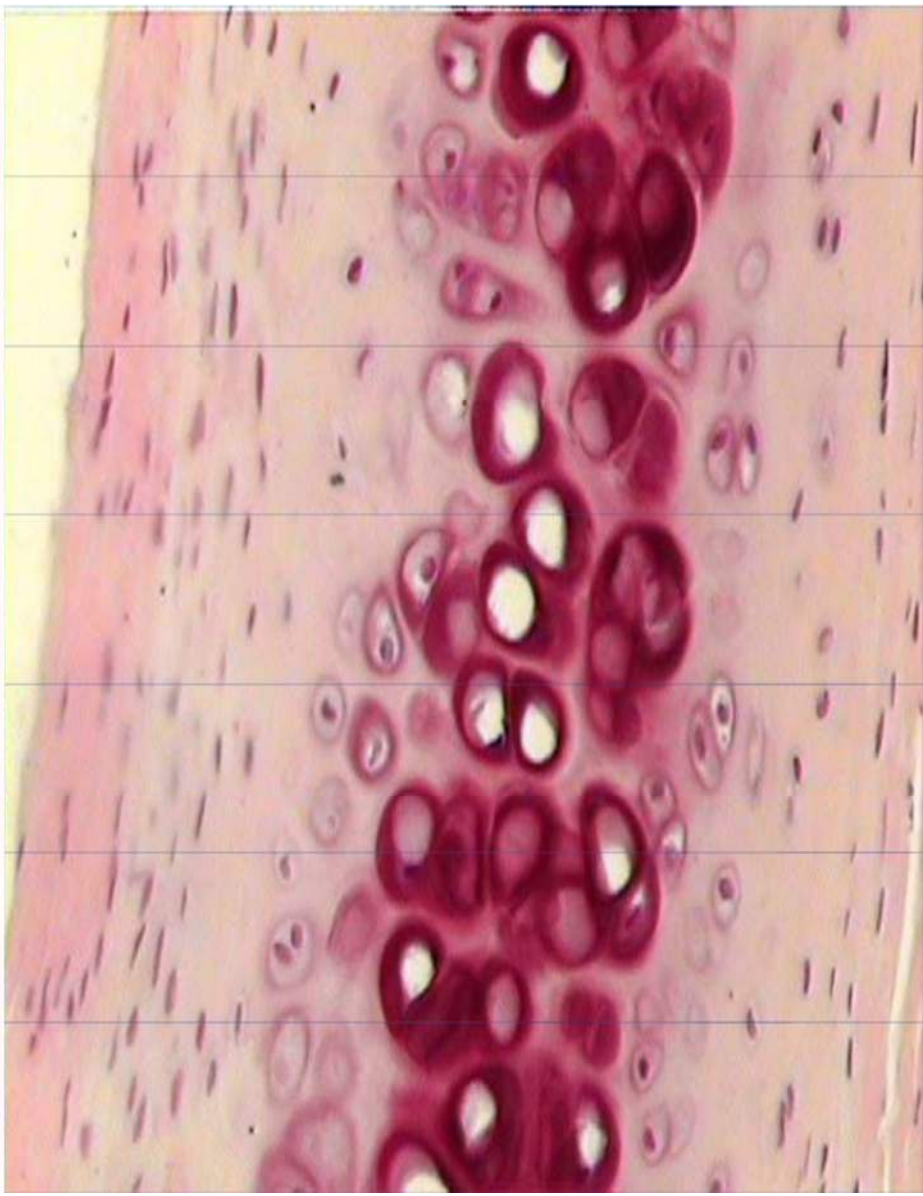



proliferating
chondrocytes
bone
marrow
maturing
cartilage
hypertrophic
cartilage
calcified cartilage
bone


Trachea H&E
fold
hyaline cartilage
perichondrium


Trachea H&E
interterritorial matrix
isogenous group
territorial matrix





Hyaline Cartilage

Matrix (amorphous & glassy)

- hyaluronic acid
- chondroitin sulfate
- keratin sulfate
- H_2O (60-78%)

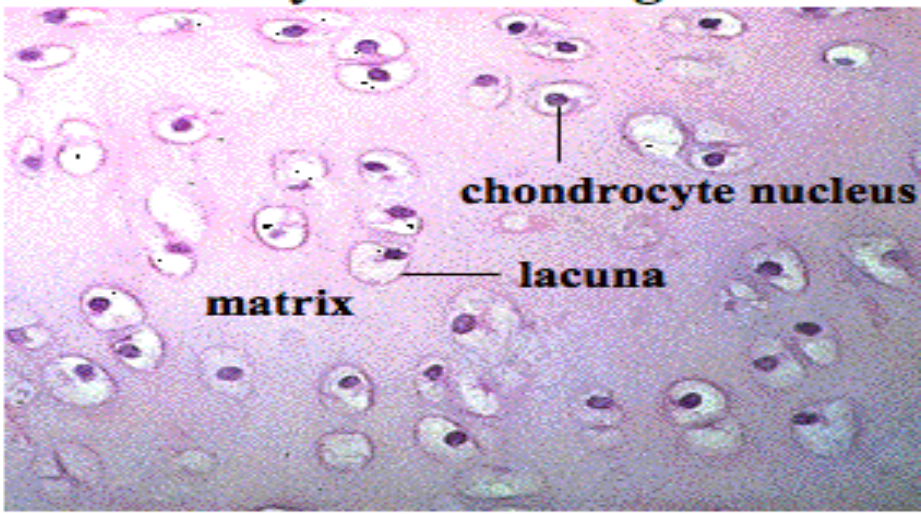
Fibers- collagenous

(invisible due to same refractive index as matrix)

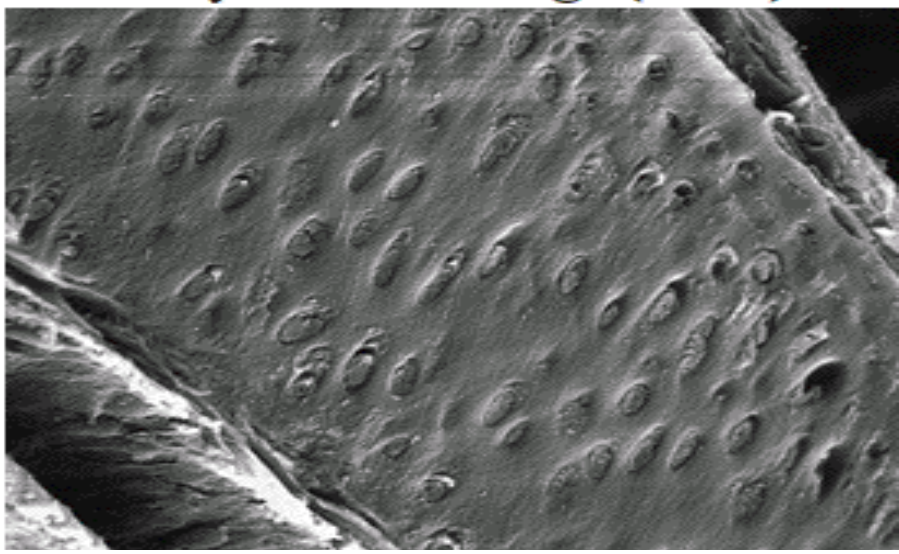
Typical Locations

- intercostals (connect ribs to the sternum)
- wall of trachea & bronchii
- articular cartilage of bone
- epiphyseal plate
- fetal axial skeleton

Hyaline Cartilage

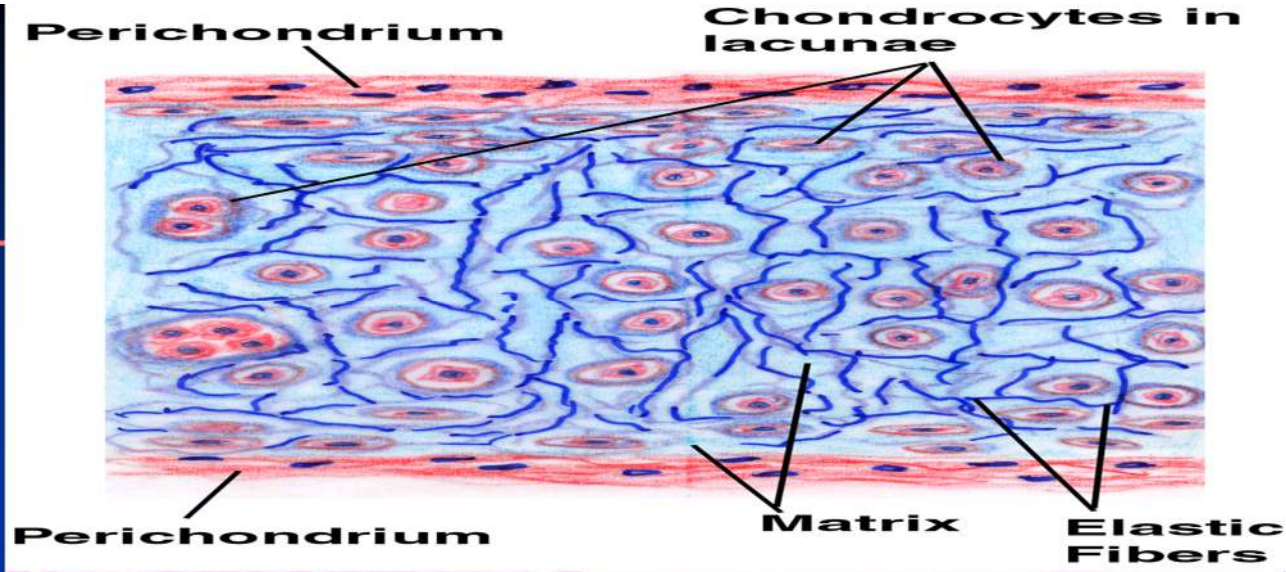


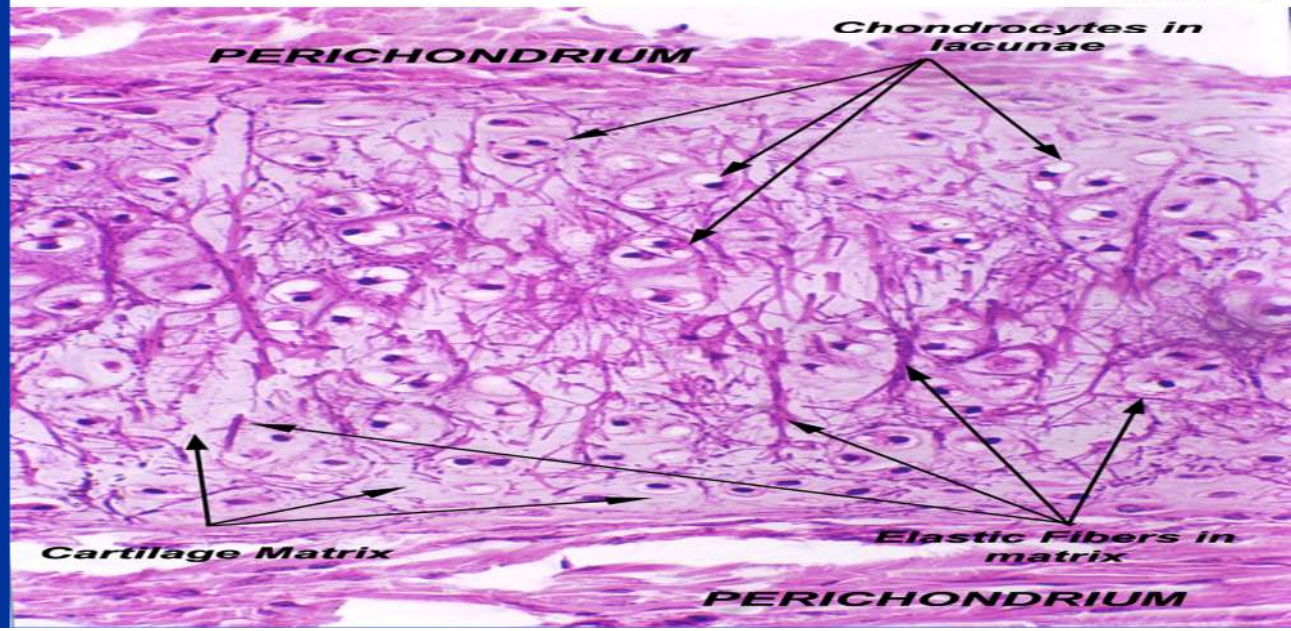
Hyaline Cartilage (SEM)

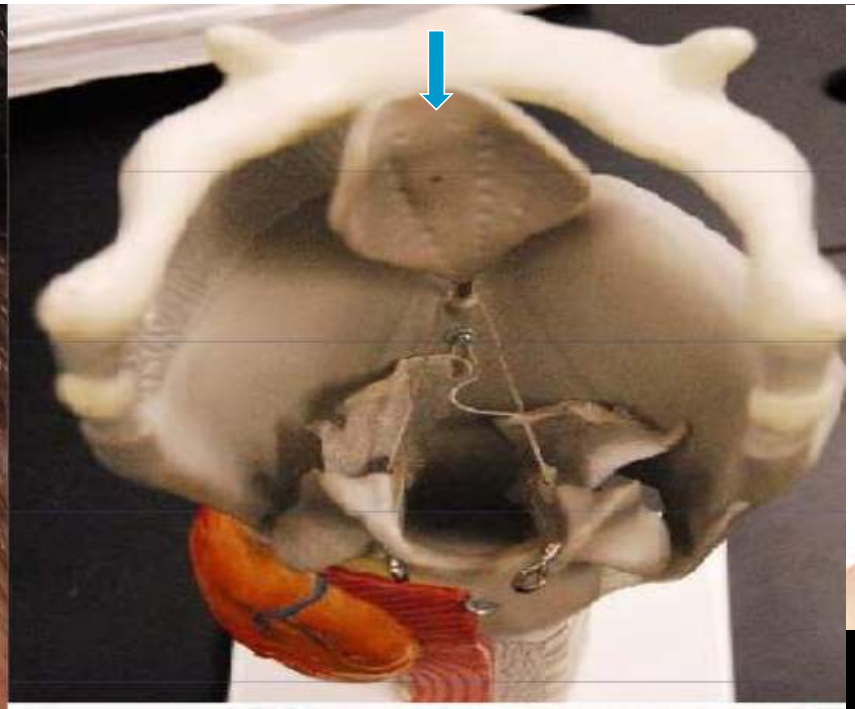


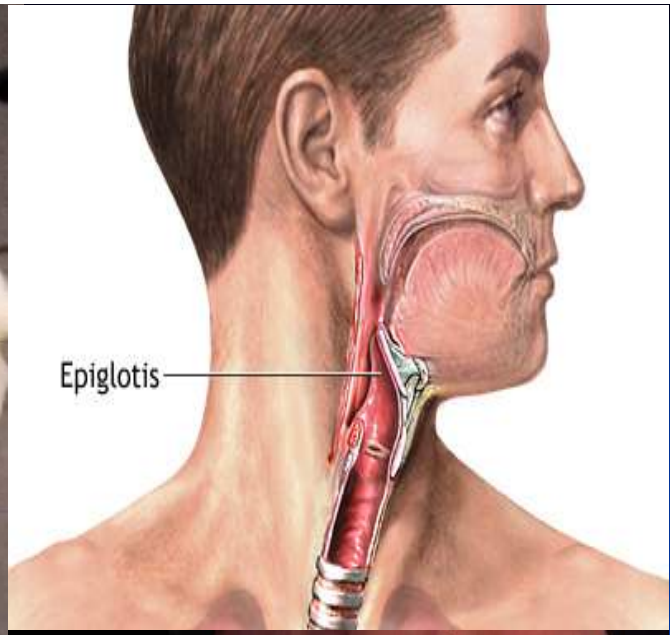
Elastic Cartilage

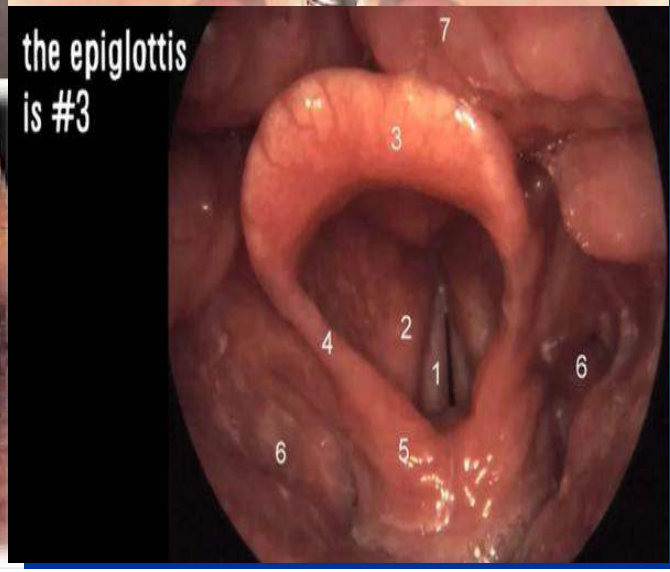
- Similar to hyaline cartilage, but contains elastic fibers + type II collagen allowing it to maintain shape after bending.
- Location:
  - External Ear (Pinna): Provides shape and support.
  - Epiglottis: Prevents food from entering the trachea during swallowing.
  - Eustachian Tube: Part of the middle ear.

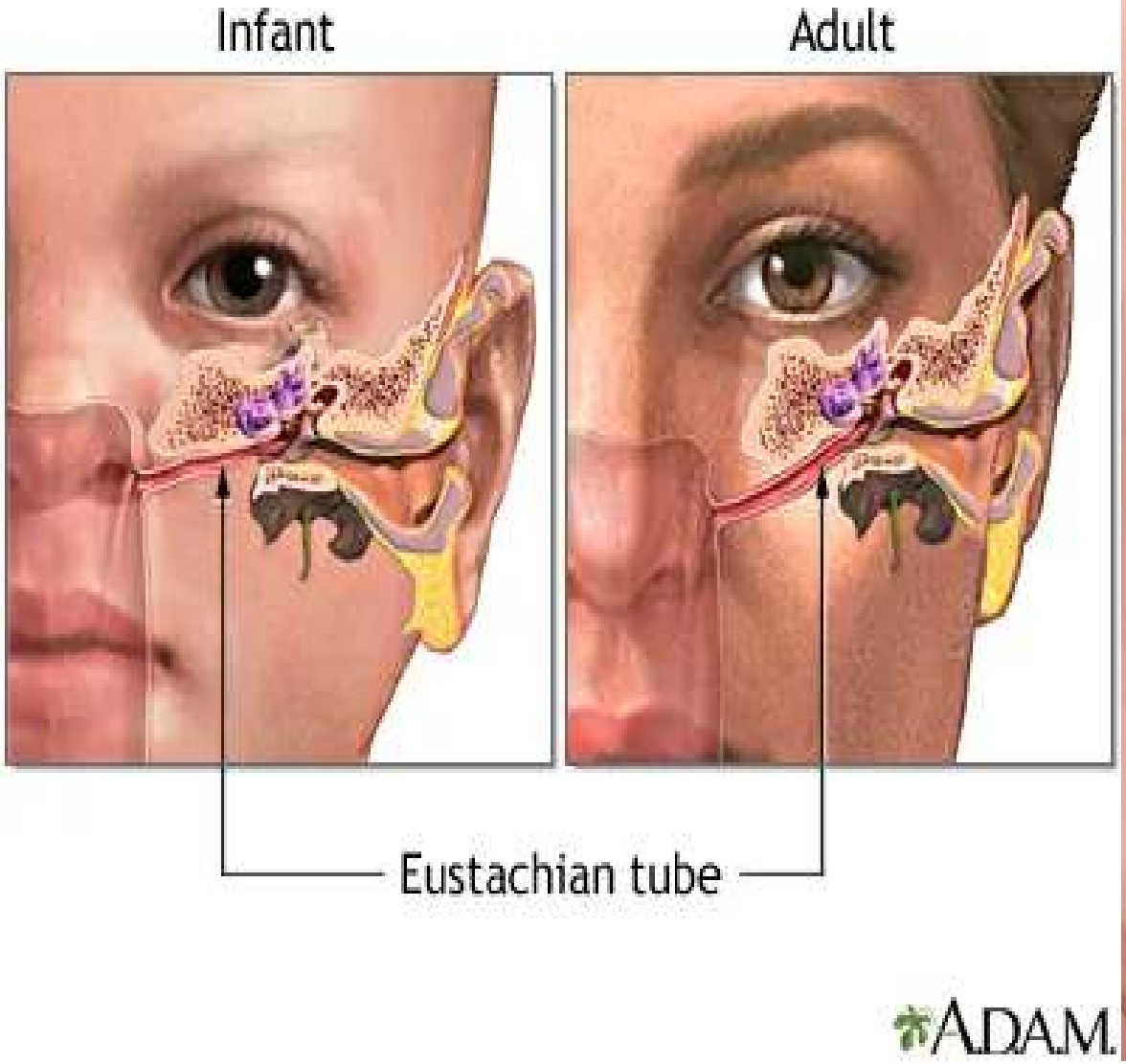


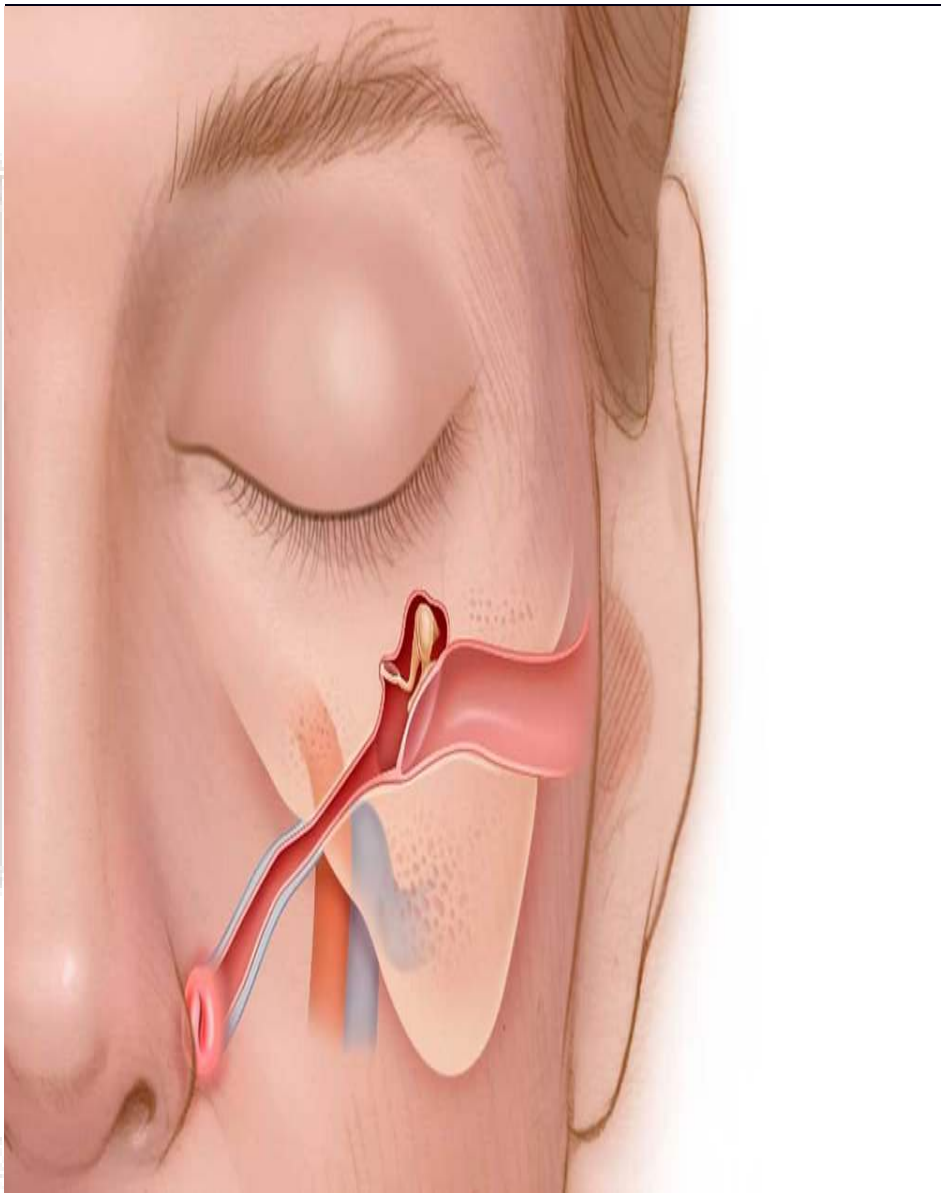


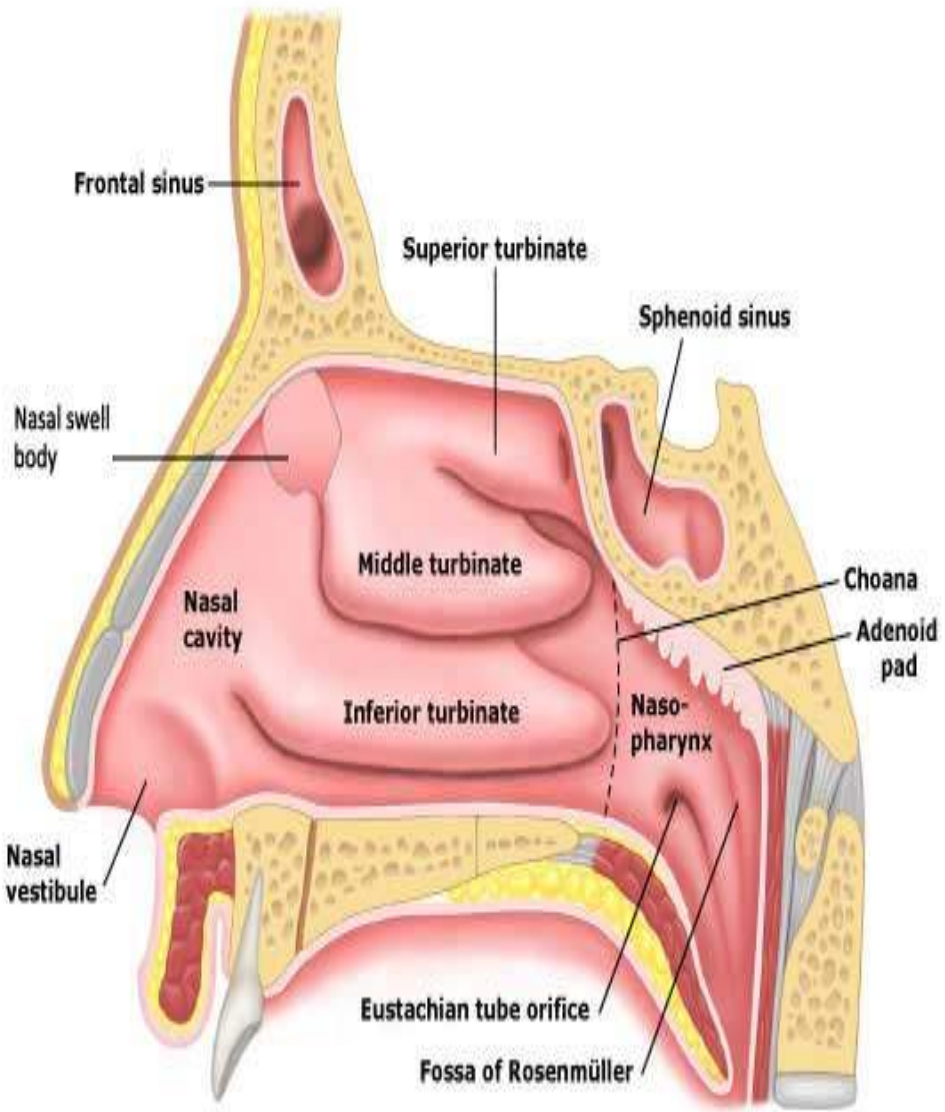


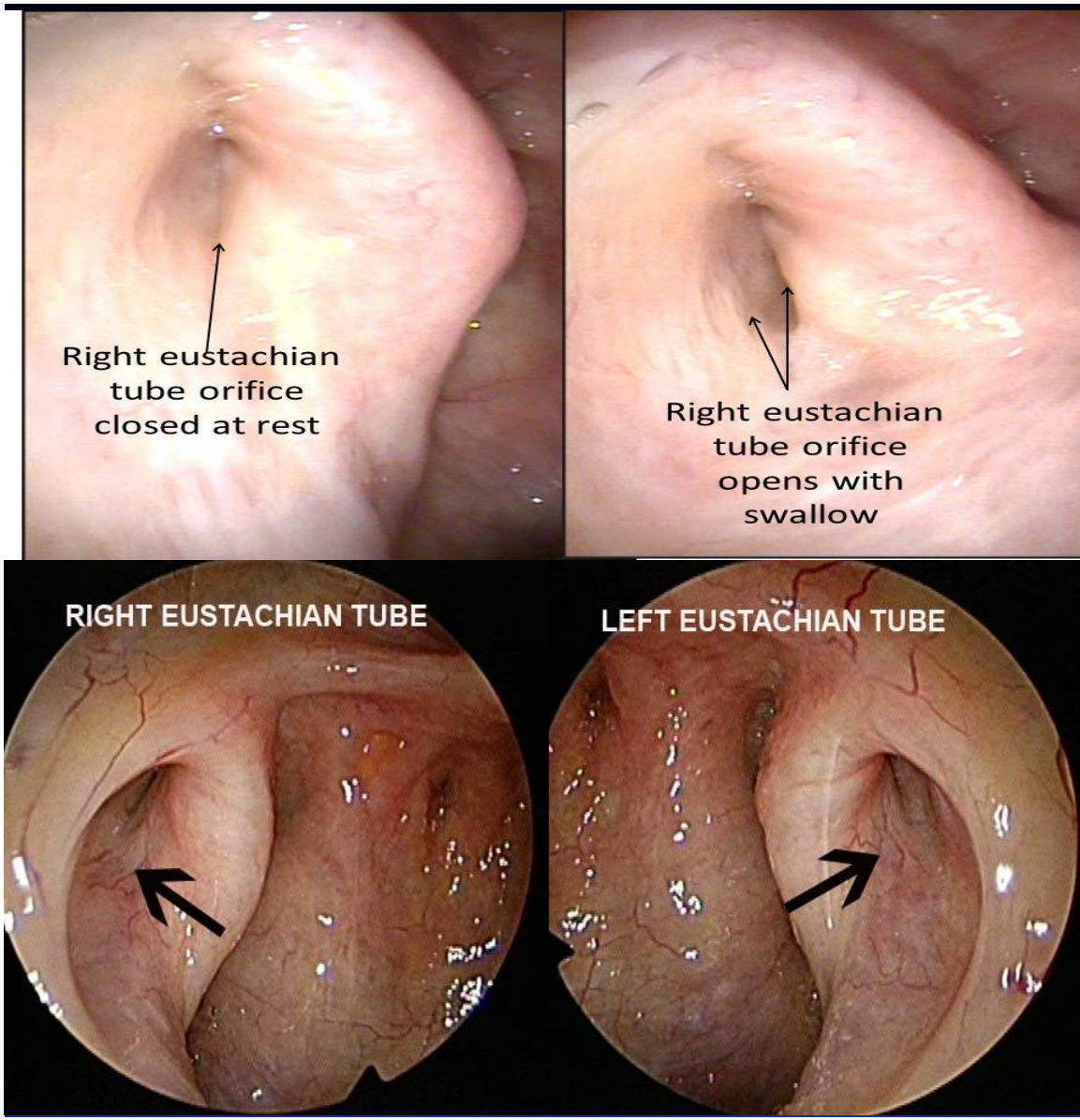

Epiglotis

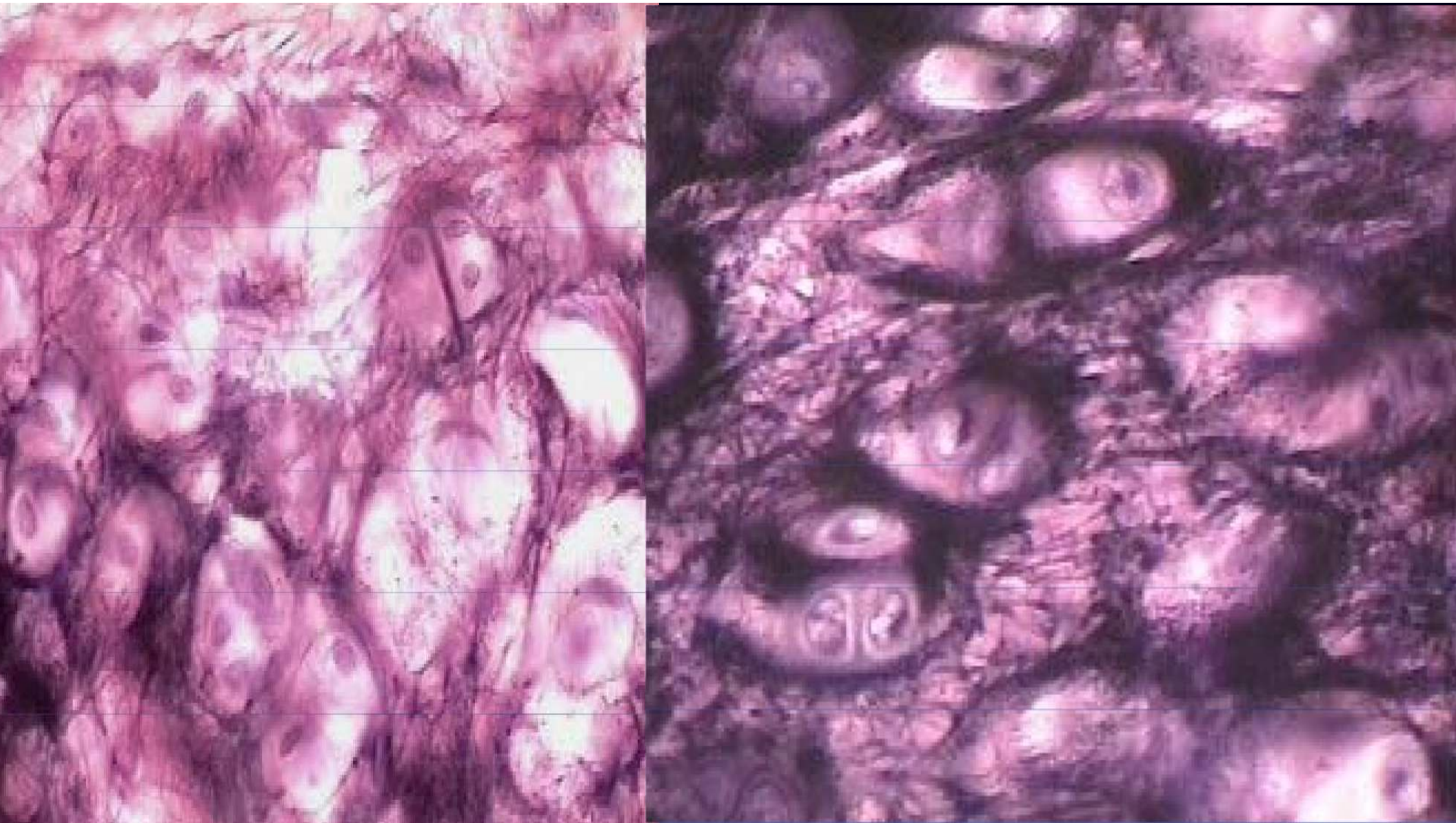

the epiglottis
is #3
7
3
4
2
1
6
6
5


Infant
Adult
Eustachian tube
A.D.A.M.




