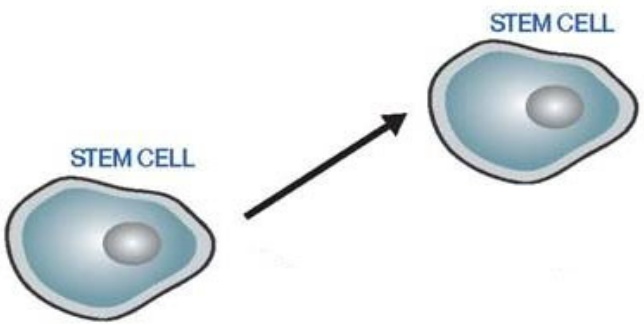
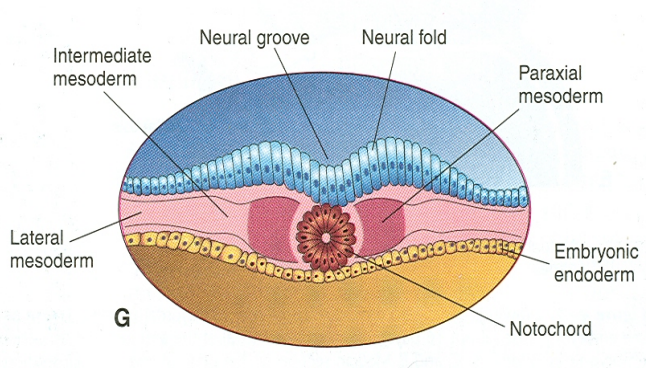
DEVELOPMENT OF MESENCHYME, FIBROUS TISSUE; CARTILAGE, BONE AND JOINTS

Prof Peter Gichangi

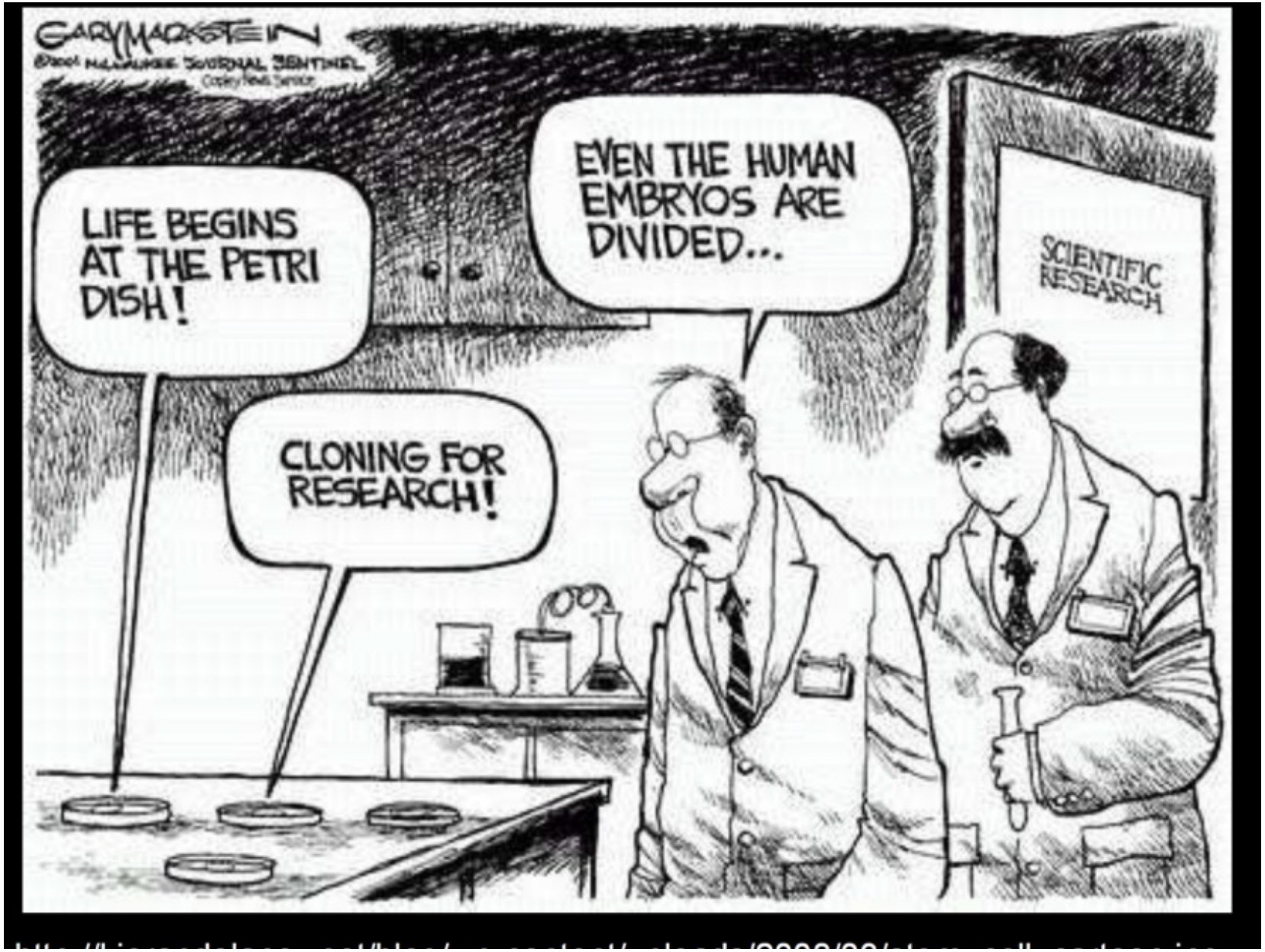
October 2016



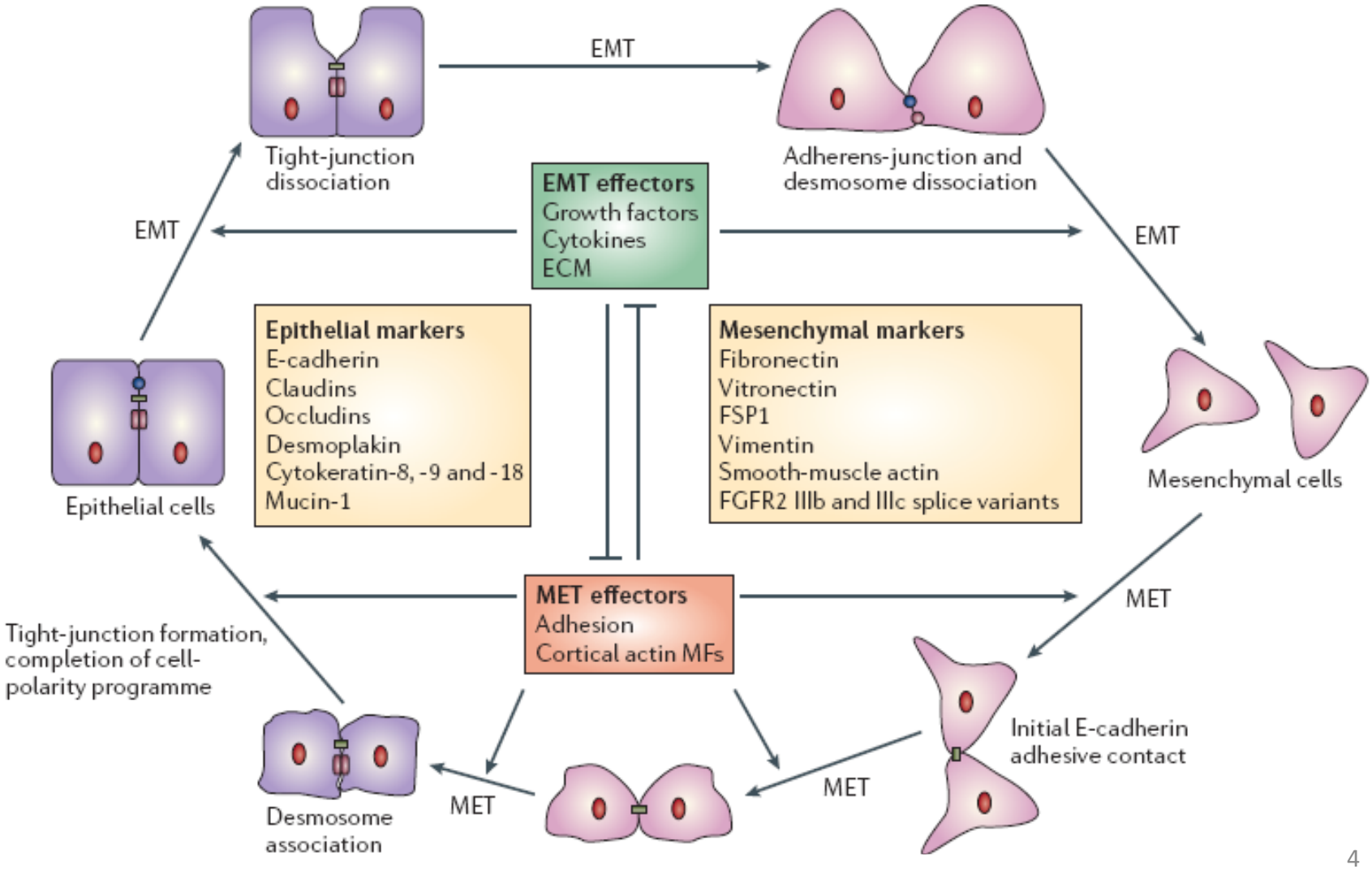


OBJECTIVES

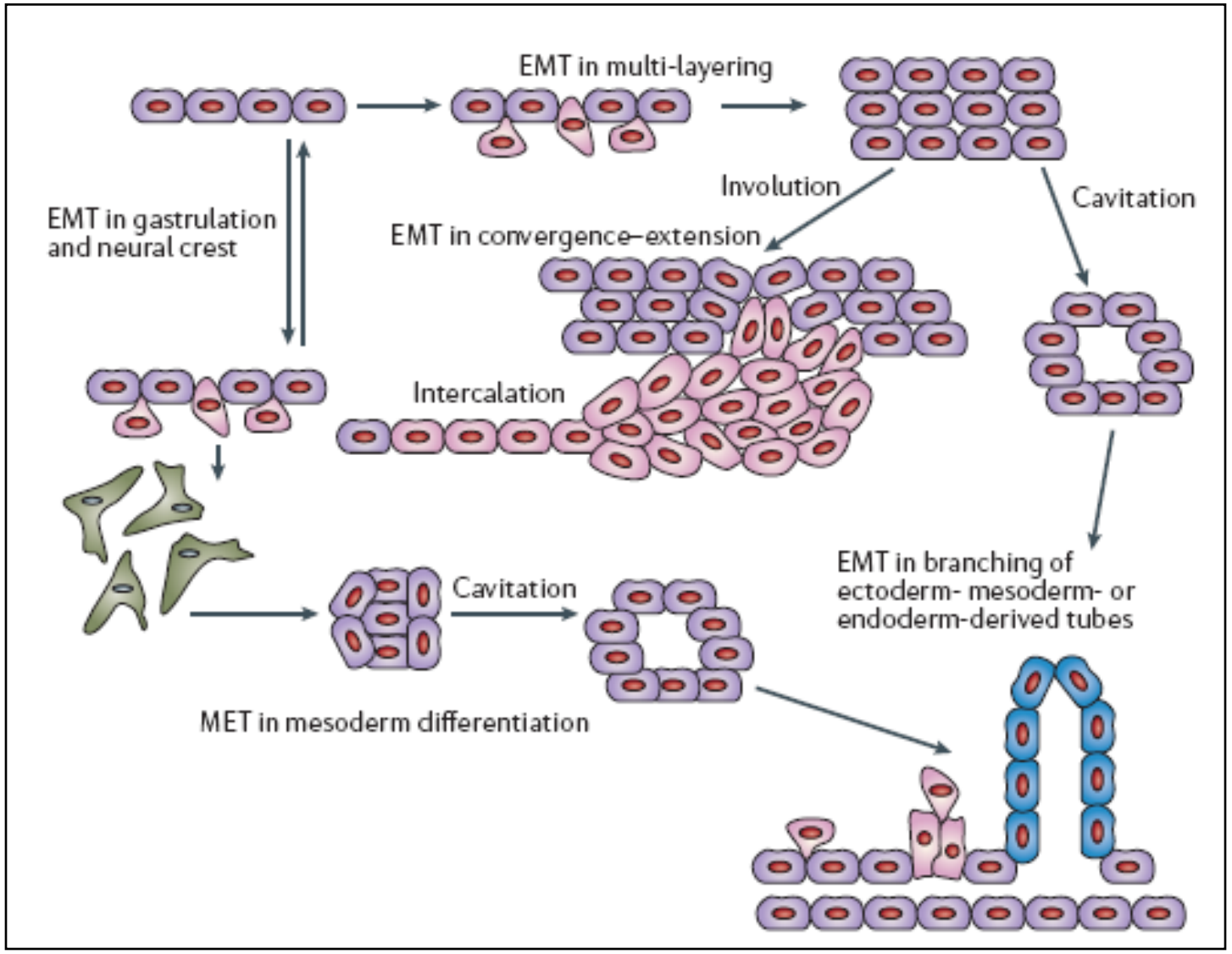
- Understand the sources of mesechyme
- Appreciate the properties of mesenchyme
- Understand development of connective tissue:
  - Fibrous
  - Cartilage
  - Bone

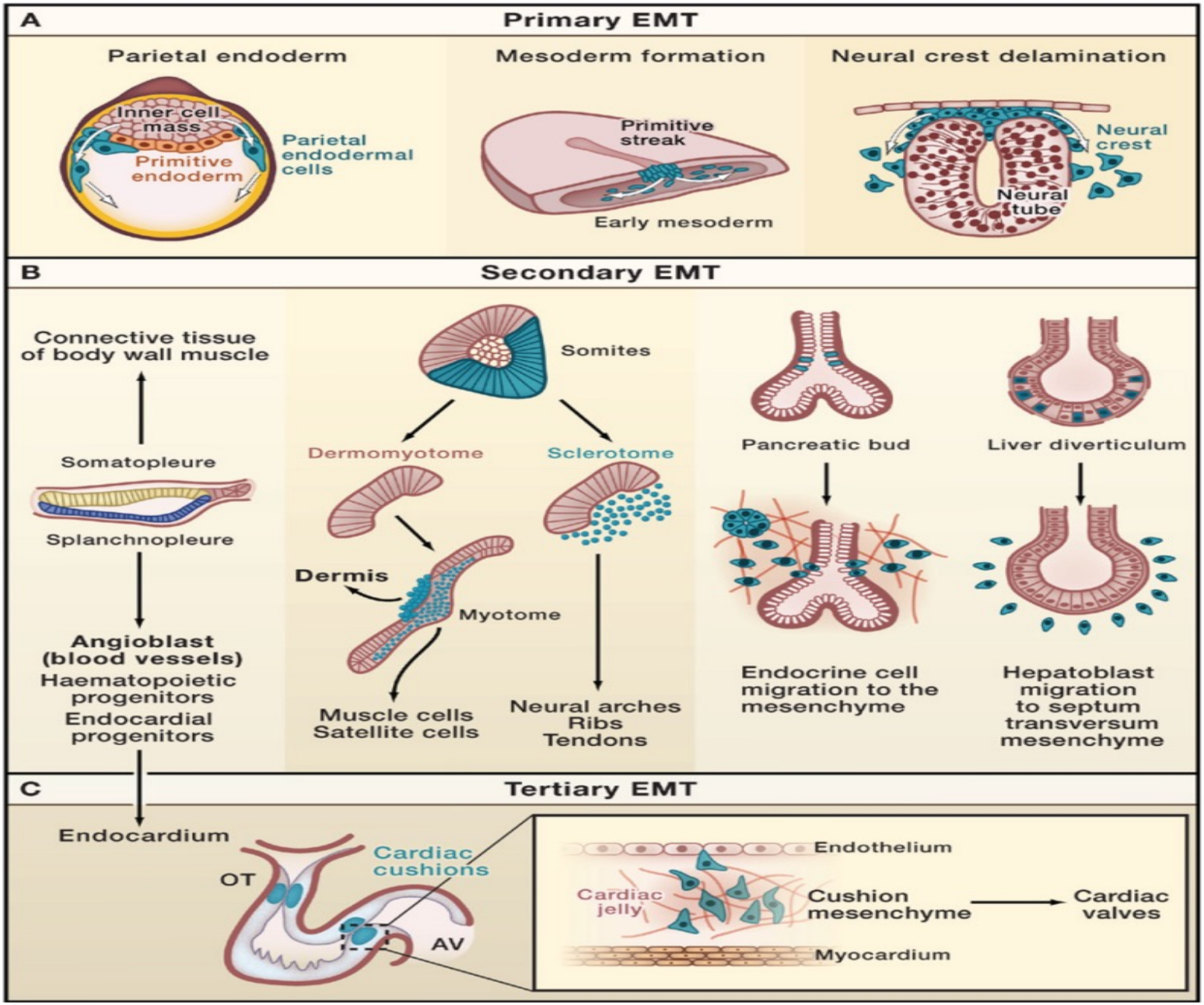

GARY MARKSTEIN
LIFE BEGINS AT THE PETRI DISH!
CLONING FOR RESEARCH!
EVEN THE HUMAN EMBRYOS ARE DIVIDED...
SCIENTIFIC RESEARCH

Epithelial–Mesenchymal Transition



EMT in Tissue Remodelling




A
Primary EMT
Parietal endoderm
Inner cell mass
Primitive endoderm
Parietal endodermal cells
Mesoderm formation
Primitive streak
Early mesoderm
Neural crest delamination
Neural crest
Neural tube
B
Secondary EMT
Connective tissue of body wall muscle
Somatopleure
Splanchnopleure
Angioblast (blood vessels)
Haematopoietic progenitors
Endocardial progenitors
Somites
Dermomyotome
Sclerotome
Dermis
Myotome
Muscle cells
Satellite cells
Neural arches
Ribs
Tendons
Pancreatic bud
Endocrine cell migration to the mesenchyme
Liver diverticulum
Hepatoblast migration to septum transversum mesenchyme
C
Tertiary EMT
Endocardium
OT
Cardiac cushions
AV
Endothelium
Cardiac jelly
Cushion mesenchyme
Cardiac valves
Myocardium

GASTRULATION

- Key event – loss of epithelial characteristics of epiblast and hyopblast.
- The main important processes of gastrulation are formation of:
  - Primitive streak
  - Germ layers
  - Notochord

THE PRIMITIVE STREAK

- It develops at the beginning of **3rd week**.
- Proliferation and migration of cells of the epiblast to the median plane of the embryonic disc.
- Cells leave the deep surface and form a loose network of embryonic connective tissue called **MESENCYME OR MESOBLAST OR MESODERM**.

SOURCES OF MESENCHYME

- **Definitions:**
  - **Mesoderm** refers to cells derived from the epiblast and extraembryonic tissues.
  - **Mesenchyme** refers to loosely organized embryonic unspecialized cells that are set in a gelatinous ground substance**.**
- Sources:
  - **Mesoderm**
    - Primitive streak
    - Somites.
      - The somites differentiate to scleretome, myotome and dermatome.
      - In early stages of differentiation, the somite cells show epithelial characteristics.
      - Later, they loose this characteristic to form a loose jelly-like tissue - MESENCHYME.
    - Mesodermal lateral plates.
  - **Neural crest cells especially in the head region**

CHARACTERISTICS OF MESENCHYME

- Mesenchyme consists of:
  - cells
  - intercellular ground substance
- Ability to differentiate in many different ways
- Ability to differentiate along a different pattern from their customary line (metaplasia)
- Ability to migrate and change their position and arrangement
- Cells are:
  - Amoeboid – ability to move
  - Different shapes:
    - Stellate (star-shaped)
    - Fusiform (spindle-shaped)
  - Joined by cellular processes.
- Initially, ground substance is fluid, later it becomes a mucoid jelly containing scanty fibrils.

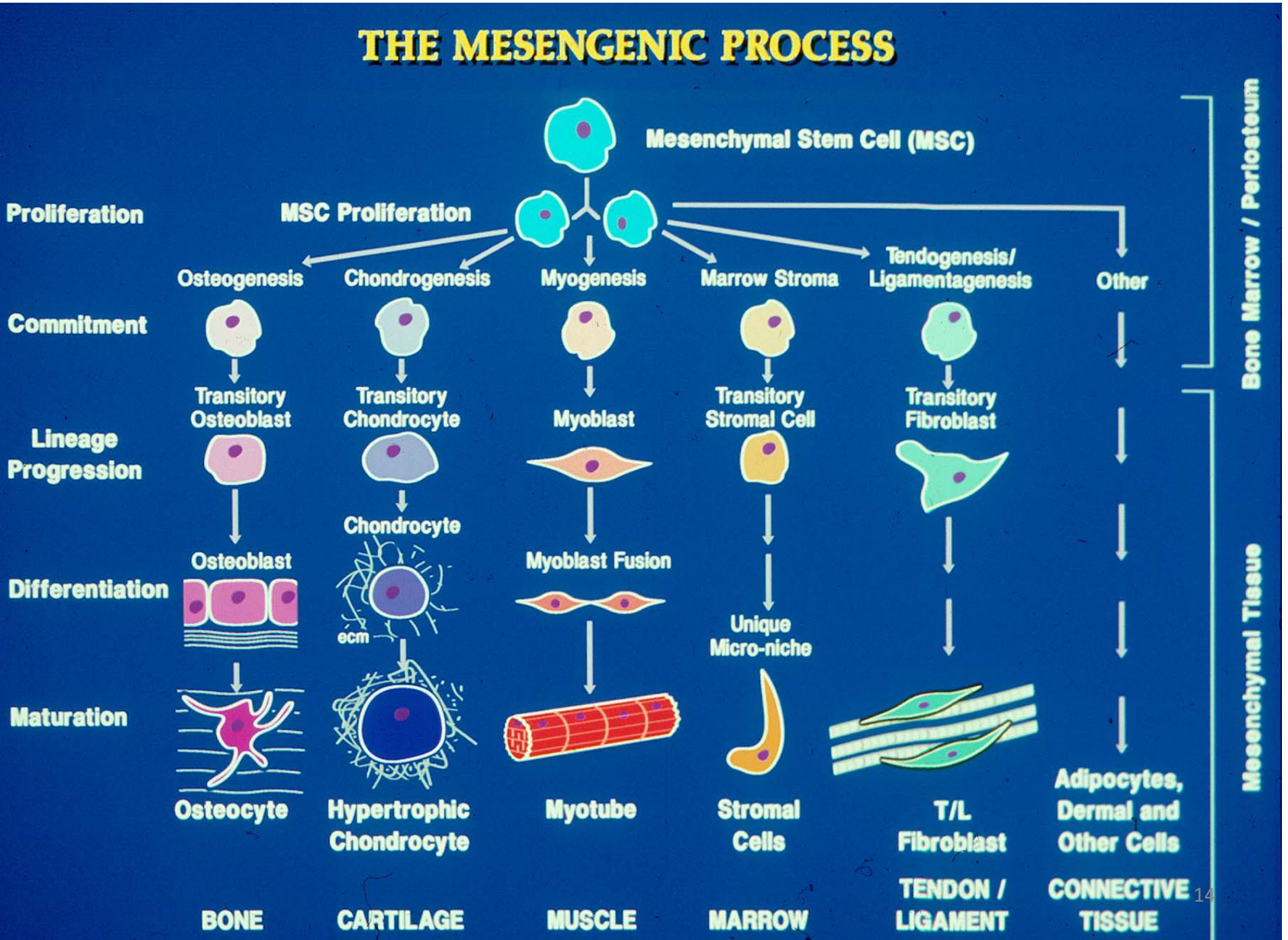
MORPHOGENESIS IS BROUGHT ABOUT BY CHANGES IN

- The direction and number of cell divisions;
- Cell shape changes;
- Cell movement;
- Cell growth;
- Cell death;
- Changes in the composition of cell membrane and extracellular matrix.

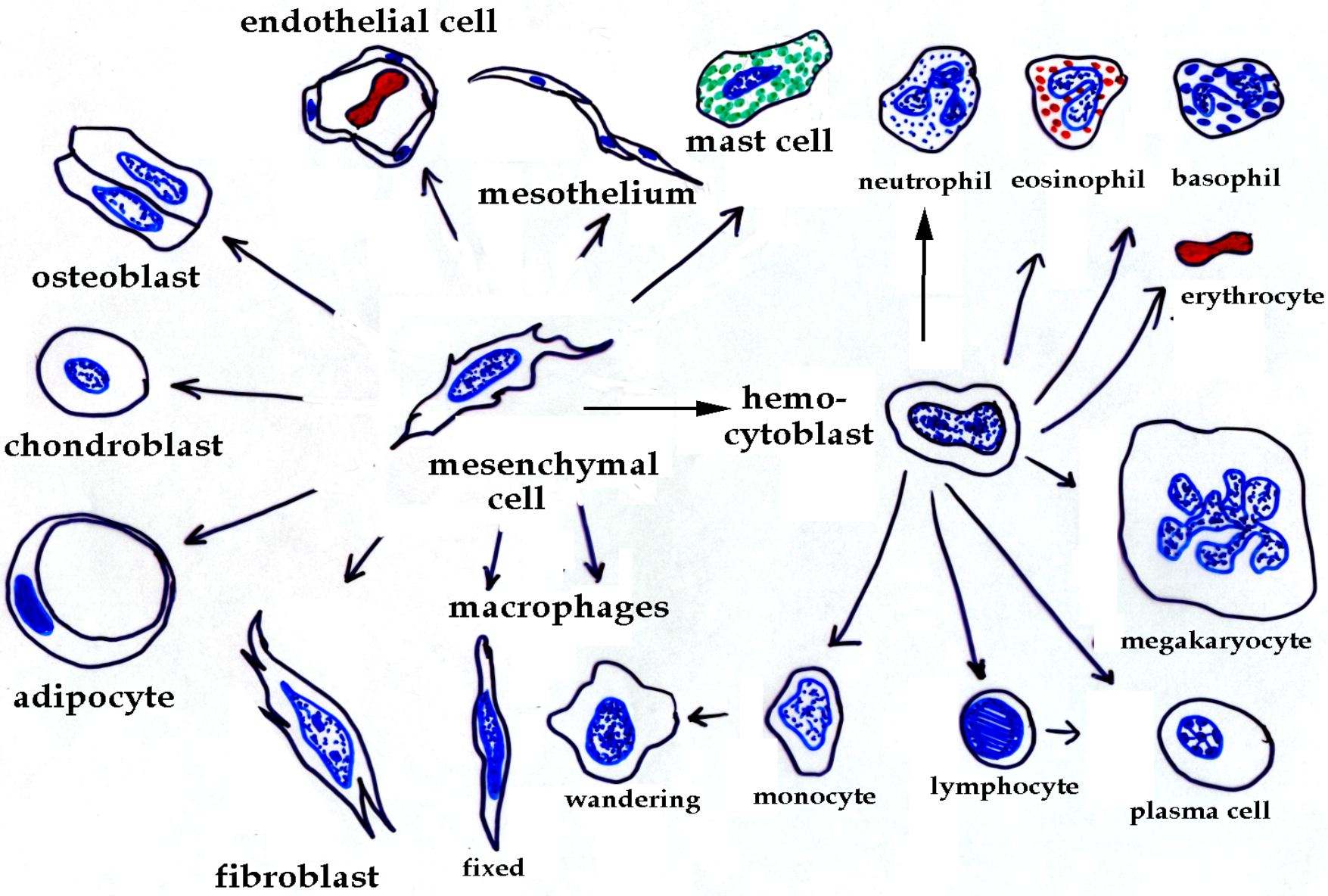
FUNCTIONS

- Forms supporting tissue of the embryo
- Forms most connective tissue of the body
- Forms stromal components or framework of glands
- Mesenchyme acts as "packing tissue" occupying all the spaces between the germ layers.
- Some mesenchymal cells persist in the adult connective tissue and under particular stimuli can differentiate along various lines.

- The mesoderm mesenchyme gives rise to:
  - Connective tissue
  - Cartilage
  - Striated and smooth muscle
  - Heart
  - Kidneys
  - Ovaries
  - Tests
  - Genital ducts
  - Serous membranes lining the body cavities (pericardial, pleural and peritoneal)
  - Spleen
  - Cortex of suprarenal glands


THE MESENGENIC PROCESS
Mesenchymal Stem Cell (MSC)
Proliferation
MSC Proliferation
Osteogenesis
Chondrogenesis
Myogenesis
Marrow Stroma
Tendogenesis/ Ligamentagenesis
Other
Commitment
Transitory Osteoblast
Transitory Chondrocyte
Myoblast
Transitory Stromal Cell
Transitory Fibroblast
Lineage Progression
Chondrocyte
Osteoblast
Differentiation
Myoblast Fusion
ecm
Unique Micro-niche
Maturation
Osteocyte
Hypertrophic Chondrocyte
Myotube
Stromal Cells
T/L Fibroblast
Adipocytes, Dermal and Other Cells
BONE
CARTILAGE
MUSCLE
MARROW
TENDON / LIGAMENT
CONNECTIVE TISSUE
Bone Marrow / Periosteum
Mesenchymal Tissue

Cell Lineage from Mesenchymal Cells

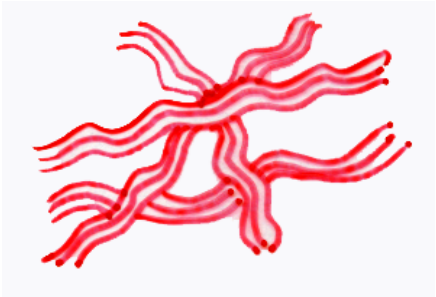


DEVELOPMENT OF CONNECTIVE TISSUE

- By 6th week of development, mesenchymal cells join with their process forming a syncytium.
- Cells are spindle shaped.
- Delicate argyrophilic fibrils or marginal filaments develop along the peripheral area of the cytoplasm.
- Cells with many fibrils are called **FIBROBLASTS**.
  - Fibroblasts are responsible for formation of fibres and ground substance of the supporting tissue.

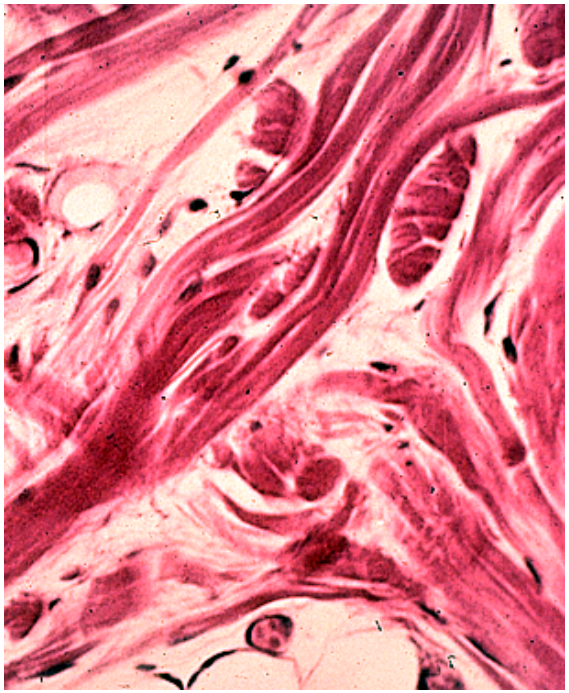
CONNECTIVE TISSUE FIBERS

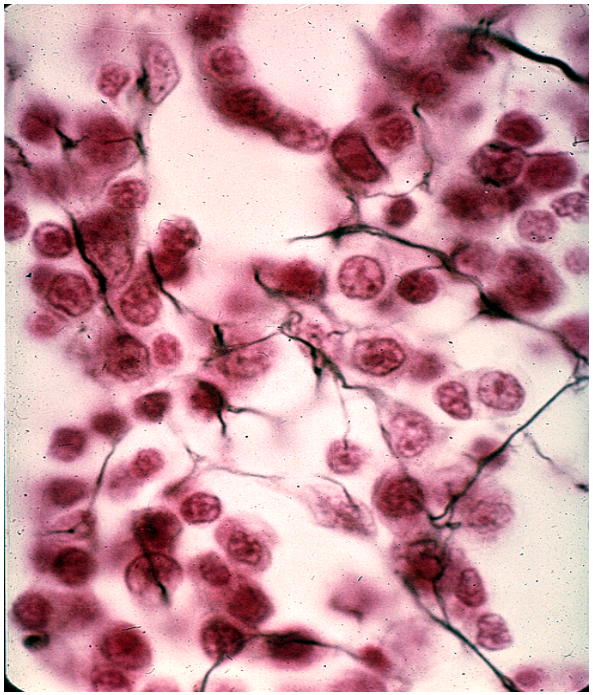
Collagenous Fibers
(bundles)

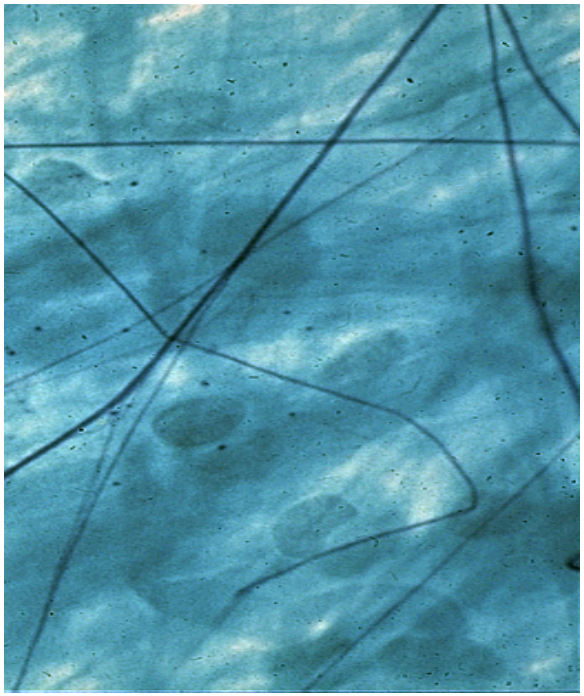


Reticular Fibers
(networks)

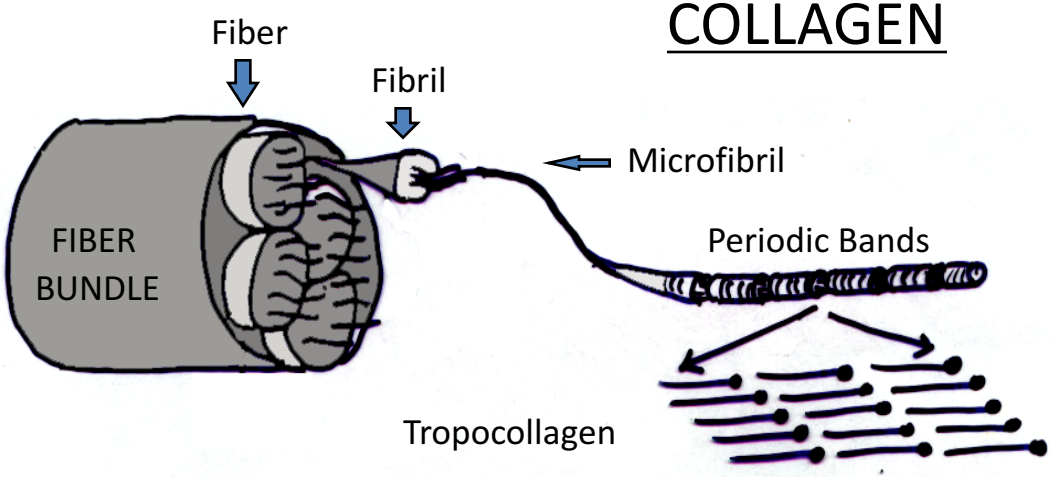
Elastic Fibers
(anastomosing bundles)

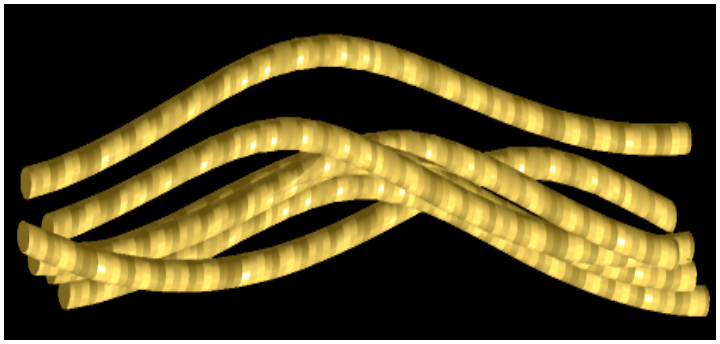






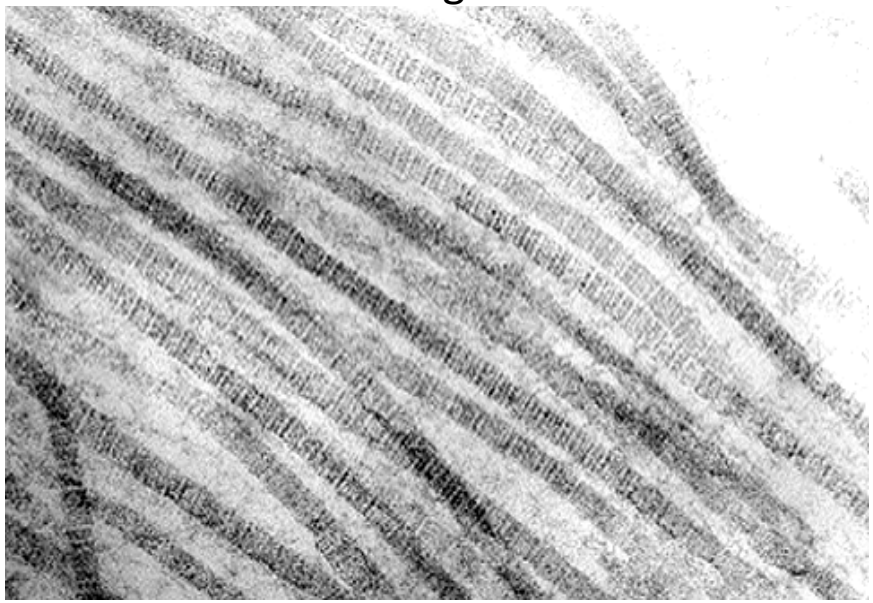
COLLAGEN



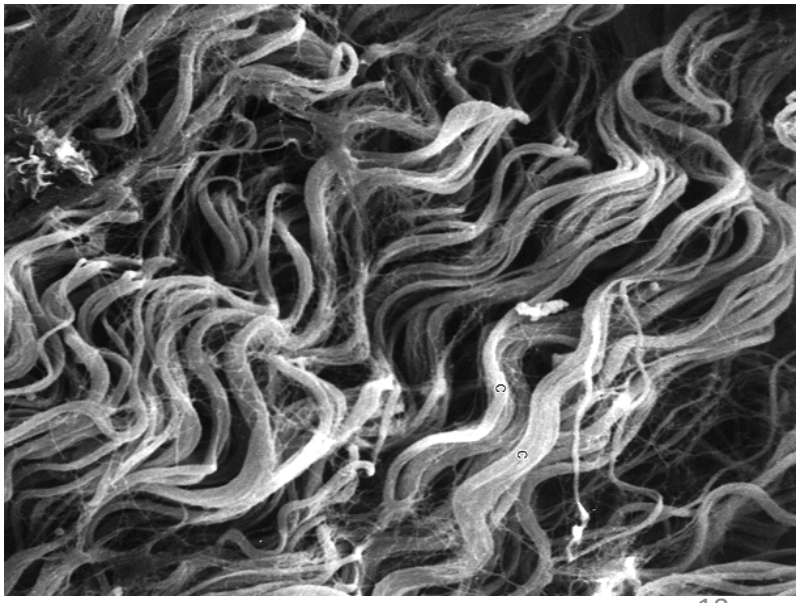


alpha 1 peptide
alpha 2 peptide

TEM of Collagen Fibers

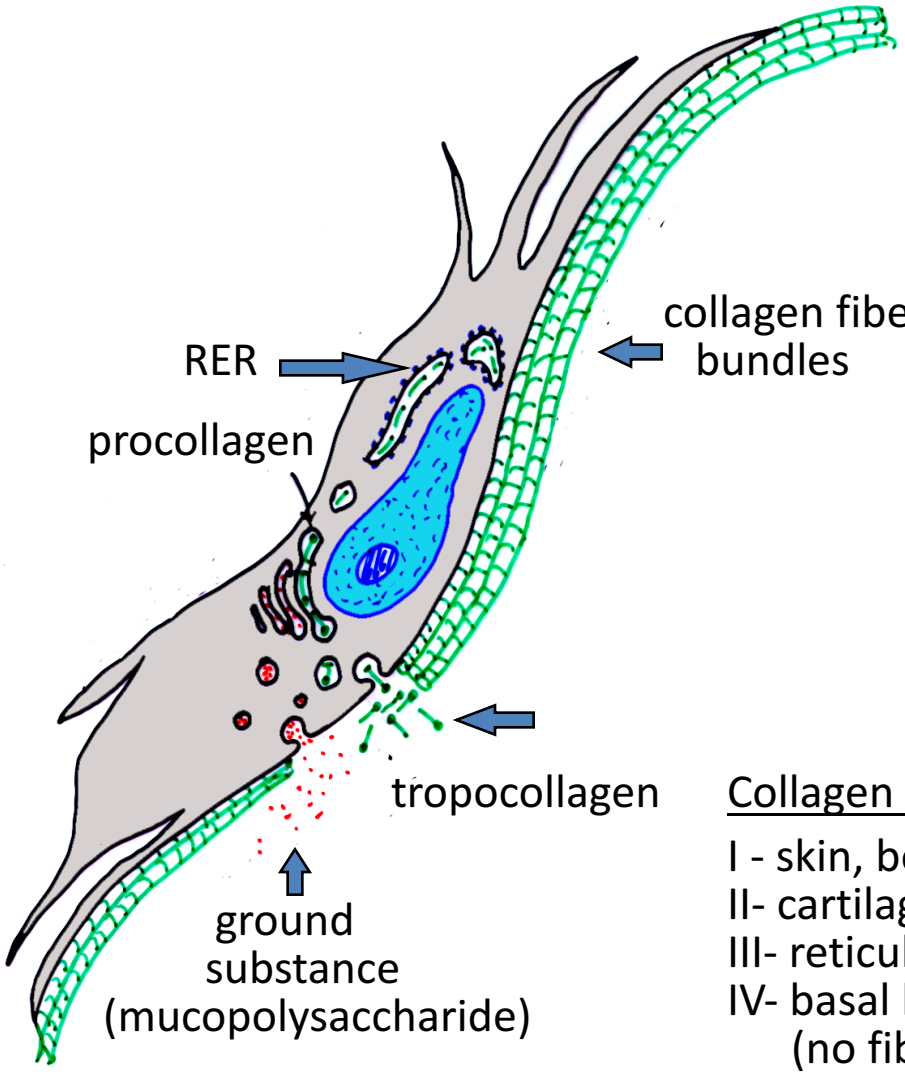


SEM of Collagen Fibers

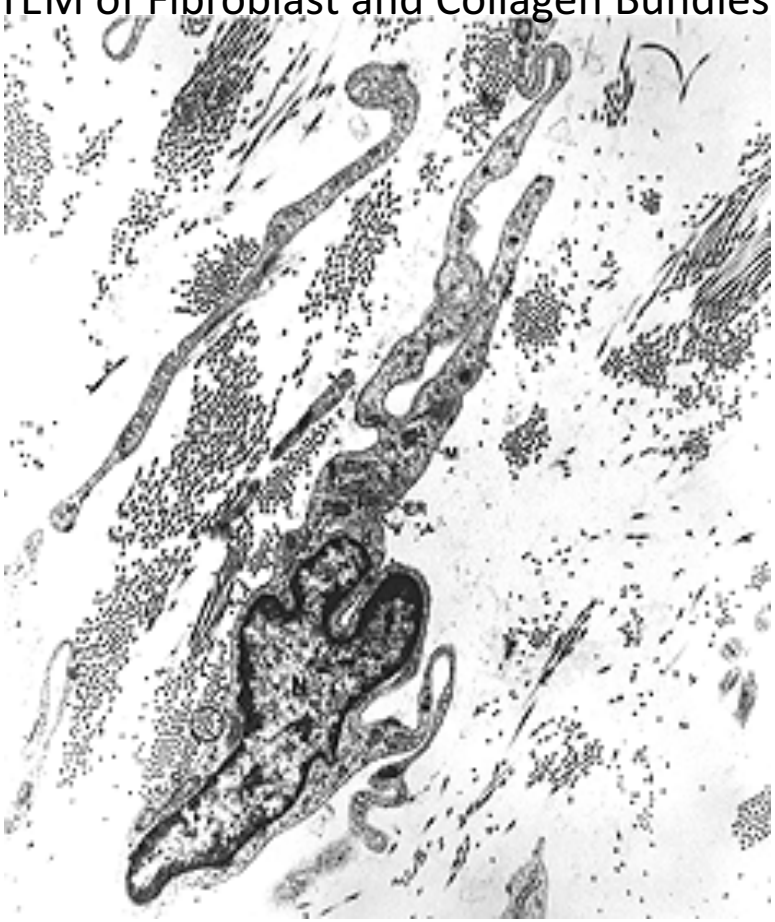


- Process of fibre formation is **fibrogenesis**
- **Fibrogenesis** begins from basic embryonic molecule called **tropocollagen**.
- By **5th month** , the fibrils have increased in number and thickness and are arranged in parallel bundles.
- The arrangement is correlated with the mechanical conditions under which the tissue will function.
- Reticular fibres arise by polymerization of tropocollagen.
  - They are the first fibres to develop during wound healing.