Frontal sinus
Superior turbinate
Sphenoid sinus
Nasal swell body
Middle turbinate
Nasal cavity
Choana
Adenoid pad
Inferior turbinate
Naso-pharynx
Nasal vestibule
Eustachian tube orifice
Fossa of Rosenmüller


Right eustachian tube orifice closed at rest
Right eustachian tube orifice opens with swallow
RIGHT EUSTACHIAN TUBE
LEFT EUSTACHIAN TUBE



Elastic Cartilage

Matrix

hyaluronic acid
chondroitin sulfate
kertatin sulfate

Fibers

elastic (elastin)

Typical Locations

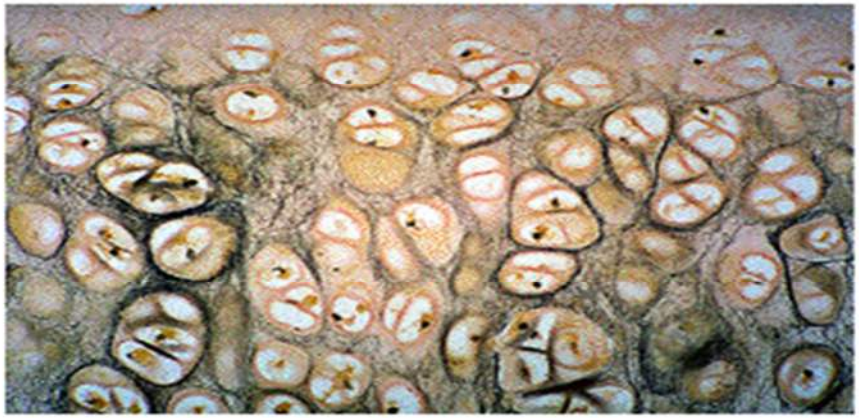
external ear
walls of external auditory canal and eustachian tubes
epiglottis & larynx
bridge of nose

Properties

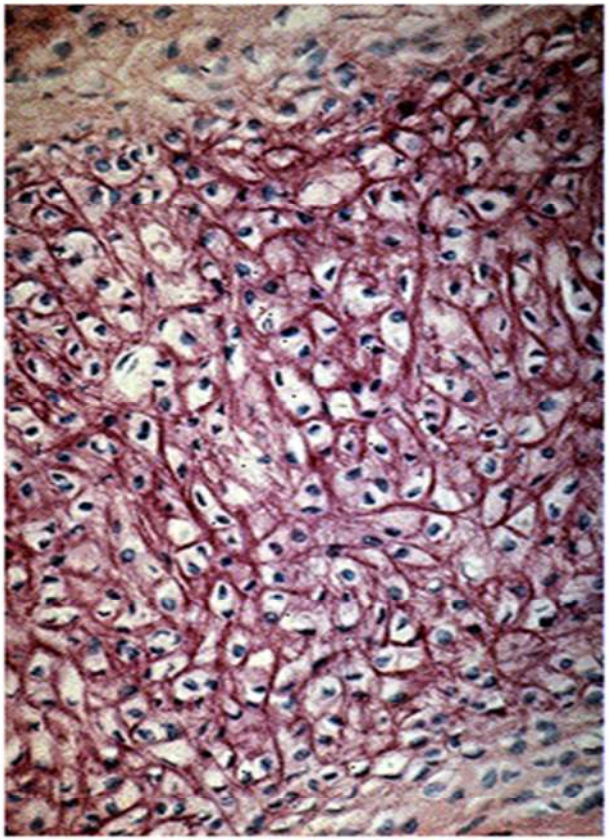
resiliency and pliability

Elastic Cartilage- pinnae of ear

Elastic Fibers- silver stain



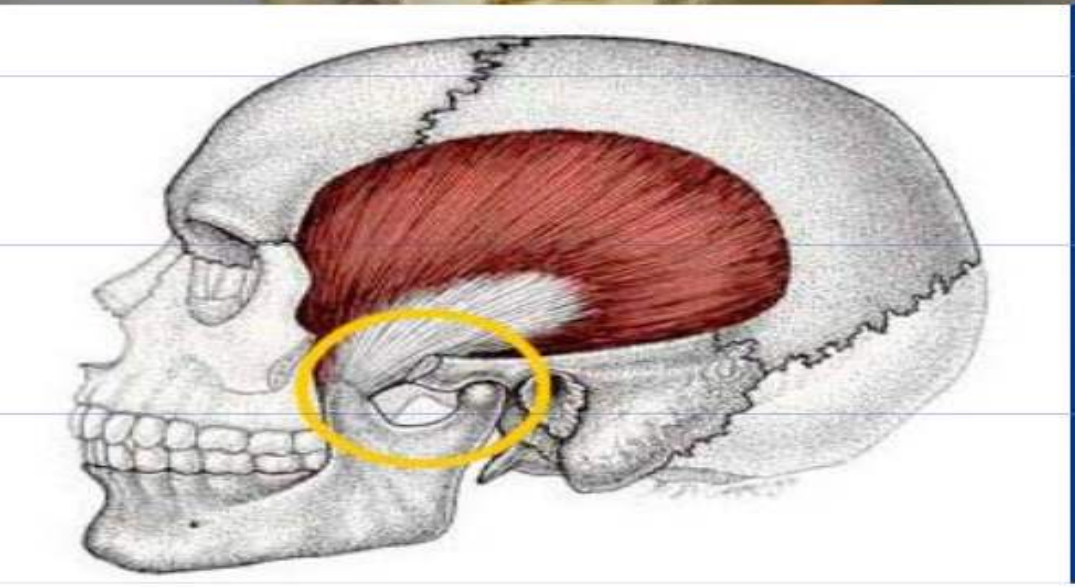
Elastic Fibers
(resorcin-fuchsin stain)

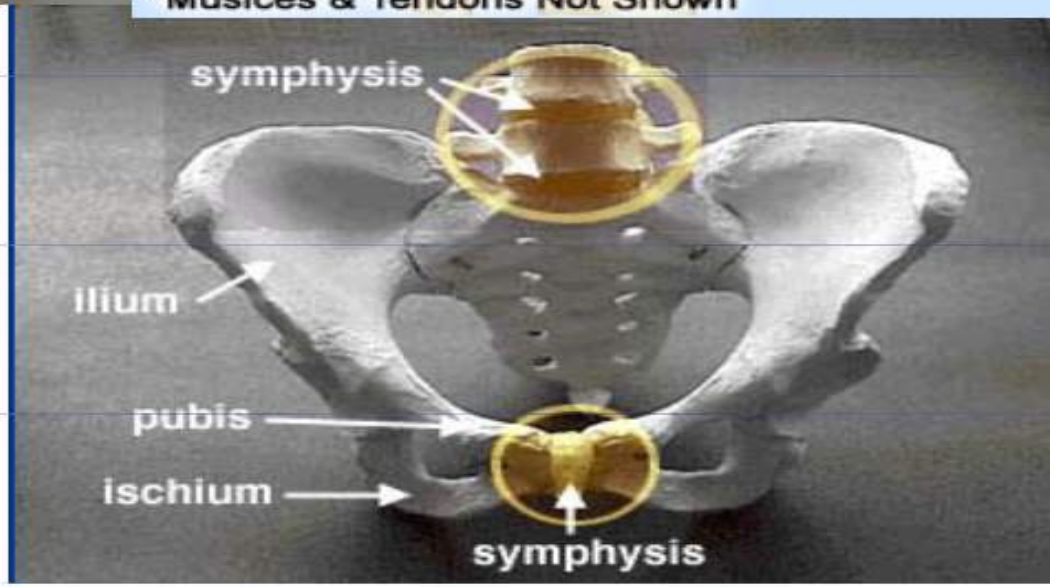


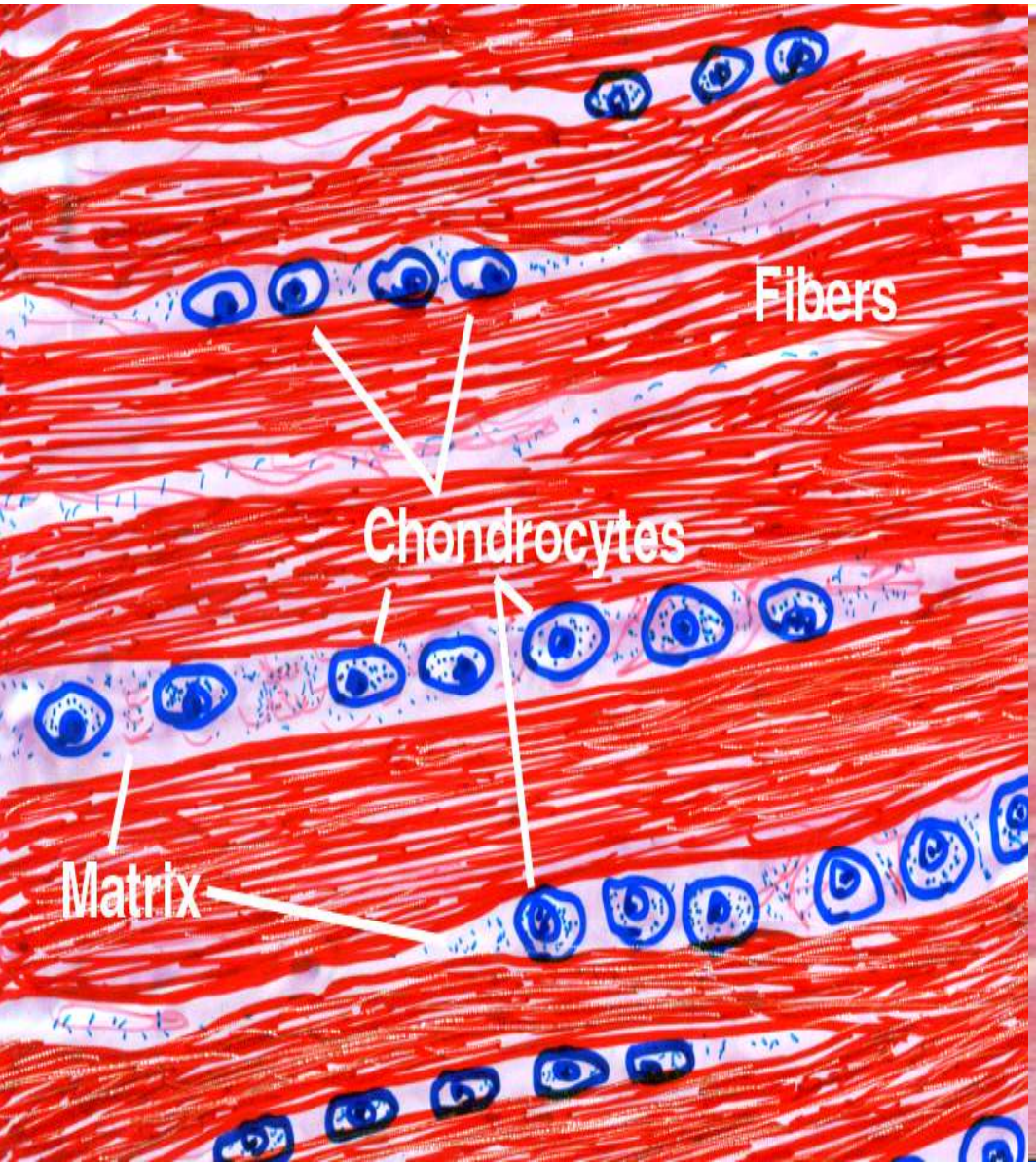
Fibrocartilage

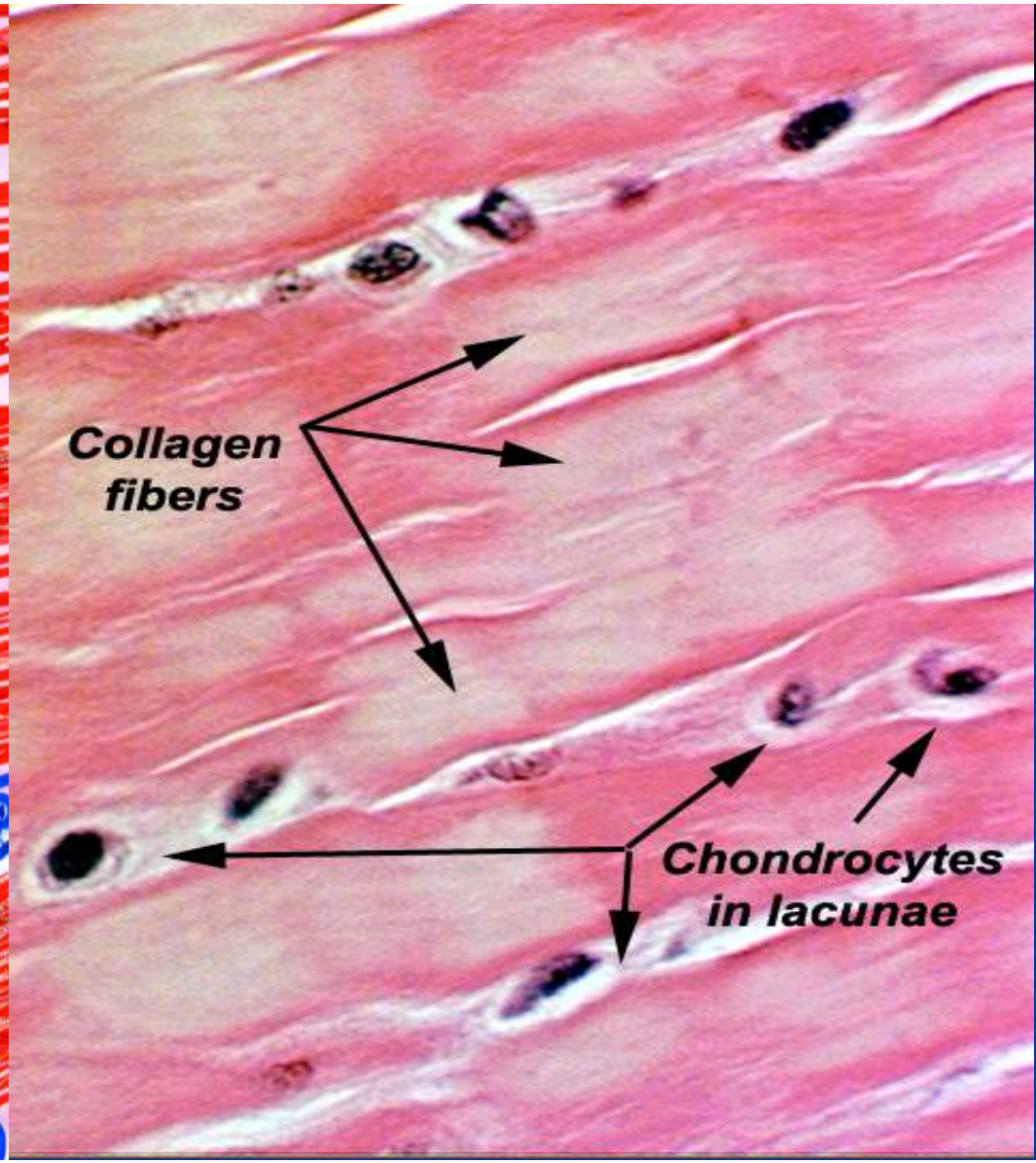
- Highly compressed with great tensile strength
- **Contains collagen fibers type I in addition to type II**
- **Composed of thick bundles of type I collagen fibers, providing great tensile strength.**
- **Location:**
  - **Intervertebral Discs:** Acts as a cushion between vertebrae.
  - **Menisci:** Crescent-shaped pads in the knee joint.
  - **Pubic Symphysis:** Connects the pubic bones anteriorly.
  - **Temporomandibular Joint:** Helps in jaw movement.

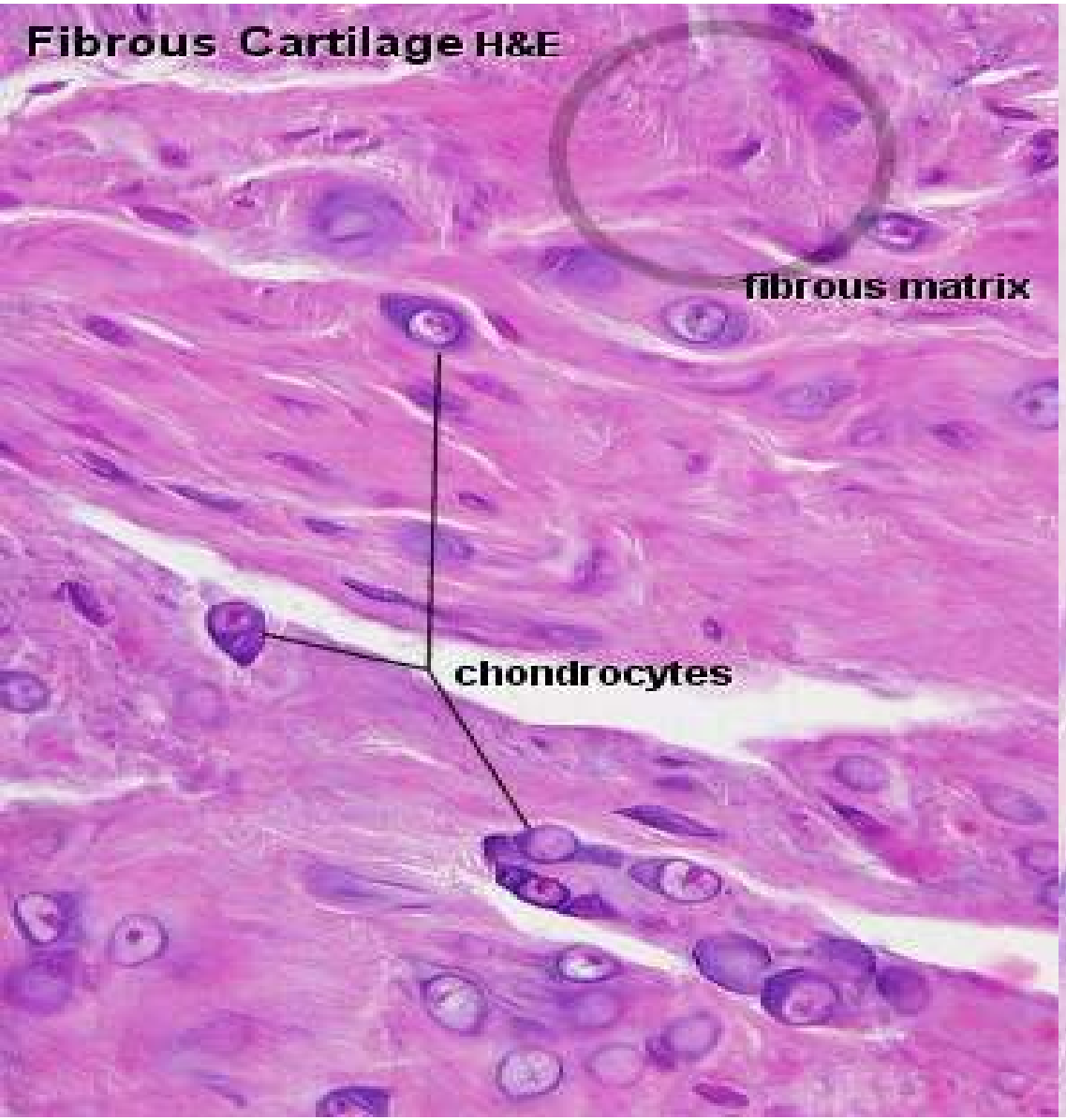

Femur
(thigh bone)
Articular
Cartilage
Cruciate
Ligaments
Patella
(knee cap)
Outer (lateral)
side of knee
Inner side
of knee
Menisci
(Menisicular
Cartilage)
Collateral
Ligaments
Tibia (shin bone)
Fibula
Collateral
Ligaments
*Muslces & Tendons Not Shown