FIBROBLAST



TEM of Fibroblast and Collagen Bundles



Collagen Types

I - skin, bone, tendon cornea (most common type)
II- cartilage, embryonic cornea
III- reticular fibers, loose c.t., blood vessel walls, dermis
IV- basal lamina of epithelium
(no fibers, matrix of randomly-oriented molecules)

TYPES OF COLLAGEN

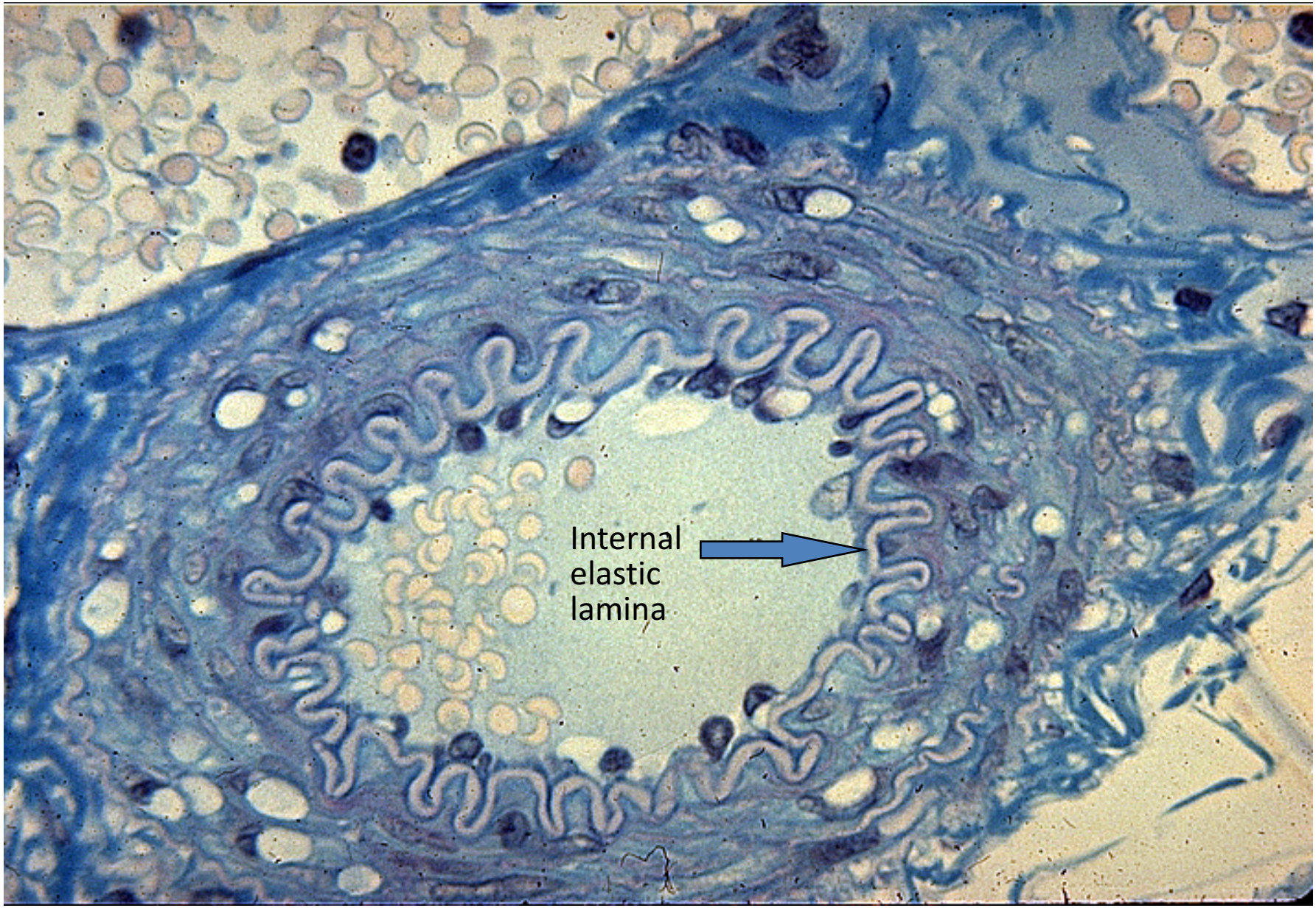
Type Tissues

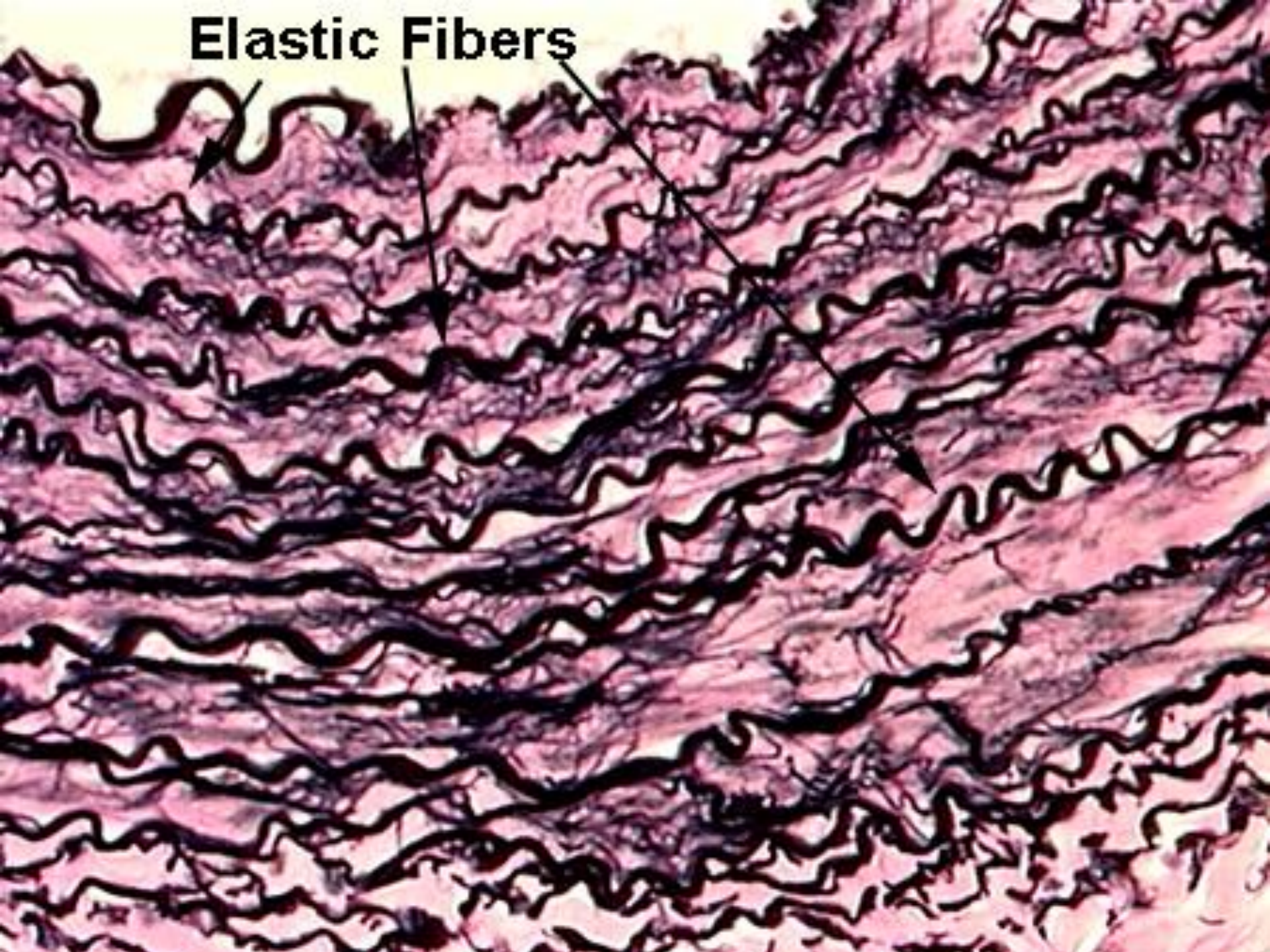
- **I** Skin, tendon, bone, meniscus, annulus fibrosus
- **II** Articular cartilage, vitreous humor, nucleus pulposus
- **III** Skin, muscle, blood vessels
- **IV** basement membrane (basal lamina)
- **V,VI,IX,X** articular cartilage
- **X** Articular cartilage, mineralization of cartilage in hypertrophic zone of physis
- **XI** Articular cartilage
- **XII** Tendon
- **XIII** endothelial cells

ELASTOGENESIS

- Production of elastic fibres (elastogenesis) follows the appearance of collagen fibres.
- Elastic fibres are produced by specialized fibroblasts referred to as **ELASTOBLASTS**.
  - The first stage of elastogenesis is represented by condensation of fusiform mesenchymal cells.
  - Later, short delicate filaments appear orientated along the axis of the tendon and among collagen fibres.
  - Formation of elastic fibres proceeds further with an increase in thickness and correspondingly more organization of the surrounding collagen fibres.
- Elastic fibres are similar to collagen in content of glycine and proline but differ in the content of valine and desmocine.

ELASTIC CONNECTIVE TISSUE IN BLOOD VESSEL WALL



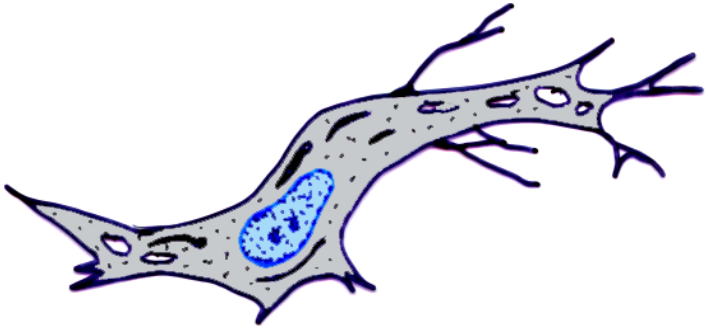

Elastic Fibers

DEVELOPMENT OF ADIPOSE TISSUE

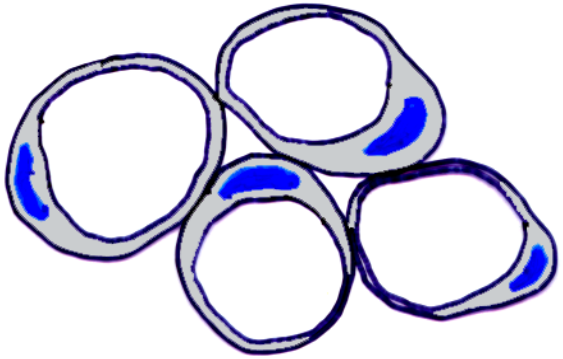
- Adipose tissue is formed by **LIPOBLASTS** which are cells capable of storing lipoidal material.
- The distribution of fat differs in both sex and varies in individuals.
- In the developing fetus, subcutaneous fat is laid down during the last two months as white adipose tissue.
- Brown adipose tissue has more cytochrome and flavoproteins which give it typical reddish-brown color.
  - It is distributed in the following areas:
    - Axilla
    - Cervical region
    - Interscapular area
    - Mediastinum
    - Aortic area
    - Pararenal area
    - Inguinal areas.
  - Brown fat is used by the infant to generate heat.

FIXED CONNECTIVE TISSUE CELL TYPES

Fibroblast
(fiber producing cell)

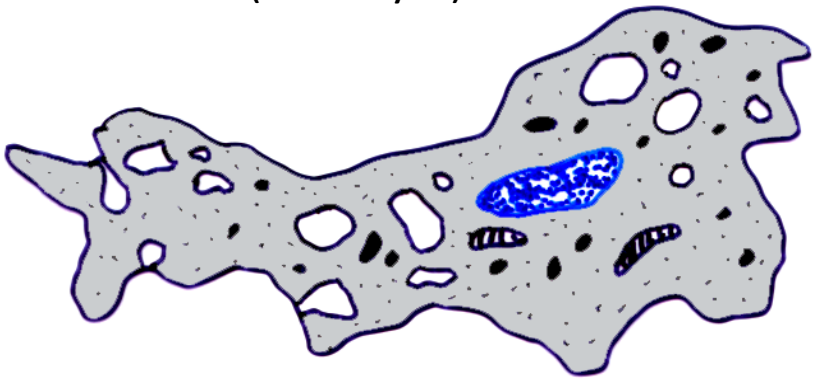


Adipocytes
(fat storage)



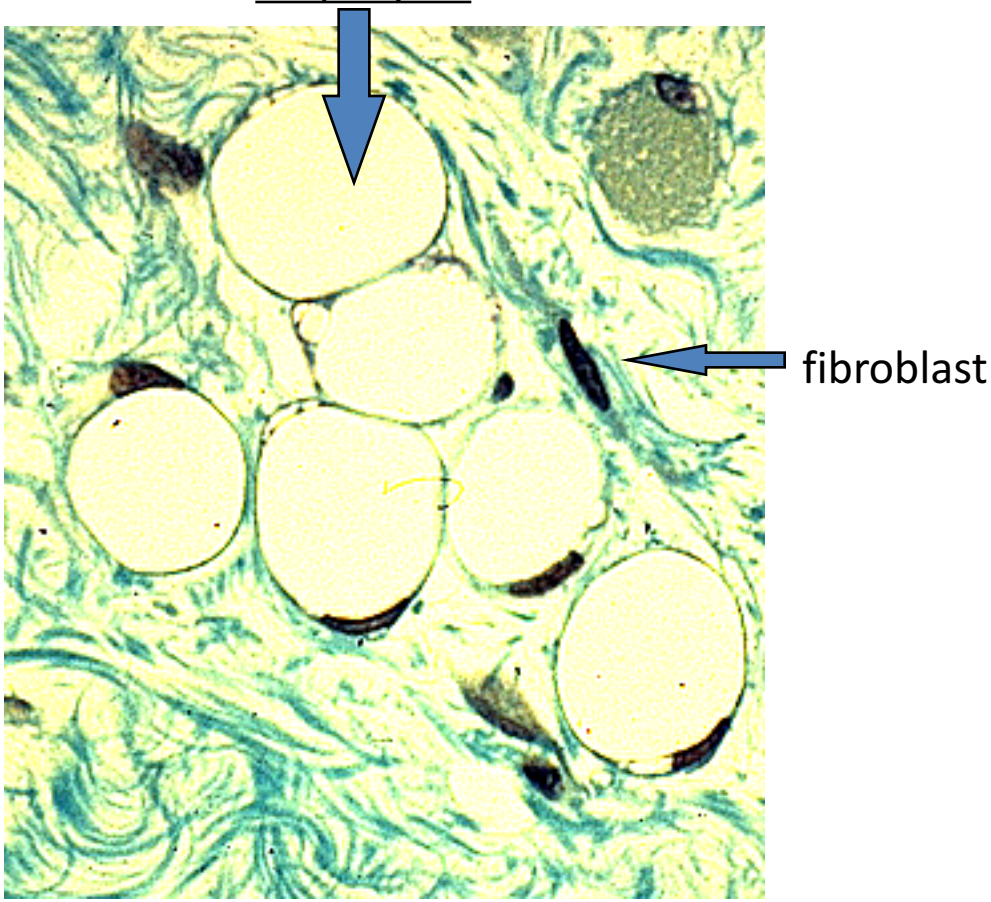
Fibrocyte
(mesenchymal- pluropotent)

Fixed Macrophage
(histiocyte)

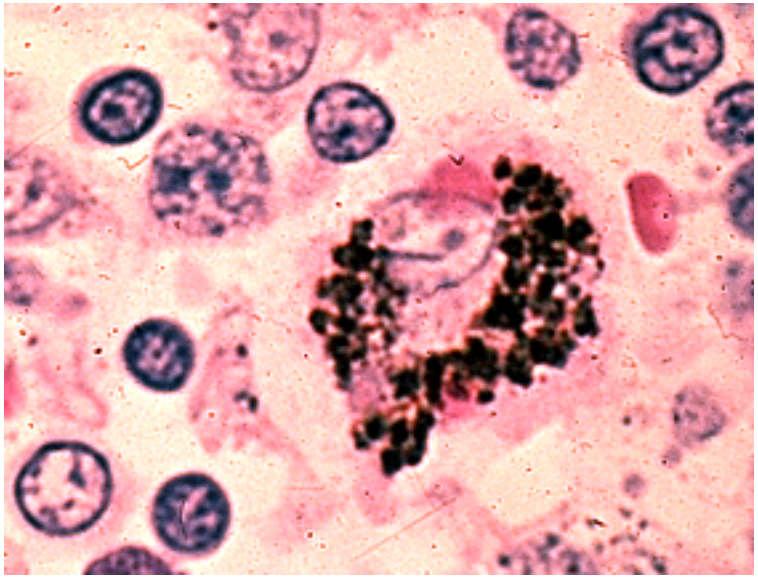


Fixed Connective Tissue Cells

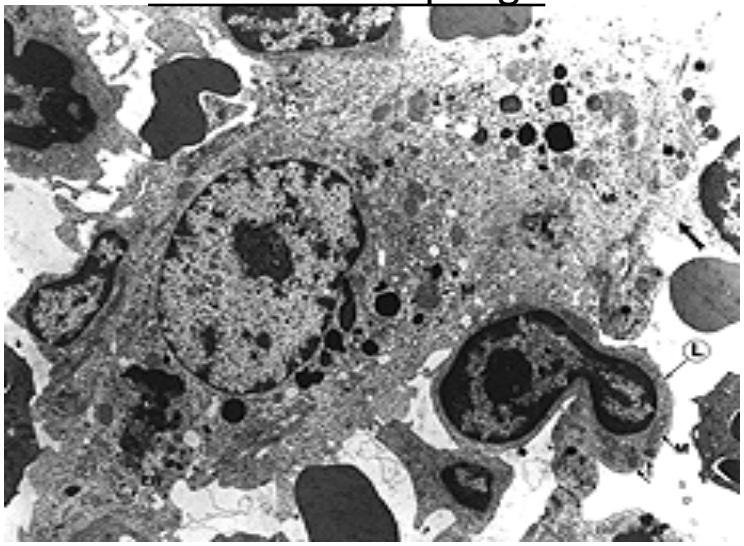
Adipocytes



Macrophage (light micrograph)



TEM of Macrophage

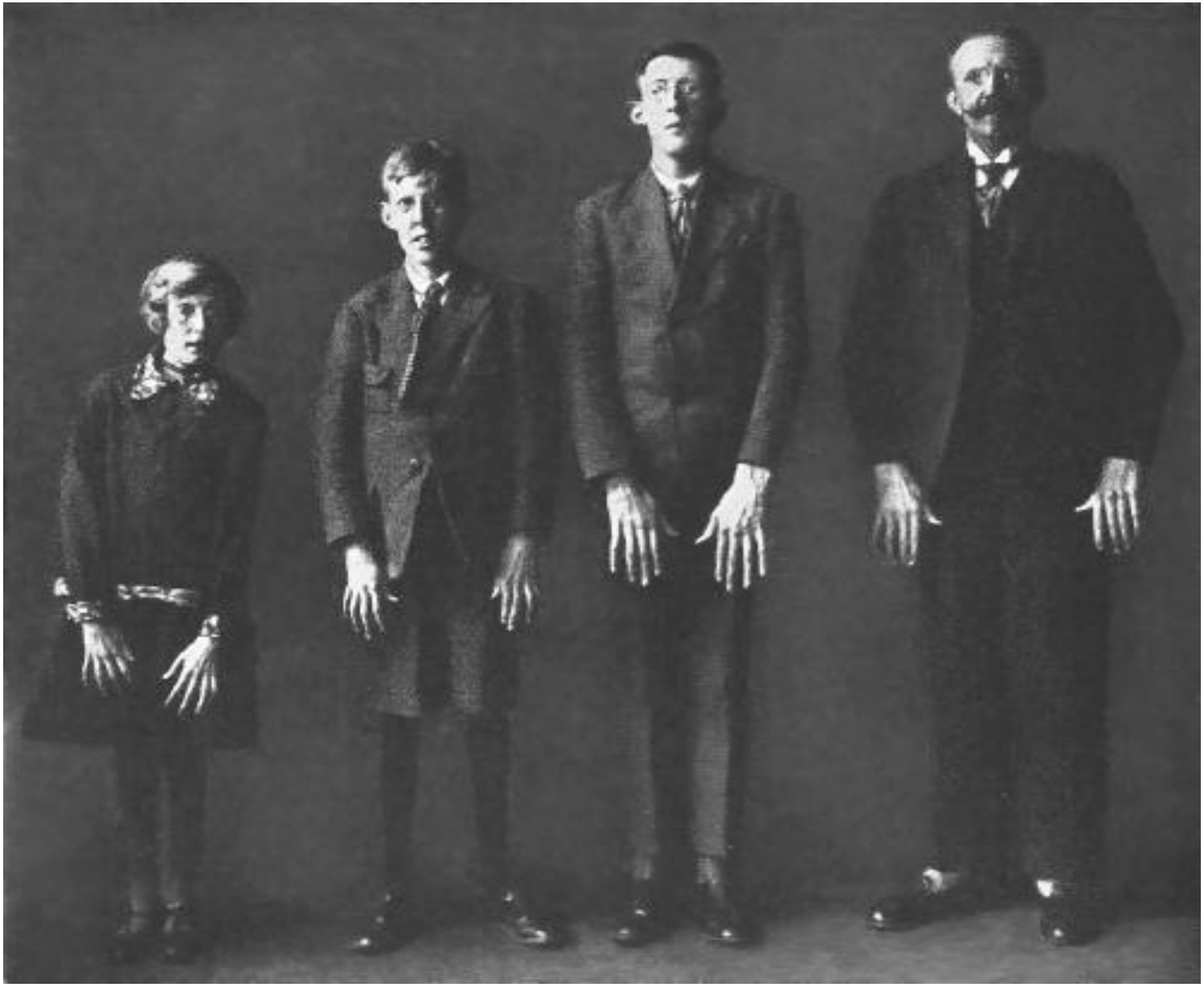


ABNORMALITIES OF DEVELOPMENT OF CONNECTIVE TISSUE

- These are dependent on the type of connective tissue involved and the organ e.g. defective collagen fibres which are of various varieties may lead to defective blood vessels, cervical incompetence, lax joints etc.

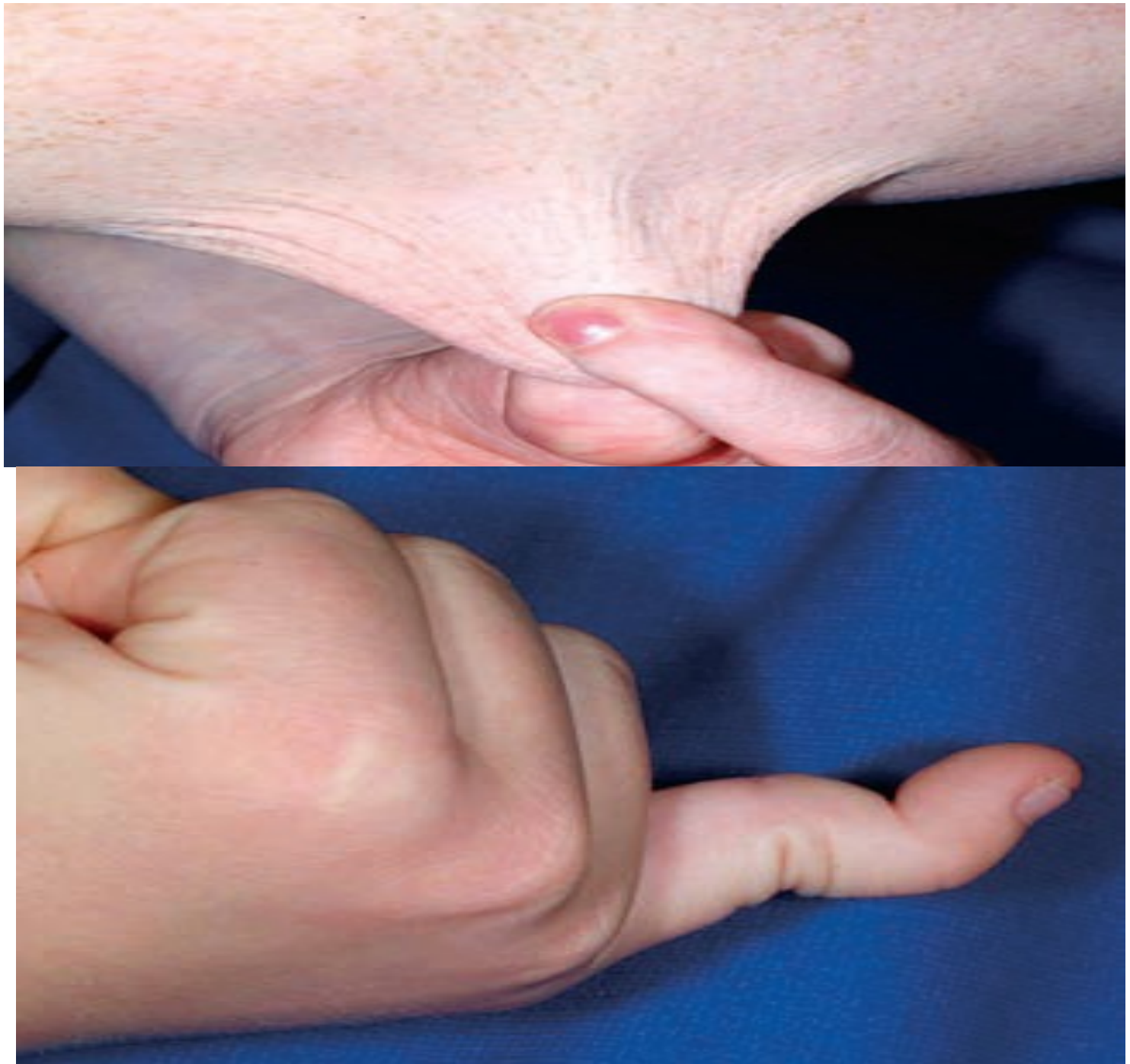
Marfan Syndrome

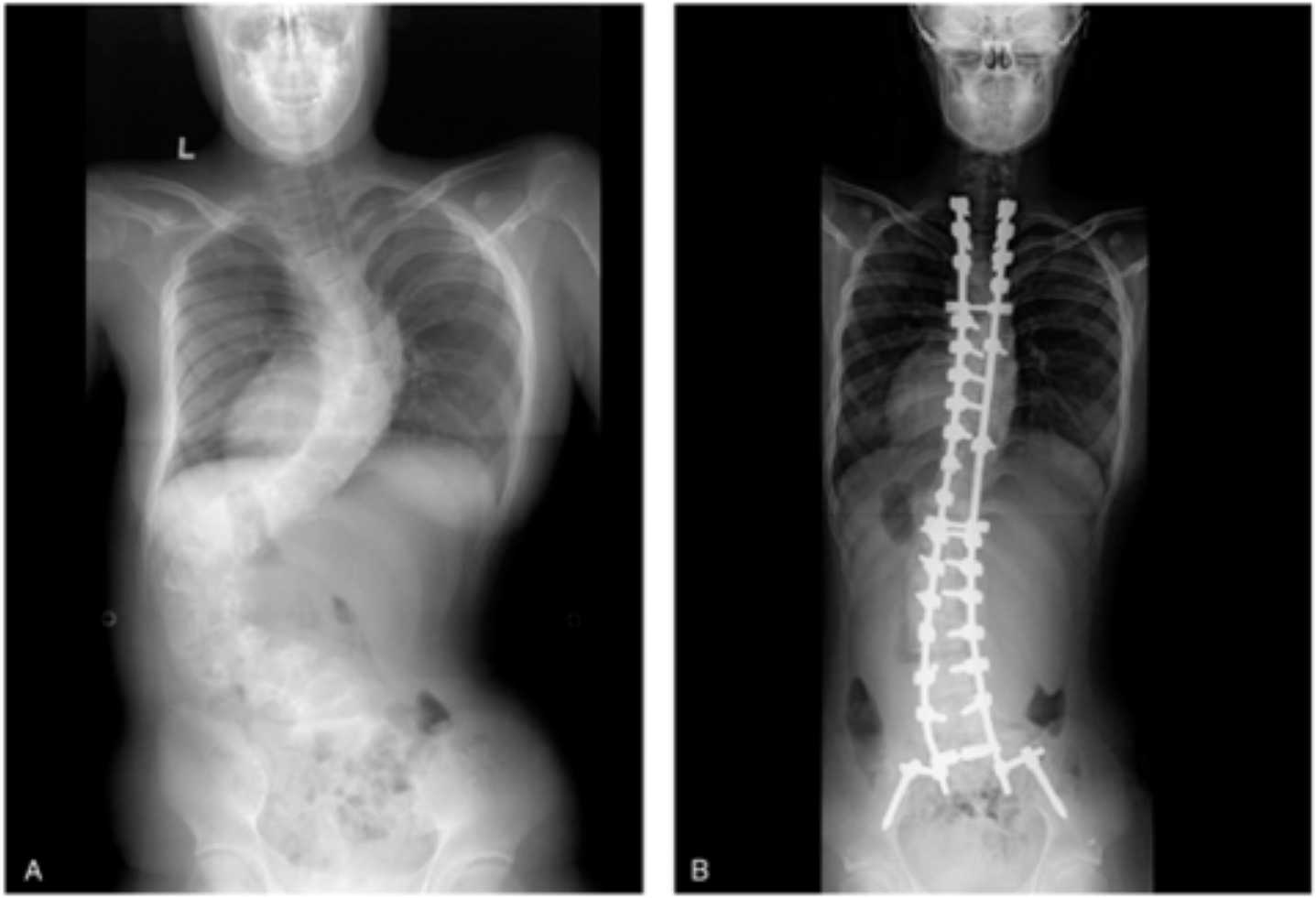
- An inherited disorder caused by a defective gene for the glycoprotein fibrillin resulting in abnormal development of elastic fibers.
- This causes tissues that contain many elastic fibers to be malformed or weak (including the covering of bone, ligament that suspends the lens of the eye, and the walls of large arteries.
- People with Marfan syndrome are often tall, have long arms, legs, fingers and toes, blurred vision, and weakened aortic walls that may burst.



EHLERS-DANLOS SYNDROME (EDS)

- Hypermobile joints, hyperextensible skin, fragile tissues extremely susceptible to trauma
- 40% to 50% of patients: mutation in COL5A1 or COL5A2 (**type V** collagen gene)
- 7 types
- Classic form: AD
- **Type VI**, AR (mutation in lysyl hydroxylase. Severe kyphoscoliosis - characteristic)
- **Type IV**, AD (mutation in COL3A1 thus abnormal collagen III; arterial, intestinal, and uterine rupture seen)



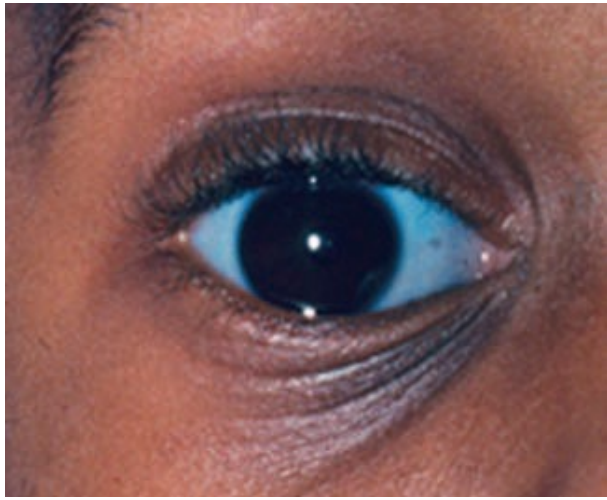

L
A
B

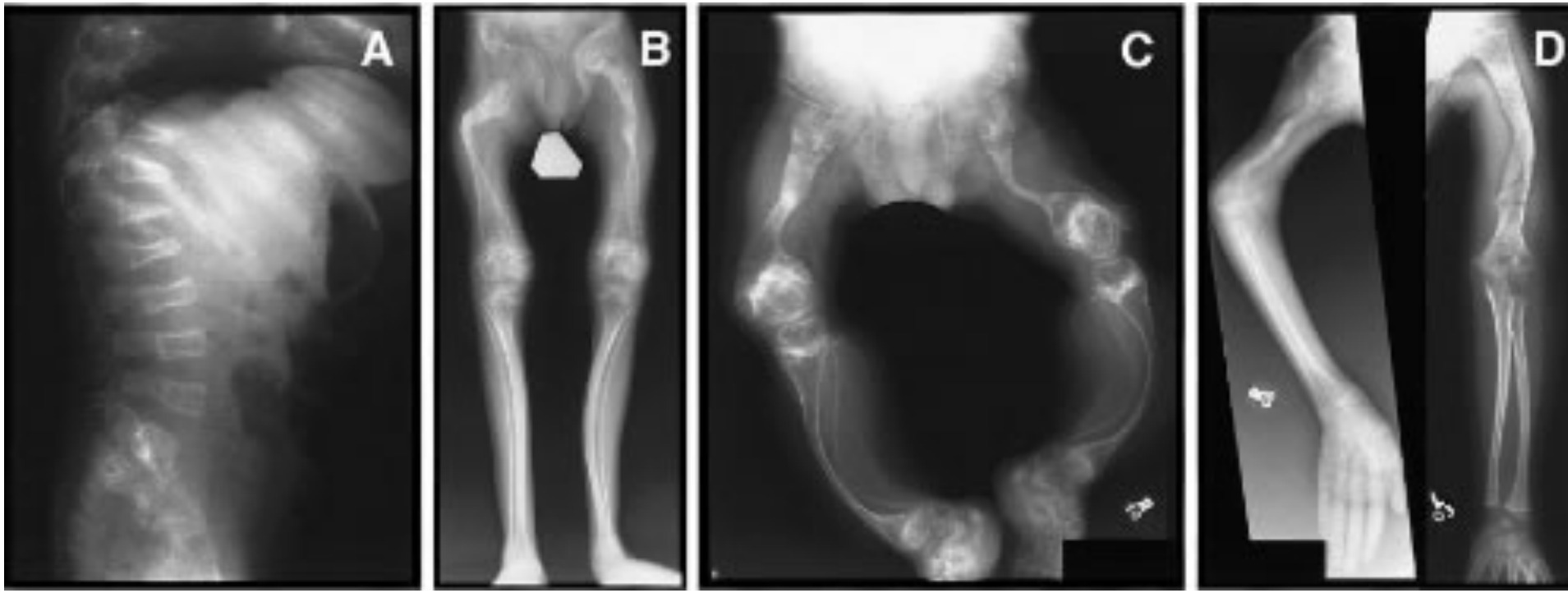
TYPES OF EHLERS-DANLOS SYNDROME

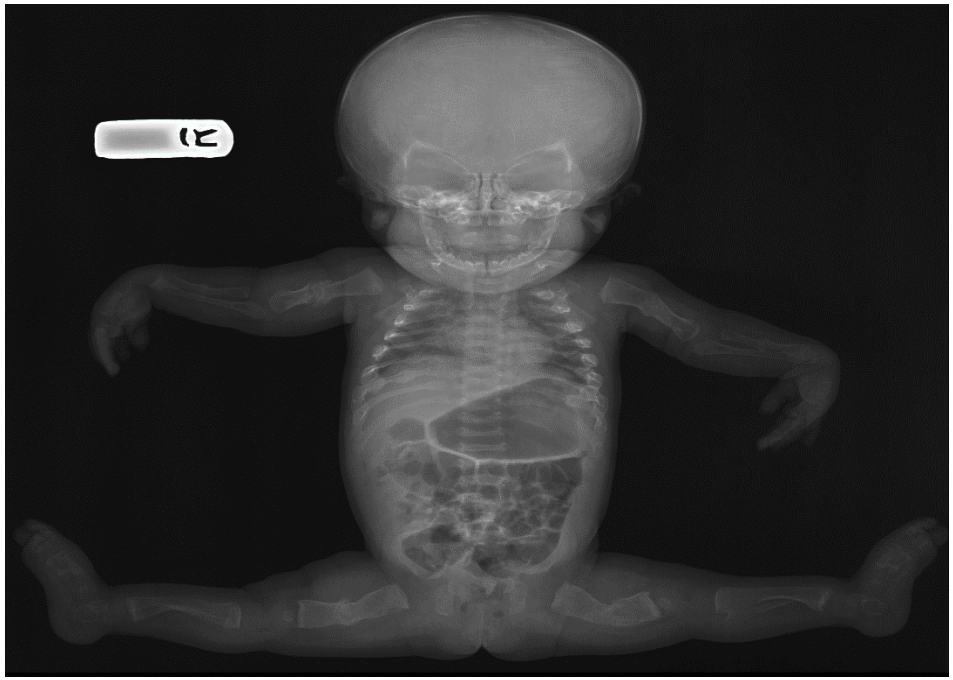
- Hypermobility Type
- Classical Type
- Vascular Type
- Kyphoscoliosis Type
- Arthrochalasia Type
- Dermatosparaxis Type
- Other Types

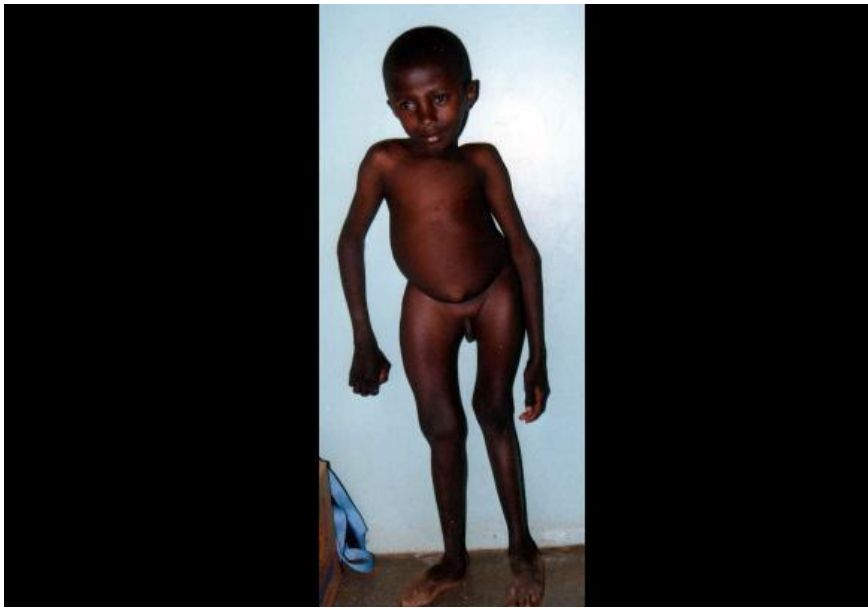
OSTEOGENESIS IMPERFECTA (OI)

- Types I through IV : mutation in the COL1A1 and COL1A2 genes
- Bone that has decreased number of trabeculae and cortical thickness (wormian bone)
- Types V through VII no collagen I mutation but
  - similar phenotype and
  - abnormal bone on microscopy




A
B
C
D





MULTIPLE EPIPHYSEAL DYSPLASIA

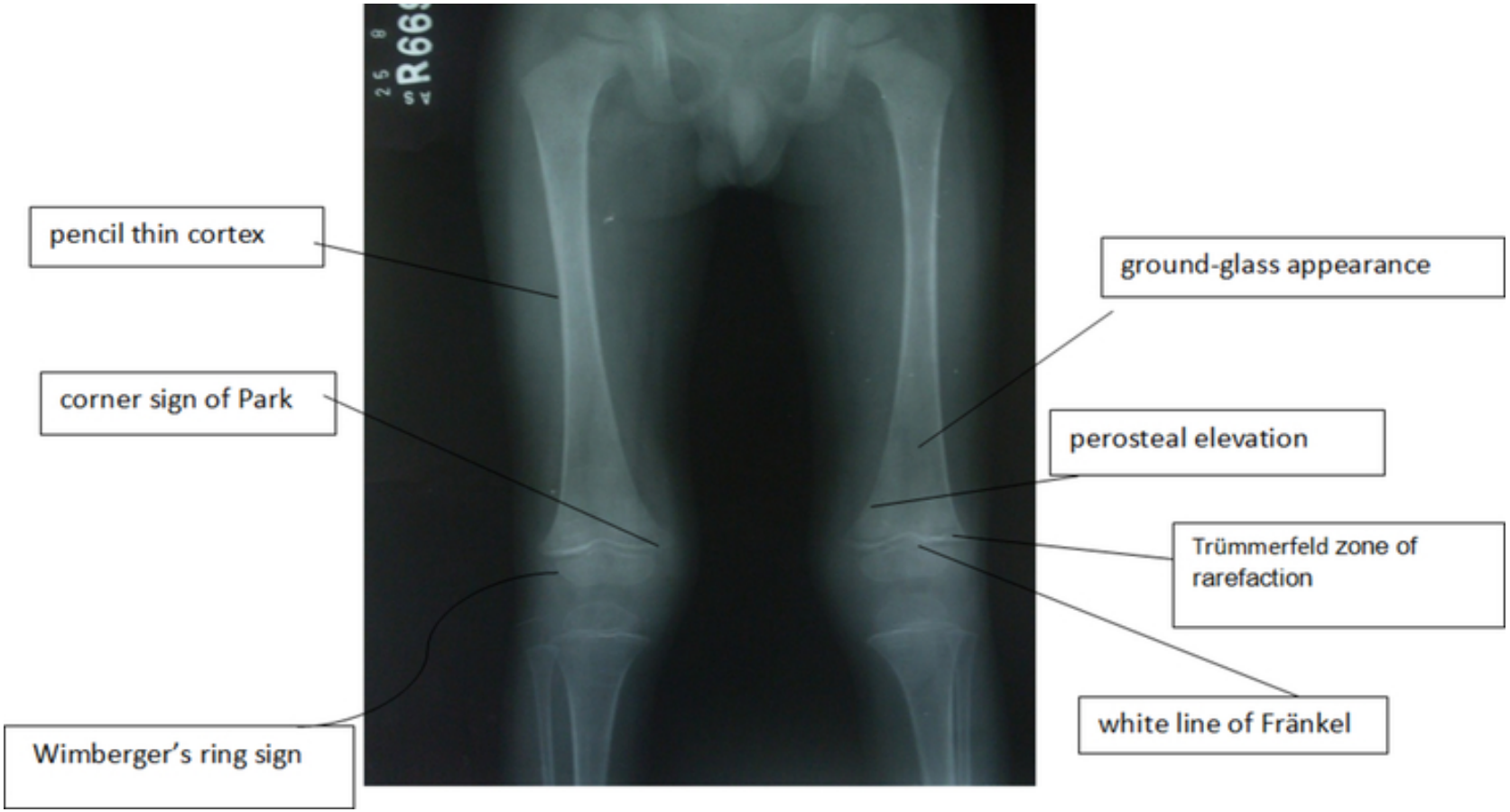
- Gene mutation is in COMP
- AD
- Radiologic findings: irregular, delayed ossification at multiple epiphyses
- P/E: Short, stunted metacarpals and metatarsals,
- Irregular proximal femora,
- Abnormal ossification (tibial “slant sign” & flattened femoral condyles, patella with double layer)
- Valgus knees (early osteotomy should be considered),
- Waddling gait, and early hip arthritis

OTHER COLLAGEN ASSOCIATED DISEASES

1. Scurvy

- Acquired: vitamin C deficiency
- Decrease in chondroitin sulfate and collagen synthesis
- Greatest deficiency seen in the metaphysis
- P/E: microfractures, hemorrhages, and collapse of the metaphysis
- Characteristic radiographic findings: line of Frankel and osteopenia of the metaphysis.