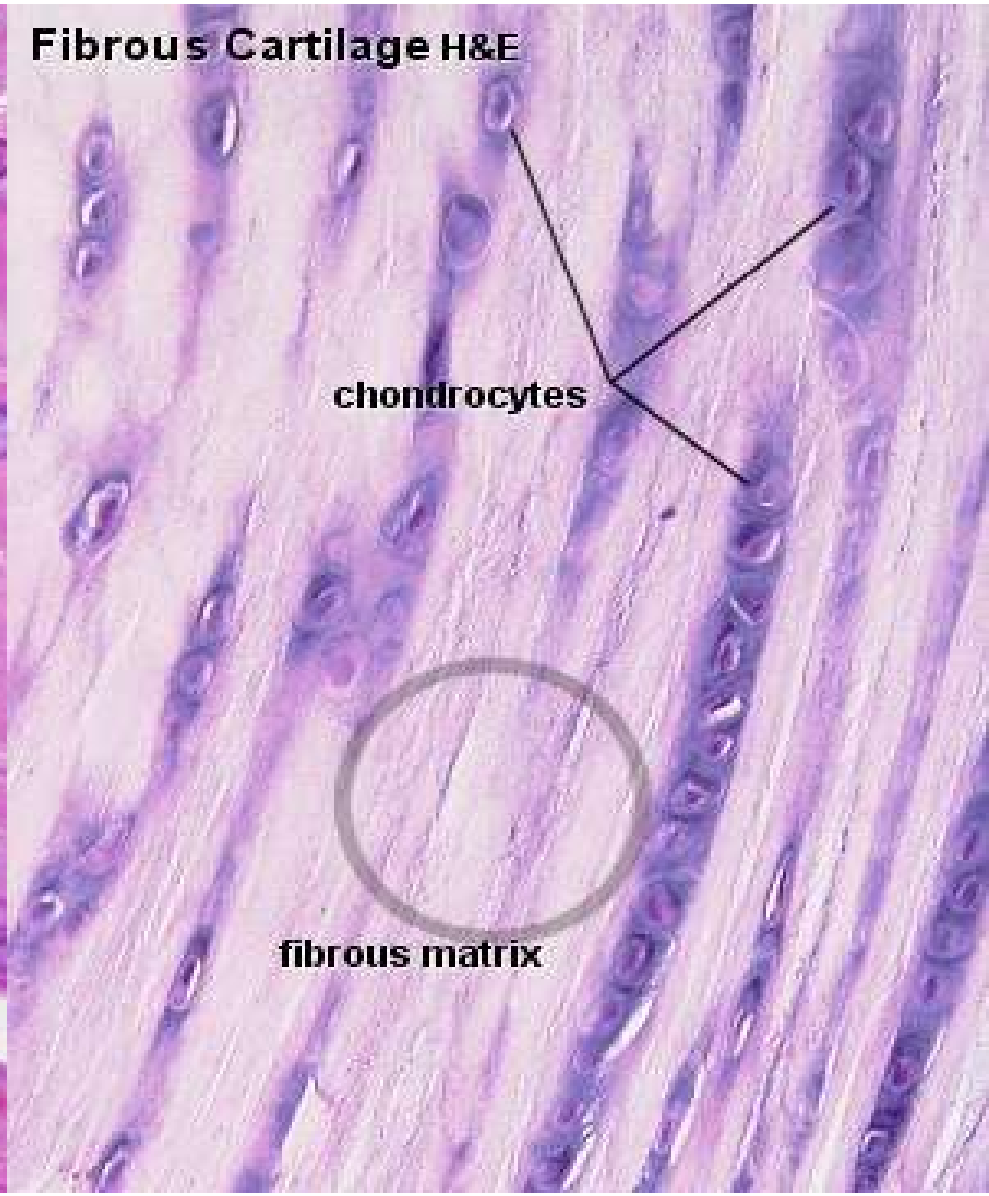


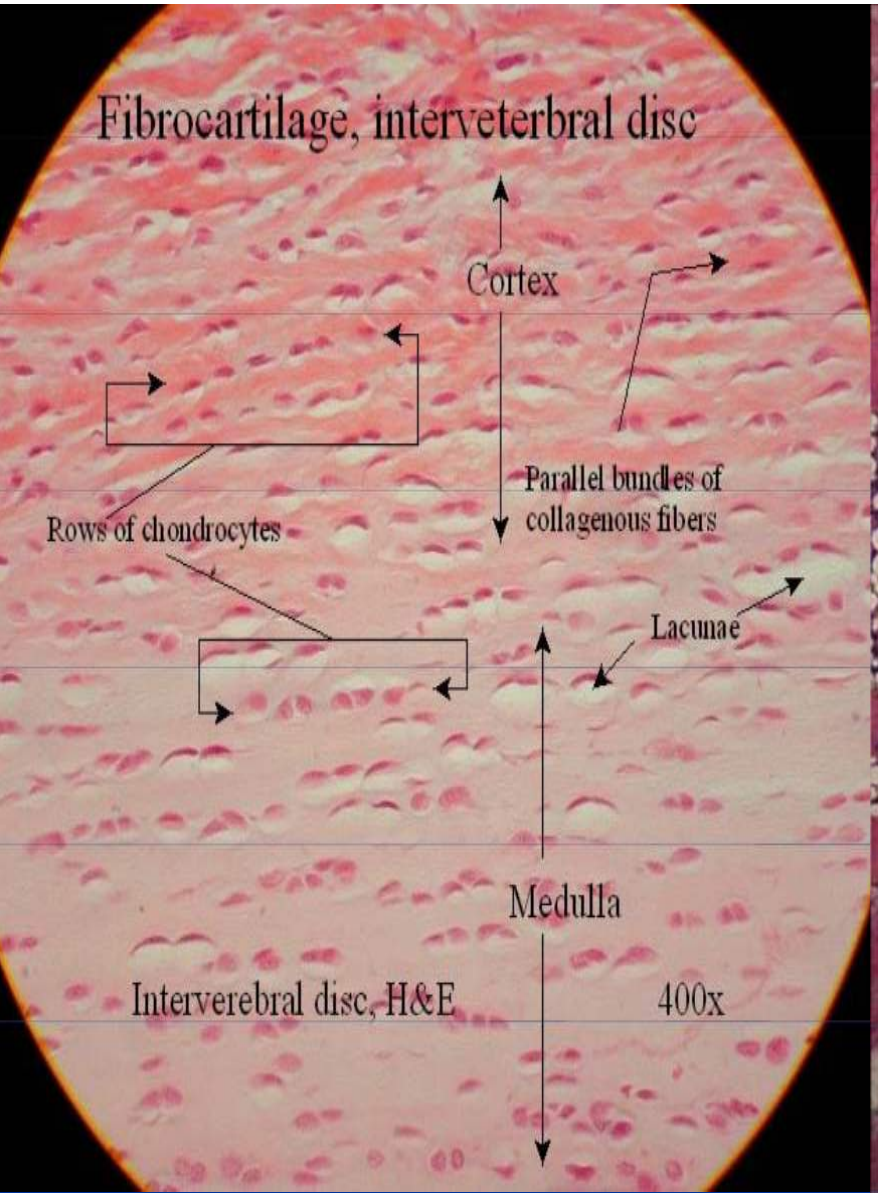

symphysis
ilium
pubis
ischium
symphysis

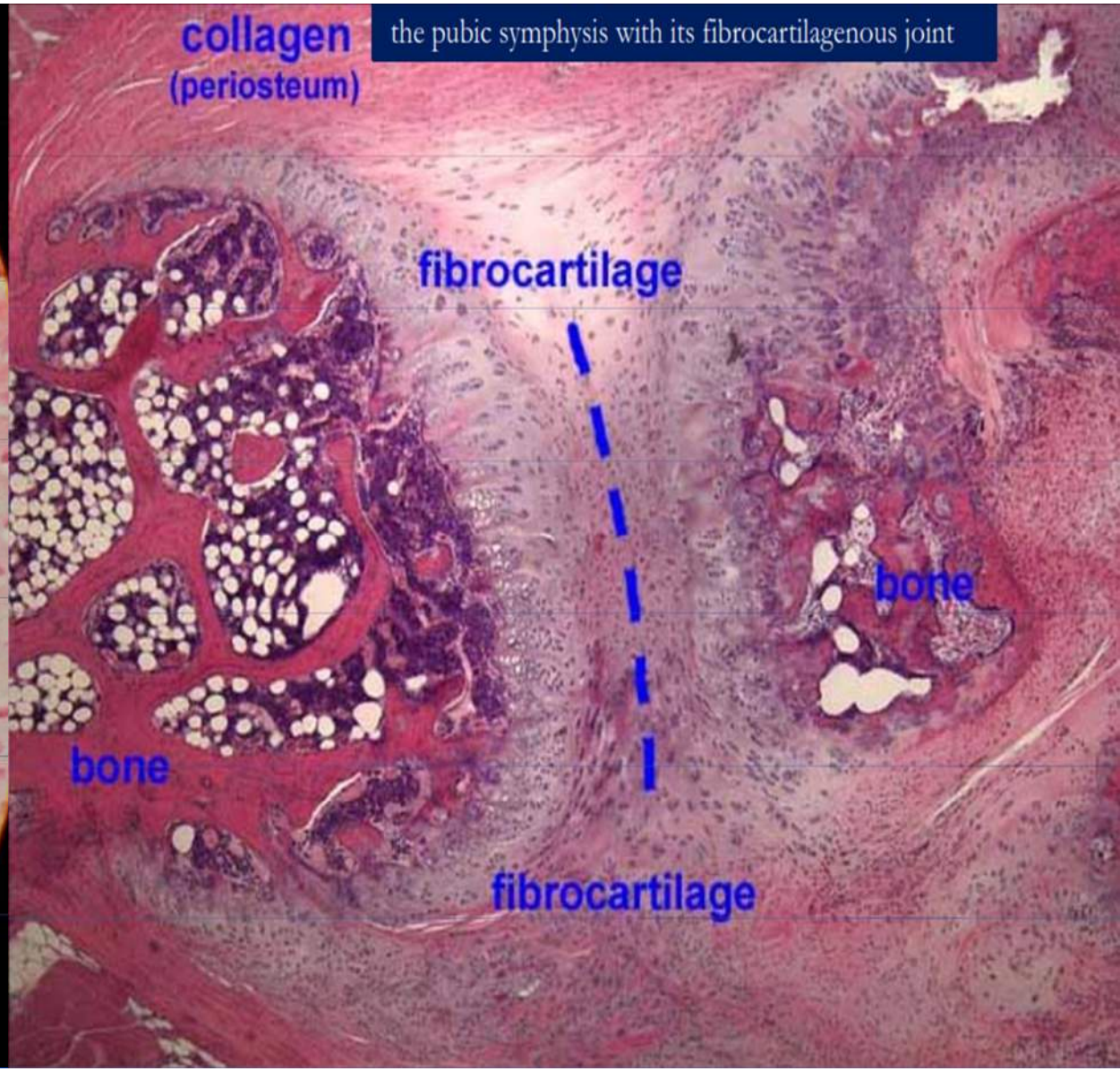

Fibers
Chondrocytes
Matrix

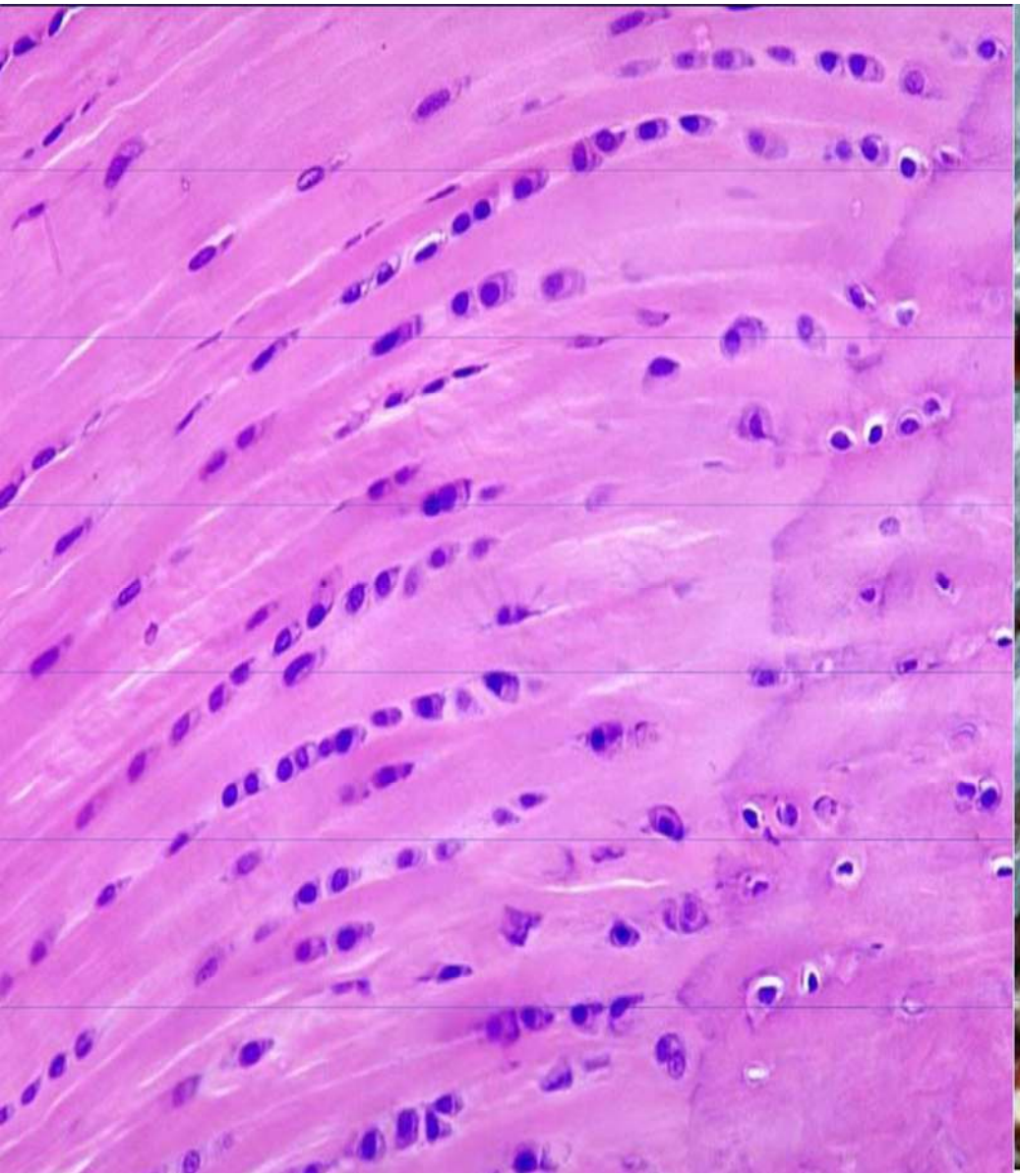

Collagen fibers
Chondrocytes in lacunae

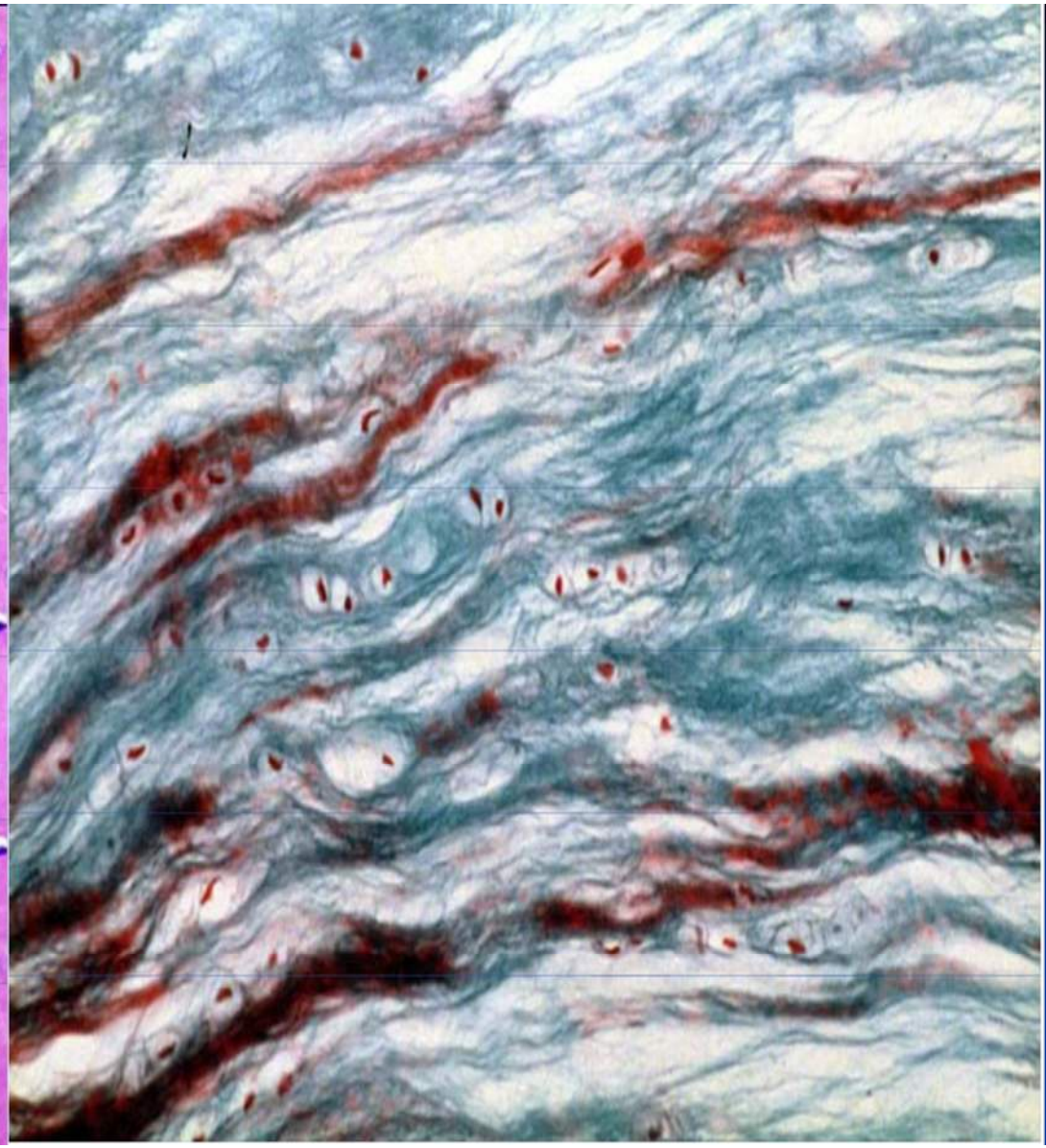

Fibrous Cartilage H&E
fibrous matrix
chondrocytes


Fibrous Cartilage H&E
chondrocytes
fibrous matrix


Fibrocartilage, interveterbral disc
Cortex
Parallel bundles of collagenous fibers
Rows of chondrocytes
Lacunae
Medulla
Interverebral disc, H&E
400x


collagen
(periosteum)
the pubic symphysis with its fibrocartilagenous joint
fibrocartilage
bone
bone
fibrocartilage





Fibrocartilage

Matrix

hyaluronic acid
chondroitin sulfate
keratin sulfate

Fibers

dense collagenous bundles

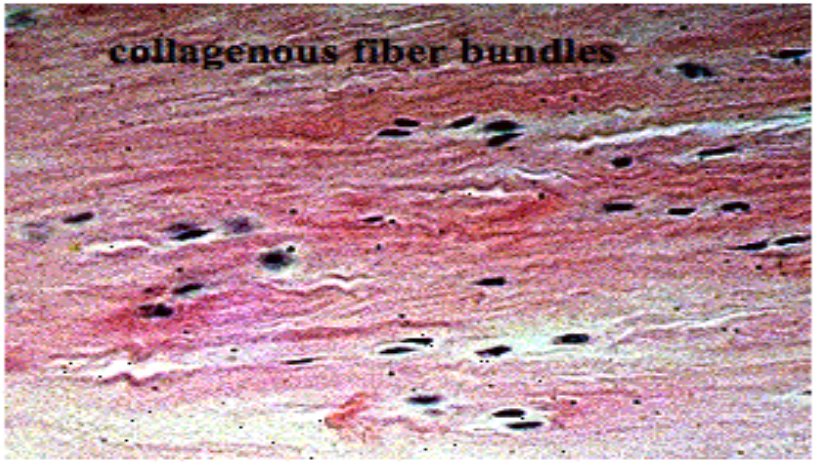
Typical Locations

intervertebral discs
pubic symphysis
meniscus of knee joint
attach tendons to bone

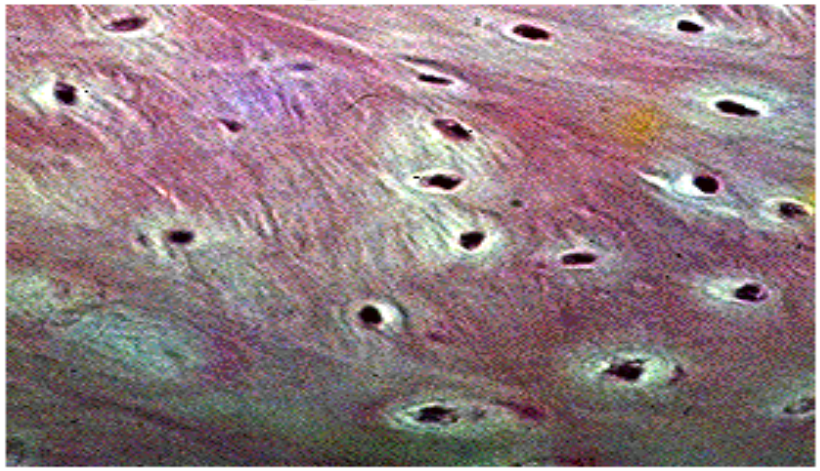
Properties

resistance to compression and shear forces

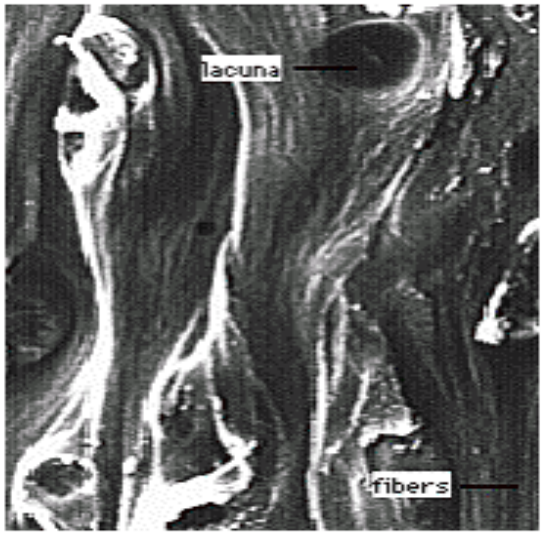
Fibrocartilage- longitudinal section

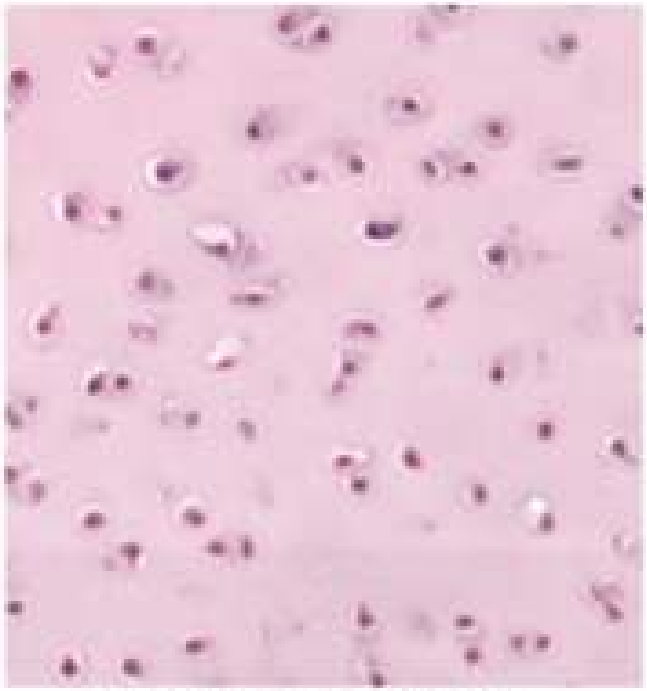


Fibrocartilage- transverse section

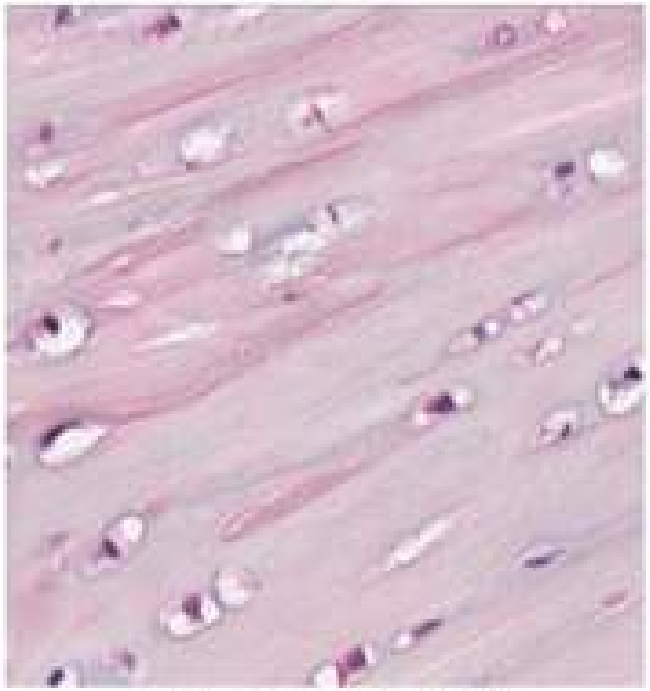


Fibrocartilage- SEM

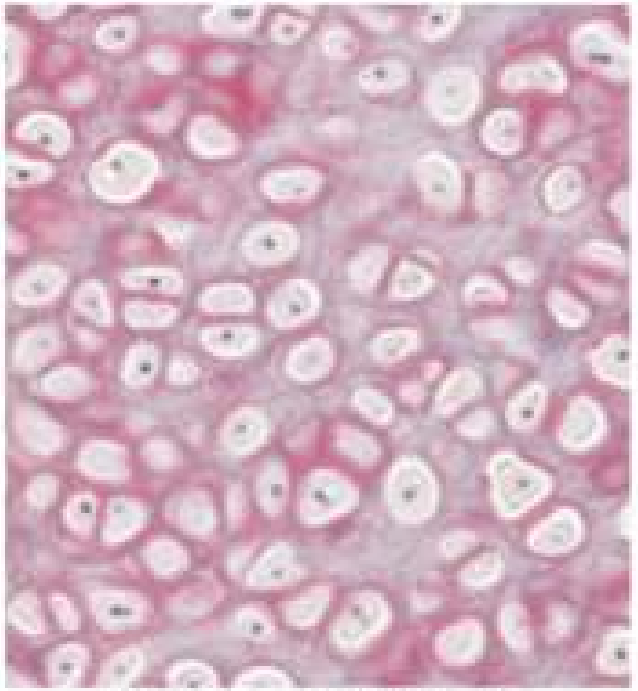




Hyaline cartilage

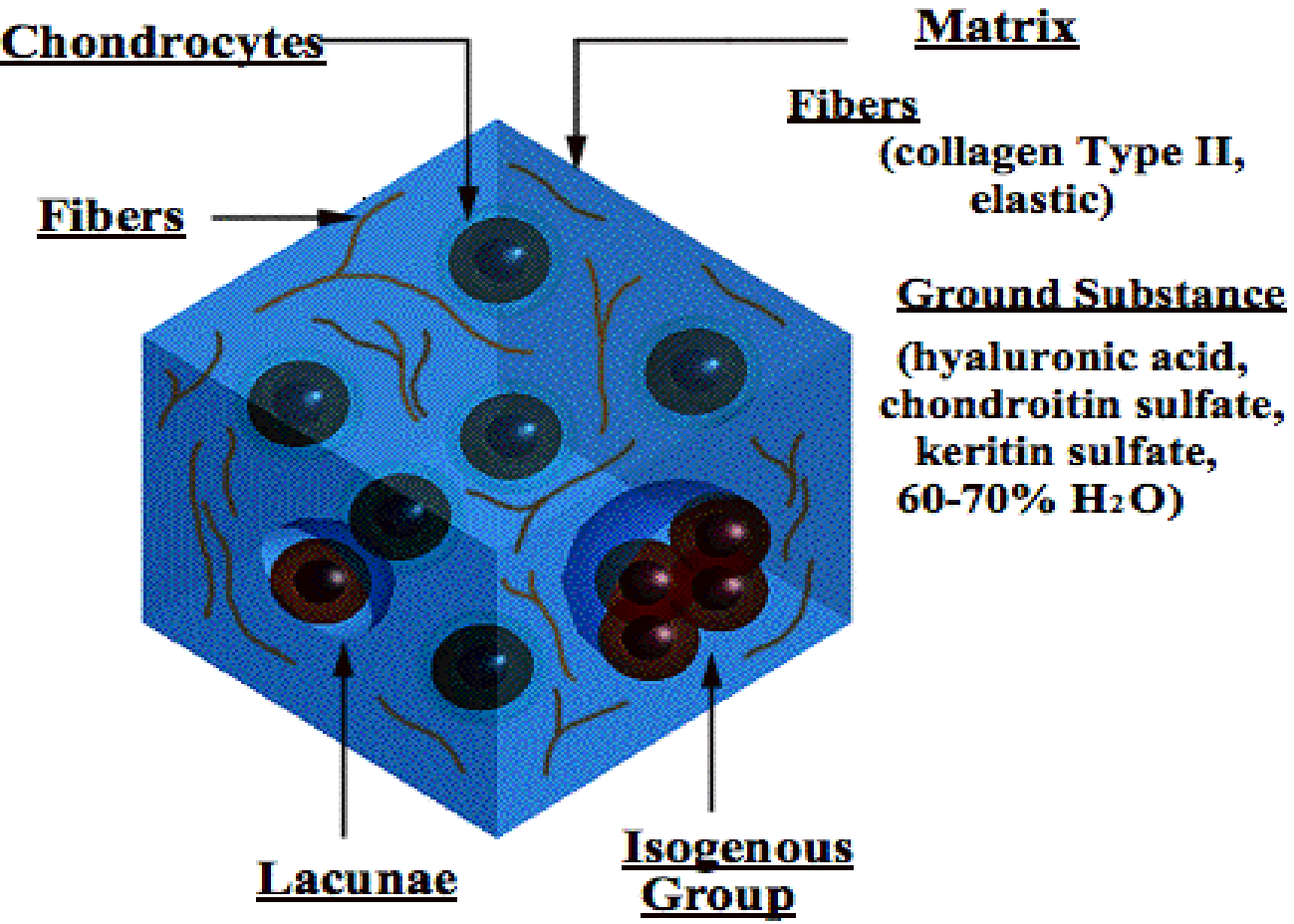


Fibrocartilage



Elastic cartilage

Cartilage



Properties of Cartilage

1. Avascular
2. Permeable
   (conducts nutirents and water)
3. Flexible but Weight-Bearing
   (resistance to compression)
4. Elasticity and Resiliency
5. Resistance to Shear Forces
6. Slippery
   (low friction at articular joints)
7. Poor Regenerative Capacity

Distribution of The Various Types Of Cartilage

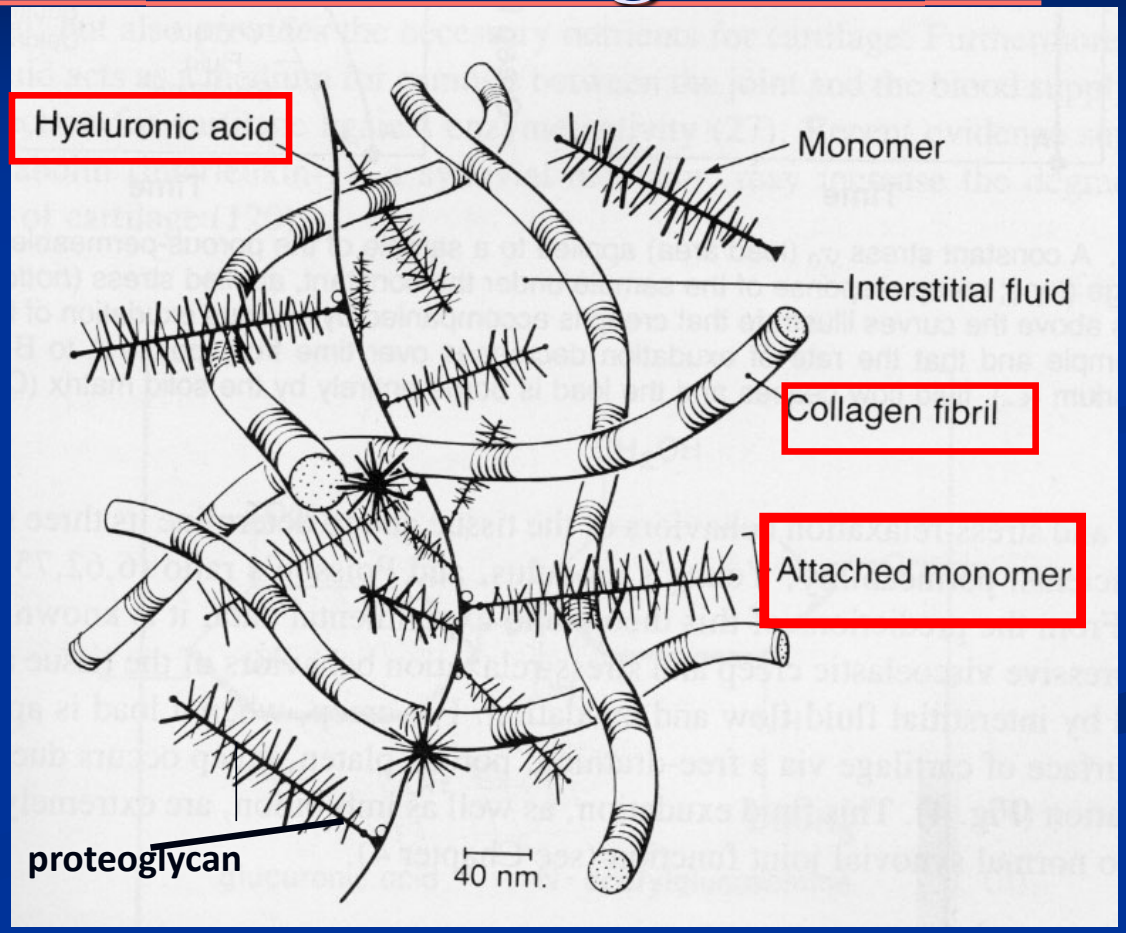
Hyaline Cartilage

- Most bones of the embryonic skeleton
- Articular cartilage (synovial jt)
- Epiphyseal Plate
- Costal Cartilage
- Xiphoid process
- Nasal Cartilages
- Most Laryngeal Cartilages
- Tracheal Ring Cartilages
- Cartilage plates in large
- and medium bronchi

- **Elastic Cartilage**
  - Pinna
  - External Auditory tube
  - Eustachian Tube
  - Epiglottis
  - Laryngeal Cartilages (2)
  - Cartilage plates in small
  - bronchi
- **Fibrocartilage**
  - Symphyses
  - - Intervertebral disks
  - - Pubic symphysis
  - Menisci

Components of Cartilage

- Water
  - 70%
- Collagen Type II, IX, XI
  - 10-20%
  - Tensile strength
  - Shear strength
- Proteoglycans
  - 5-10%
  - Compressive strength
- Chondrocytes
  - Cells ~5%
  - Maintenance of tissue



Collagen Types

TABLE 2. Some Types of Collagen and their Characteristics

Collagen Type	Molecular Structure*	Tissues	Function
Type I	$[\alpha1(I)]_2\ \alpha2(I)$	Bone, tendon, ligament,	Support tensile loads
Type II	$[\alpha1(II)]_3$	Cartilage	Support tensile loads; primary collagenous constituent of articular cartilage
Type VI	$\alpha1(VI)\ \alpha2(VI)\ \alpha3(VI)$	Cartilage	Pericellular adhesion molecule
Type IX	$\alpha1(IX)\ \alpha2(IX)\ \alpha3(IX)$	Cartilage	Fibril association; stabilizes Type II
Type X	$[\alpha1(X)]_3$	Cartilage	Hypertrophic zone of growth plate; role in calcification postulated
Type XI	$\alpha1(XI)\ \alpha2(XI)\ \alpha1(II)$	Cartilage	Core of Type II; controls fibril growth

(Mayne 1993)

Major type of collagen in articular cartilage (~80%)

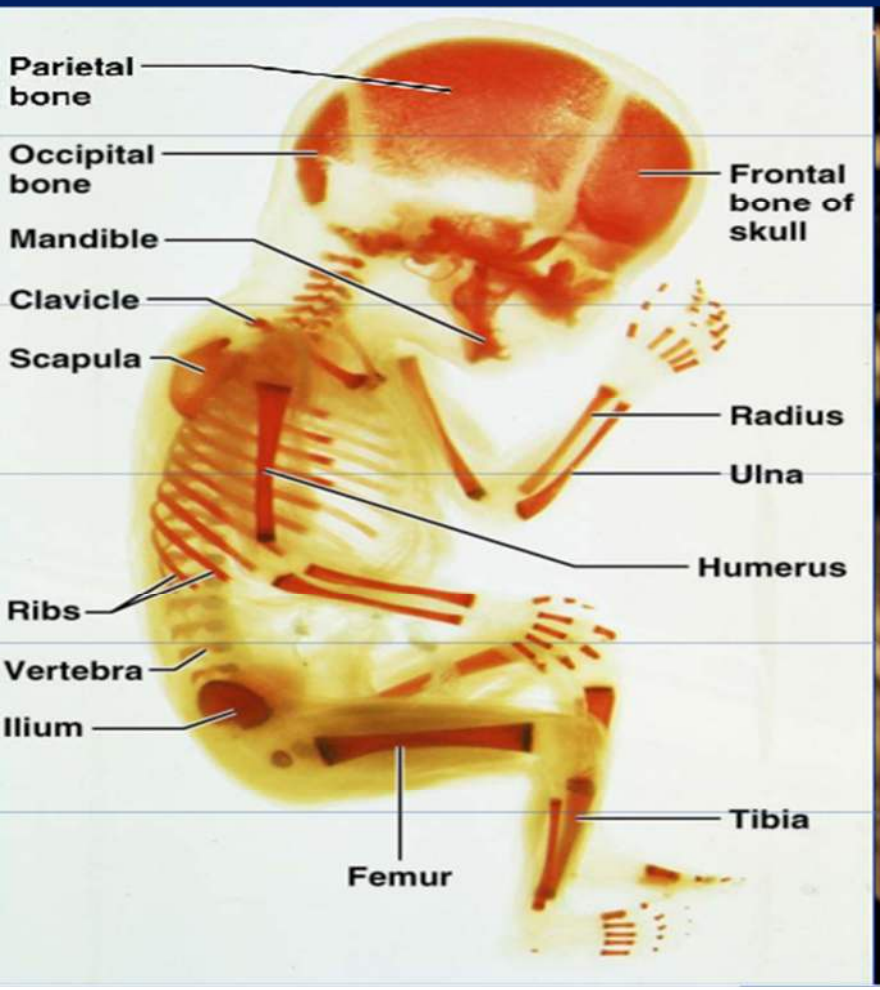
Stabilizes and forms core of the collagen type II fibril

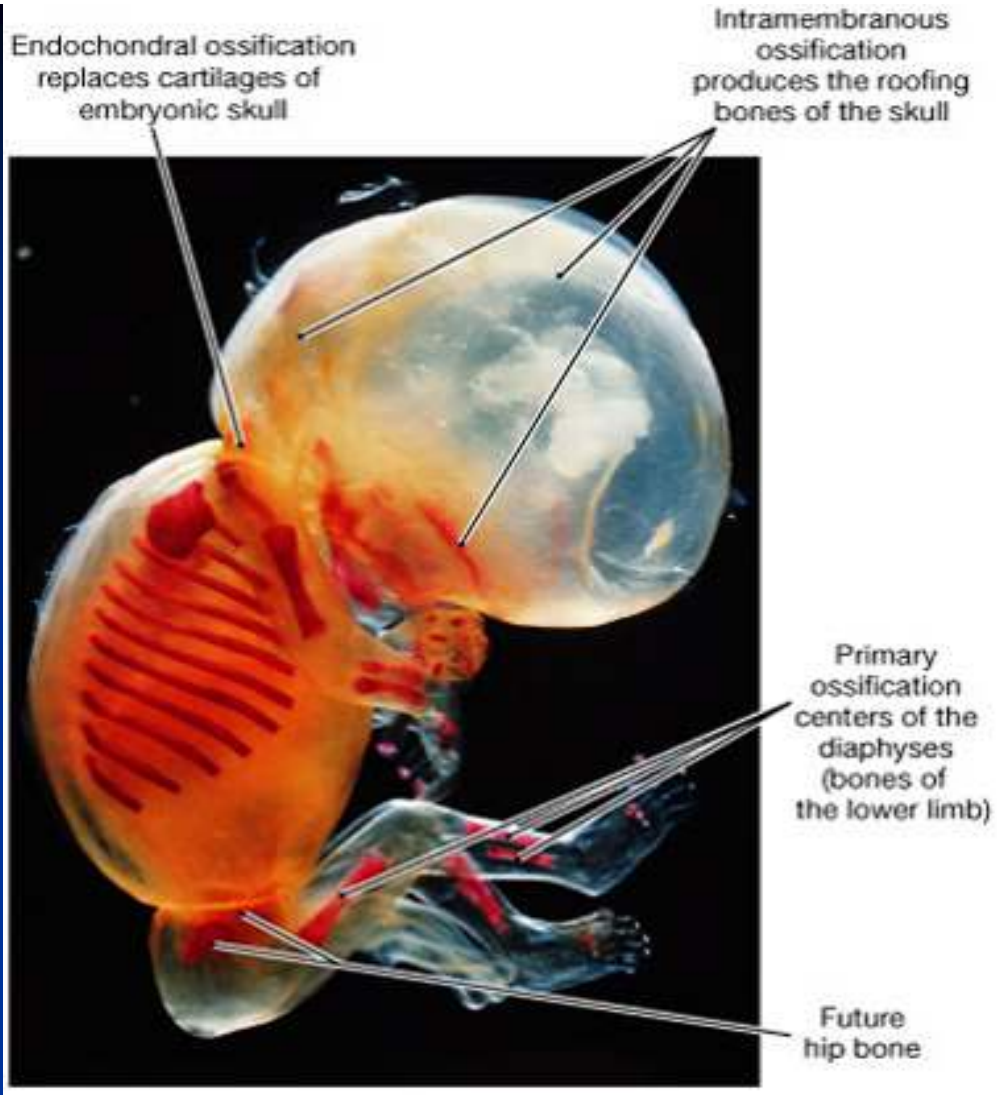
	Water		Proteoglycans
Articular Cartilage	68-85%	10-20% (type I)	5-10%
Meniscus	60-70%	15-25% (type II)	1-2%

Bone Development

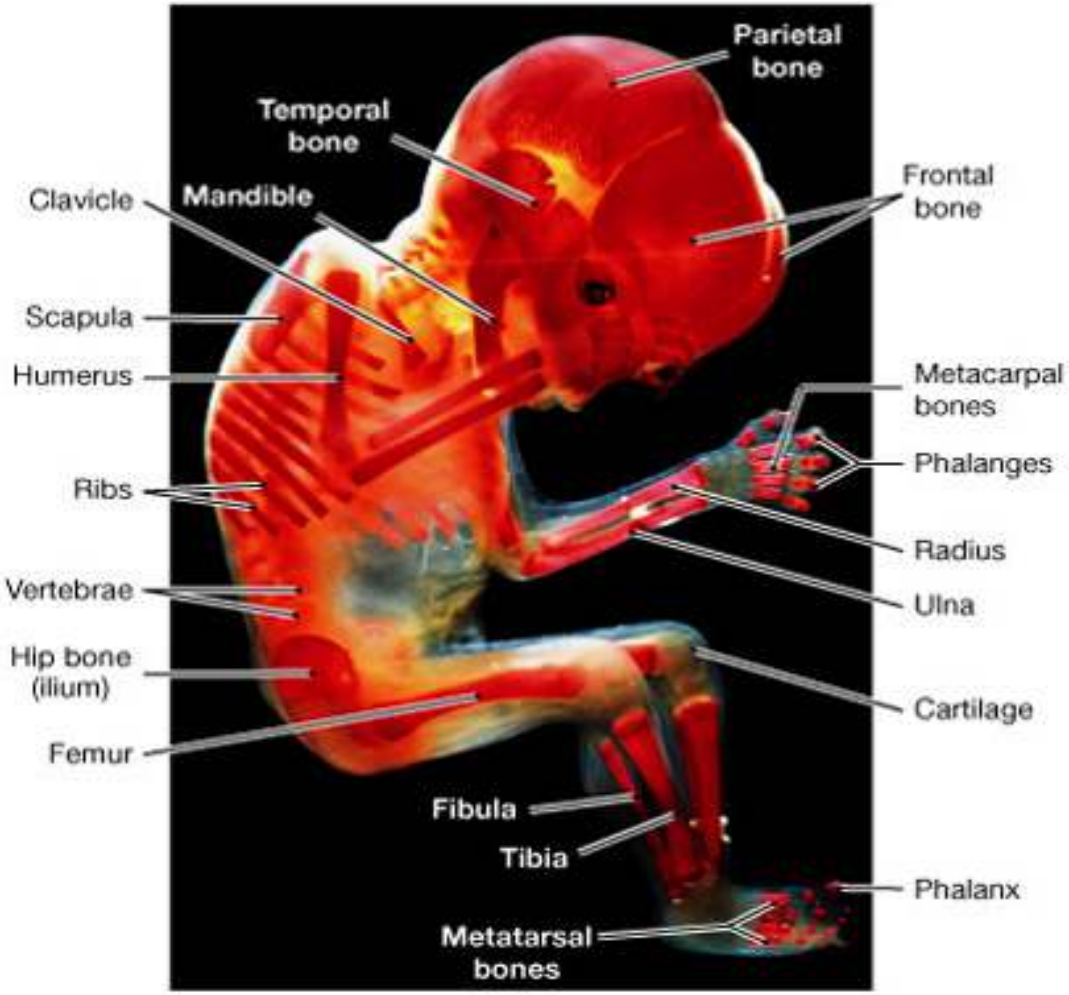
- **Osteogenesis and ossification**
  - the process of bone tissue formation, which leads to:
    - **The formation of the bony skeleton in embryos**
    - **Bone growth until early adulthood**
    - **Bone thickness, remodeling, and repair**
  - **It involves the**
    - **differentiation of osteoprogenitor cells into osteoblasts,**
    - **which secrete the extracellular matrix of bone, and then the mineralization of that matrix to form bone.**
  - **There are two primary mechanisms of bone formation: intramembranous ossification and endochondral ossification.**

Fetal Primary Ossification Centers



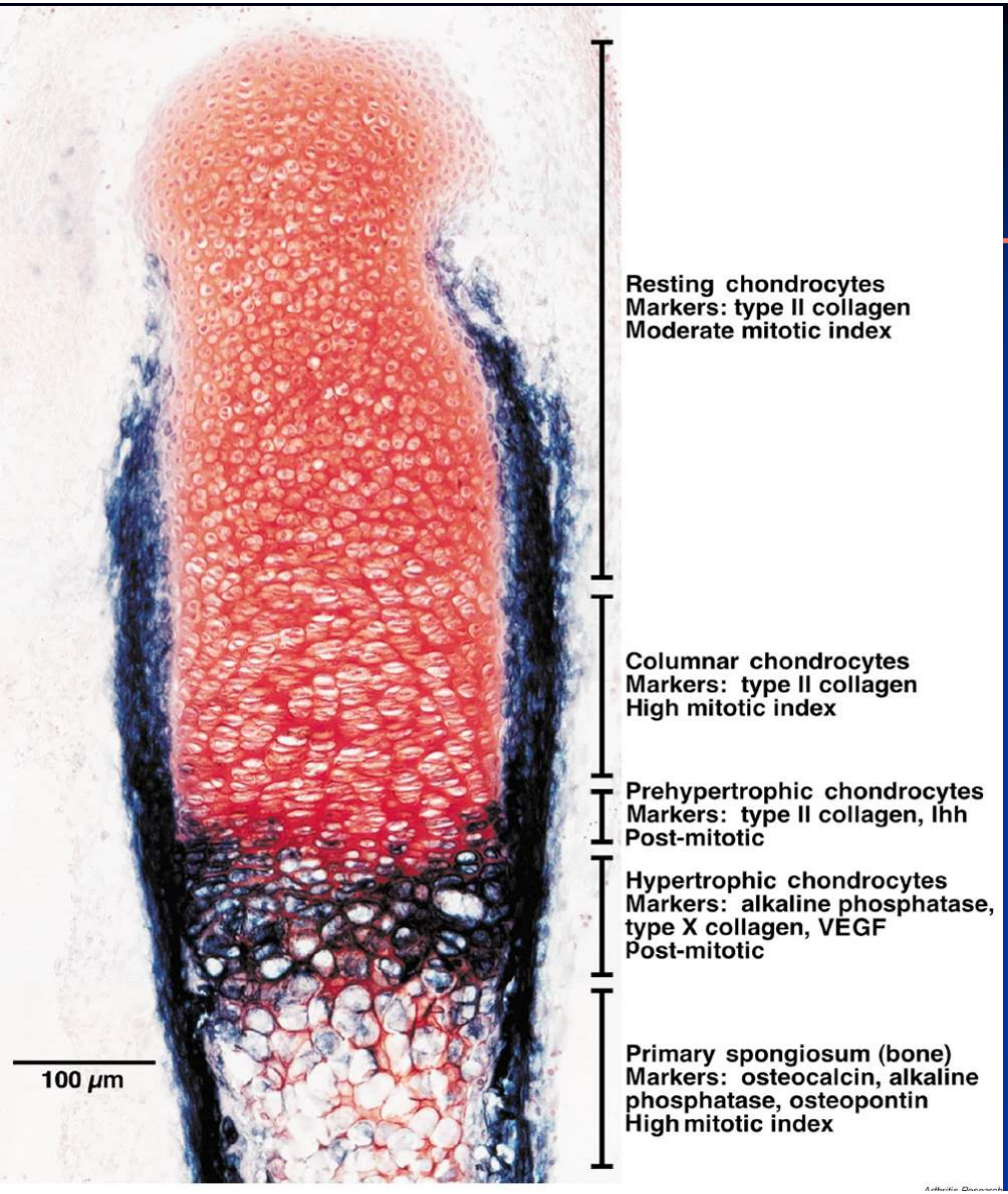

Endochondral ossification replaces cartilages of embryonic skull
Intramembranous ossification produces the roofing bones of the skull
Primary ossification centers of the diaphyses (bones of the lower limb)
Future hip bone

(a)


Parietal bone
Temporal bone
Frontal bone
Clavicle
Mandible
Scapula
Humerus
Metacarpal bones
Phalanges
Ribs
Radius
Ulna
Vertebrae
Hip bone (ilium)
Cartilage
Femur
Fibula
Tibia
Phalanx
Metatarsal bones

(b)


SPINE



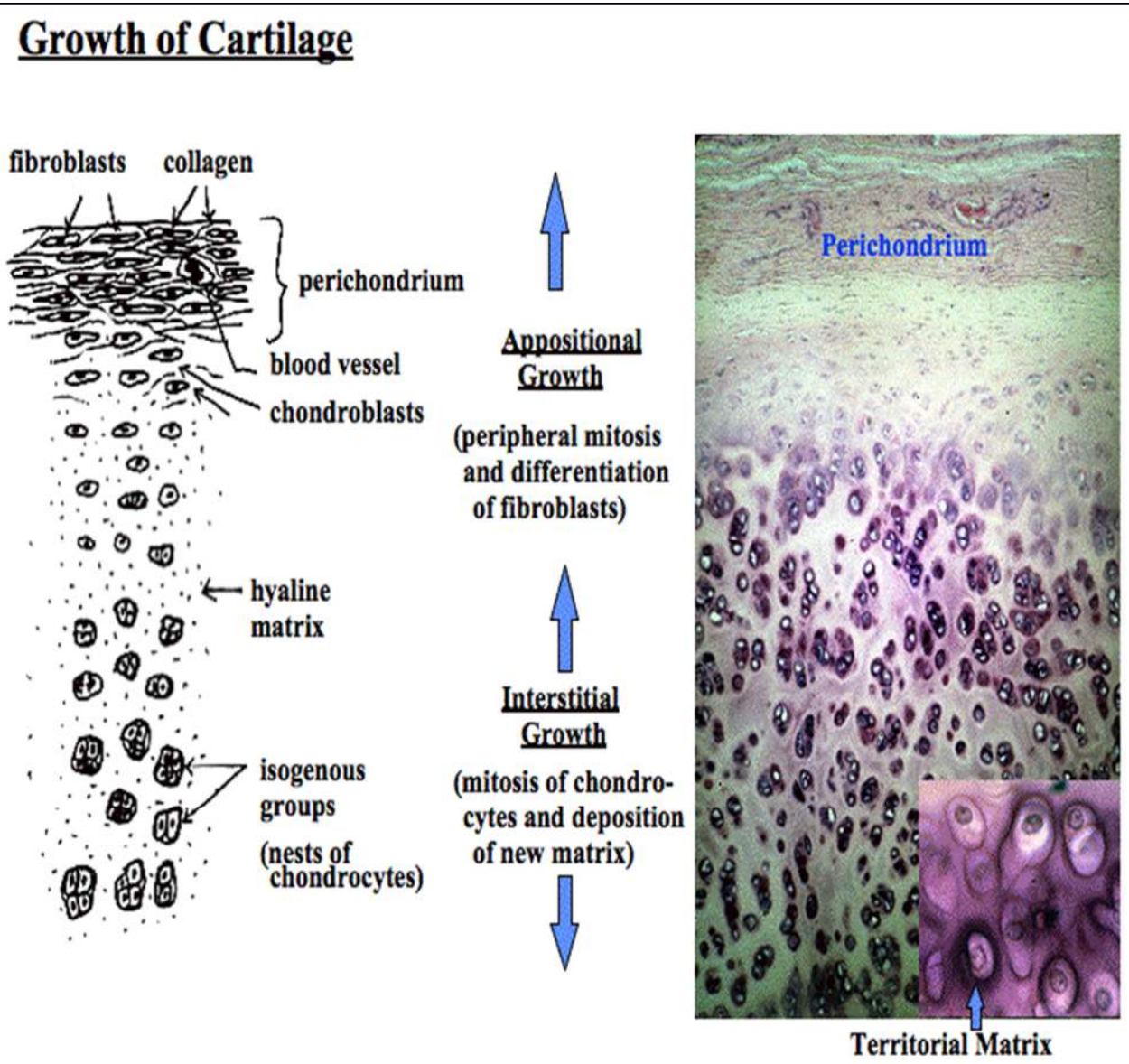
A section through the growth plate of a fetal mouse metatarsal, 17 days post fertilization. Blue staining indicates endogenous alkaline phosphatase activity in the hypertrophic chondrocytes, diaphyseal perichondrium and bone collar, and primary spongiosa.

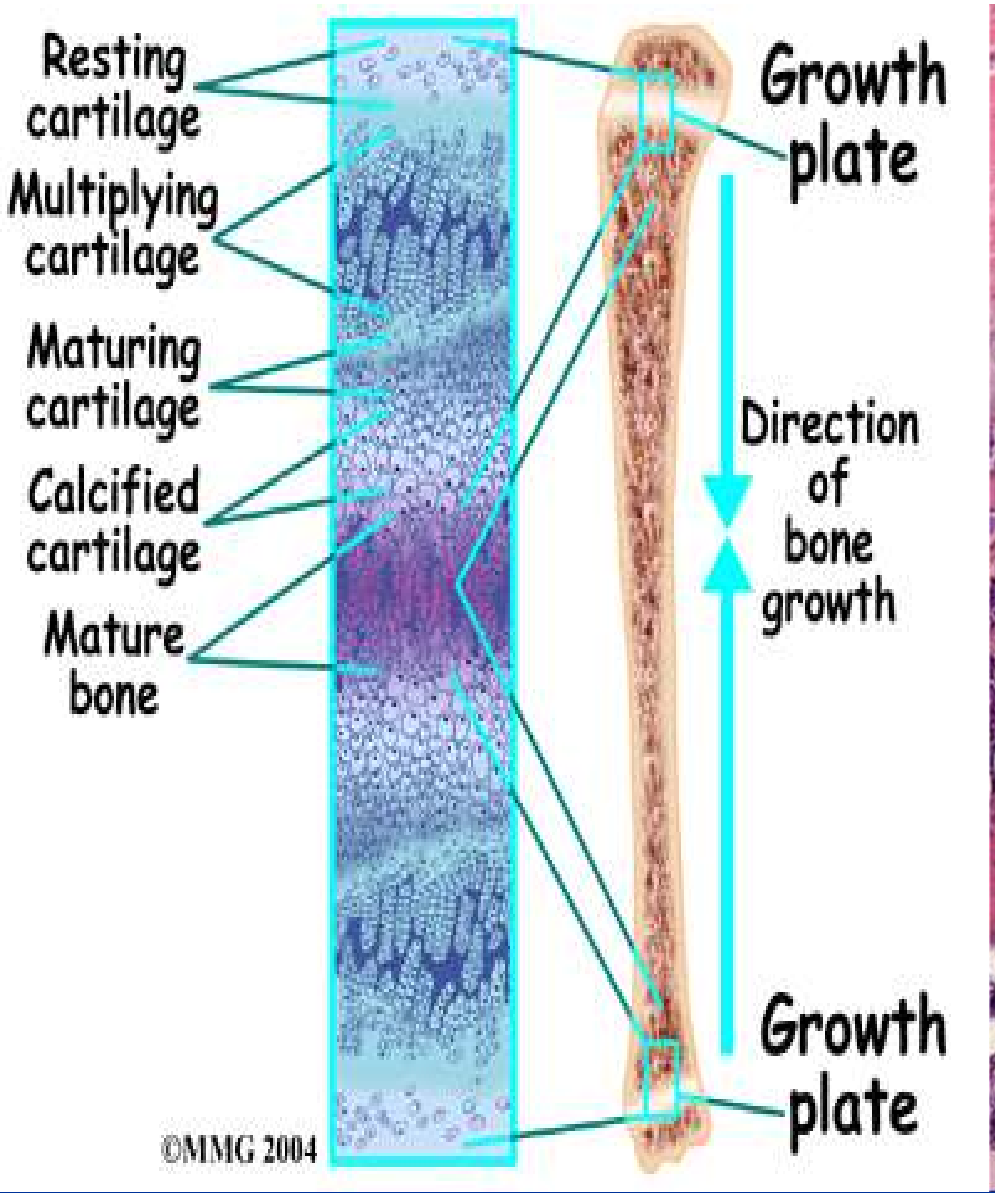
Safranin O staining of chondromucin in the cartilage matrix is red.

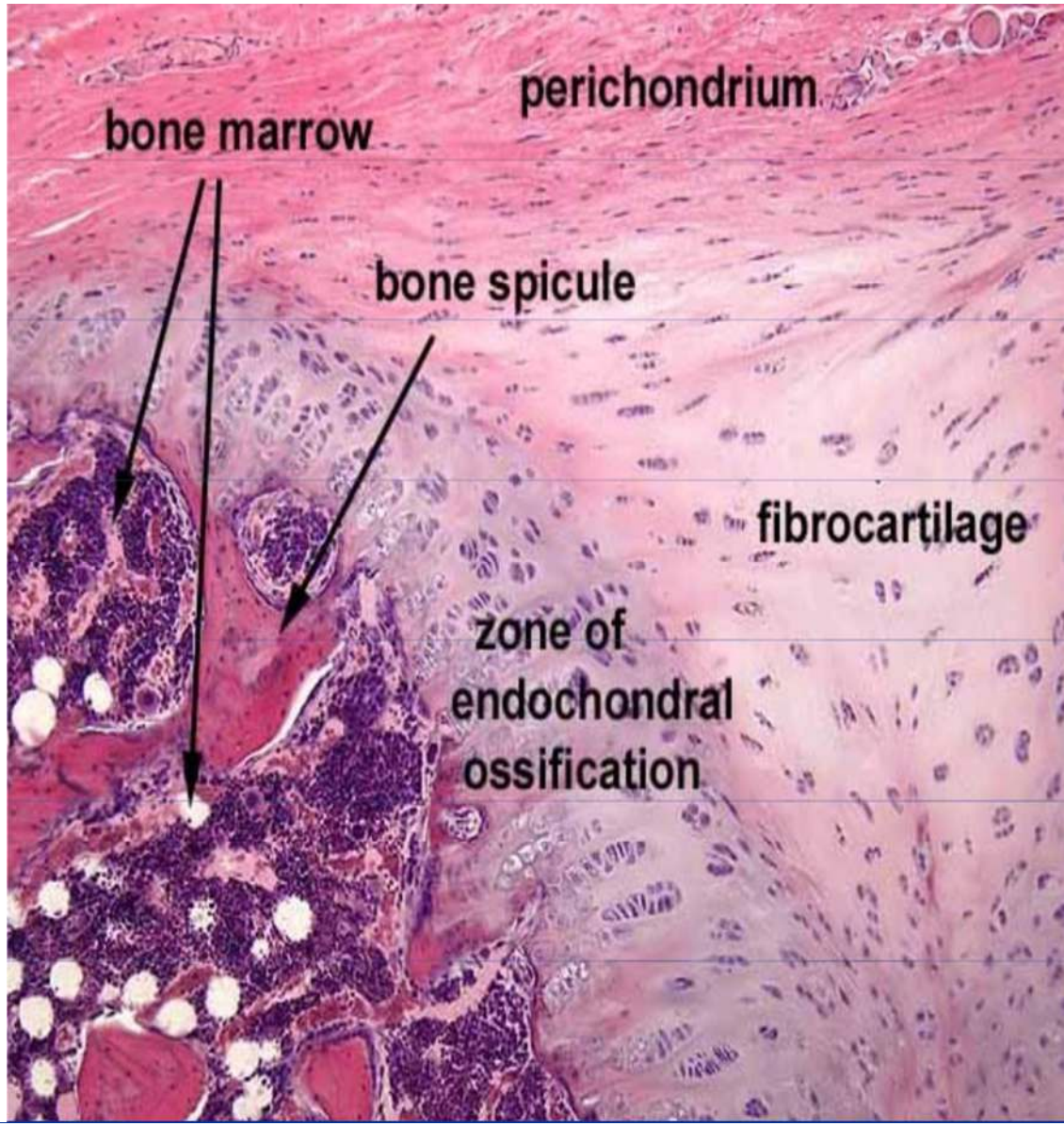
The regions populated by each stage of the chondrocyte lineage are shown.

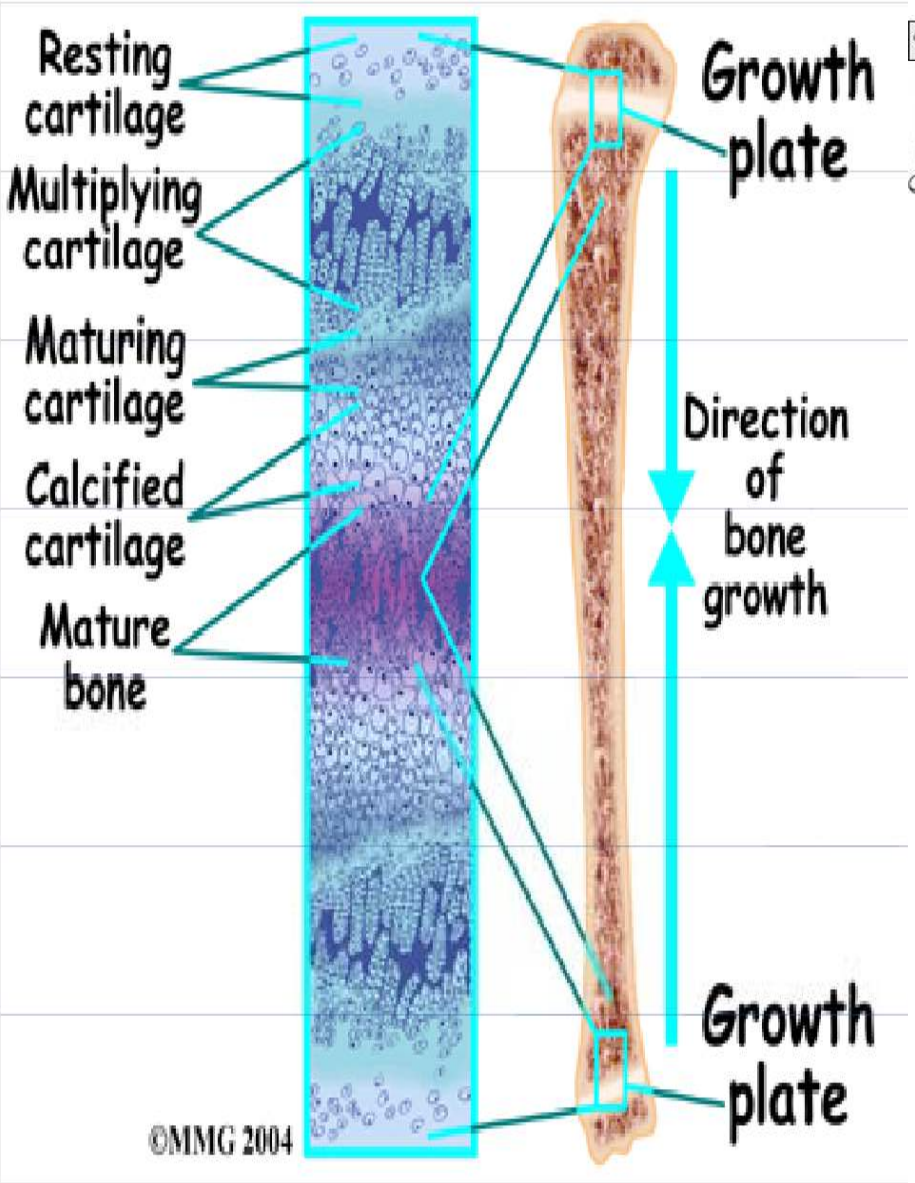
Growth of Cartilage

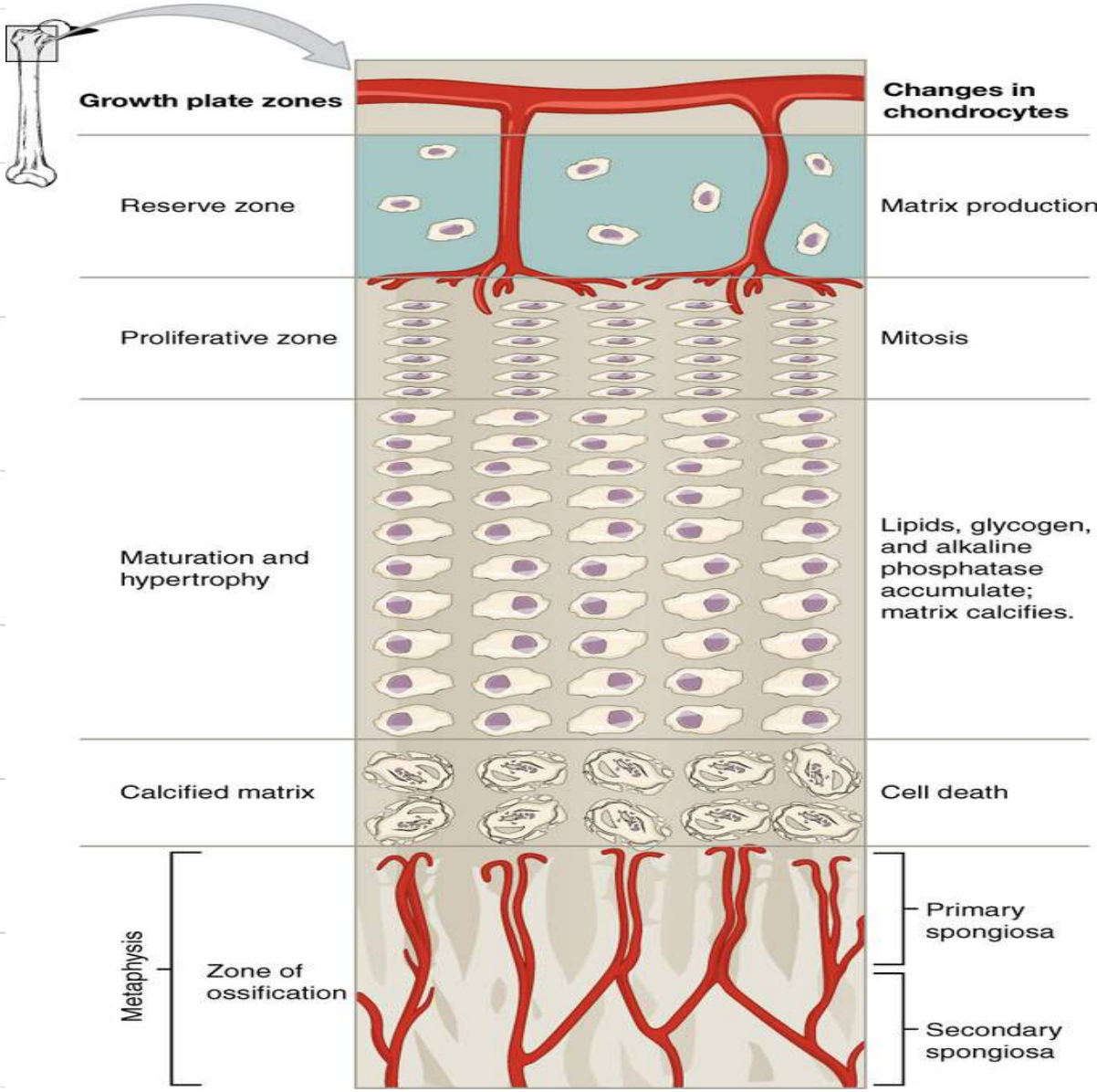
- **Appositional** – cells in the perichondrium secrete matrix against the external face of existing cartilage
- **Interstitial** – lacunae-bound chondrocytes inside the cartilage divide and secrete new matrix, expanding the cartilage from within
- Calcification of cartilage occurs
  - During normal bone growth
  - During old age

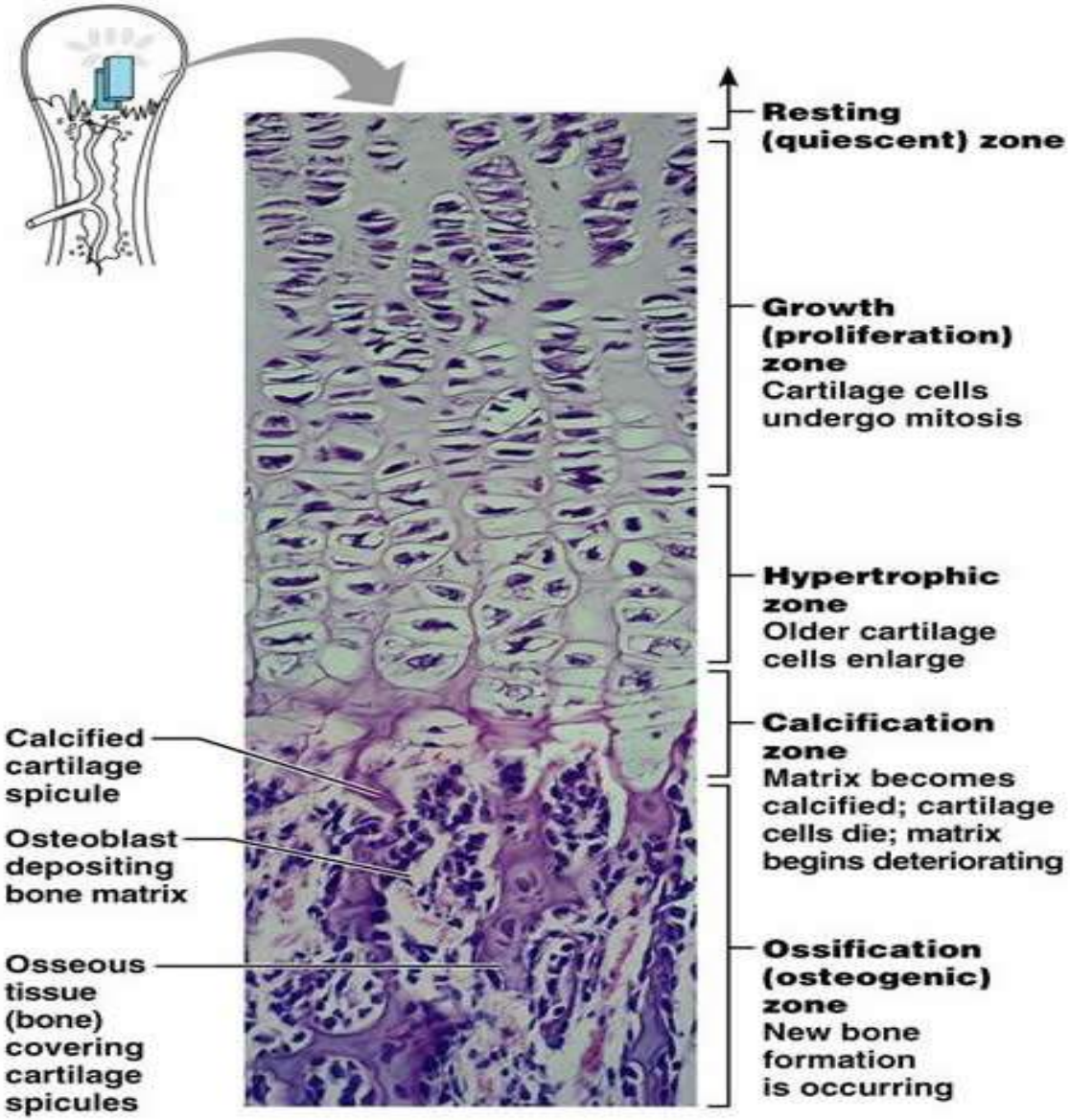



Resting cartilage
Multiplying cartilage
Maturing cartilage
Calcified cartilage
Mature bone
Growth plate
Direction of bone growth
Growth plate
©MMG 2004

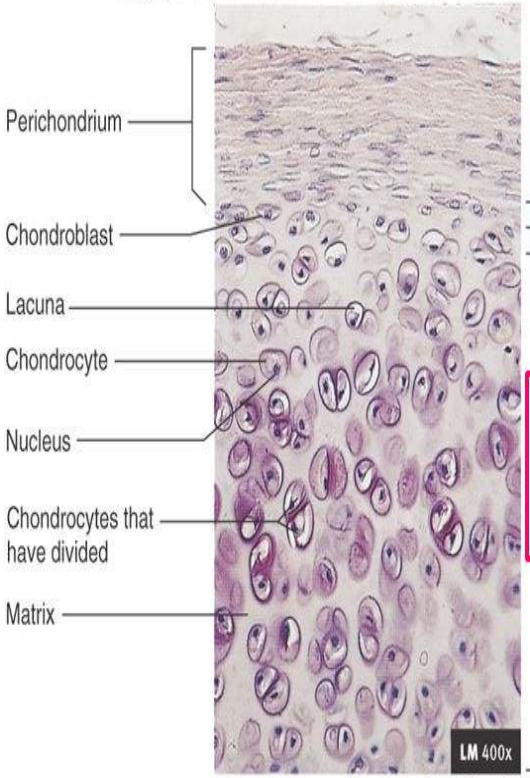

perichondrium
bone marrow
bone spicule
fibrocartilage
zone of endochondral ossification