FEATURES OF SCURVY ON X-RAY OF LONG BONES



Summary of connective tissue disorders

MarfanSyndrome
- Fibrillin

Ehrlos-Danlos
- Type I/III collagen

OsteogenesisImperfecta
- Insufficient Type I collagen

Alportsyndrome
- Type IV collagen
- Basement membrane disease
- Hearing/vision loss, glomerulonephritis

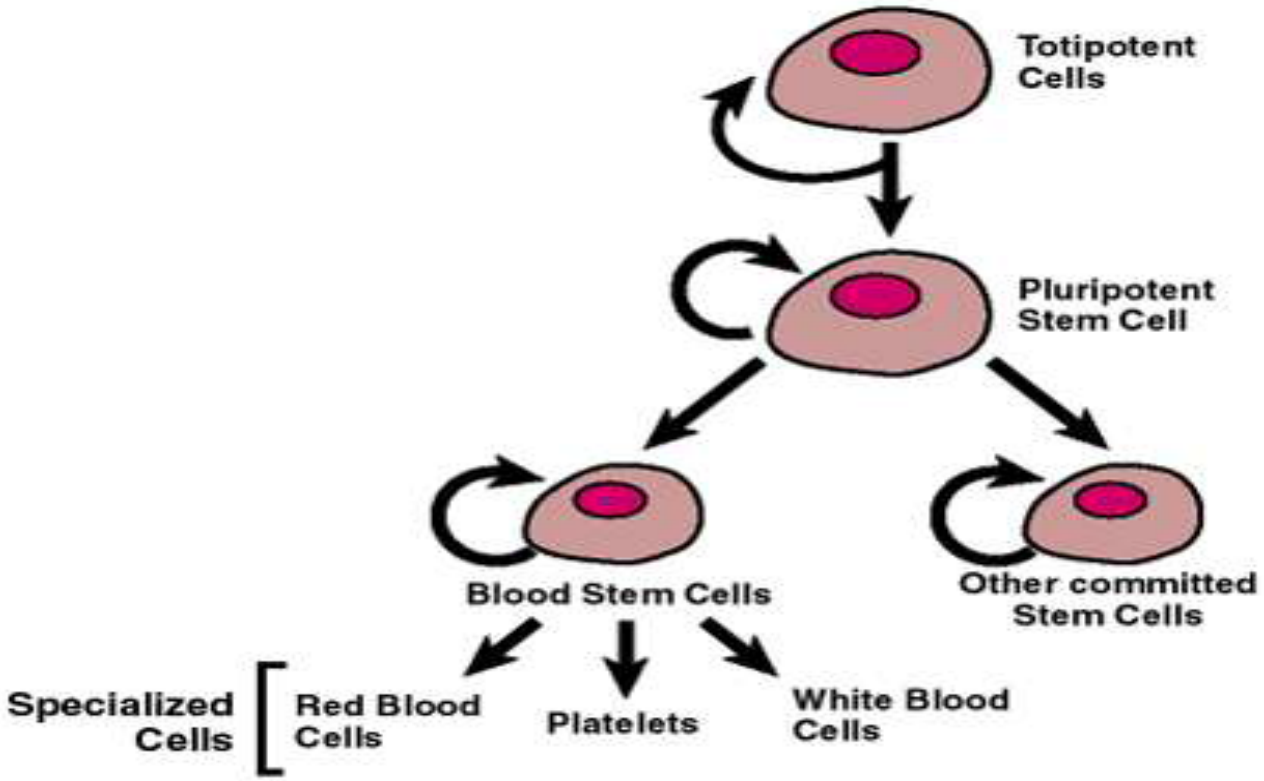
WHAT ARE STEM CELLS?

- Undifferentiated cells found throughout the body that…
  1. Divide to create new stem cells
  2. Differentiate into other cell types

STEM CELLS: 3 BROAD CATEGORIES

- Defined by Cell's Ability to Differentiate
- **Totipotent**
  - found only in early embryo
  - can create a complete organism, e.g. identical twin
- **Pluripotent**
  - exist in undifferentiated inner cell mass of the blastocyst
  - can form any of >200 different cell types found in the body
- **Multipotent**
  - derived from fetal tissue, cord blood, and adult tissues
  - ability to differentiate more limited than pluripotent cells

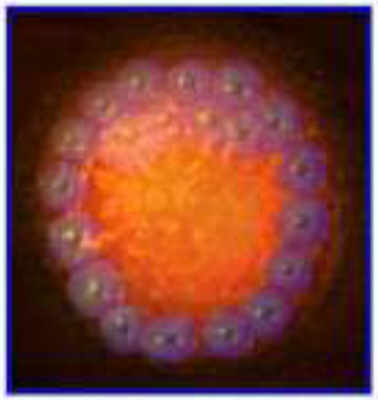
STEM CELL HIERARCHY



STEM CELL TIMELINE

Single Cell Embryo

Totipotent



5-7 Day Embryo

Embryonic Stem (ES) Cells

Pluripotent

Infant

Adult

"Adult" Stem Cells

Multipotent

Cord Blood Stem Cells

Placental Stem Cells

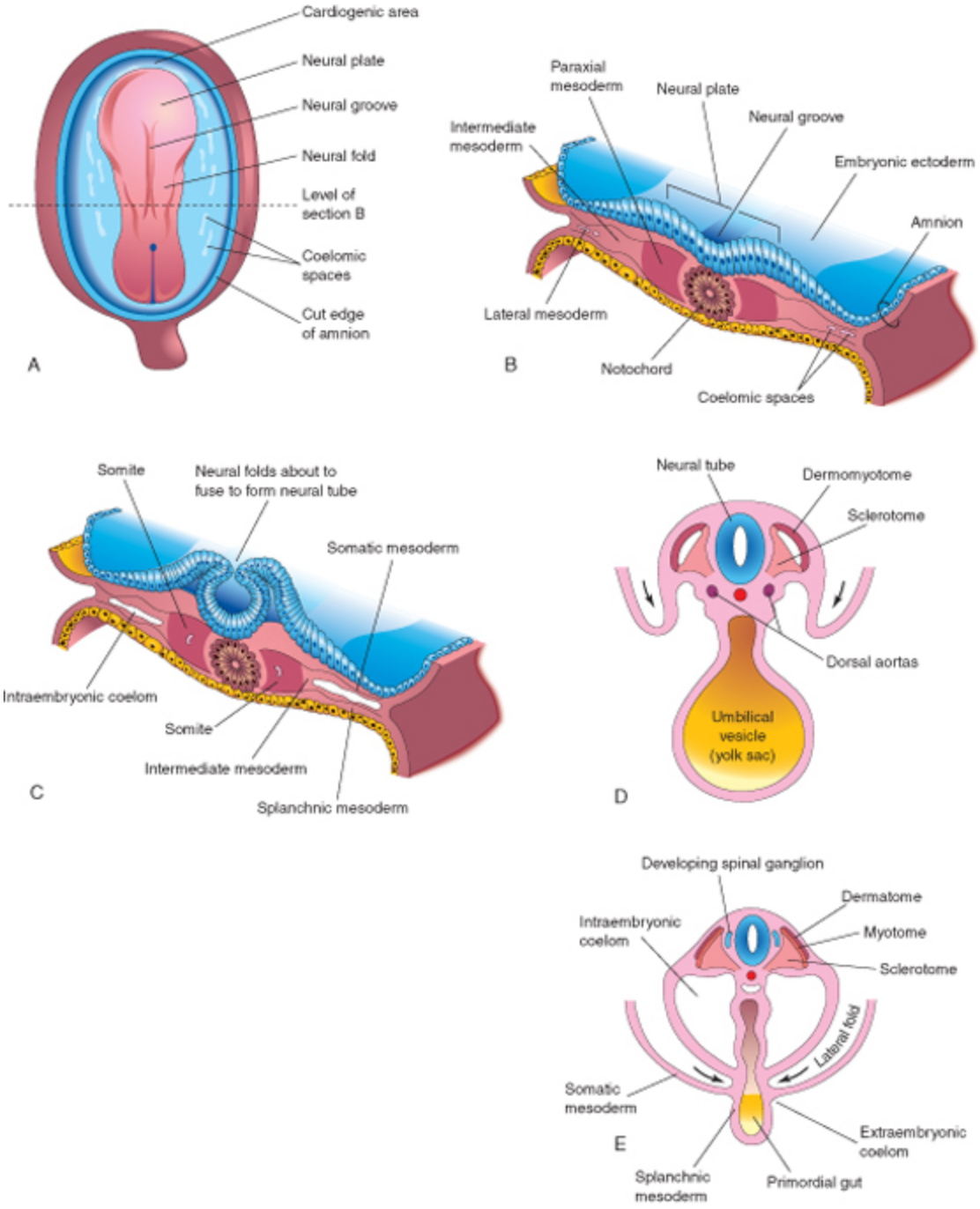
Multipotent

DEVELOPMENT OF BONE, CARTILAGE AND JOINTS

Prof Peter Gichangi

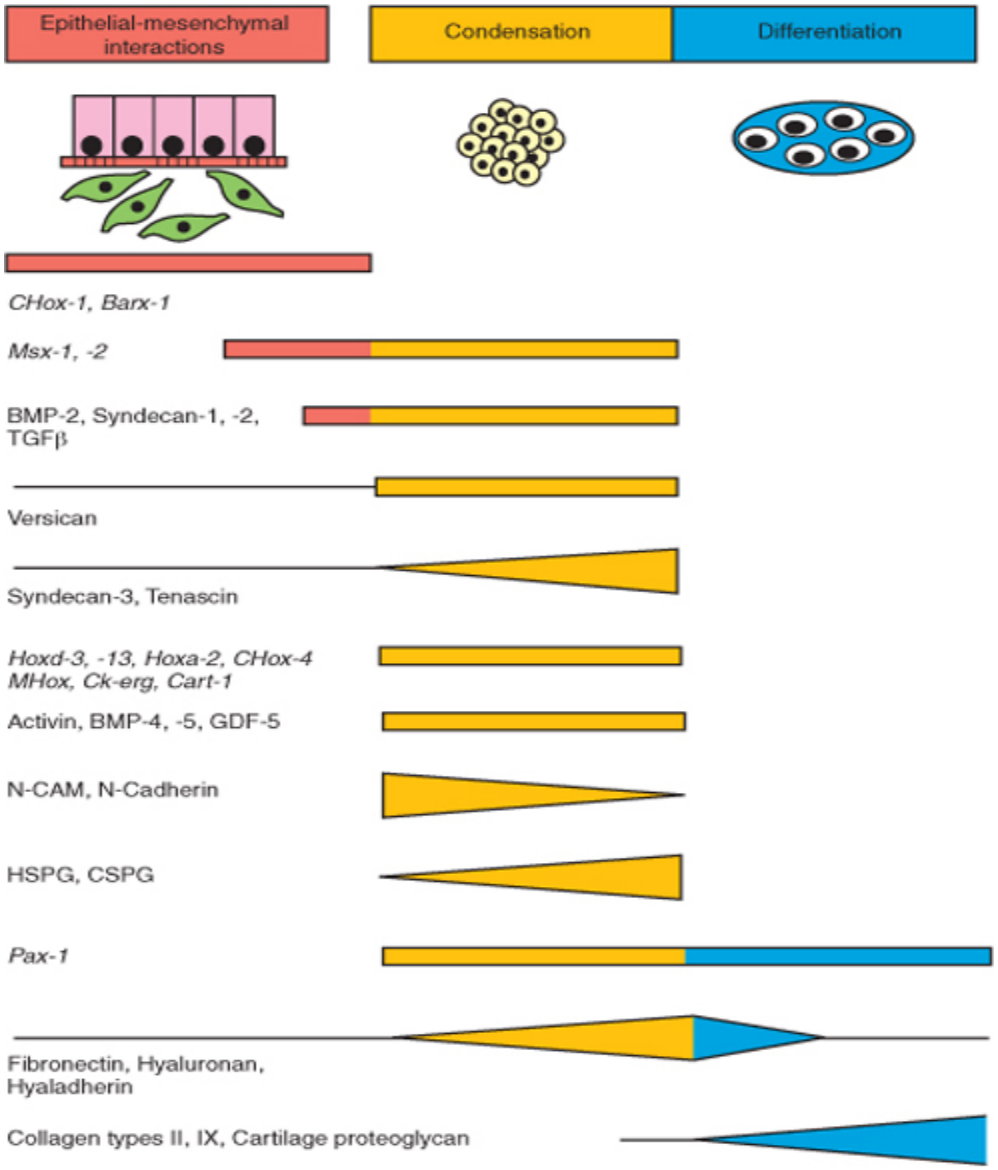
OBJECTIVES

- Understand the process of cartilage, bone and JOINT development
- Understand the embryological basis of cartilage and bone congenital malformation



HISTOGENESIS OF CARTILAGE

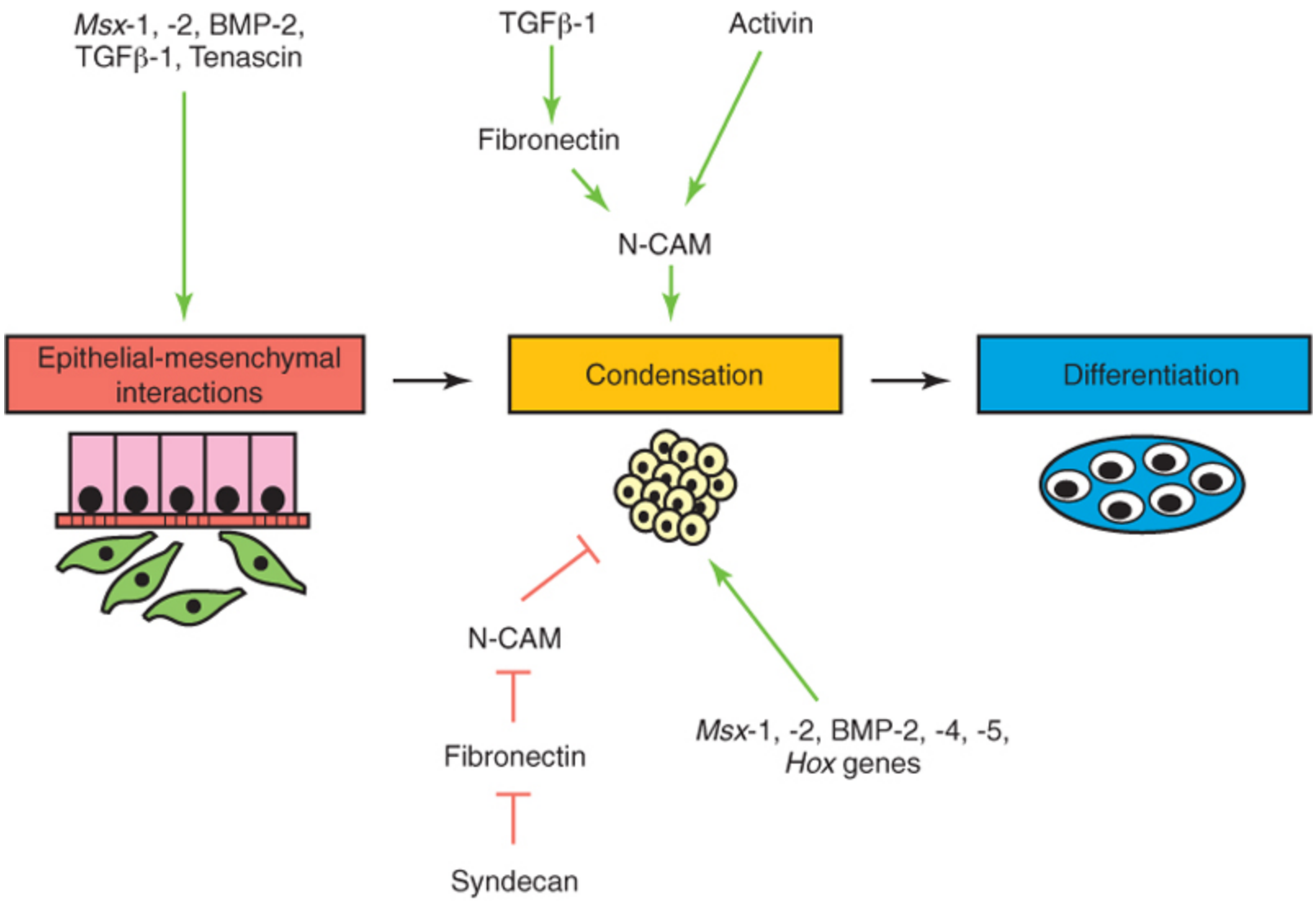
- Cartilage develops from mesenchyme.
- First appears in embryos during the **5th week**.
- In areas where cartilage is to develop, the mesenchyme condenses to form **chondrification centers**.
- The mesenchymal cells differentiate into **chondroblasts** that secrete collagenous fibrils and the ground substance.
- Collagenous and/or elastic fibers are deposited in the intercellular substance or matrix.
- Three types of cartilage are distinguished according to the type of matrix that is formed:
  - **Hyaline cartilage**, the most widely distributed type (e.g., in joints)
  - **Fibrocartilage** (e.g., in intervertebral discs)
  - **Elastic cartilage** (e.g., in auricle of ear)



Summary of chondrogenesis in the craniofacial skeleton

- The three phases are precondensation, characterized by epithelial-mesenchymal interactions (brown); condensation (yellow); and differentiation (blue).
- The precondensation phase is characterized by expression of *Hox* genes (*CHox-1* [*Hoxa 4*], *Barx-1*), Msx-1, -2, the growth factors bone morphogenetic protein [BMP]-2 and[transforming growth factor β [TGF-β], and syndecan-1. Versican, syndecan-3, and tenascin, which are present in low concentrations precondensation, are up-regulated at condensation.
- Other *Hox* genes and transcription factors (*Hoxd-3*, *-13*, *Hoxa-2*, Cdxa [*Chox*-4], *Mhox*, *Ck-erg*, and *Cart-1*) and other growth factors (activin, BMP-4, -5, and GDF-5) are expressed at condensation.
- The cell adhesion molecules neural cell adhesion molecule (N-CAM) and N-cadherin also appear with condensation but are down-regulated during condensation.
- Heparan sulfate and chondroitin sulfate proteoglycans appear at condensation and are up-regulated during condensation.
- The transcriptional factor *Pax*-1 is present during and after condensation.
- Extracellular matrix molecules such as fibronectin, hyaluronan, and hyaladherin increase during condensation (yellow) but are down-regulated thereafter (blue).
- Collagen types II and IX and cartilage proteoglycan appear postcondensation, although mRNAs for the collagens and for the core protein of the proteoglycan are up-regulated during condensation.

CONDENSATION FORMATION



DIFFERENTIATION

HISTOGENESIS OF BONE

- Bone primarily develops in two types of connective tissue, mesenchyme and cartilage, but can also develop in other connective tissues.
- Like cartilage, bone consists of cells and an organic intercellular substance-the **bone matrix**-that comprises collagen fibrils embedded in an amorphous component.
- Osteogenesis and chondrogenesis are programmed early in development and are independent events under the influence of vascular events.

BONE FORMATION

- Bone formation is termed *osteogenesis* or *ossification.*
- It is a process of transforming mesenchyme to bone.
- Bone first appearance - **condensations of mesenchymal cells.**
  - *Condensation* marks the beginning of selective gene activity, which precedes cell differentiation.
- Two types of ossification occur.
  - ***Intramembranous ossification*** is the formation of bone directly from or within fibrous connective tissue membranes.
  - ***Endochondrial ossification*** is the formation of bone from hyaline cartilage models.

- ***Intramembranous ossification –*** no bone model.
- ***Endochondrial ossification –*** first form hyaline cartilage bone model.
- Bone morphogenetic proteins (BMP-5 and BMP-7), the growth factor Gdf5, members of the transforming growth factor β (TGF-β) superfamily, and other signaling molecules have been implicated as *endogenous regulators of chondrogenesis and skeletal development.*

INTRAMEMBRANOUS OSSIFICATION

- Mesenchyme forms a membranous sheath, hence, the name intramembranous ossification.
- Also called dermal ossification because it normally occurs in the deeper layers of connective tissue of the dermis of the skin.
- The mesenchyme condenses and becomes highly vascular.
- Some cells differentiate into **osteoblasts** (bone-forming cells) and begin to deposit unmineralized matrix - **osteoid**.
- Calcium phosphate is then deposited in the osteoid tissue as it is organized into bone.

- Osteoblasts are trapped in the matrix and become **osteocytes**.
- At first, new bone has no organized pattern.
- Spicules of bone soon become organized and coalesce into lamellae (layers).
- **Concentric lamellae** develop around blood vessels, forming **osteons** (haversian systems).
- Some osteoblasts remain at the periphery of the developing bone and continue to lay down lamellae, forming plates of compact bone on the surfaces.
- Between the surface plates, the intervening bone remains spiculated or spongy.