Resting cartilage
Multiplying cartilage
Maturing cartilage
Calcified cartilage
Mature bone
Growth plate
Direction of bone growth
Growth plate
©MMG 2004


Growth plate zones
Changes in chondrocytes
Reserve zone
Matrix production
Proliferative zone
Mitosis
Maturation and hypertrophy
Lipids, glycogen, and alkaline phosphatase accumulate; matrix calcifies.
Calcified matrix
Cell death
Metaphysis
Zone of ossification
Primary spongiosa
Secondary spongiosa



Cartilage grows by appositional and interstitial growth



Appositional growth
(new cartilage is added to the surface of the cartilage by chondroblasts from the inner layer of the perichondrium)

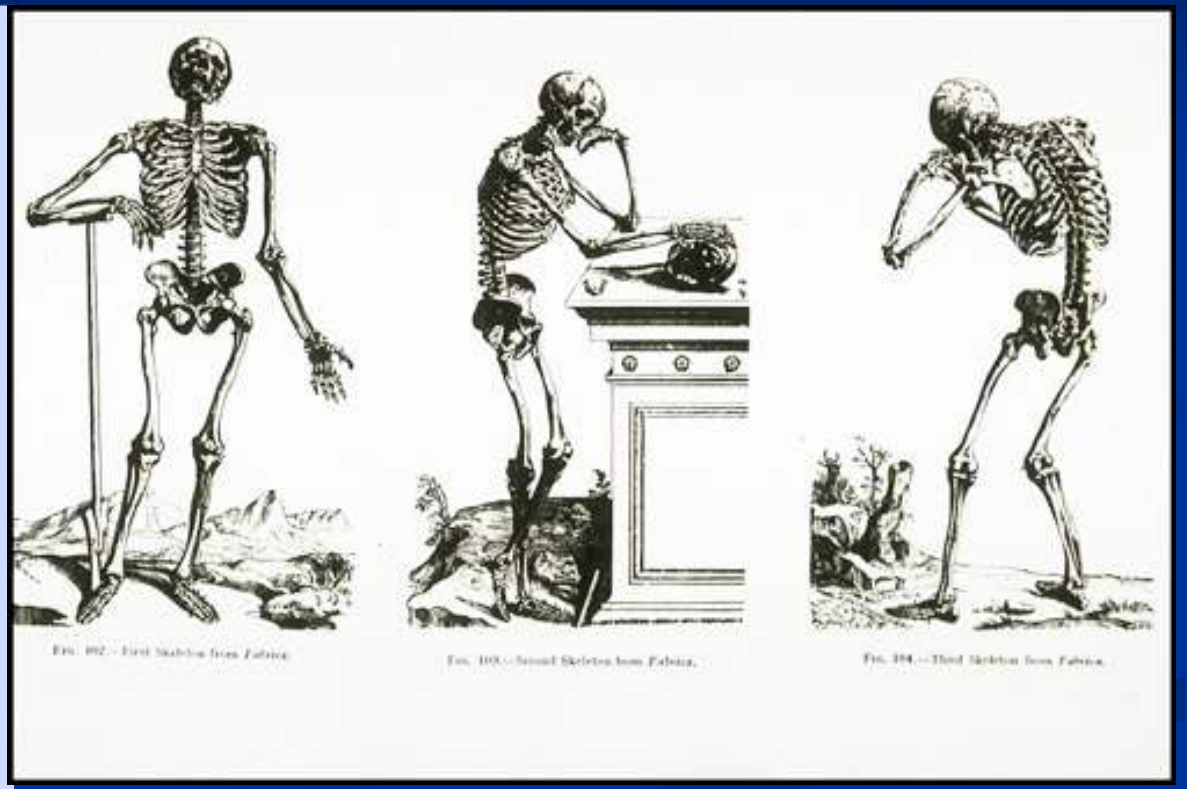
Interstitial growth
(new cartilage is formed within the cartilage by chondrocytes that divide and produce additional matrix)

© Ed Reschke

Fig. 6.1

Bone Development

- **Osteogenesis** (a.k.a. ossification) is the process of bone tissue formation.
- **In embryos this leads to the formation of the bony skeleton.**
- **In children and young adults, ossification occurs as part of bone growth.**
- **In adults, it occurs as part of bone remodeling and bone repair.**

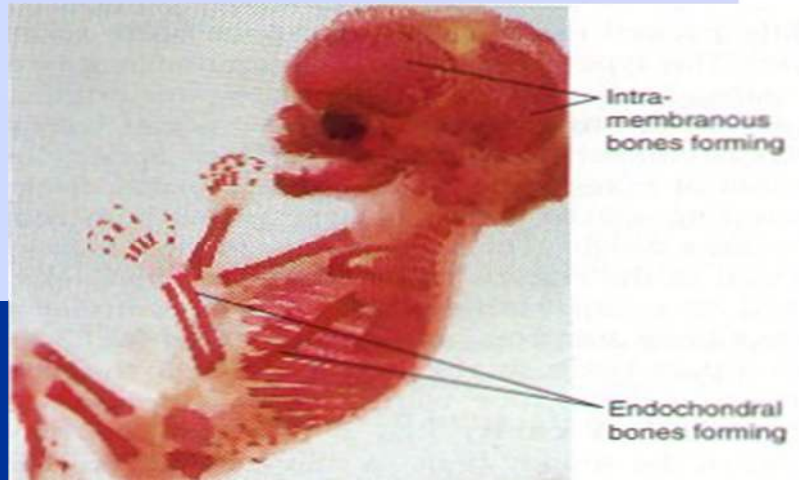


Formation of the Bony Skeleton

- Begins at week 8 of embryo development
- Intramembranous ossification – bone develops from a fibrous membrane
  - Formation of most of the flat bones of the skull and the clavicles
  - Fibrous connective tissue membranes are formed by mesenchymal cells
- Endochondral ossification – bone forms by replacing hyaline cartilage
- By age 25, nearly all bones are completely ossified
- In old age, bone resorption predominates
- A single gene that codes for vitamin D docking determines both the tendency to accumulate bone mass early in life, and the risk for osteoporosis later in life

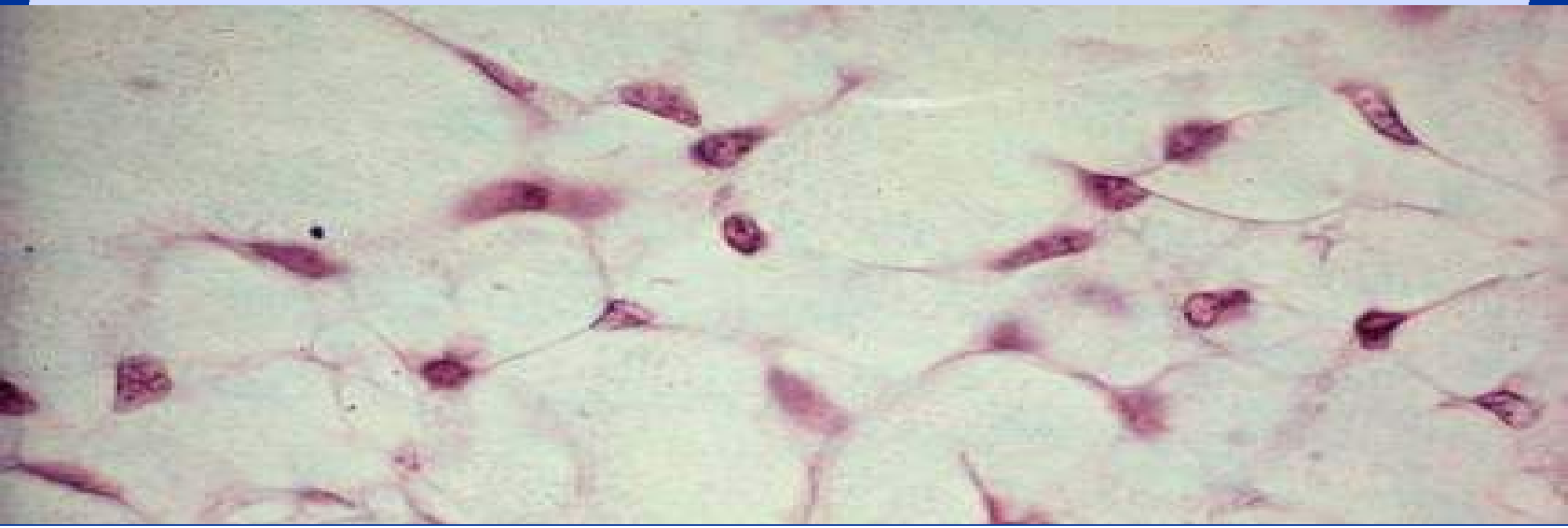
Developmental Aspects of Bones

- **Mesoderm** gives rise to embryonic **mesenchymal cells,** which produce membranes and cartilages that form the embryonic skeleton
- The embryonic skeleton ossifies in a predictable timetable that allows fetal age to be easily determined from sonograms
- **At birth, most long bones are well ossified (except for their epiphyses)**



Intramembranous Ossification

- Some bones of the skull (frontal, parietal, temporal, and occipital bones), the facial bones, the clavicles, the pelvis, the scapulae, and part of the mandible are formed by intramembranous ossification
- Prior to ossification, these structures exist as fibrous membranes made of embryonic connective tissue known as **mesenchyme**.



Intramembranous Ossification

•**Definition**: Direct formation of bone within mesenchymal tissue.
•**Process**:

- **Mesenchymal Cell Differentiation**: Mesenchymal cells cluster together and differentiate into osteoprogenitor cells, which then become osteoblasts.
- **Osteoid Formation**: Osteoblasts secrete osteoid, an unmineralized bone matrix composed of collagen and other proteins.
- **Mineralization**: The osteoid becomes calcified, trapping osteoblasts within it, which then differentiate into osteocytes.
- **Bone Trabeculae Formation**: The bone matrix forms trabeculae (spongy bone) around blood vessels, creating woven bone.
- **Periosteum Development**: Mesenchyme at the surface forms the periosteum, which gives rise to compact bone as the woven bone is replaced by lamellar bone.

•**Locations**: This type of ossification primarily occurs in flat bones such as the skull, mandible, and clavicles.

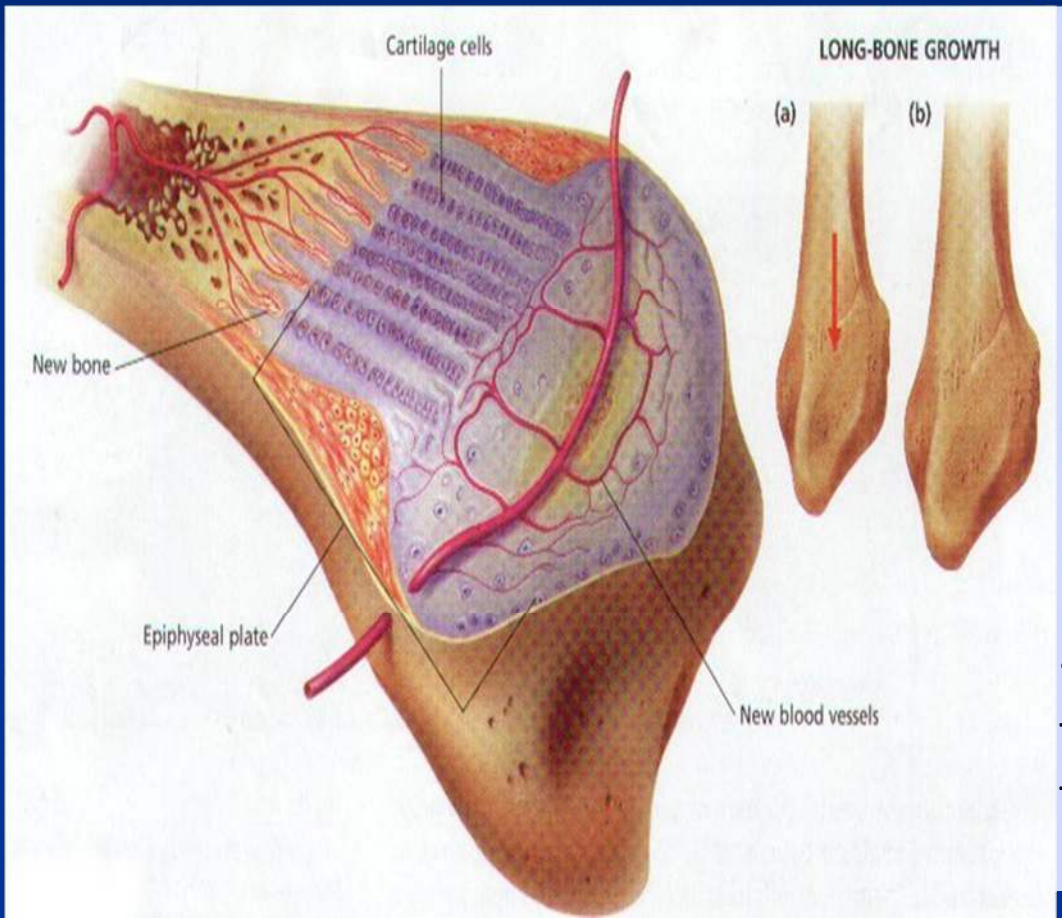
Intramembranous Ossification

- Formation of most of the flat bones of the skull and the clavicles
- Fibrous connective tissue membranes are formed by mesenchymal cells

Stages of Intramembranous Ossification

- An ossification center appears in the fibrous connective tissue membrane
- Bone matrix is secreted within the fibrous membrane
- Woven bone and periosteum form
- Bone collar of compact bone forms, and red marrow appears

Endochondral Ossification



- **Begins in the second month of development**
- Uses hyaline cartilage "bones" as models for bone construction
- Requires breakdown of hyaline cartilage prior to ossification

•**Locations**: This process is typical for the formation of long bones such as the femur, tibia, and humerus.

Endochondral Ossification

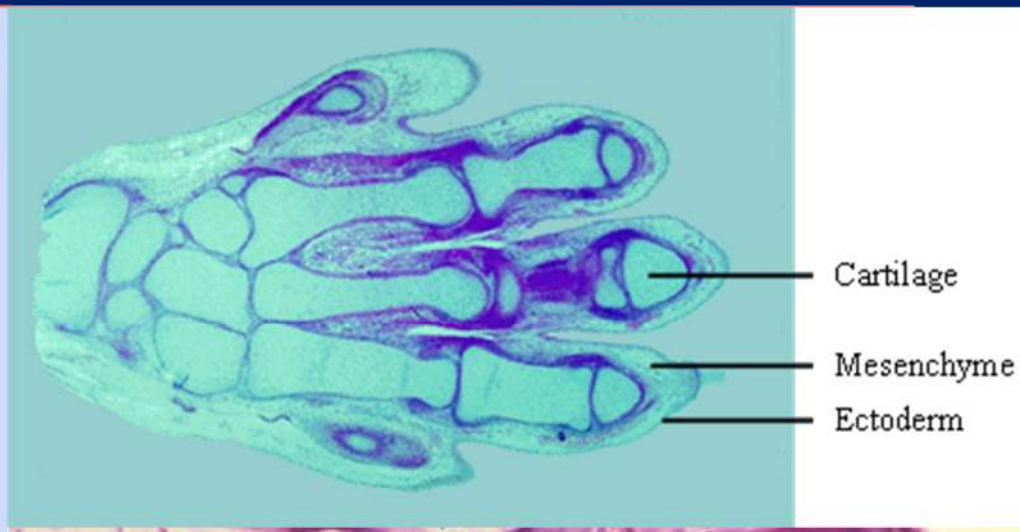
•**Definition**: Bone formation that involves the replacement of hyaline cartilage with bone.

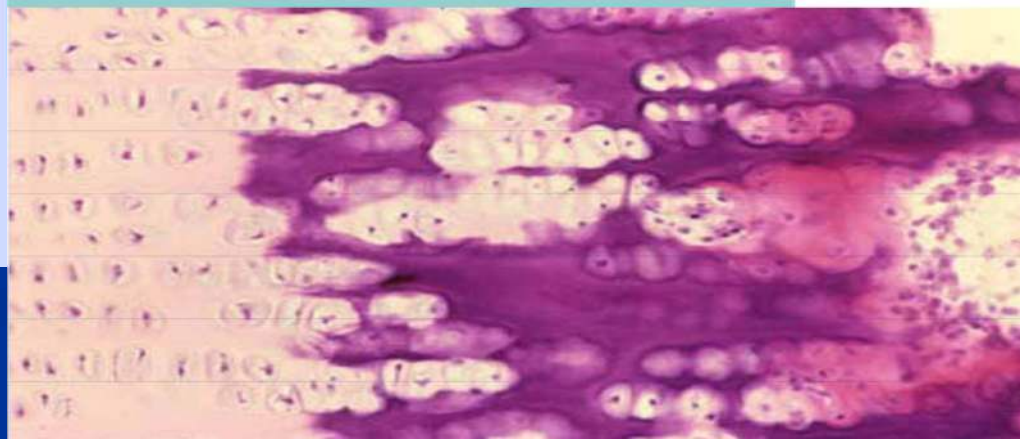
•**Process**:

- **Cartilage Model Development**: Mesenchymal cells differentiate into chondrocytes, forming a hyaline cartilage model of the future bone.
- **Growth of Cartilage Model**: The cartilage model grows in length and width through appositional and interstitial growth.
- **Primary Ossification Center**: Blood vessels invade the perichondrium, converting it to a periosteum. Osteoblasts form a bone collar around the diaphysis. Chondrocytes in the center hypertrophy and calcify, leading to their death.
- **Medullary Cavity Formation**: Osteoclasts break down the newly formed trabeculae, creating a medullary cavity. Secondary ossification centers develop in the epiphyses.
- **Secondary Ossification Centers**: Similar to the primary center, except it occurs in the epiphyses without the formation of a medullary cavity.
- **Epiphyseal Plate**: Hyaline cartilage remains only at the epiphyseal plates (growth plates) and articular surfaces. The plate allows for continued longitudinal growth until it ossifies at adulthood.

Endochondral Ossification

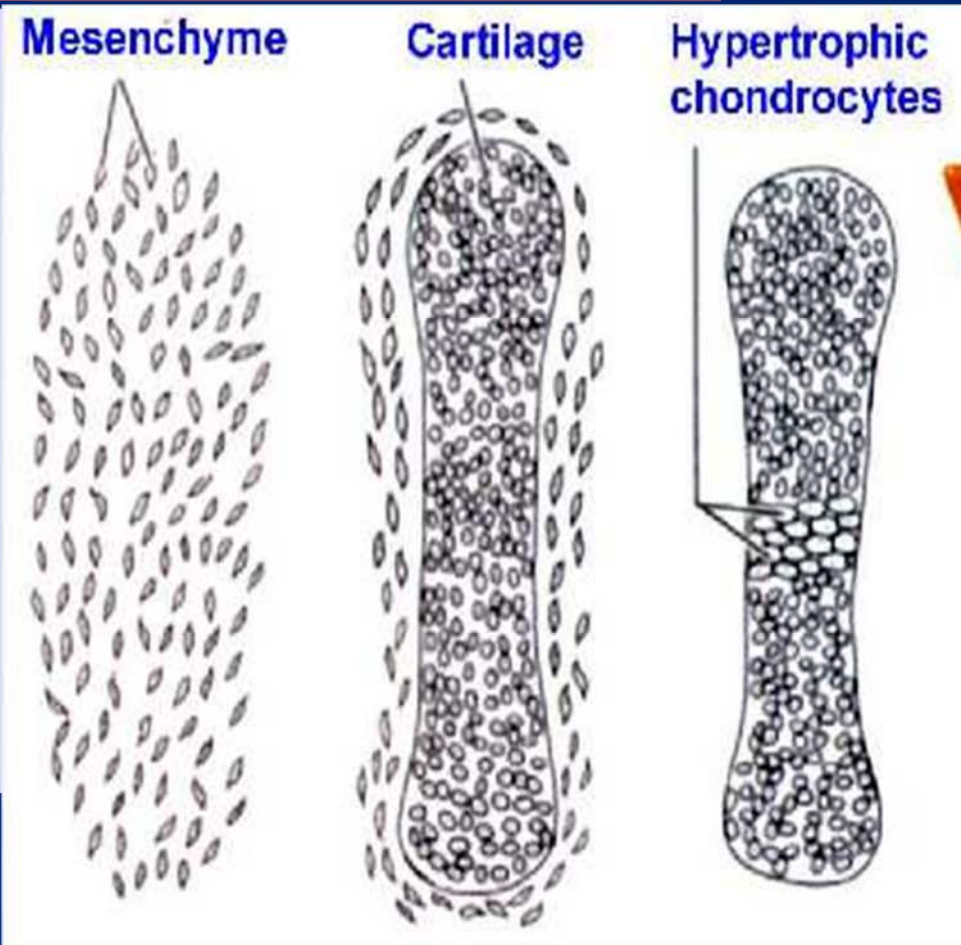
- Begins with the formation of a hyaline cartilage model which will later be replaced by bone.
- Most bones in the body develop via this model.
- More complicated than intramembranous because the hyaline cartilage must be broken down as ossification proceeds.
- We'll follow limb bone development as an example.



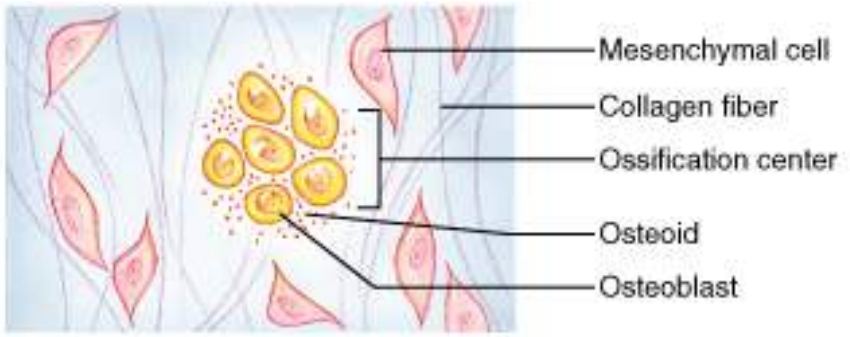


Stages of Endochondral Ossification

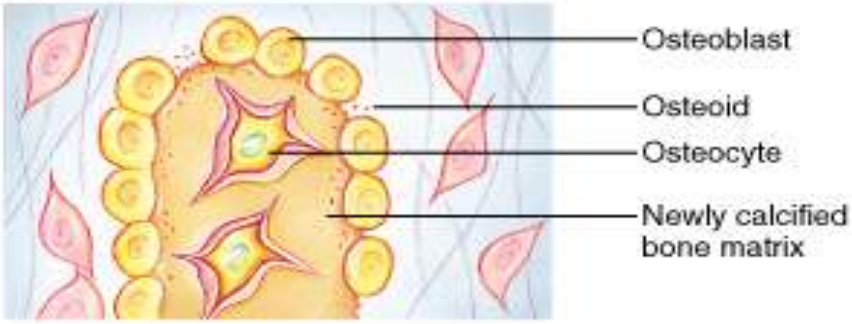
- Formation of bone collar
- Cavitation of the hyaline cartilage
- Invasion of internal cavities by the periosteal bud, and spongy bone formation
- Formation of the medullary cavity; appearance of secondary ossification centers in the epiphyses
- Ossification of the epiphyses, with hyaline cartilage remaining only in the epiphyseal plates



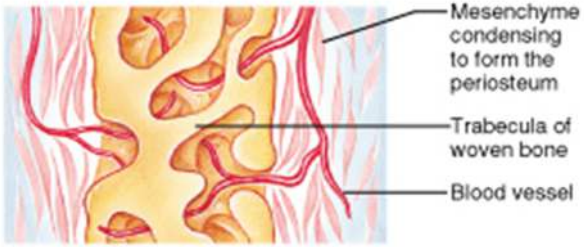
- Mesenchymal cells first cluster together and start to secrete the organic components of bone matrix which then becomes mineralized through the crystallization of calcium salts. As calcification occurs, the mesenchymal cells differentiate into osteoblasts.
- The location in the tissue where ossification begins is known as an ossification center.
- Some osteoblasts are trapped w/i bony pockets. These cells differentiate into osteocytes.



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



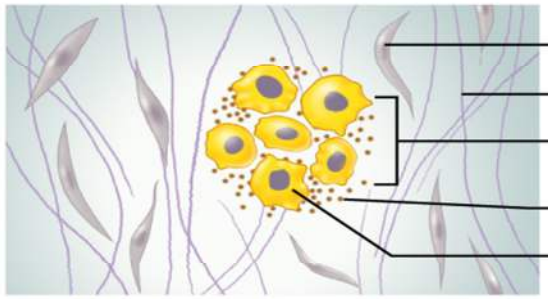
② Bone matrix (osteoid) is secreted within the fibrous membrane.



③ Woven bone and periosteum form.

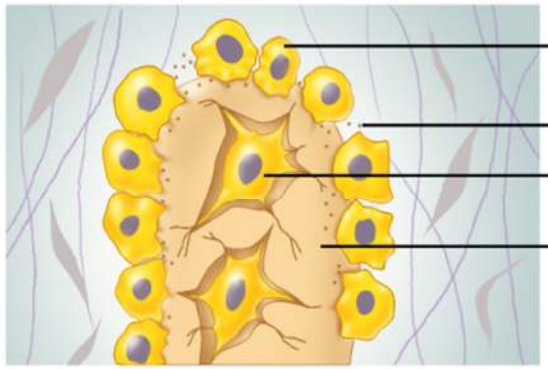
- The developing bone grows outward from the ossification center in small struts called spicules.
- Mesenchymal cell divisions provide additional osteoblasts.
- The osteoblasts require a reliable source of oxygen and nutrients. Blood vessels trapped among the spicules meet these demands and additional vessels branch into the area.
- These vessels will eventually become entrapped within the growing bone.

Stages of Intramembranous Ossification



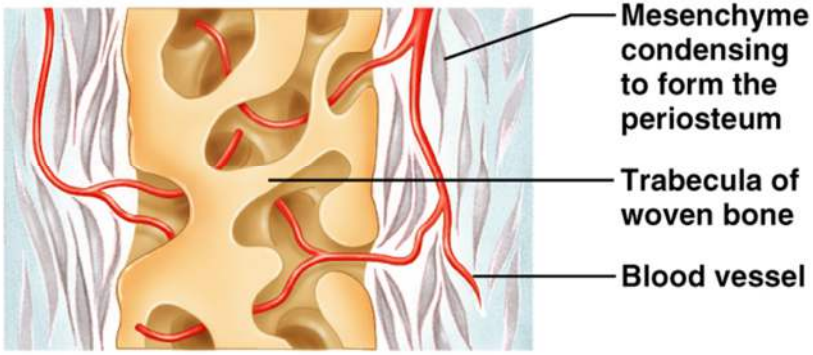
① An ossification center appears in the fibrous connective tissue membrane.

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



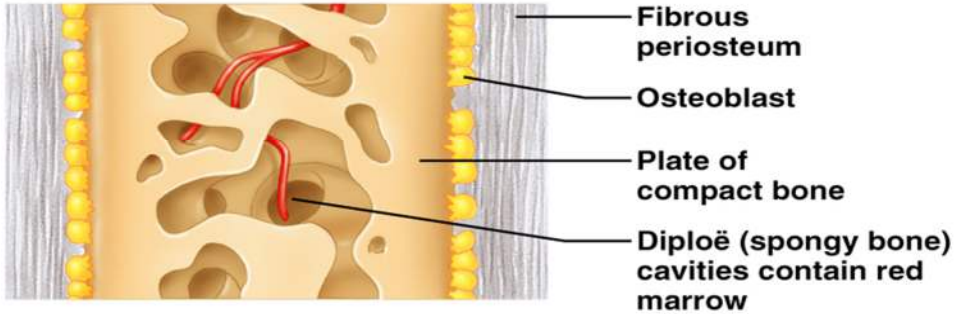
② Bone matrix (osteoid) is secreted within the fibrous membrane.

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



③ Woven bone and periosteum form.

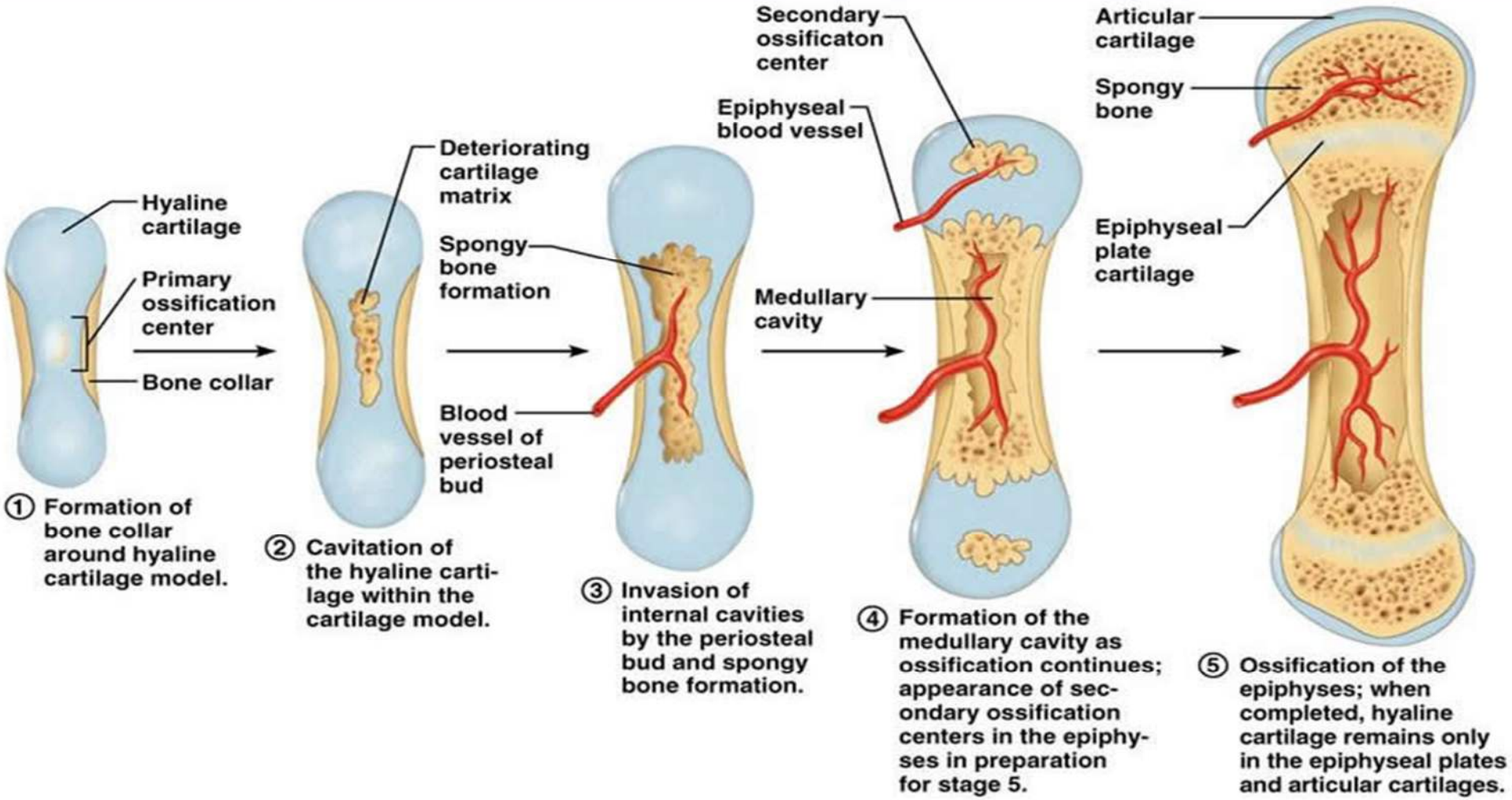
- Accumulating osteoid is laid down between embryonic blood vessels, which form a random network. The result is a network (instead of lamellae) of trabeculae.
- Vascularized mesenchyme condenses on the external face of the woven bone and becomes the periosteum.

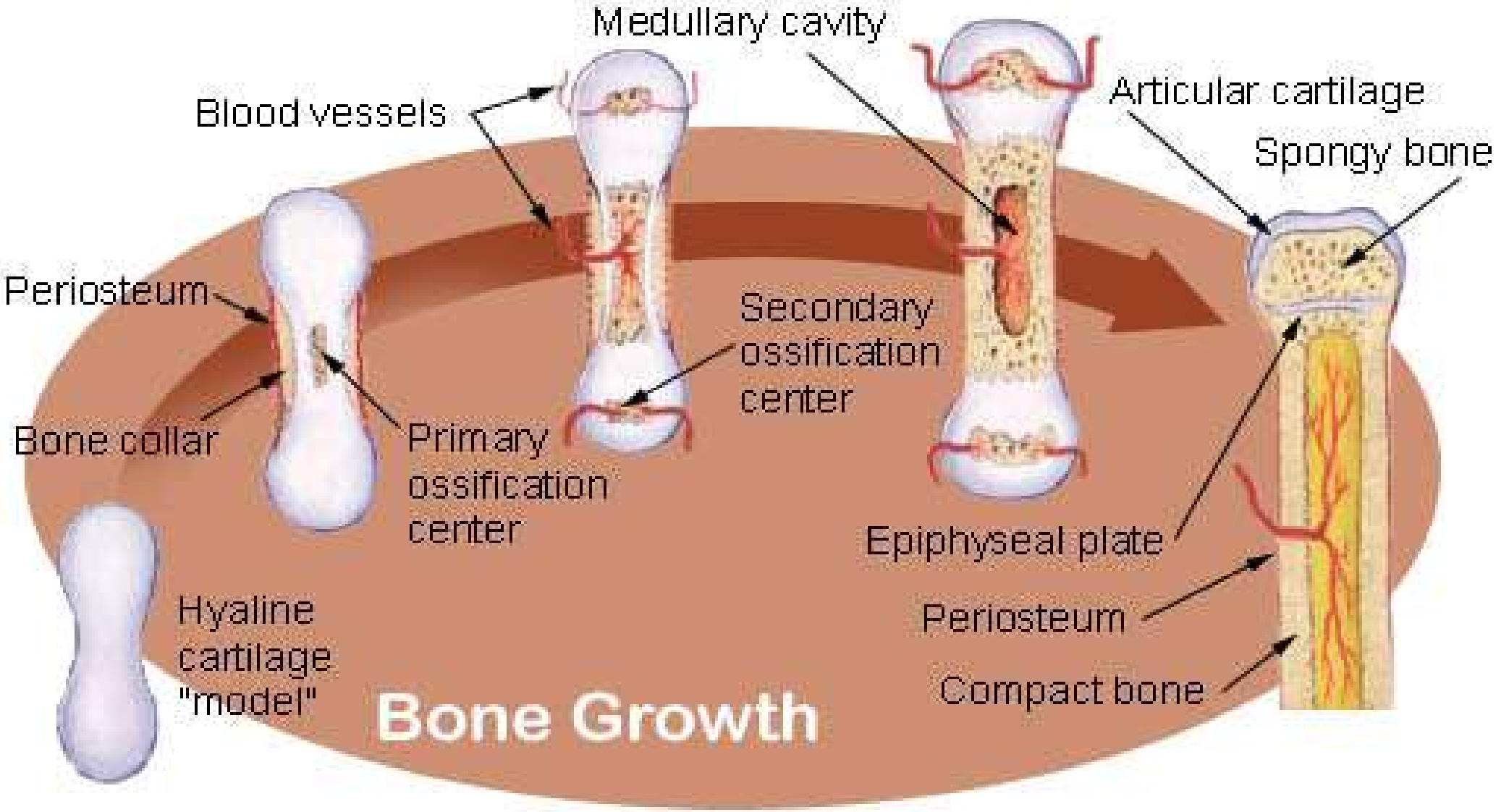


④ Bone collar of compact bone forms and red marrow appears.

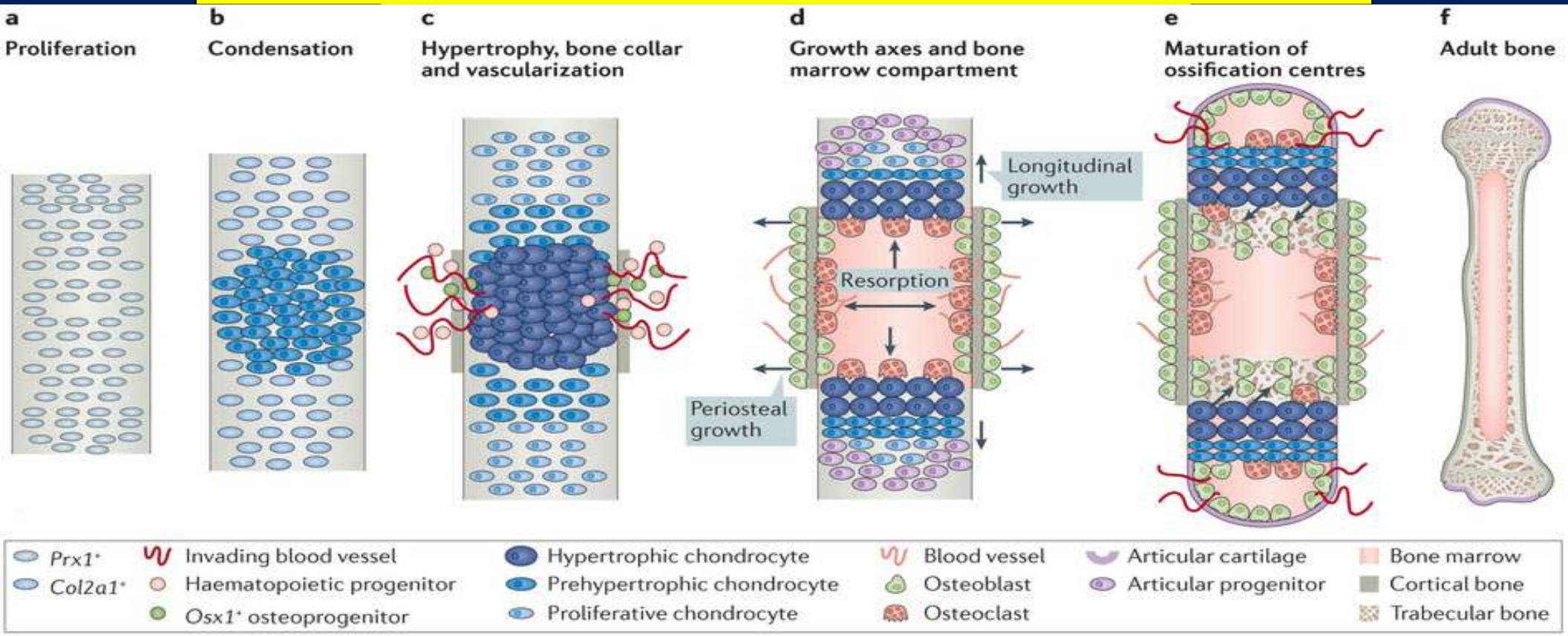
- Trabeculae just deep to the periosteum thicken, forming a woven bone collar that is later replaced with mature lamellar bone.
- Spongy bone (diploë), consisting of distinct trabeculae, persists internally and its vascular tissue becomes red marrow.

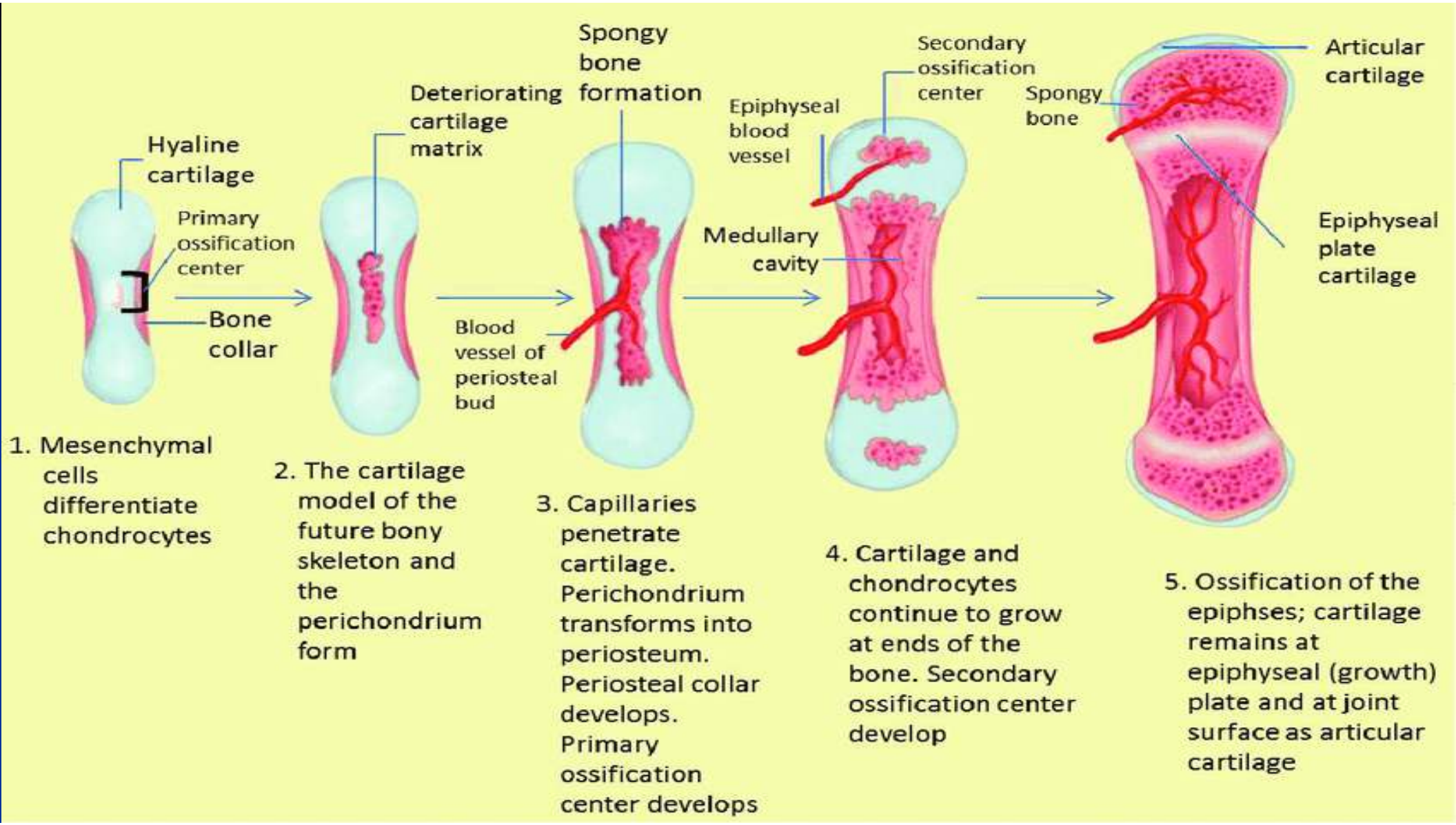
Stages of Endochondral Ossification




Medullary cavity
Blood vessels
Articular cartilage
Spongy bone
Periosteum
Secondary ossification center
Bone collar
Primary ossification center
Epiphyseal plate
Hyaline cartilage "model"
Periosteum
Compact bone
Bone Growth

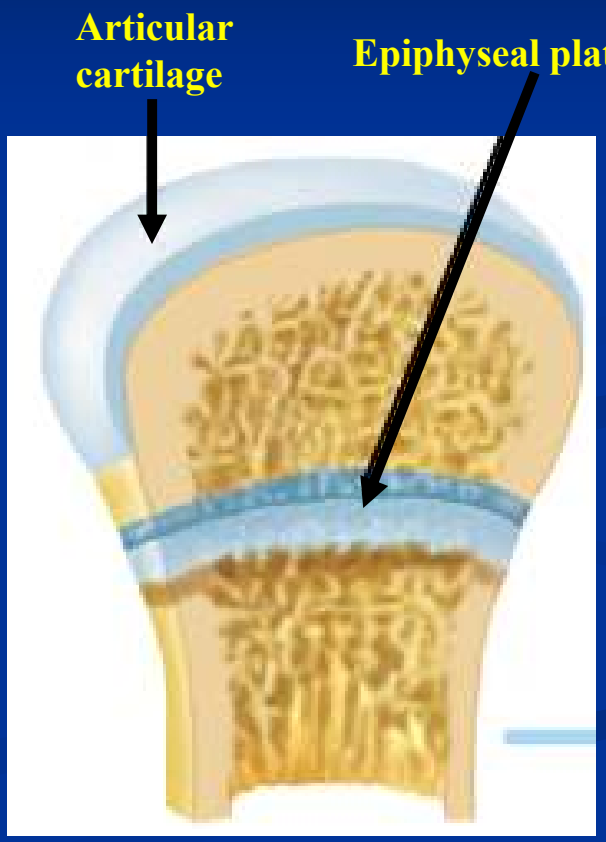
Endochondral Ossification

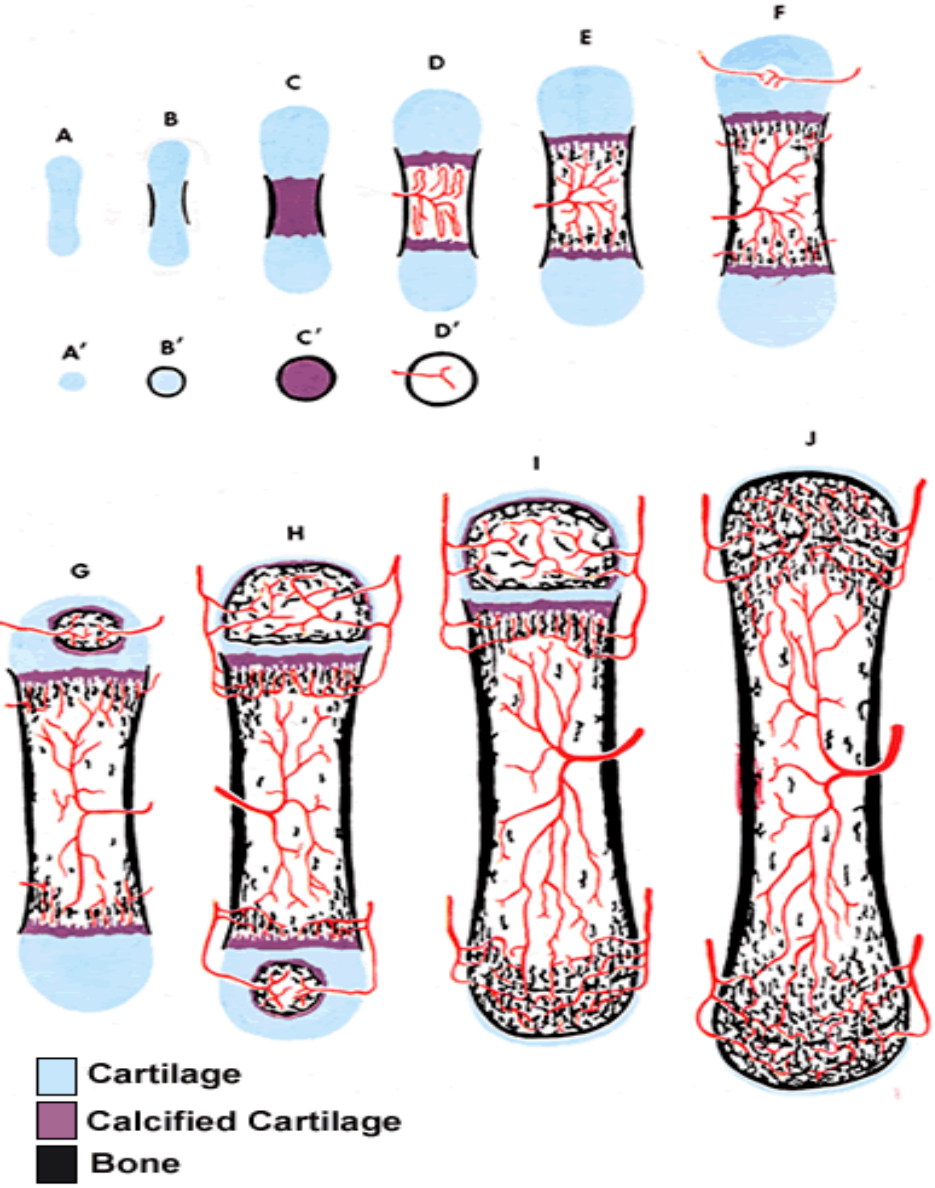



Hyaline cartilage
Primary ossification center
Bone collar
Deteriorating cartilage matrix
Spongy bone formation
Blood vessel of periosteal bud
Epiphyseal blood vessel
Secondary ossification center
Medullary cavity
Spongy bone
Articular cartilage
Epiphyseal plate cartilage
1. Mesenchymal cells differentiate chondrocytes
2. The cartilage model of the future bony skeleton and the perichondrium form
3. Capillaries penetrate cartilage. Perichondrium transforms into periosteum. Periosteal collar develops. Primary ossification center develops
4. Cartilage and chondrocytes continue to grow at ends of the bone. Secondary ossification center develop
5. Ossification of the epiphses; cartilage remains at epiphyseal (growth) plate and at joint surface as articular cartilage

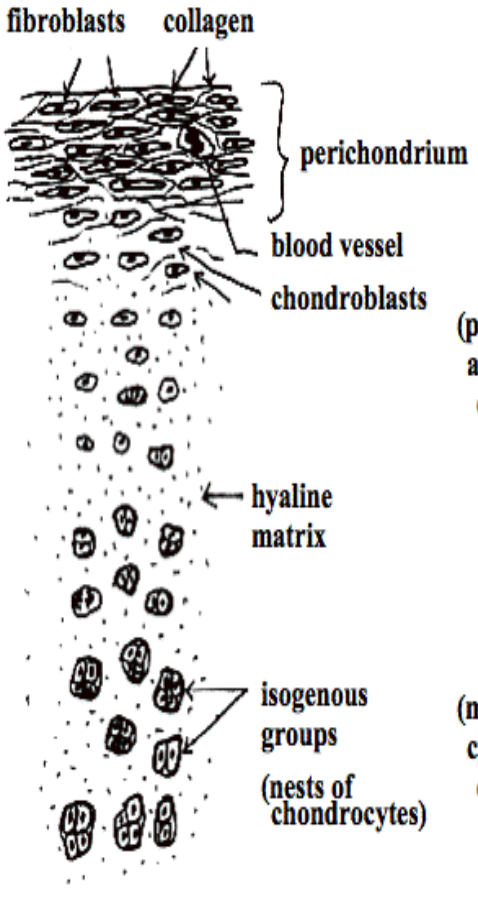
Endochondral Ossification – Step 5

- **Around birth, most long bones have a bony diaphysis surrounding remnants of spongy bone**, a widening medullary cavity, and 2 cartilaginous epiphyses.
- At this time, capillaries and osteoblasts will migrate into the epiphyses and create secondary ossification centers.
- The epiphysis will be transformed into spongy bone.
- However, a small cartilaginous plate, known as the epiphyseal plate, will remain at the juncture between the epiphysis and the diaphysis.





Growth of Cartilage

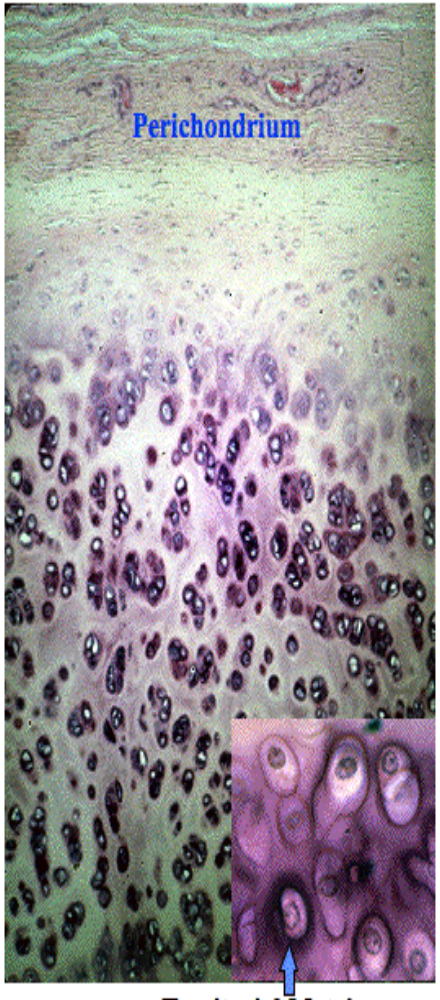


Appositional Growth

(peripheral mitosis and differentiation of fibroblasts)

Interstitial Growth

(mitosis of chondrocytes and deposition of new matrix)



Steps in Endochondral Ossification:

Cartilage Model Formation: Initially, a cartilage model of the bone forms.

Primary Ossification Center: Blood vessels invade the cartilage model, leading to the formation of the primary ossification center in the diaphysis (shaft) of the bone.

Osteoblasts and Osteoclasts: Osteoblasts (bone-forming cells) deposit bone matrix, while osteoclasts (bone-resorbing cells) remove cartilage.

Secondary Ossification Centers: These form in the epiphyses (ends) of long bones.

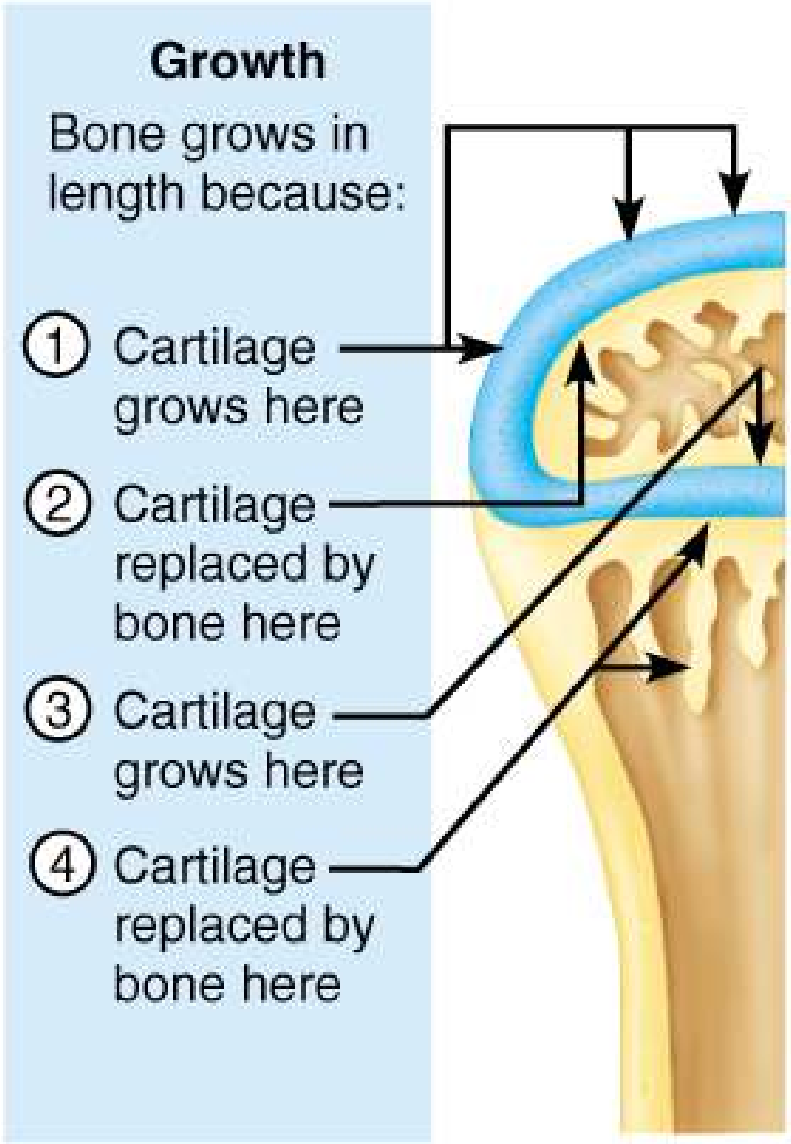
Epiphyseal Plates (Growth Plates): These are cartilage regions between the diaphysis and epiphyses. They allow for longitudinal bone growth.

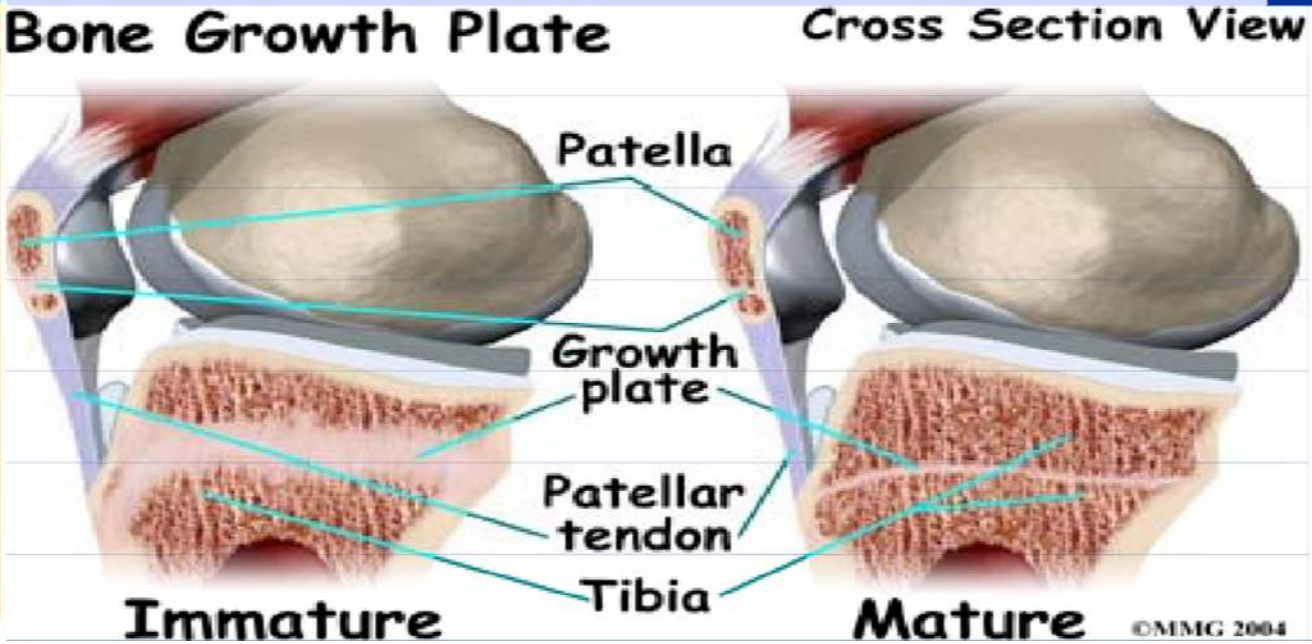
Bone Remodeling: Throughout life, bone is continuously remodeled by osteoblasts and osteoclasts.

https://study.com/academy/lesson/steps-of-intramembranous-ossification.html

Growth in Bone Length

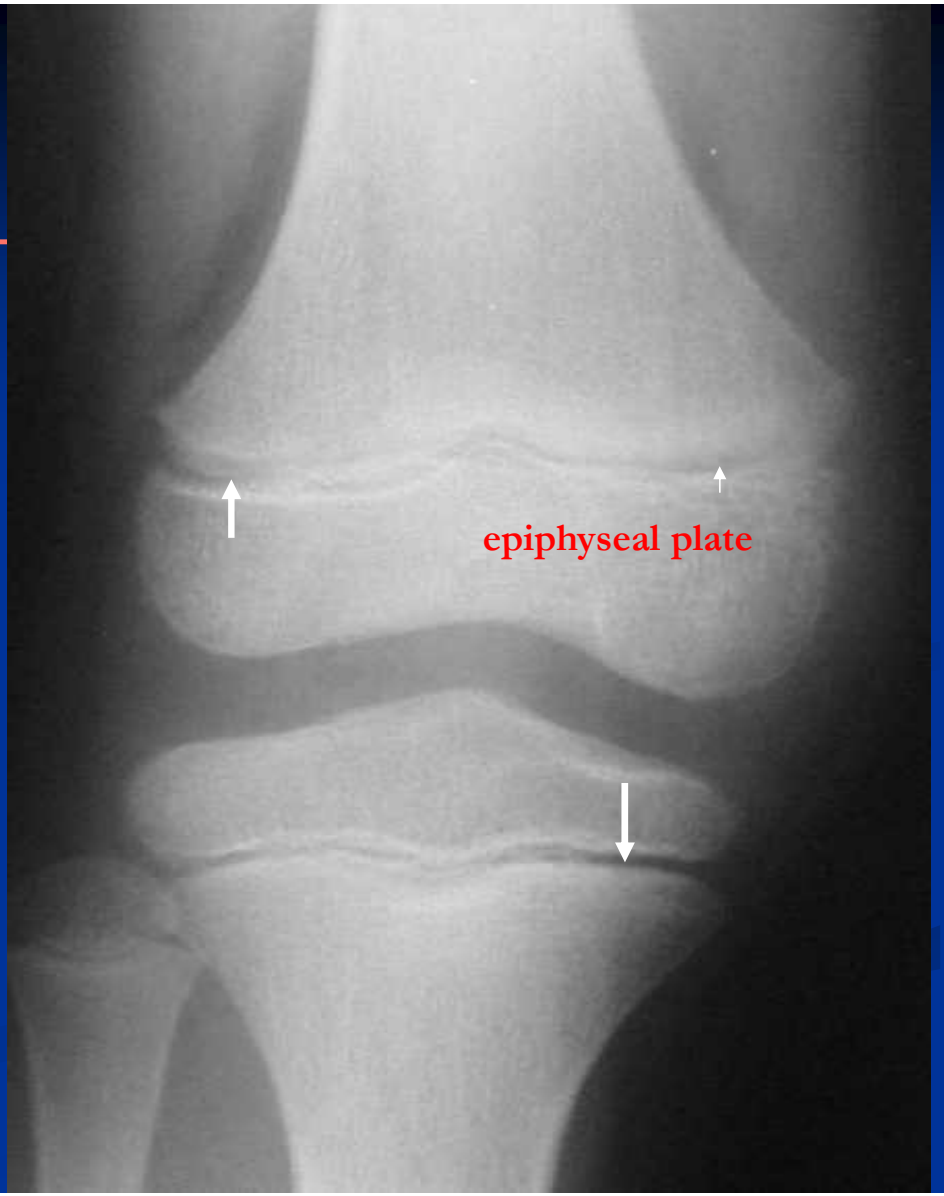
- **Epiphyseal cartilage (close to the epiphysis) of the epiphyseal plate divides to create more cartilage, while the diaphyseal cartilage (close to the diaphysis) of the epiphyseal plate is transformed into bone.**
- **This increases the length of the shaft.**



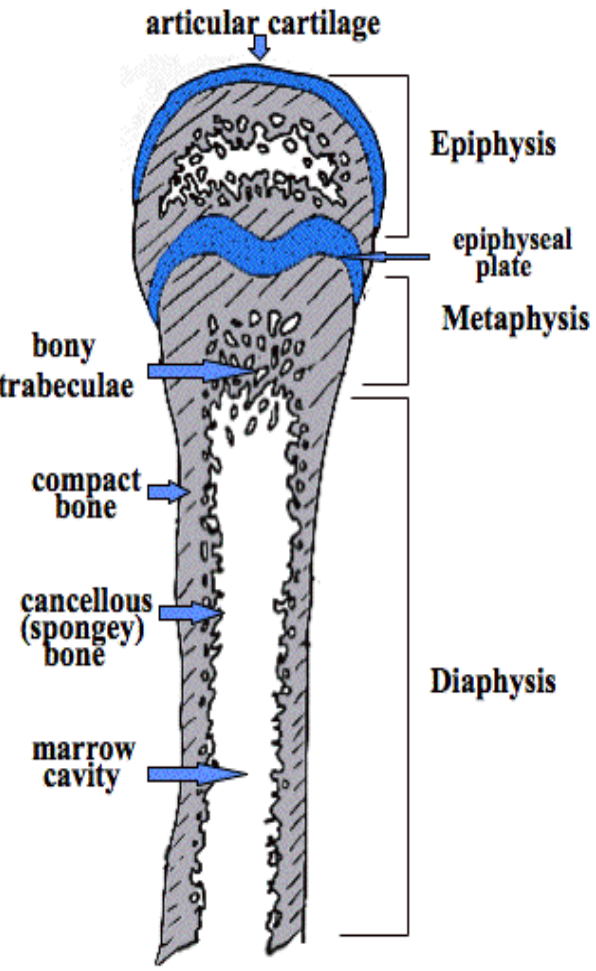


At puberty, growth in bone length is increased dramatically by the combined activities of growth hormone, thyroid hormone, and the sex hormones.