- Osteoclasts are multinucleated cells with a hematopoietic origin.
- In the interstices of spongy bone, the mesenchyme differentiates into **bone marrow**.
- During fetal and postnatal life, there is continuous remodeling of bone by the coordinated action of osteoclasts and osteoblasts.
- All roofing bones of the Skull

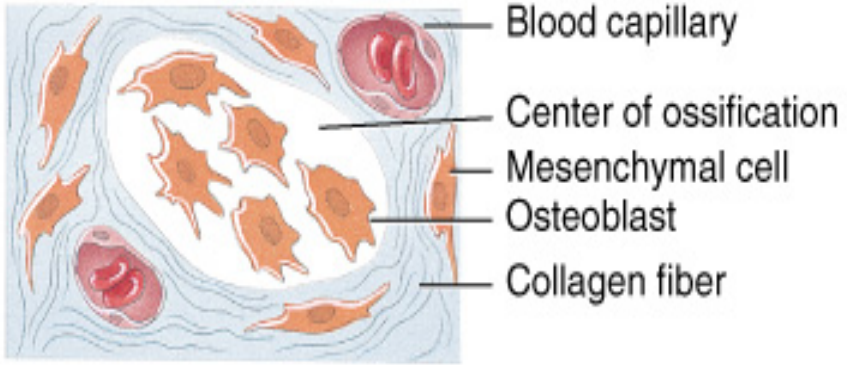
  Frontal bone

  Parietal bones

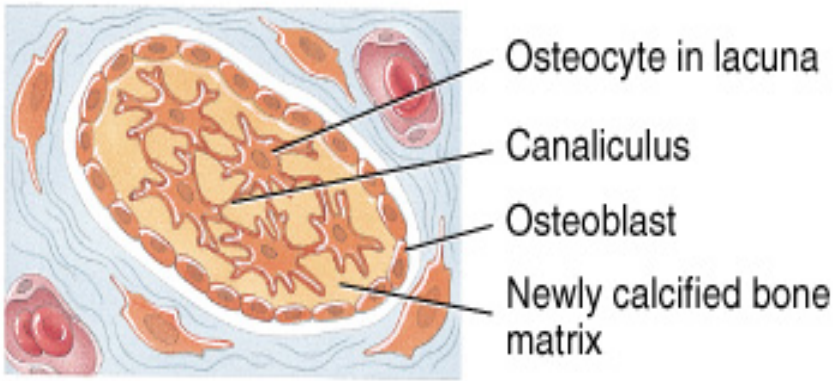
  Occipital bone

  Temporal bones
- Mandible
- Clavicle – lateral third

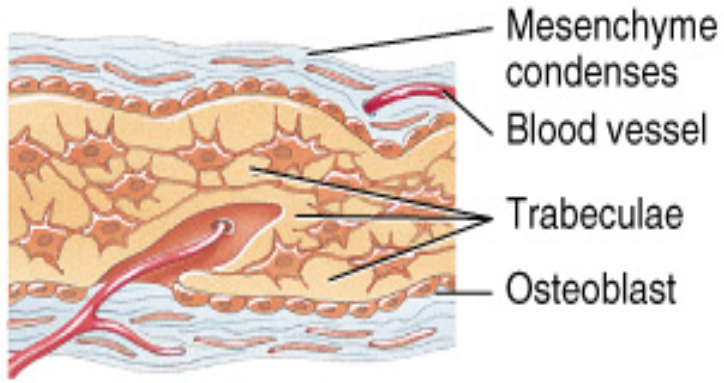
Intramembranous Ossification



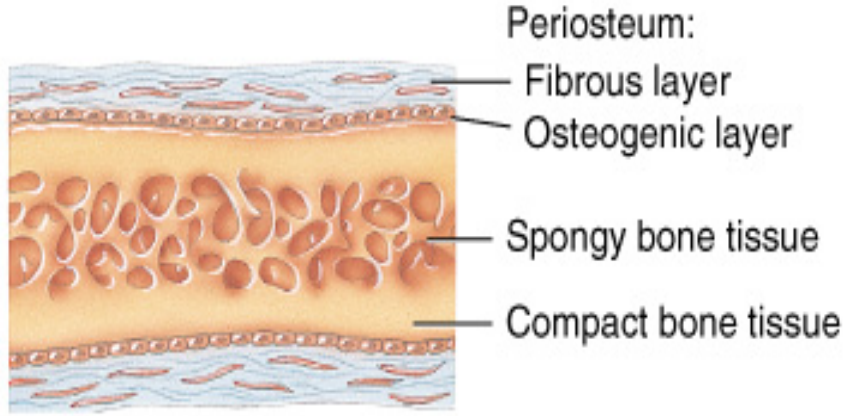
1 Development of center of ossification



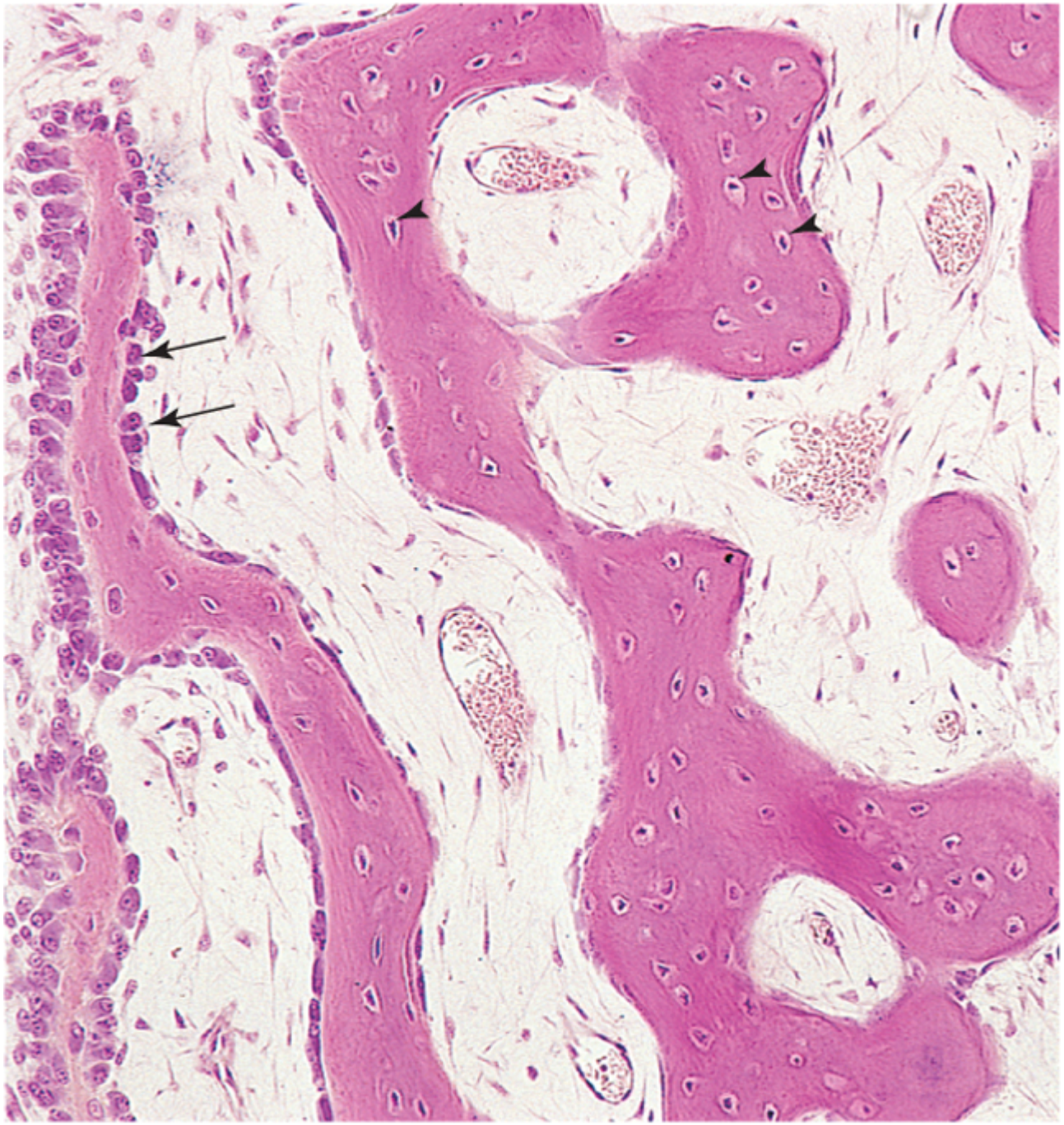
2 Osteocytes deposit mineral salts (calcification)



3 Formation of trabeculae

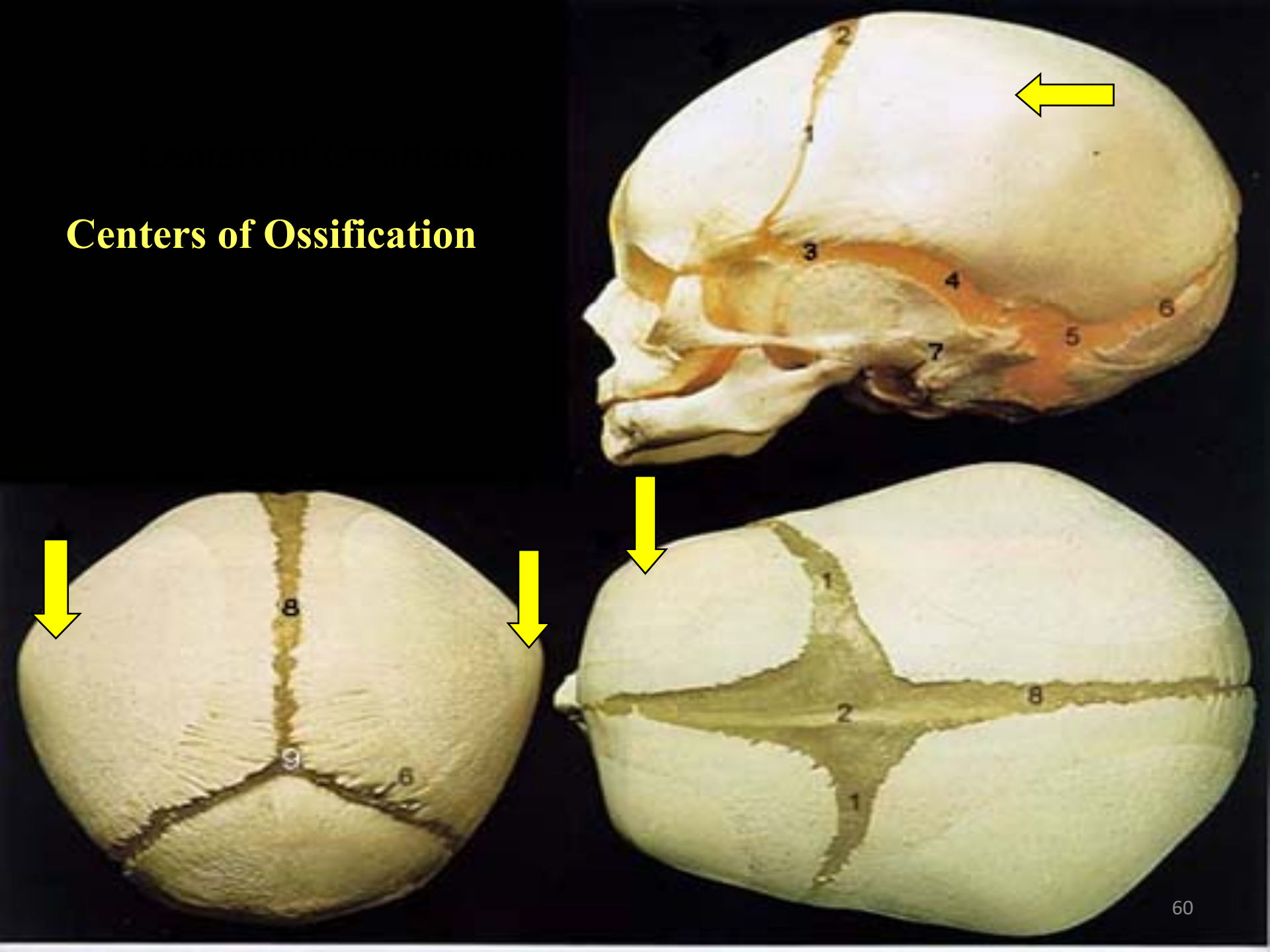


4 Development of periosteum, spongy bone, and compact bone tissue



Light micrograph of intramembranous ossification (×132). Trabeculae of bone are being formed by osteoblasts lining their surface (*arrows*). Observe osteocytes trapped in lacunae (*arrowheads*) and that primordial osteons are beginning to form. The osteons (canals) contain blood capillaries.

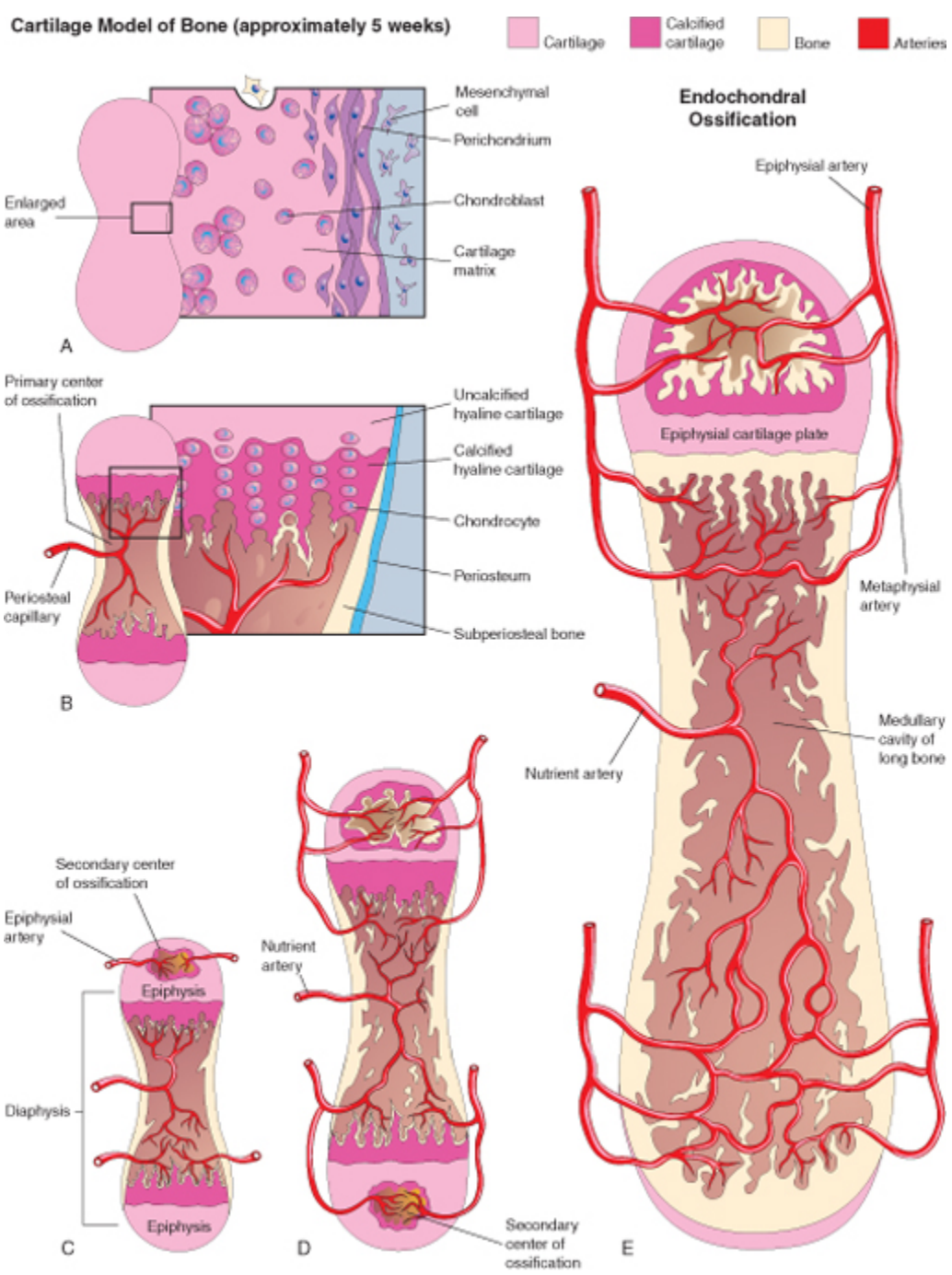
Centers of Ossification



ENDOCHONDRAL OSSIFICATION

- Endochondral ossification is formation of bone from preexisting cartilaginous models.
- In a long bone, for example, the **primary center of ossification** appears in the **diaphysis -** the part of a long bone between its ends - that forms the shaft of the bone.
- At the center of ossification, chondrocytes increase in size (hypertrophy), the matrix becomes calcified, and the cells die.
- Concurrently, a thin layer of bone is deposited under the **perichondrium** surrounding the diaphysis; thus, the perichondrium becomes the **periosteum**.

- Invasion by vascular connective tissue from blood vessels surrounding the periosteum also breaks up the cartilage.
- Some invading cells differentiate into **hemopoietic cells,** blood cells, of the bone marrow.
- Transformation of cartilage model to bone proceeds towards the **epiphyses** (ends of the bone).
- The spicules of bone are remodeled by the action of osteoclasts and osteoblasts.



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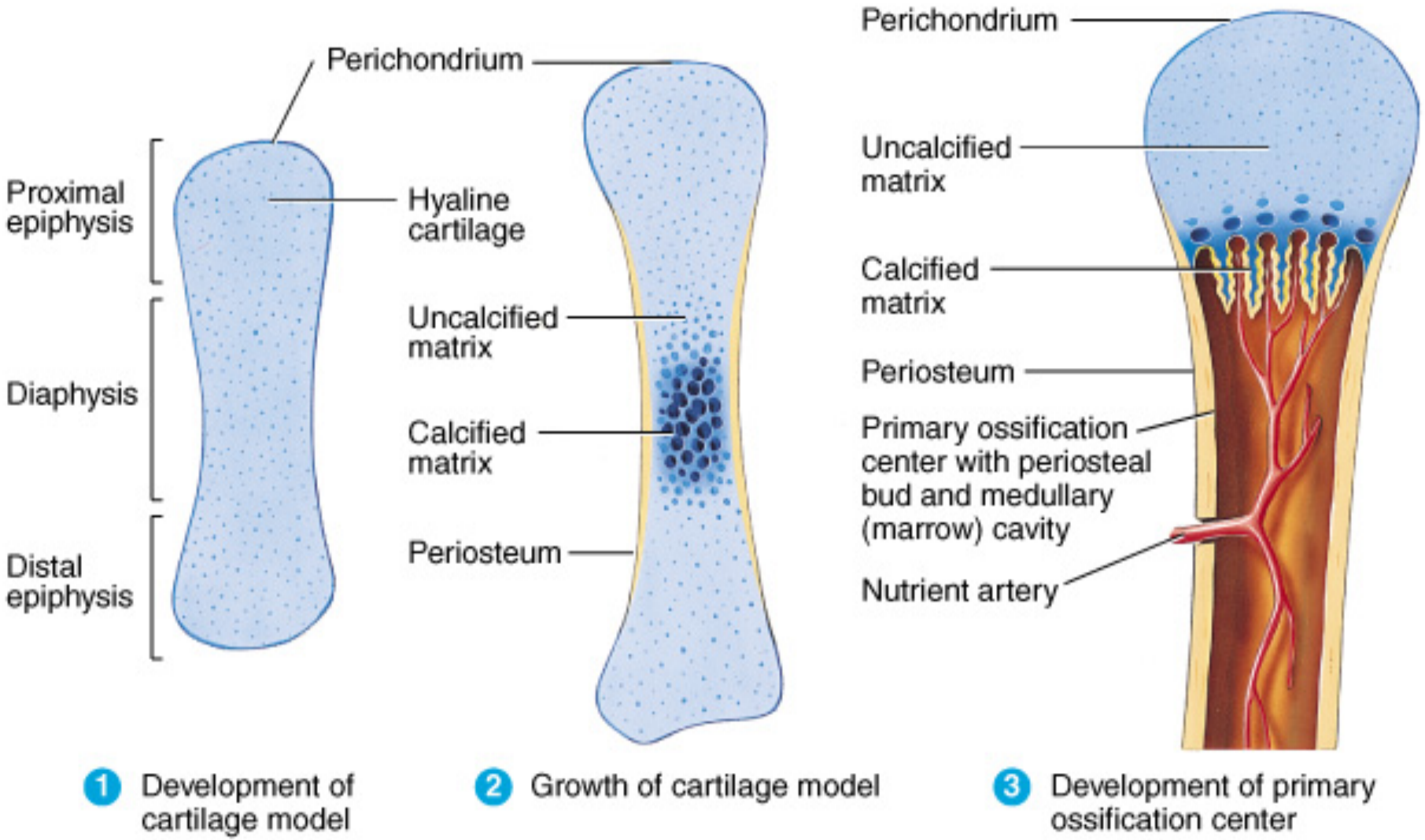
A to **E,** Schematic longitudinal sections illustrating endochondral (intracartilaginous) ossification in a developing long bone.