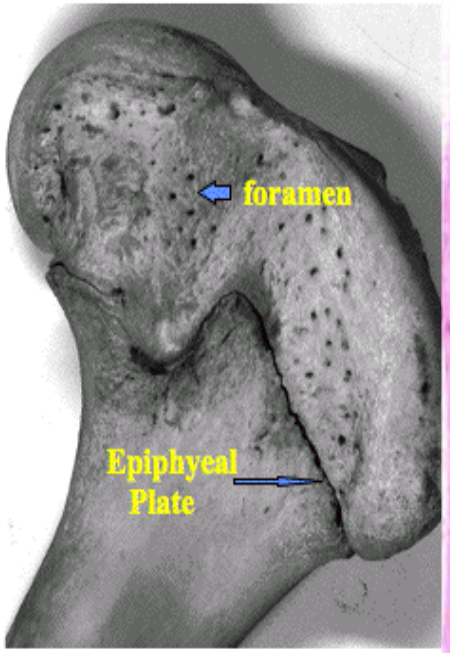
•As a result osteoblasts begin producing bone faster than the rate of epiphyseal cartilage expansion. Thus the bone grows while the epiphyseal plate gets narrower and narrower and ultimately disappears. A remnant **(epiphyseal line for adult)** is visible on X-rays *(do you see them in the adjacent femur, tibia, and fibula?)*

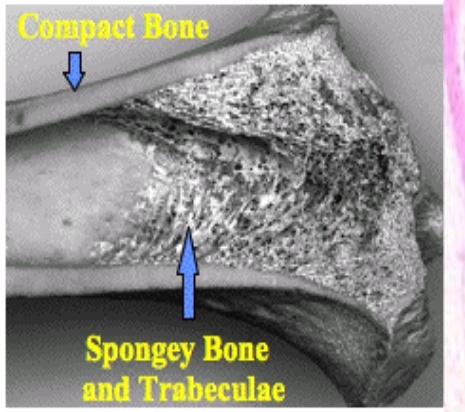


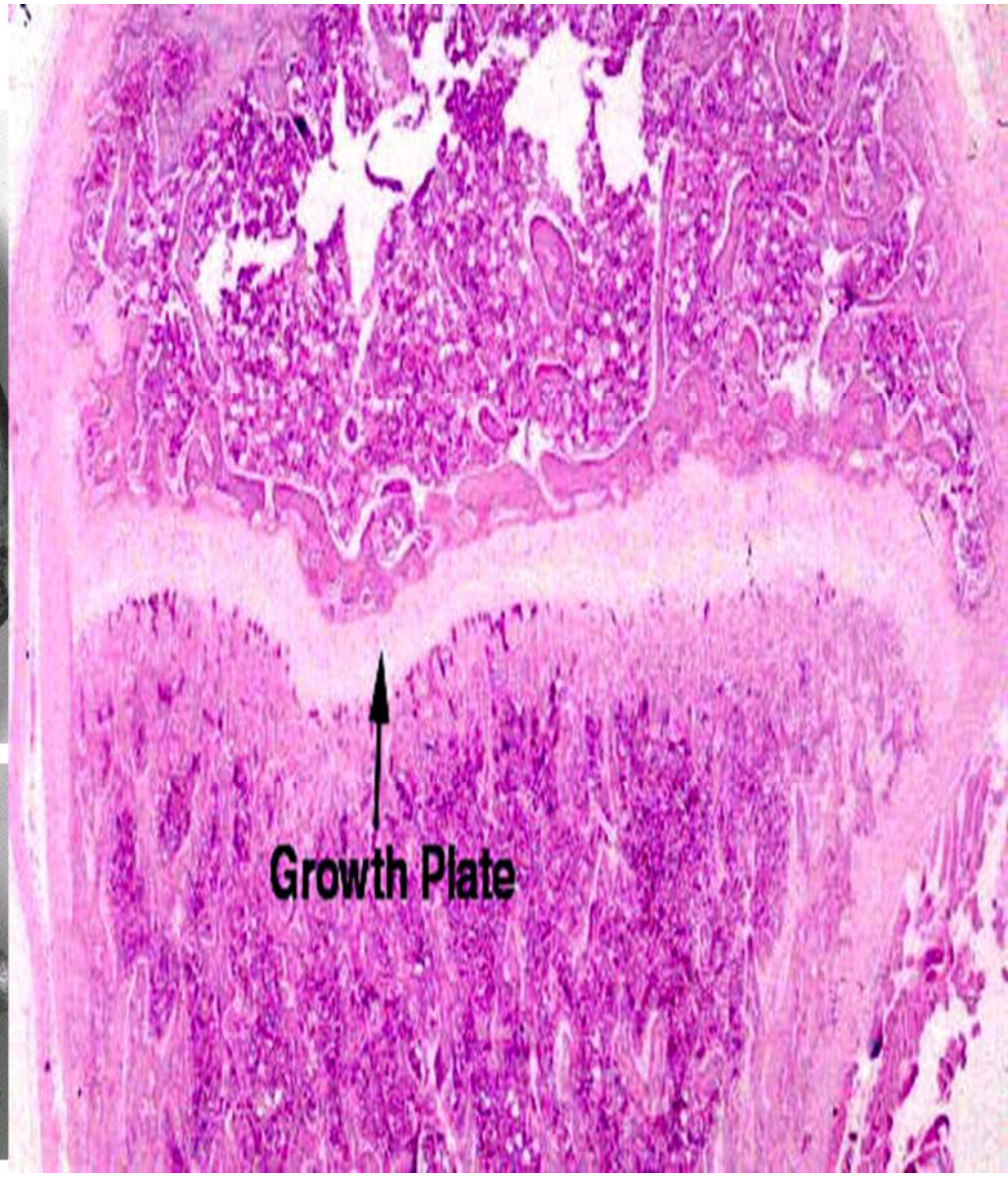
BONE ANATOMY

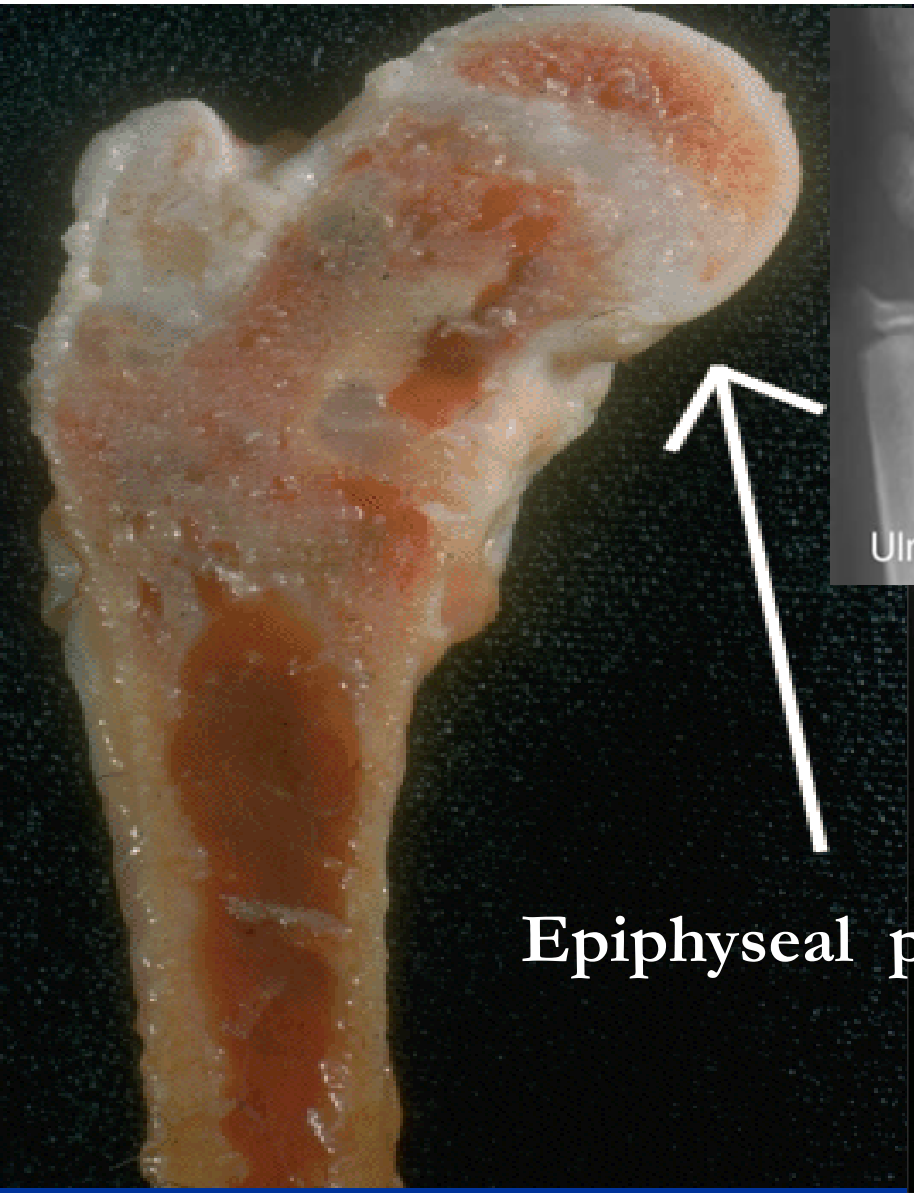


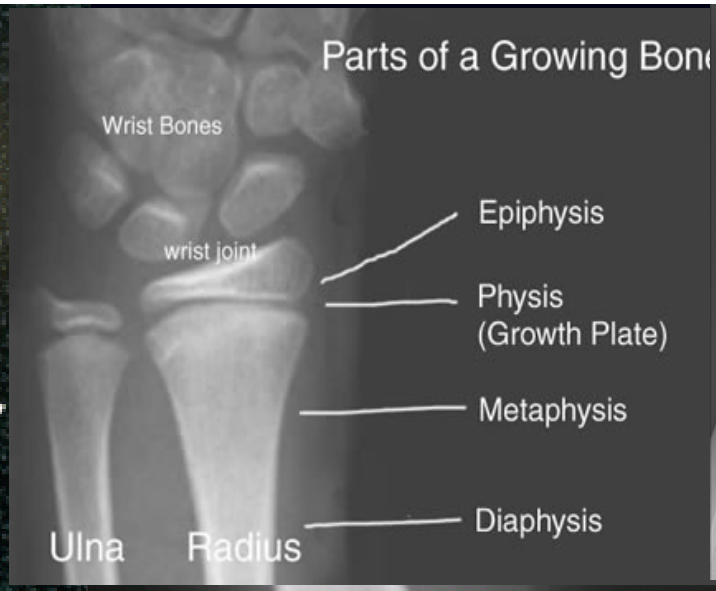
Epiphysis and Metaphysis

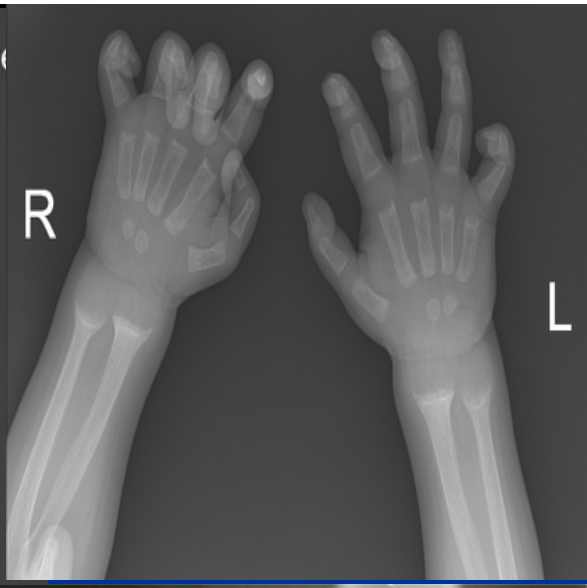


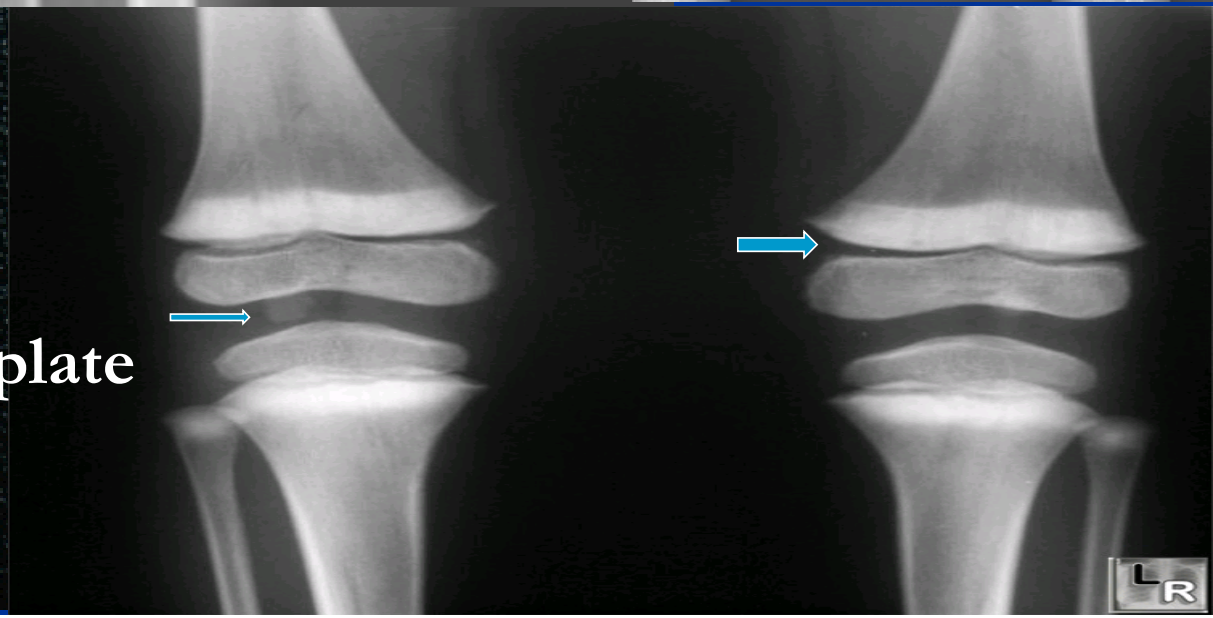


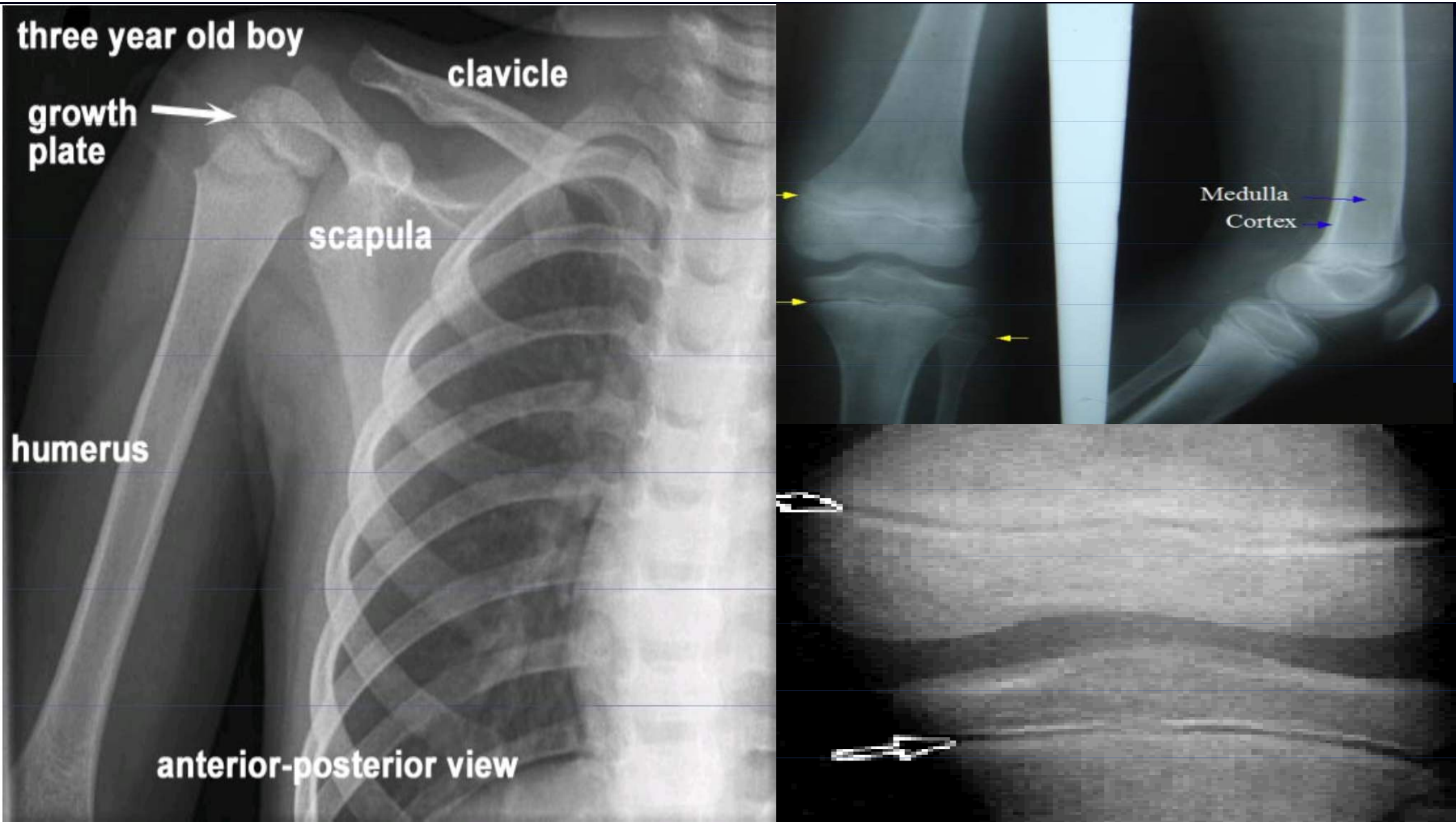



Epiphyseal plate


Parts of a Growing Bon
Wrist Bones
wrist joint
Epiphysis
Physis
(Growth Plate)
Metaphysis
Diaphysis
Ulna
Radius


R
L




three year old boy
clavicle
growth plate
scapula
humerus
anterior-posterior view
Medulla
Cortex

Clinical Significance

1.Bone Growth and Development:

1. Proper bone formation is crucial for the overall growth and development of the skeletal system.
2. Disorders of ossification, such as **achondroplasia, can lead to abnormal bone development and growth.**

2.Fracture Healing:

1. Understanding osteogenesis is essential in managing bone fractures and developing strategies for effective bone healing.
2. Fracture healing involves a combination of intramembranous and endochondral ossification.

1.Osteoporosis and Other Bone Diseases:

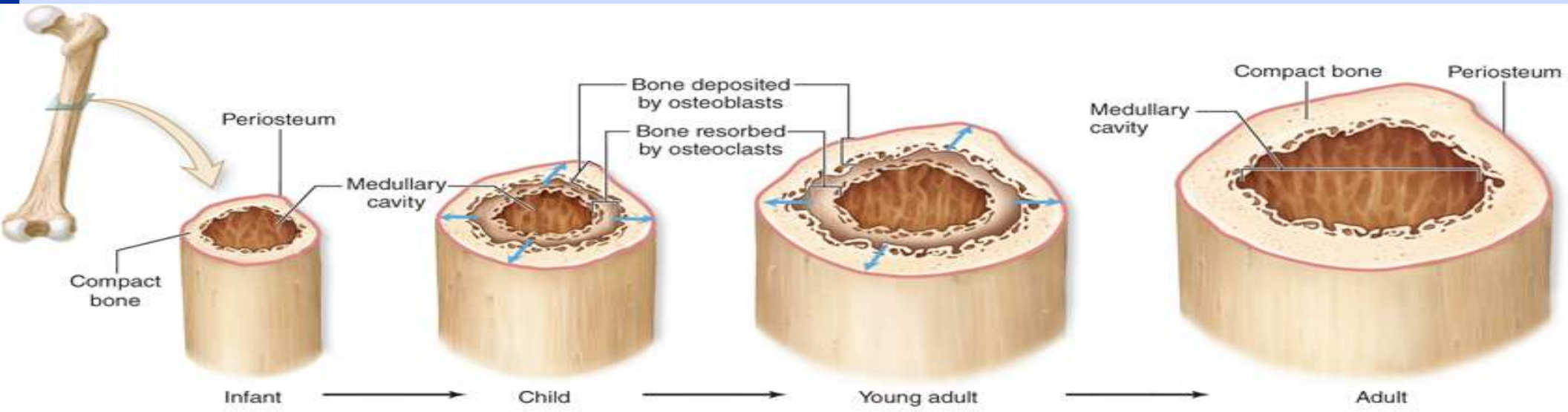
1. Osteogenesis is affected in various bone diseases such as osteoporosis, where the balance between bone resorption and formation is disrupted.
2. Treatments often aim to enhance bone formation or reduce bone resorption.

2.Bone Grafting and Tissue Engineering:

1. Knowledge of osteogenesis is applied in bone grafting procedures and the development of bone tissue engineering techniques.
2. Synthetic and natural scaffolds are designed to support the growth of new bone tissue through principles of osteogenesis.

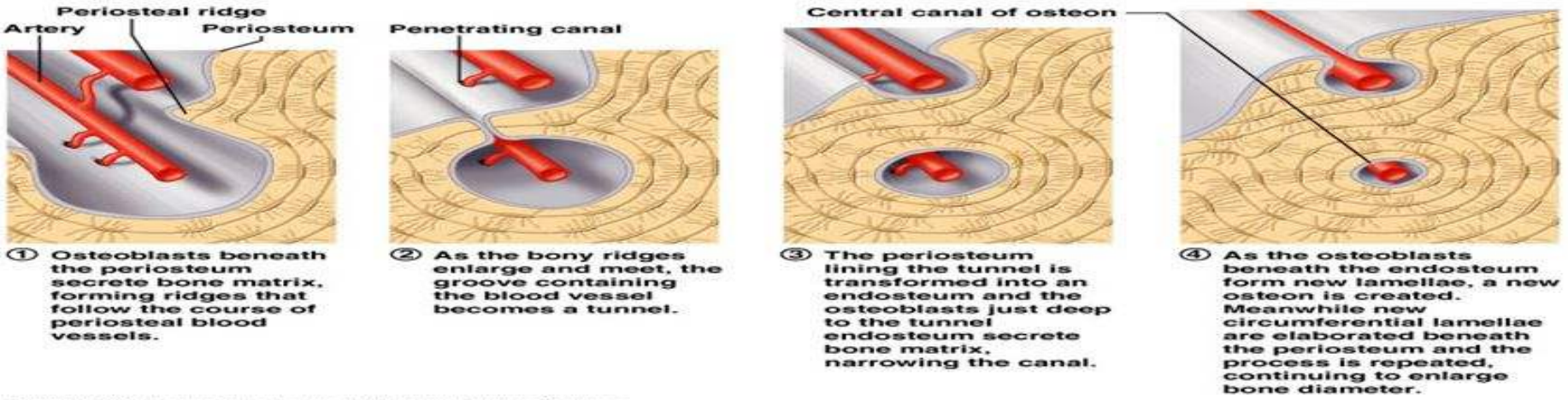
Growth in Bone Thickness

- **Osteoblasts beneath the periosteum secrete bone matrix on the external surface of the bone. This obviously makes the bone thicker.**
- At the same time, osteoclasts on the endosteum break down bone and thus widen the medullary cavity.
- This results in an increase in shaft diameter even though the actual amount of bone in the shaft is relatively unchanged.



Source: Anthony L. Mescher: Junqueira's Basic Histology, 14th Edition.
www.accessmedicine.com

Growth in Width (Thickness)



- Growing bones widen as they lengthen
- ***Increases in thickness by appositional growth***

Postnatal Bone Growth

- **Growth in length of long bones**
  - Cartilage on the side of the **epiphyseal plate closest to the epiphysis is relatively inactive**
  - Cartilage abutting the shaft of the bone organizes into a pattern that allows fast, efficient growth
  - Cells of the epiphyseal plate proximal to the resting cartilage form three functionally different zones: growth, transformation, and osteogenic

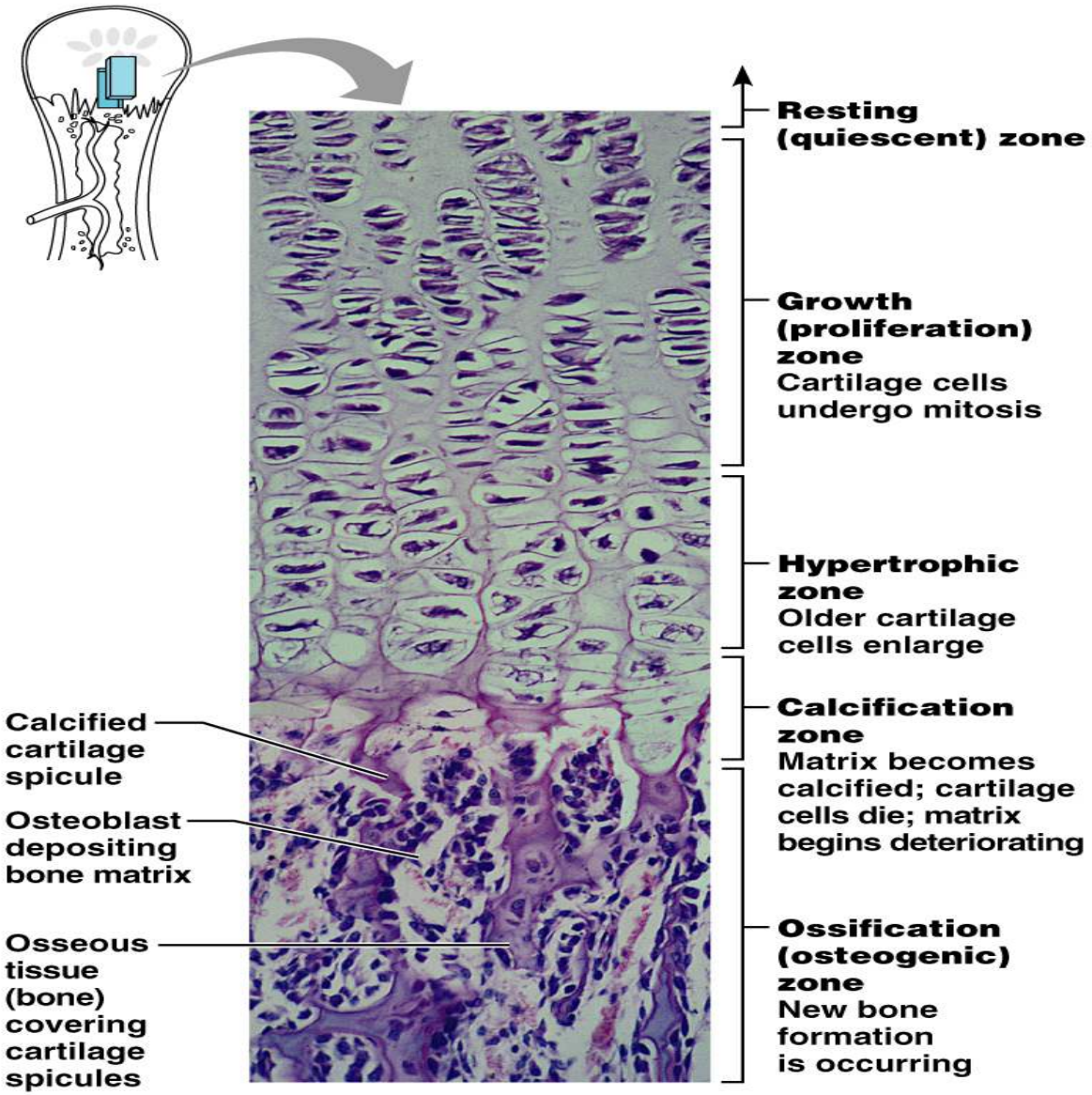
Functional Zones in Long Bone Growth

- **Growth zone** – cartilage cells undergo mitosis, pushing the epiphysis away from the diaphysis
- **Transformation zone** – older cells enlarge, the matrix becomes calcified, cartilage cells die, and the matrix begins to deteriorate
- **Osteogenic zone** – new bone formation occurs

Long Bone Growth and Remodeling

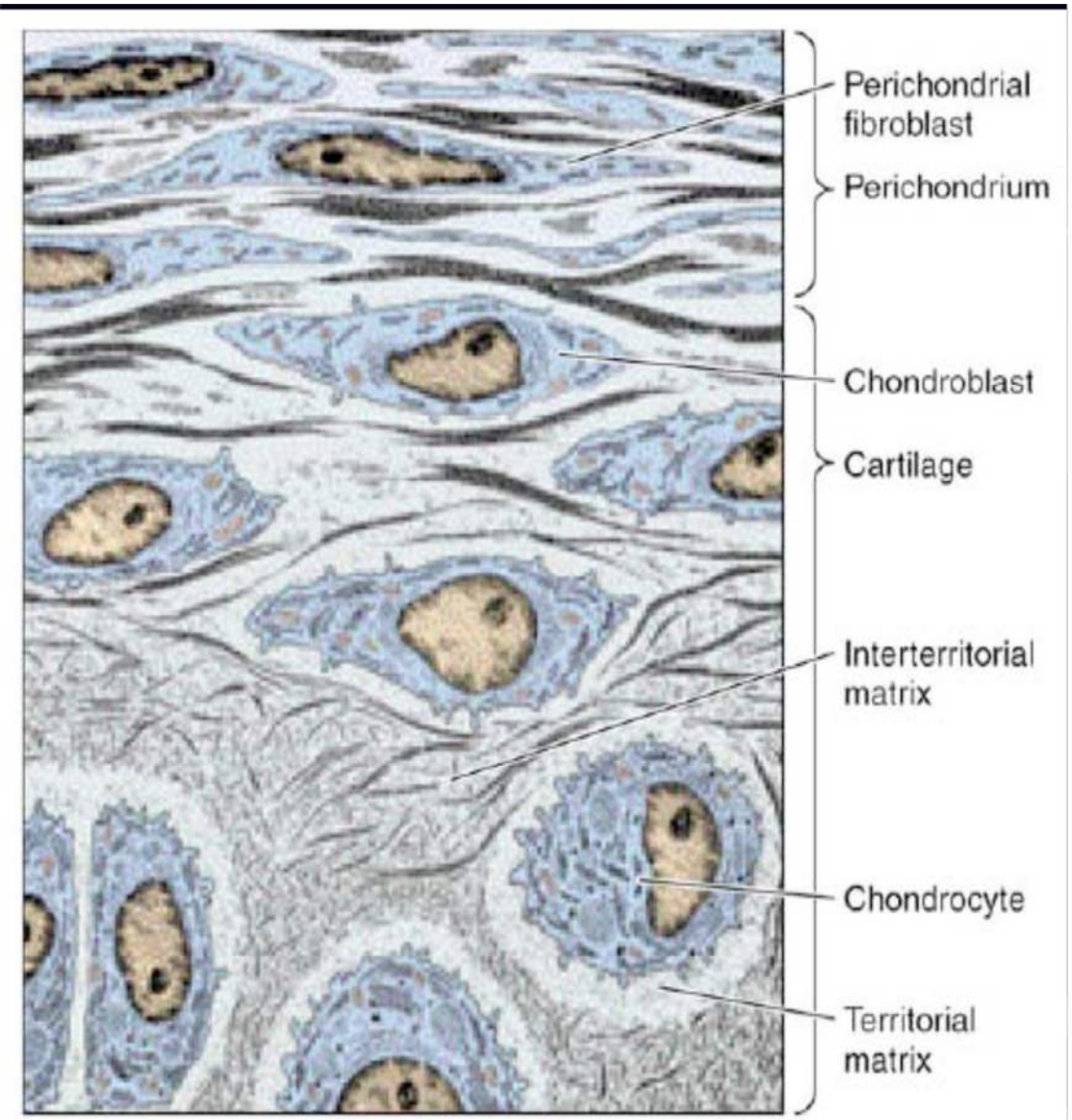
- **Growth in length** – cartilage continually grows and is replaced by bone as shown