ENDOCHONDRAL OSSIFICATION



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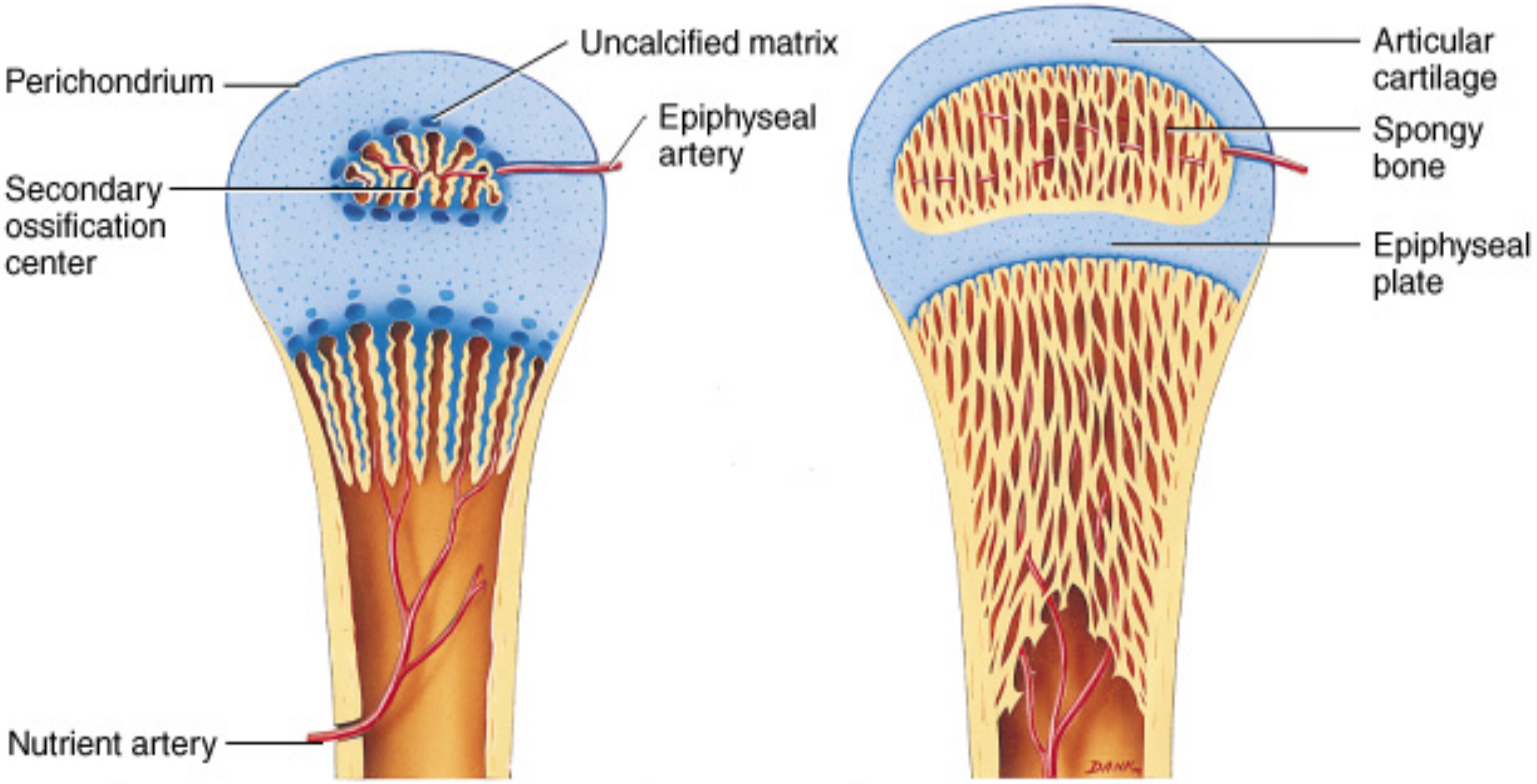
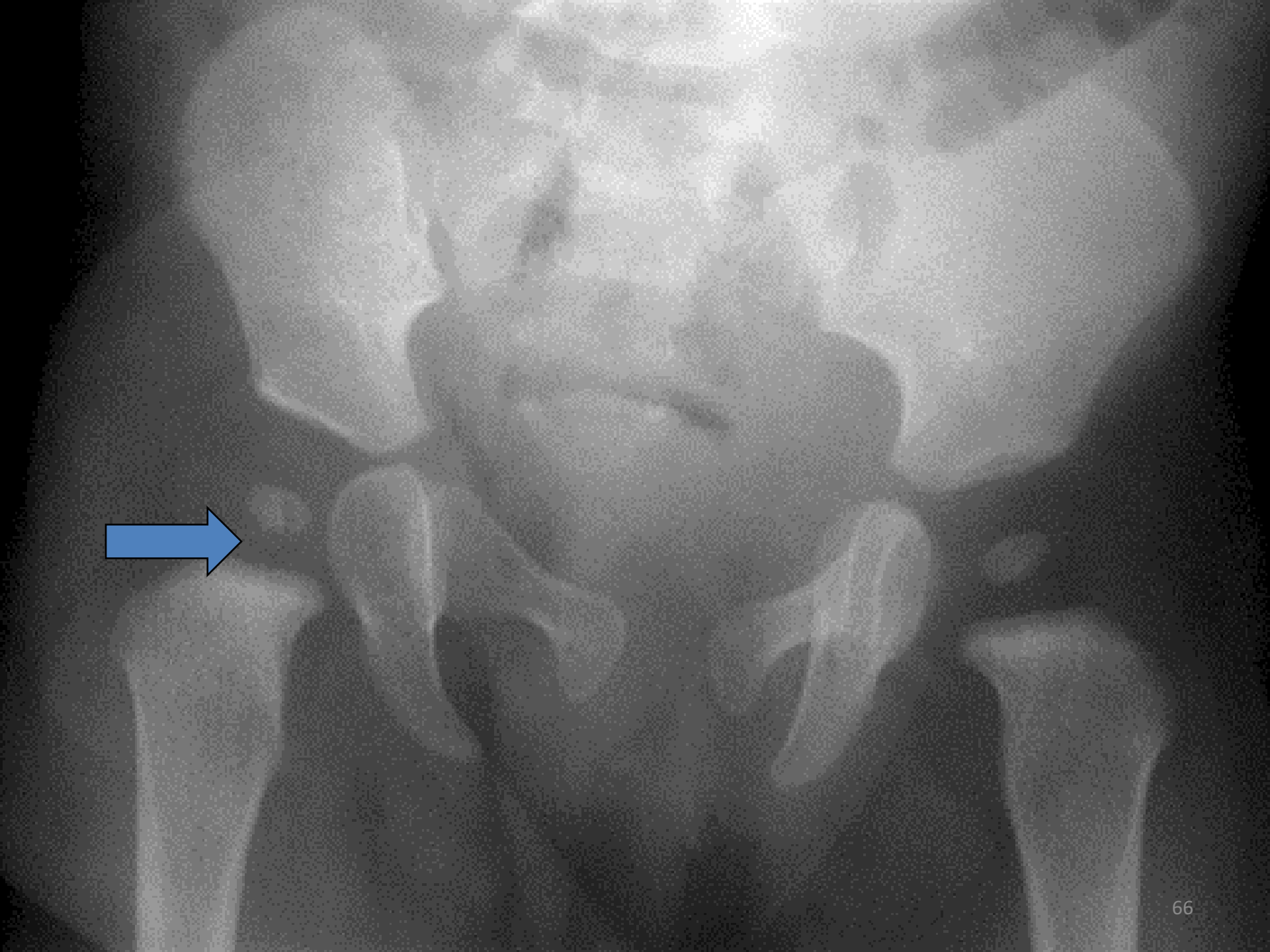


4 Development of secondary ossification center in epiphysis

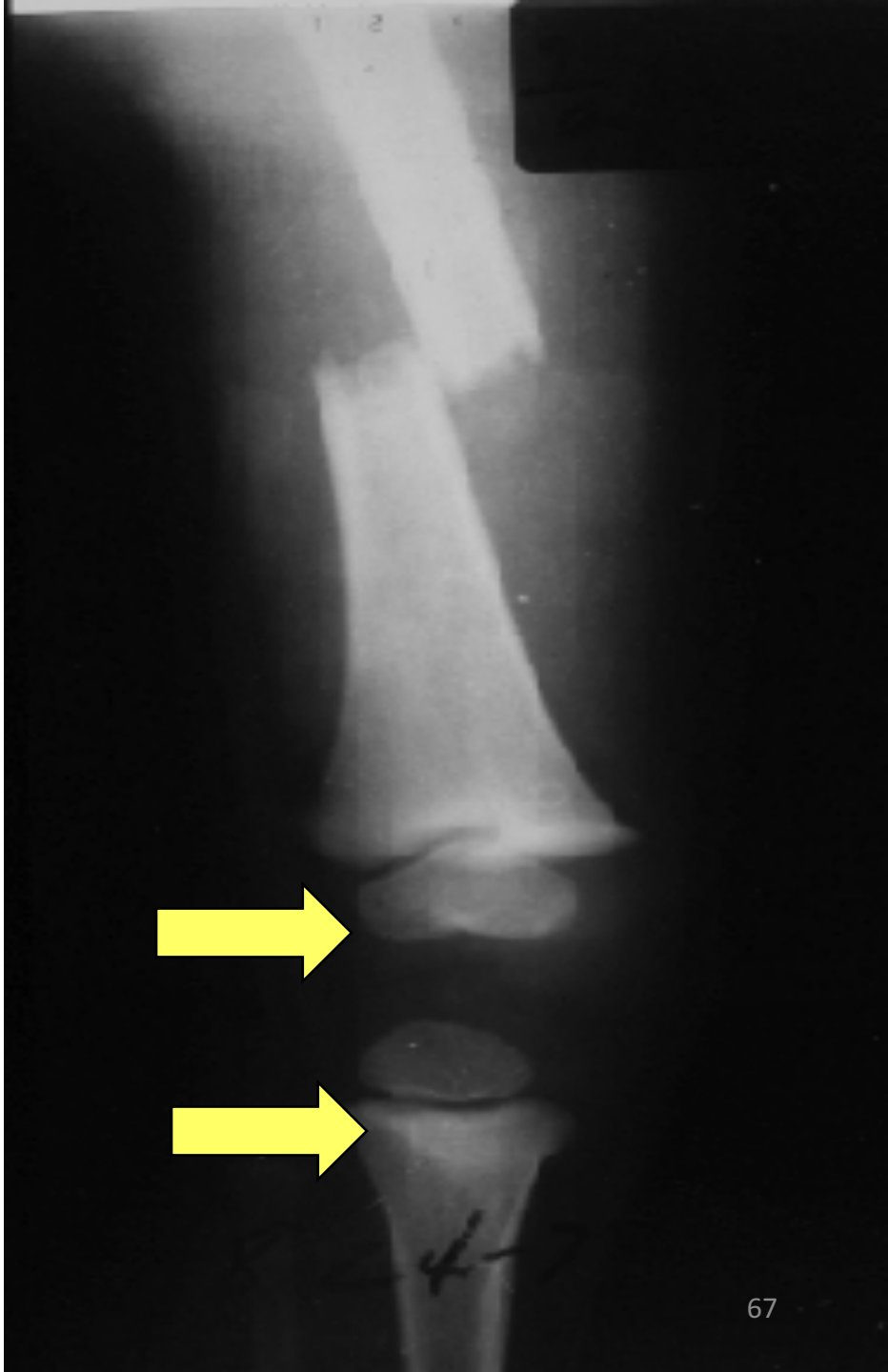
5 Formation of articular cartilage and epiphyseal plate



Growth at epiphyseal plates

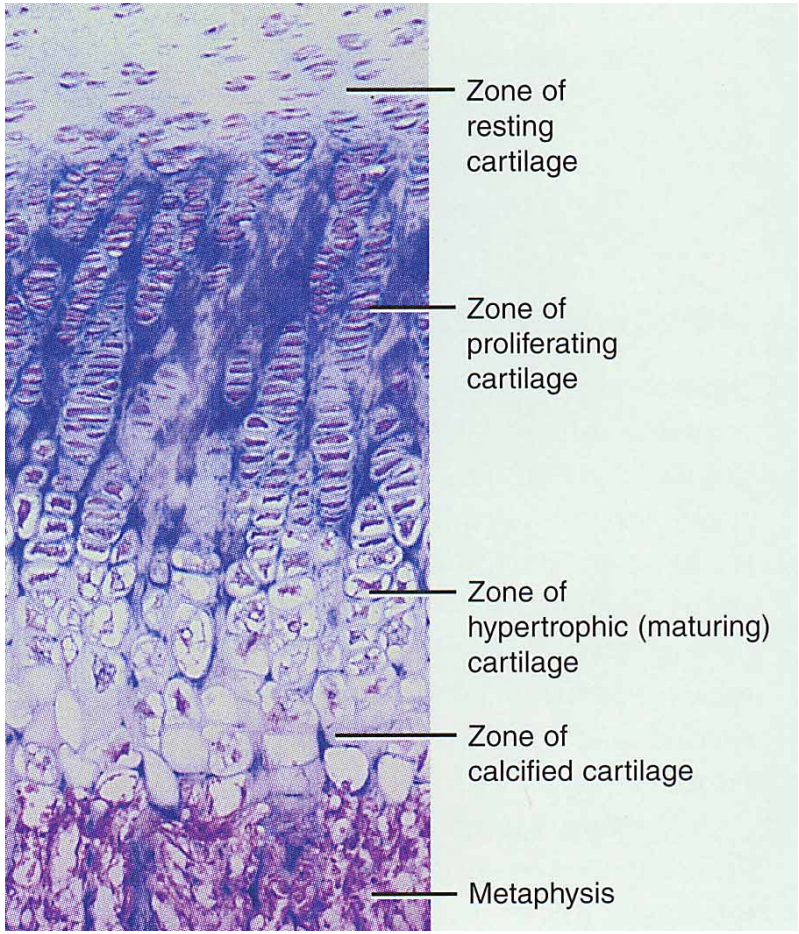
Zones of epiphyseal plates

Zone of Resting Cartilage
Zone of Proliferating Cartilage
Zone of Hypertrophic Cartilage
Zone of Calcified Cartilage



Zones of Growth in Epiphyseal Plate

- Zone of resting cartilage
  - anchors growth plate to bone
- Zone of proliferating cartilage
  - rapid cell division (stacked coins)
- Zone of hypertrophic cartilage
  - cells enlarged & remain in columns
- Zone of calcified cartilage
  - thin zone, cells mostly dead since matrix calcified
  - osteoclasts removing matrix
  - osteoblasts & capillaries move in to create bone over calcified cartilage



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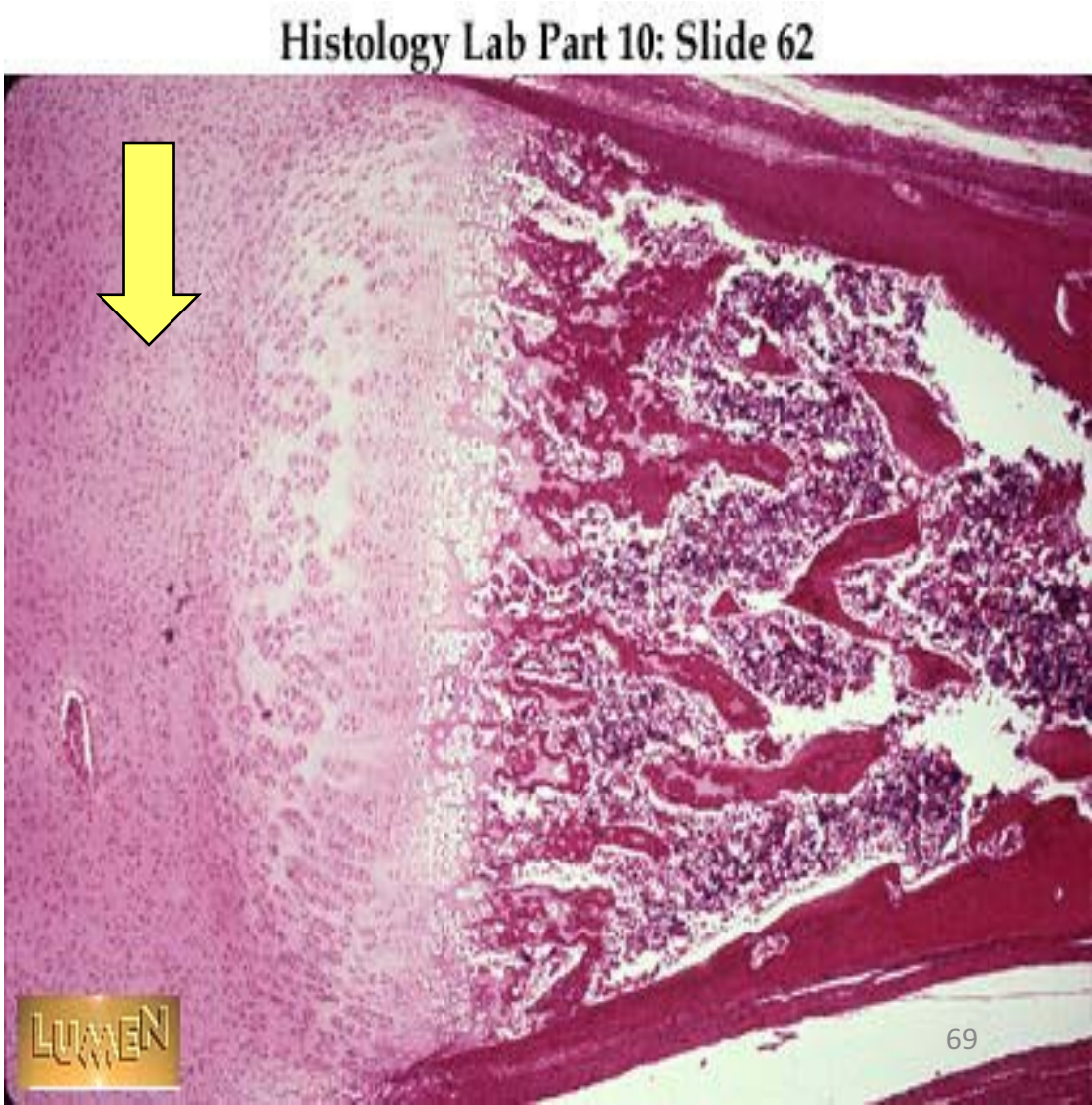

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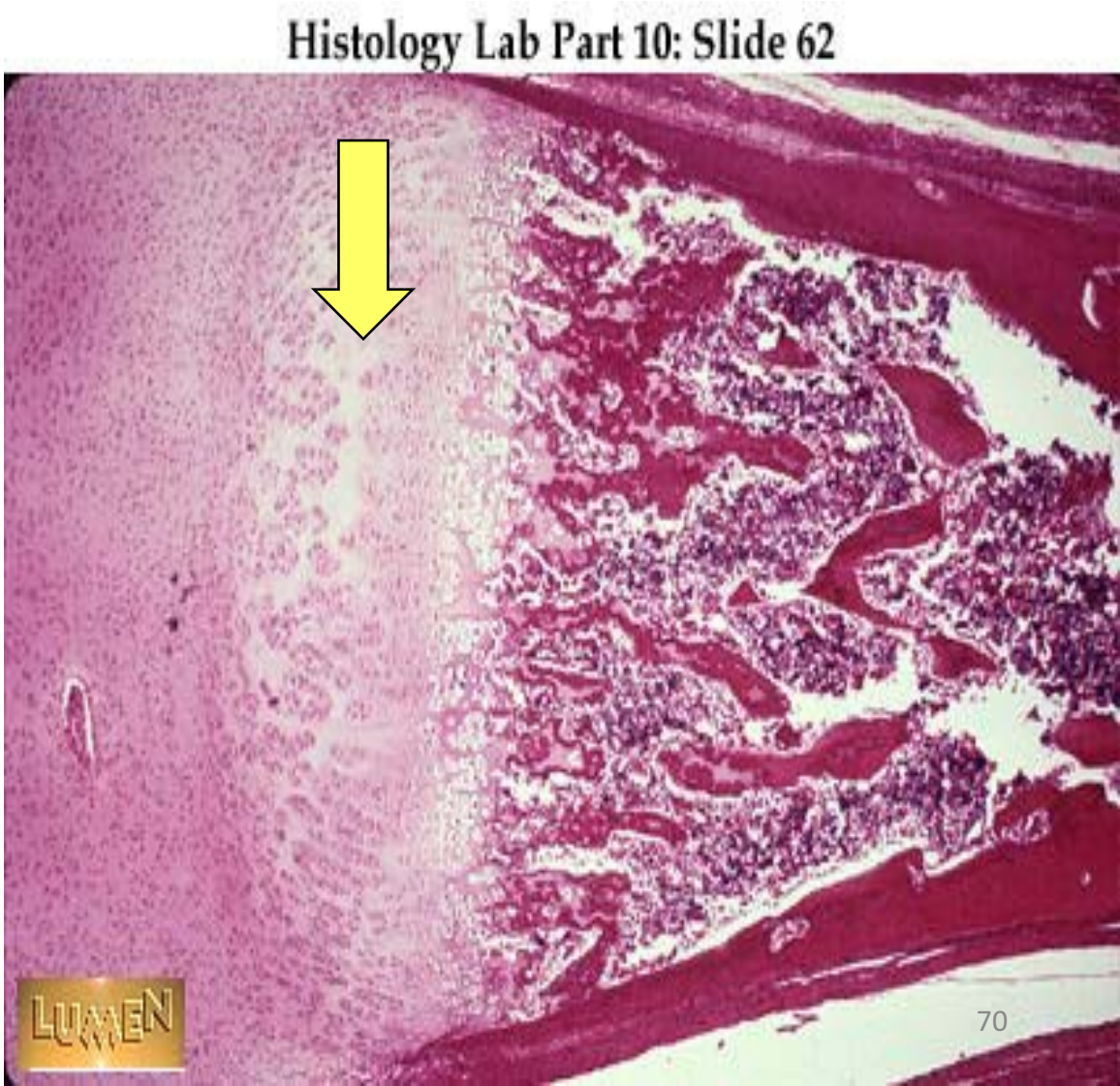

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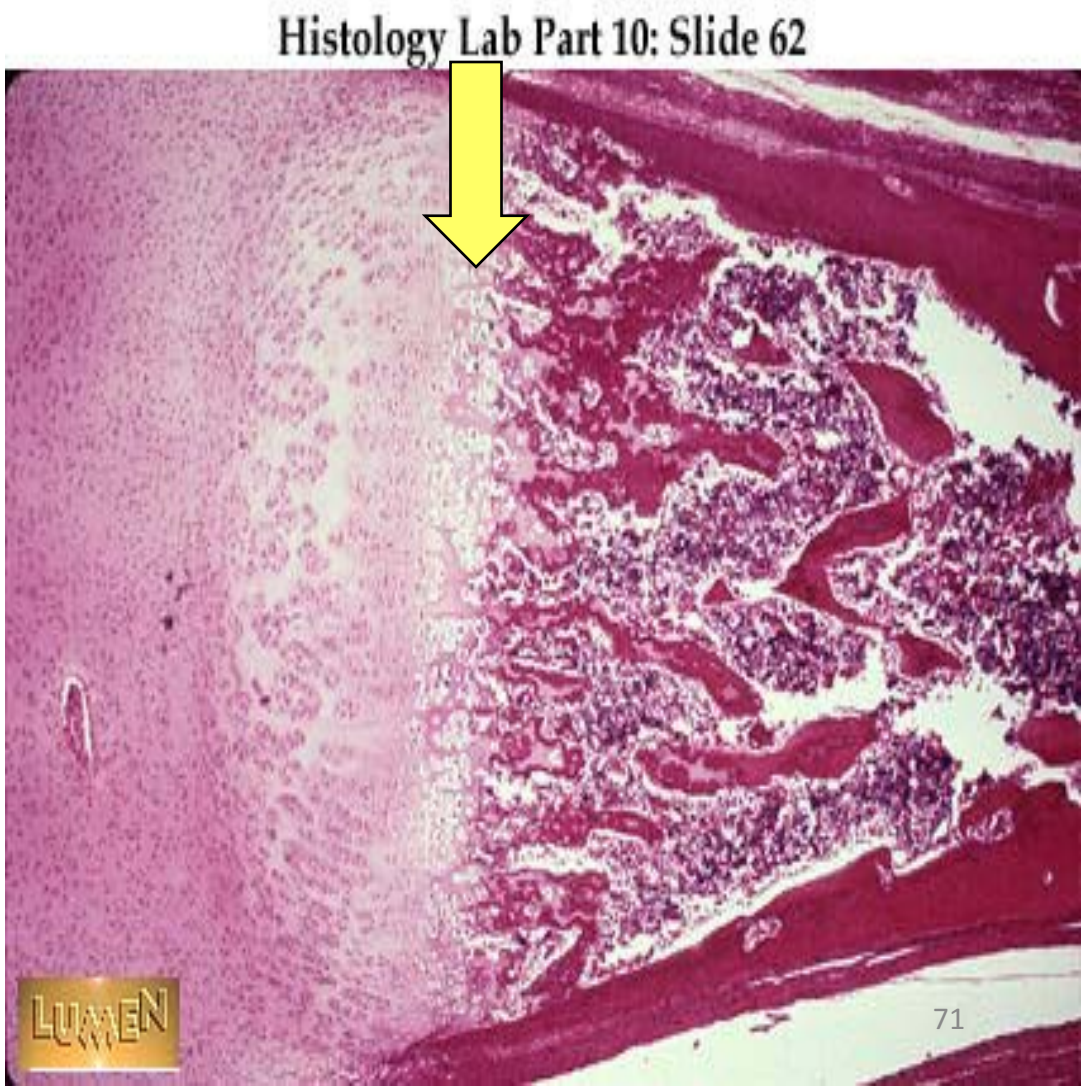

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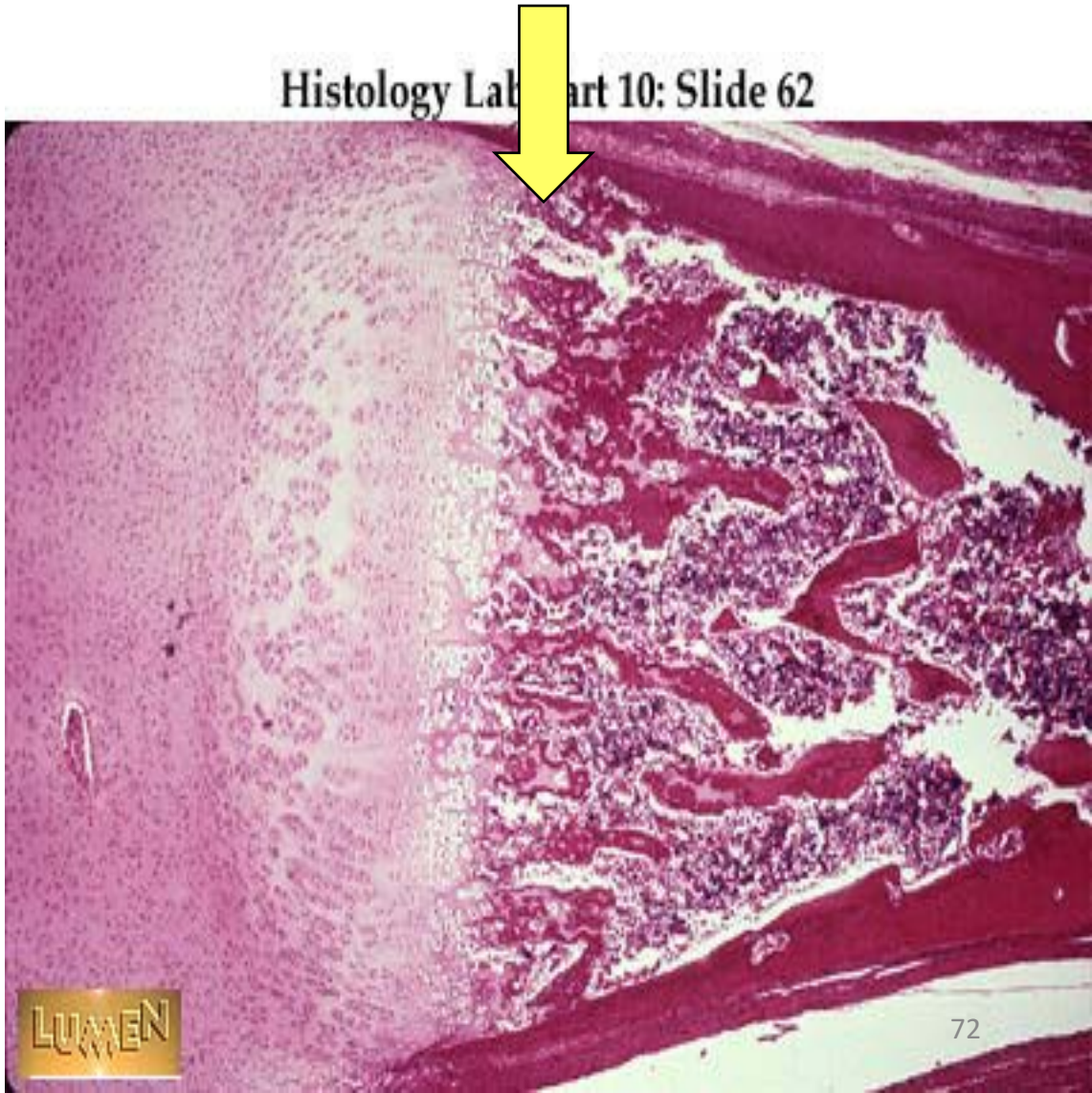
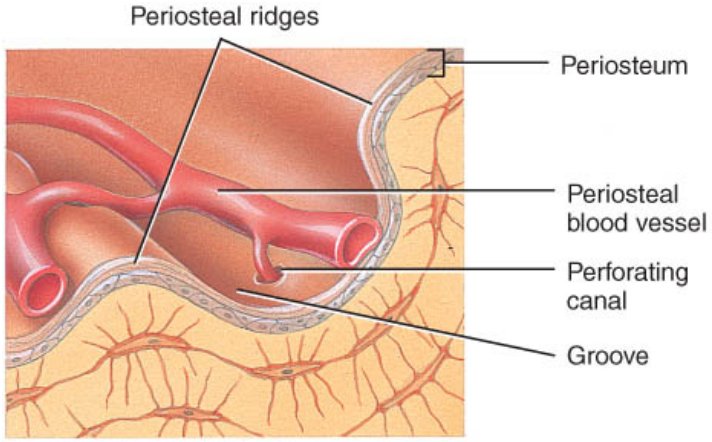
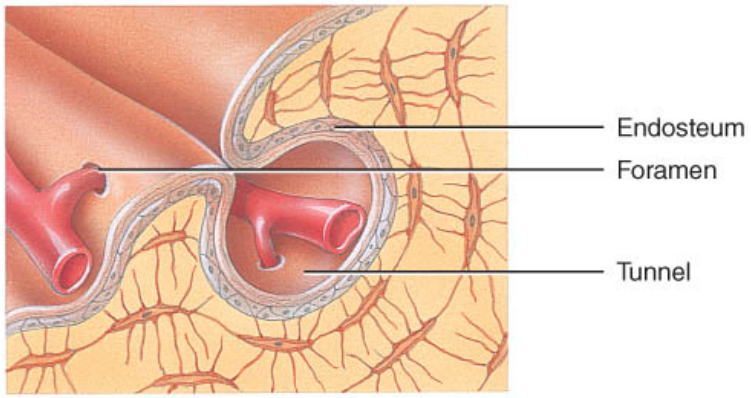


GROWTH IN THICKNESS

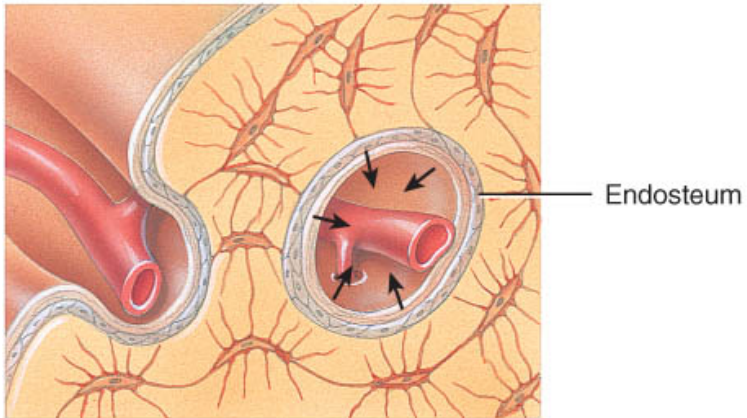
- Bone grow in thickness or diameter by *appositional growth*.
- The steps in these process are:
  - Periosteal cells differentiate into osteoblasts which secrete collagen fibers and organic molecules to form the matrix.
  - Ridges fuse and the periosteum becomes the endosteum.
  - New concentric lamellae are formed.
  - Osetoblasts under the periosteum form new circumferential lamellae.

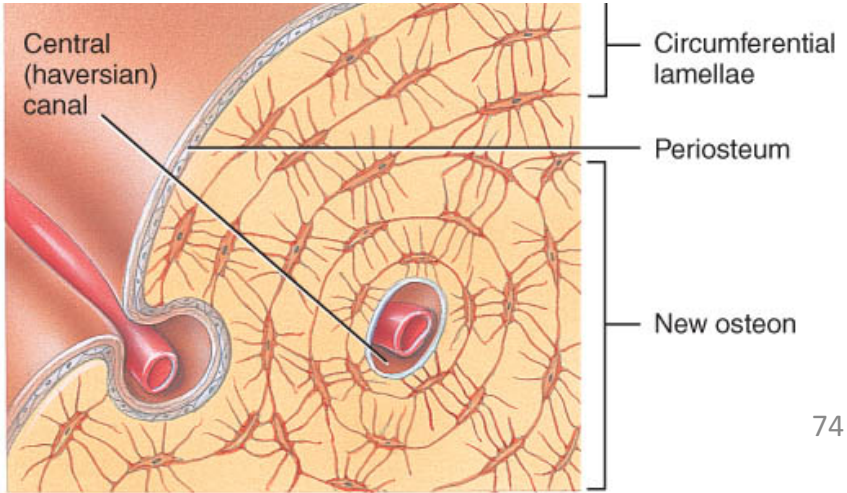
Bone Growth in Width





- By appositional growth at the bone's surface
- Periosteal cells differentiate into osteoblasts and form bony ridges and then a tunnel around periosteal blood vessel.
- Concentric lamellae fill in the tunnel to form an osteon.





- Lengthening of long bones occurs at the **diaphysial-epiphysial junction**.
- Cartilage cells in the **diaphysial-epiphyseal region** proliferate by mitosis.
- Toward the diaphysis, the cartilage cells hypertrophy and the matrix becomes calcified.
- Spicules are isolated from each other by vascular invasion from the **medullary (marrow) cavity**.
- Bone is deposited on these spicules by osteoblasts; resorption of this bone keeps the spongy bone masses relatively constant in length and enlarges the medullary cavity.

- **Ossification of limb bones** begins at the end of the embryonic period and thereafter makes demands on the maternal supply of calcium and phosphorus.
- Pregnant women are therefore advised to maintain an adequate intake of these elements to preserve healthy bones and teeth.
- At birth, the diaphyses are largely ossified, but most of the epiphyses are still cartilaginous.
- **Secondary ossification centers** appear in the epiphyses in most bones during the first few years after birth.
- Ossification spreads radially, and only the articular cartilage and a transverse plate of cartilage, the **epiphysial cartilage plate**, remain cartilaginous.
- Upon completion of growth, this plate is replaced by spongy bone; the epiphyses and diaphysis are united, and no further elongation of the bone occurs.

- In most bones, the epiphyses have fused with the diaphysis by the age of 20 years.
- The rate of deposition and resorption is balanced to regulate the thickness of the compact bone and the size of the medullary cavity.
- The internal reorganization of bone continues throughout life.
- In addition to membranous and endochondral ossification, **chondroid tissue**, which also differentiates from mesenchyme, is now recognized as an important factor for skeletal growth.

FACTORS THAT AFFECT BONE GROWTH

- Minerals
- Vitamins
- Hormones
- Exercise

Minerals

Calcium	Makes bone matrix hard Hypocalcemia: low blood calcium levels. Hypercalcemia: high blood calcium levels.
Phosphorus	Makes bone matrix hard
Magnesium	Deficiency inhibits osteoblasts
Boron	May inhibit calcium loss, increase levels of estrogens
Manganese	Inhibits formation of new bone tissue

Vitamins

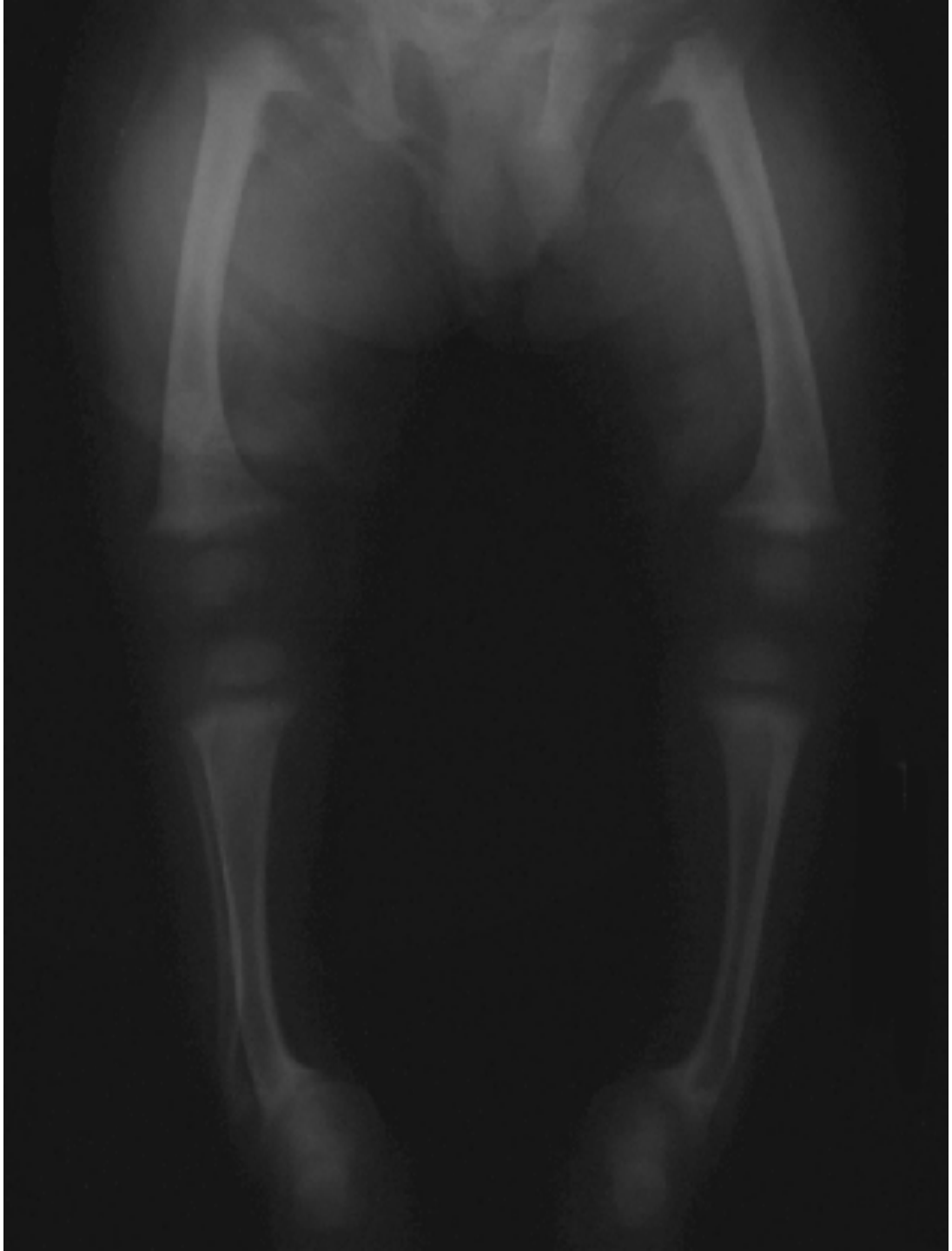
Vitamin A	Controls activity, distribution, and coordination of osteoblasts/osteoclasts
Vitamin B12	May inhibit osteoblast activity
Vitamin C	Helps maintain bone matrix, deficiency leads to decreased collagen production which inhibits bone growth and repair (scury) disorder due to a lack of Vitamin C
Vitamin D	(Calcitriol) Helps build bone by increasing calcium absorption. Deficiencies result in “Rickets” in children

Hormones

Human Growth Hormone	Promotes general growth of all body tissue and normal growth in children
Insulin-like Growth Factor	Stimulates uptake of amino acids and protein synthesis
Insulin	Promotes normal bone growth and maturity
Thyroid Hormones	Promotes normal bone growth and maturity
Estrogen and Testosterone	Increases osteogenesis at puberty and is responsible for gender differences of skeletons

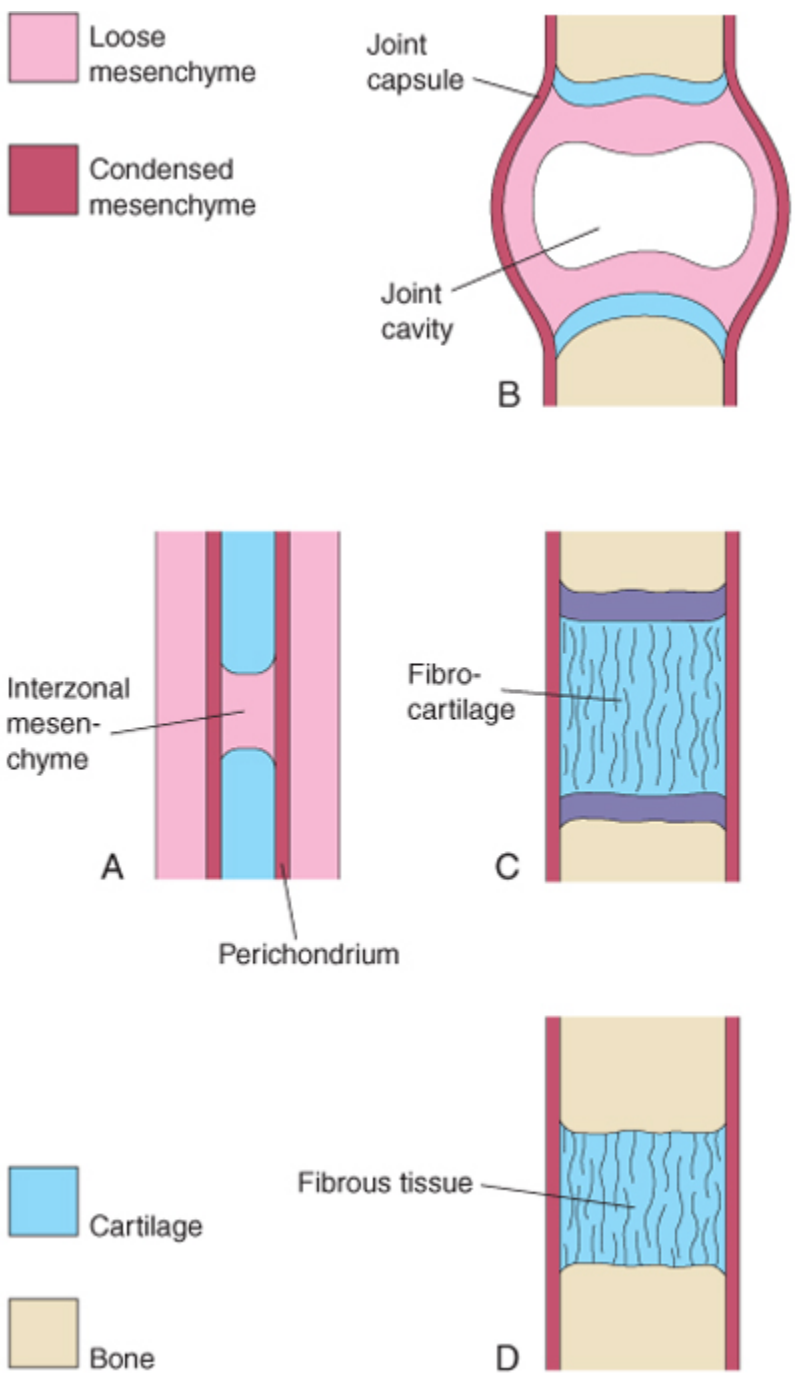
RICKETS

- Rickets is a disease that occurs in children who have a vitamin D deficiency.
- This vitamin is required for calcium absorption by the intestine.
- The resulting calcium deficiency causes disturbances of ossification of the epiphysial cartilage plates (i.e., they are not adequately mineralized), and there is disorientation of cells at the metaphysis.
- The limbs are shortened and deformed, with severe bowing of the limb bones.



DEVELOPMENT OF JOINTS

- Joints begin to develop with the appearance of the **interzonal mesenchyme** during the 6th week, and by the end of the 8th week, they resemble adult joints.
- Joints are classified as fibrous joints, cartilaginous joints, and synovial joints.
- Joints with little or no movement are classified according to the type of material holding the bones together, for example, the bones involved in fibrous joints are joined by fibrous tissue.



Development of joints during the 6th and 7th weeks. **A,** Condensed interzonal mesenchyme in the gap between the developing bones. This primordial joint may differentiate into:
a synovial joint (**B**),
a cartilaginous joint (**C**),
or a fibrous joint (**D**).

FIBROUS JOINTS

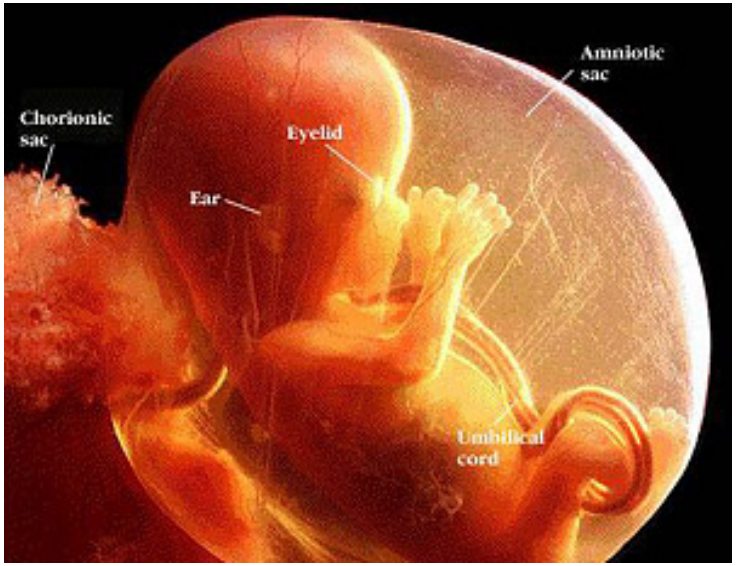
- During the development of fibrous joints, the **interzonal mesenchyme** between the developing bones differentiates into dense fibrous tissue, for example, the sutures of the cranium are fibrous joints.

CARTILAGINOUS JOINTS

- During the development of cartilaginous joints, the interzonal mesenchyme between the developing bones differentiates into **hyaline cartilage** (e.g., the costochondral joints) or **fibrocartilage** (e.g., the pubic symphysis).

SYNOVIAL JOINTS

- During the development of synovial joints (e.g., the knee joint), the interzonal mesenchyme between the developing bones differentiates as follows:
  - Peripherally it forms the capsular and other ligaments.
  - Centrally it disappears, and the resulting space becomes the **joint cavity** or synovial cavity.
  - Where it lines the joint capsule and articular surfaces, it forms the **synovial membrane** (which secretes synovial fluid), a part of the joint capsule (fibrous capsule lined with synovial membrane)
- An abnormal intrauterine environment restricting embryonic and fetal movements may interfere with limb development and cause joint fixation.



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