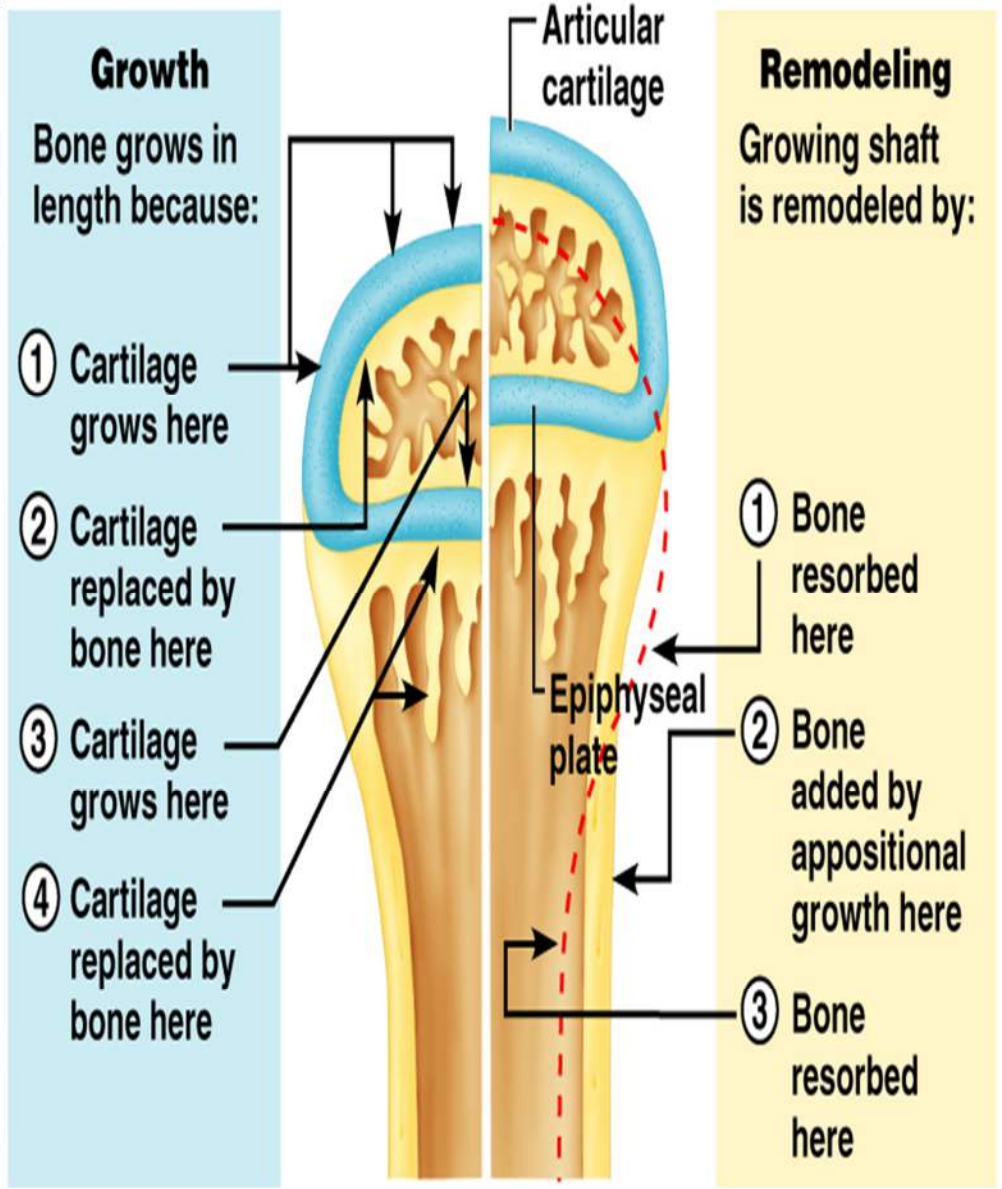
- **Remodeling** – bone is resorbed and added by appositional growth as shown



Growth in Length of Long Bone

Figure 6.9


Perichondrial fibroblast
Perichondrium
Chondroblast
Cartilage
Interterritorial matrix
Chondrocyte
Territorial matrix

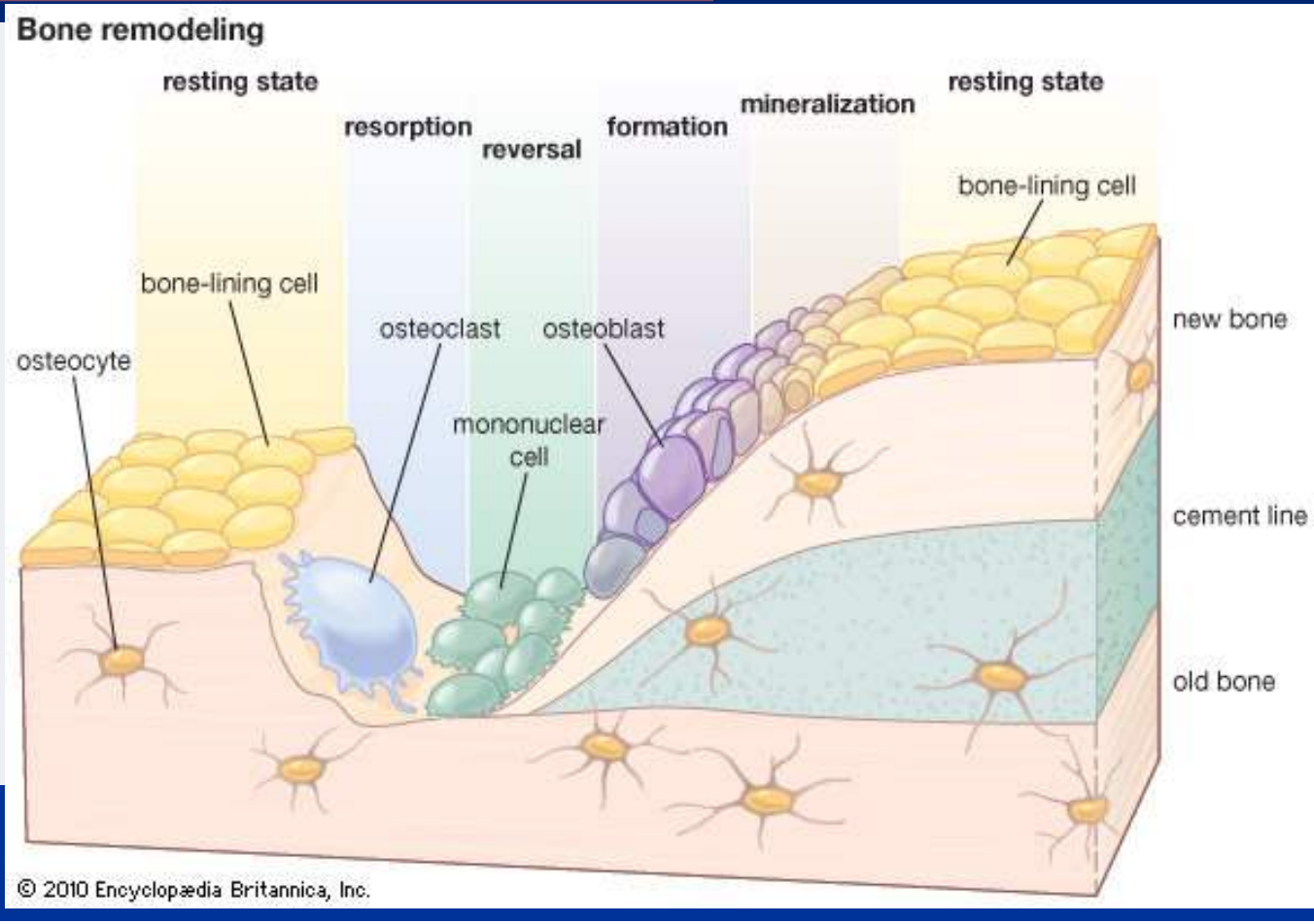

Growth
Bone grows in length because:
① Cartilage grows here
② Cartilage replaced by bone here
③ Cartilage grows here
④ Cartilage replaced by bone here
Articular cartilage
Epiphyseal plate
Remodeling
Growing shaft is remodeled by:
① Bone resorbed here
② Bone added by appositional growth here
③ Bone resorbed here

Hormonal Regulation of Bone Growth During Youth

- During infancy and childhood, epiphyseal plate activity is stimulated by **growth hormone**
- **During puberty, testosterone and estrogens:**
  - Initially promote adolescent growth spurts
  - Cause masculinization and feminization of specific parts of the skeleton
  - **Later induce epiphyseal plate closure, ending longitudinal bone growth**

Bone Remodeling

- **Remodeling units** – adjacent osteoblasts and osteoclasts deposit and resorb bone at periosteal and endosteal surfaces



Bone Deposition

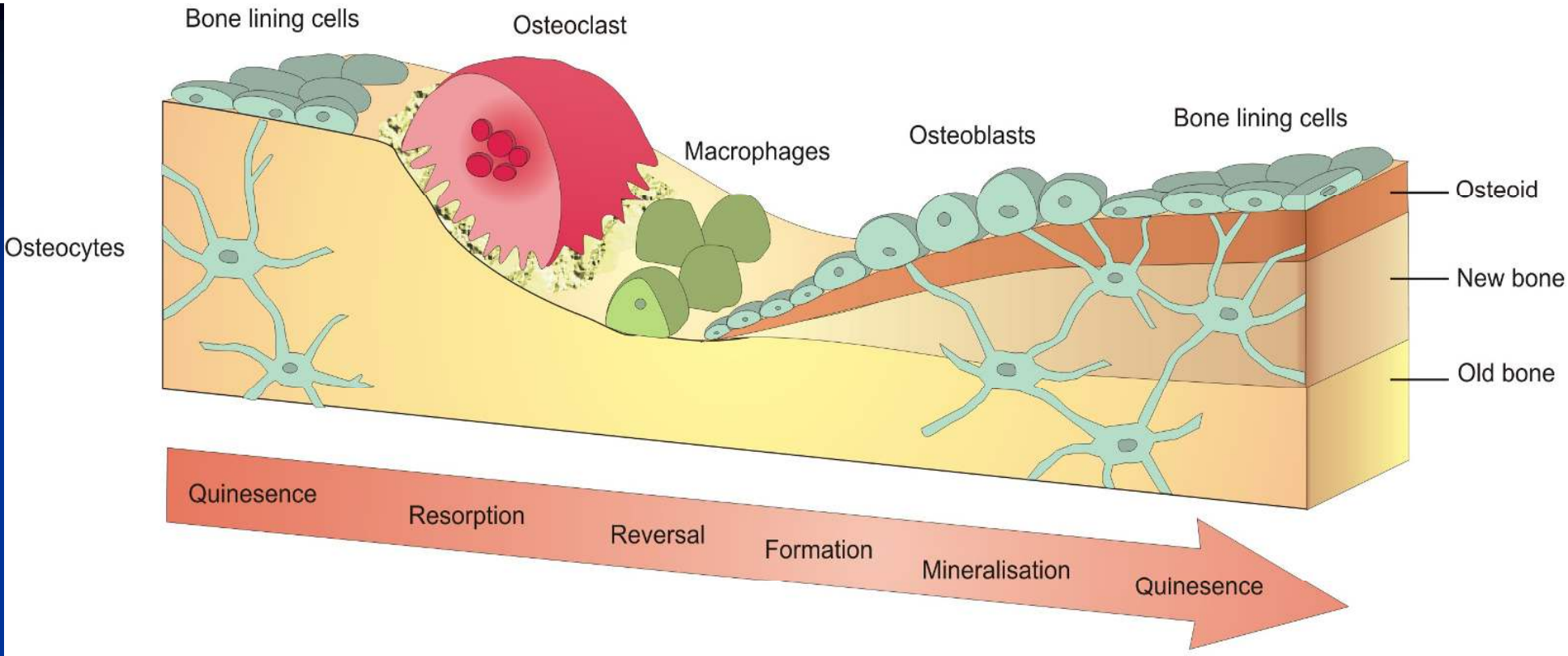
- Occurs where bone is injured or added strength is needed
- Requires a diet rich in protein, vitamins C, D, and A, calcium, phosphorus, magnesium, and manganese
- Alkaline phosphatase is essential for mineralization of bone

- Sites of new matrix deposition are revealed by the:
  - **Osteoid seam – unmineralized band of bone matrix**
  - Calcification front – abrupt transition zone between the osteoid seam and the older mineralized bone

Bone Resorption

- **Accomplished by osteoclasts**
- Resorption bays – grooves formed by osteoclasts as they break down bone matrix
- **Resorption involves osteoclast secretion of:**
  - **Lysosomal enzymes that digest organic matrix**
  - **Acids that convert calcium salts into soluble forms**

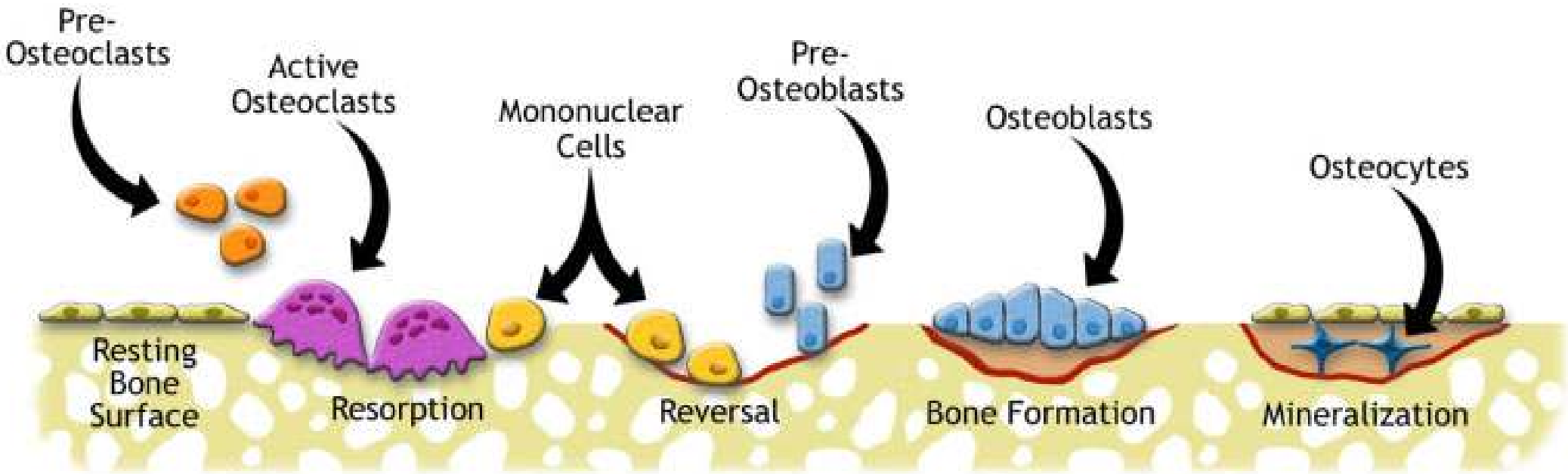
- **Dissolved matrix is transcytosed across the osteoclast's cell where it is secreted into the interstitial fluid and then into the blood**



The bone remodelling process.

Bone is continuously remodelled at discrete sites in the skeleton in order to maintain the integrity of the tissue. During this process, old bone is resorbed by osteoclasts and replaced with new osteoid, secreted by osteoblasts. First osteoclasts are activated, and the resorption phase takes approximately 10 days. Following resorption, unclassified macrophage-like cells are found at the remodelling site in the intermediate, or reversal phase. Osteoblast precursors are then recruited , which proliferate and differentiate into mature osteoblasts, before secreting new bone matrix. The matrix then mineralises to generate new bone and this completes the remodelling process.

Bone Remodeling Cycle



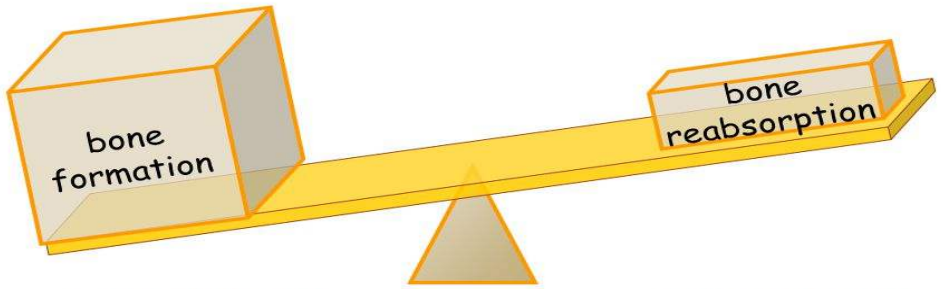

AMGEN


AMGEN

Response to Mechanical Stress

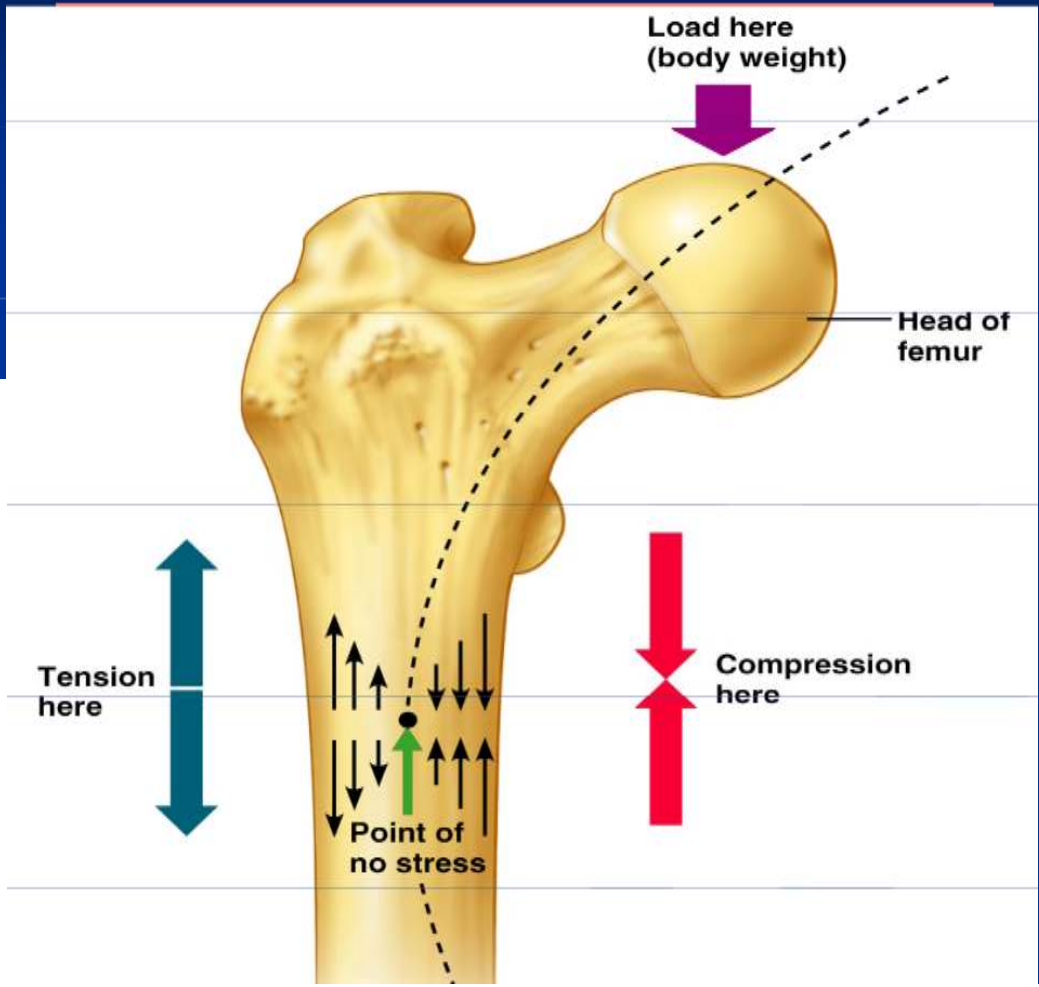
- Trabeculae form along lines of stress
- Large, bony projections occur where heavy, active muscles attach

Stress effects

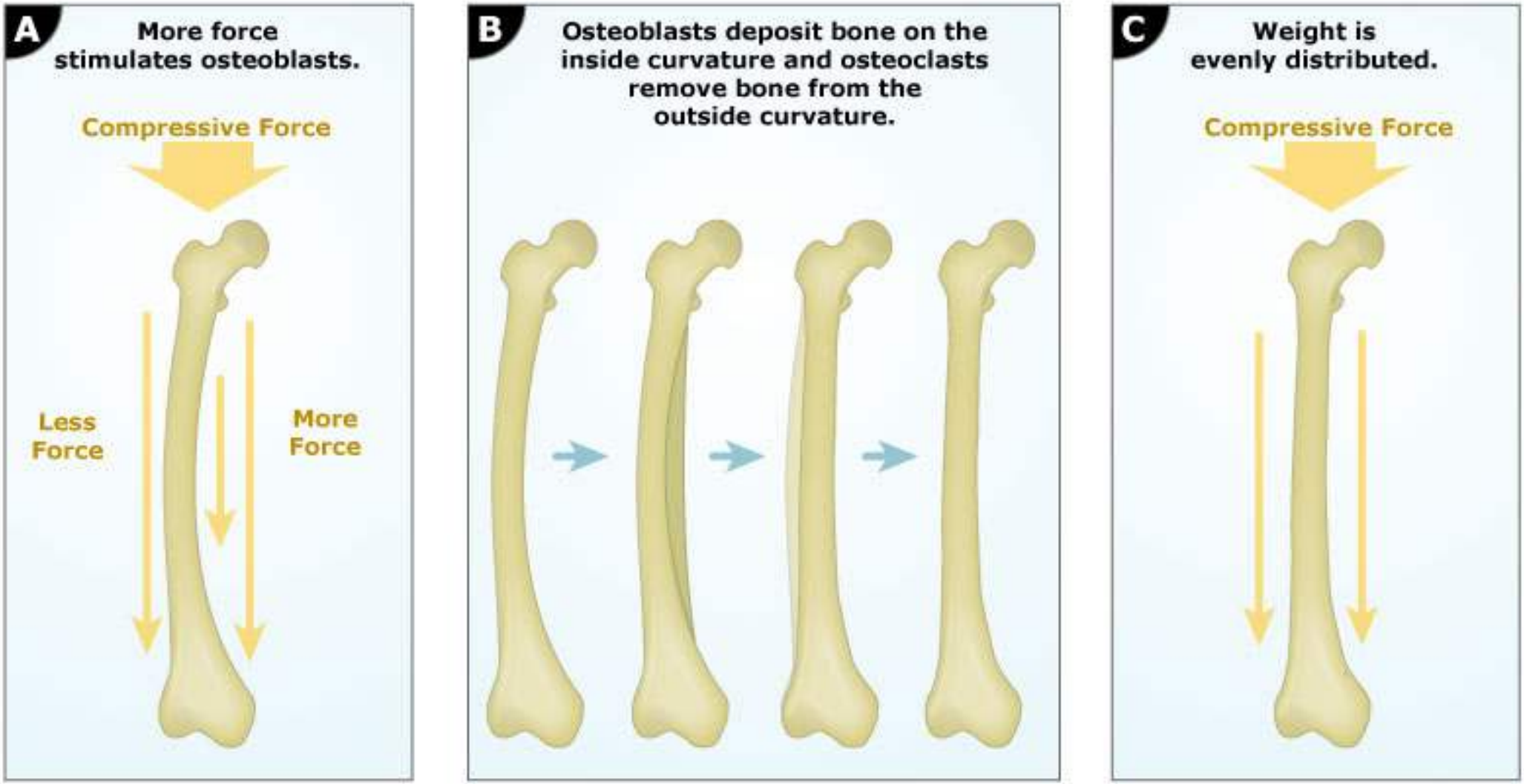


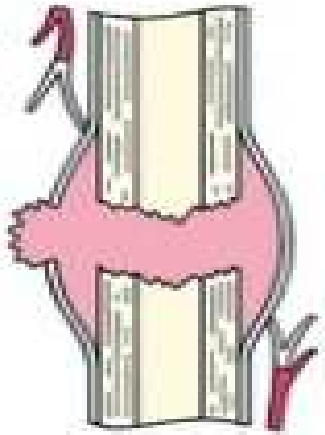
Stress increases bone density

Response to Mechanical Stress

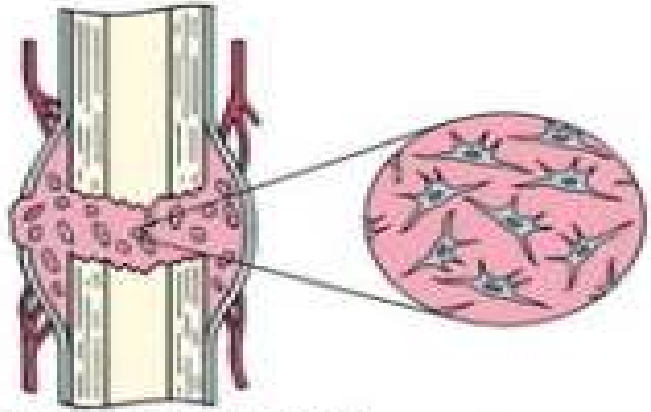


Bone Remodeling

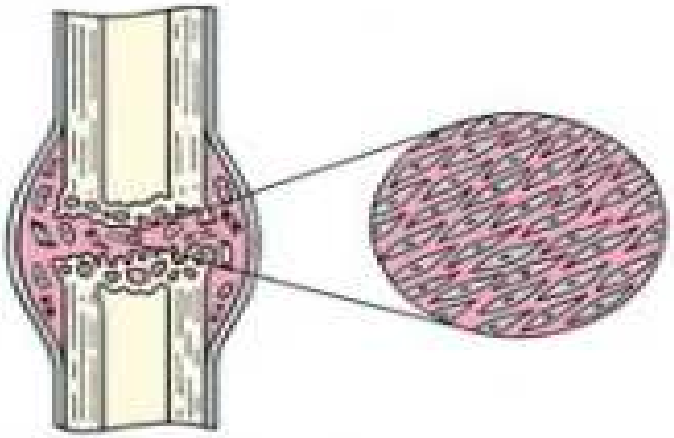




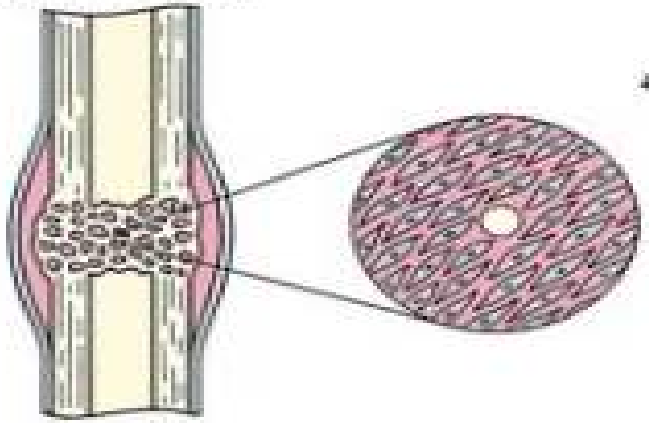
-Fracture occurrence
-Blood vessel disruption
-Hematoma formation



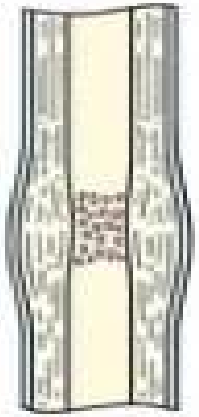
-Chemotactic invasion of osteoprogenitor
-Mitogenic and osteogenic molecules released
-Cellular proliferation begins
-Formation of granulation tissue
-Neovascularization



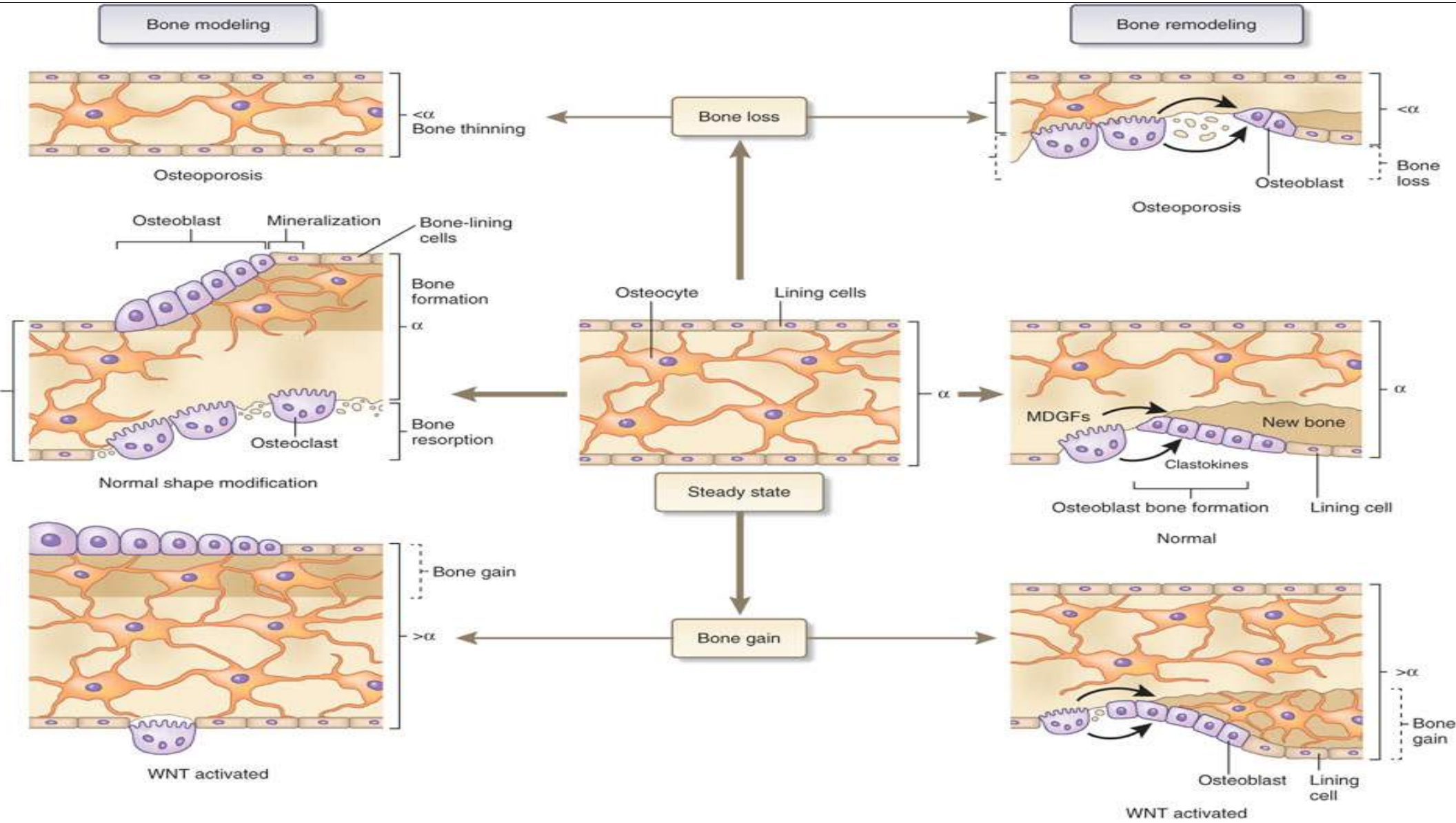
-Soft callus is formed
-Differentiation starts



-Hard callus is formed



-Remodeling


Bone modeling
Bone remodeling
Bone loss
<α
Bone thinning
Osteoporosis
Osteoblast
Bone loss
Osteoporosis
Osteoblast
Mineralization
Bone-lining cells
Bone formation
α
Bone resorption
Osteoclast
Normal shape modification
Osteocyte
Lining cells
α
MDGFs
New bone
Clastokines
Osteoblast bone formation
Lining cell
Normal
Steady state
Bone gain
>α
WNT activated
Bone gain
Osteoblast
Lining cell
WNT activated

Bone formation occurs through two main processes: intramembranous ossification and endochondral ossification.

Intramembranous Ossification: This process is responsible for the formation of flat bones, such as those in the skull and clavicles.
Here's a simplified overview:

- Mesenchymal cells differentiate directly into osteoblasts within a connective tissue membrane.
- Osteoblasts secrete osteoid (a matrix of collagen fibers) which becomes mineralized.
- Osteoblasts become trapped within the mineralized matrix and differentiate into osteocytes.
- The trabeculae formed by the mineralized matrix condense and fuse, forming spongy bone.
- Compact bone may later form on the surface, completing the bone structure.

2.Endochondral Ossification: This process is responsible for the formation of long bones, such as those in the arms and legs.

Here's a simplified overview:

•A hyaline cartilage model of the bone forms first.
•Cartilage in the center of the diaphysis begins to break down, allowing for the formation of the primary ossification center.
•Blood vessels invade the disintegrating cartilage bringing osteogenic cells.
•Osteoblasts replace the cartilage with spongy bone.
•Secondary ossification centers form in the epiphyses.
•Epiphyseal plates (growth plates) remain between the diaphysis and epiphysis to allow for bone lengthening until adulthood.
•Ossification of the epiphyseal plates leads to the closure of growth plates and the completion of bone growth.