Bone and cartilage

Danil Hammoudi.MD

Introduction and generality

The framework of bones and cartilage that protects our internal organs and allows us to move is called the SKELETAL SYSTEM. Functions of the skeletal system include:

1. Bones provide a hard **framework** that **supports** the body.
2. Bones provide **protection** to internal organs. The cranium protects the brain, the vertebrae protect the spinal cord, the rib cage protects the thoracic cavity organs, and the hip bones protect pelvic cavity organs.
3. Skeletal muscle uses the bones as levers for **movement**.
4. Bone serves as a **reservoir of minerals**, especially calcium.
5. Red bone marrow **manufactures blood cells and platelets**.
6. **Fat** is stored in the **yellow bone marrow** as an **energy reserve**.

The shape and structure of bones is governed by many factors, **genetic, metabolic and mechanical.** Genetic determination of primary shape can be demonstrated by organ culture of bone rudiments, which subsequently grow into recognisable bones, i.e. roughly the finished shape in all major respects. Fine tuning is by muscular action. The muscles are active in utero, although it is difficult to isolate their effect at this stage. After birth, however, and up to adolescence there is a correlation between activity and growth. this is seen in reverse if we look at people who are bedridden, or who have paralyses (such as poliomyelitis).

Metabolic factors are also important: calcium, phosphorous, vitamins A,C and D and the secretions of the pituitary, thyroid, parathyroid adrenals and gonads are all involved. Dwarves and giants are controlled by aberrant hormones, but there is much variation in normal height. Absence of adequate supplies of vitamin D may lead to rickets, and absence of calcium in the diet to week bone liable to fracture.

Skeletal system contains 4 types of tissue:

- **cartilage**
- **osseous tissue**
- **bone marrow**

– periosteum/endosteum

<u>Structurally, the skeletal system consists of 3 types of connective tissue:</u>

- **BONE,**
- **CARTILAGE**
- **LIGAMENTS**.

- **Most LIGAMENTS are cords of DENSE REGULAR CONNECTIVE TISSUE that attach bone to bone at joints.**

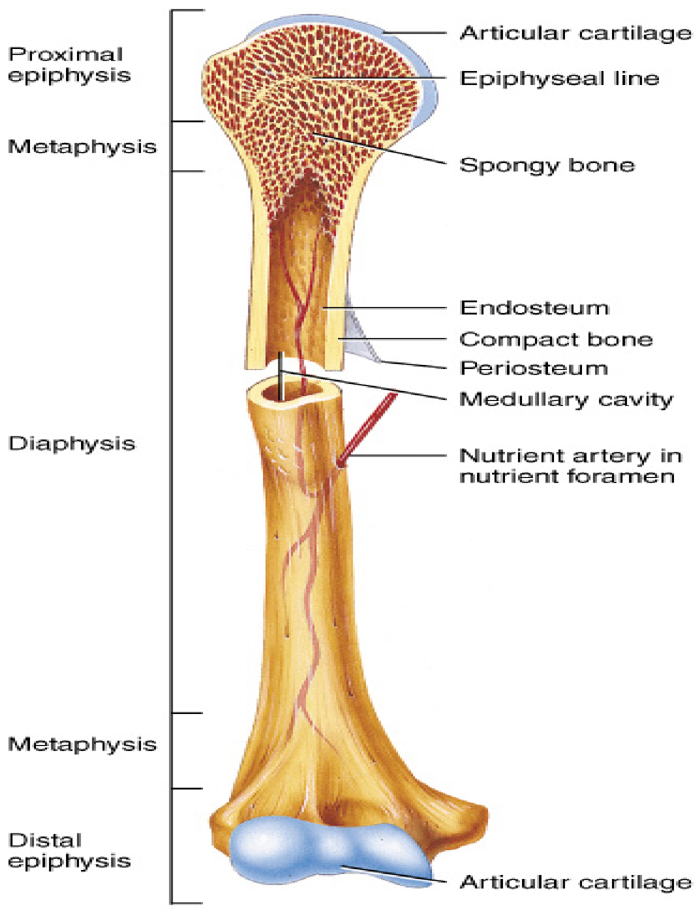
- **The ligaments between the vertebrae, however, are made of ELASTIC CONNECTIVE TISSUE .**
- Like all connective tissue, BONE TISSUE contains a great deal of extracellular matrix.
- The **extracellular matrix** of bone consists of **25% water, 50% mineral salts & 25% collagen**.
- The **mineral salts** include primarily **calcium** salts, like calcium phosphate and calcium carbonate.
- There are also small amounts of **magnesium** and **fluoride**.
- The mineral salts give bone its hardness, which allows bone to **resist compression**.
- **Collagen** contributes to the bone's great **tensile strength**, making the bone more resilient and pliable, and less brittle.

Function

1. As a lever. The bones of the upper and lower limbs pull and push, with the help of muscles.
2. As a calcium store. 97% of the body's calcium is stored in bone. Here it is easily available and turns over fast. In pregnancy the demands of the fetus for calcium require a suitable diet and after menopause hormonal control of calcium levels may be impaired: calcium leaches out leaving brittle osteoporotic bones.
3. Protective? This is often quoted in books: in fact protection against outside forces is rarely needed, and if it is we usually wear a cycling helmet, or a crash hat, or a hard hat. Or sit in a very strong structure like a formula 1 carbon fibre tub or a Volvo. So the bone can't be that good. In practice these are exceeded by the almost continuous large forces exerted by our own muscles. Respiratory movements need ribs. If a thigh bone or a humerus fractures the pull exerted by the muscles, even though not in active use, will be enough to overlap or otherwise displace the broken ends and we need considerable force, traction, to reduce the fracture i.e. to un-overlap the bits so that they can be lined up. The force exerted by the masticatory muscles is sufficient to support the bodyweight.
4. As a marrow holder. This is secondary to production of maximum strength for minimum weight: the cavities produced in unstressed areas (like the holes in the tubes of a bicycle frame) are used for marrow, or in some places (mastoid) just for air storage. The saving is small in man but considerable in an elephant. Occurrence of bone in two main forms, compact and cancellous. Both can be seen in our old lady's vertebra. That section was produced like this. Around the outside is a layer of strong, hard, heavy compact bone. In the middle is a branching network of cancellous or trabecular bone which usually, like iron filings, follow lines of force. Marrow sits in the interconnecting cavities between these plates or rods of bone.

Origin of bone is again in two main forms. Some bone (in broad terms almost everything except the top of the skull) is preformed in cartilage - replacement or endochondral bone. Details will come in histology lectures. In the skull and one or two other places, however, bone forms direct in

membranous connective tissue - membrane bone.
Look at the history of the skeleton to see why. Calcified skeletal tissues replaced silicacious in the Cambrian period, presumably because physiological changes either in the beasts or the oceans in which they lived allowed retention of Ca ions. Brachiopods, nautiloids, trilobites gradually converted. Later the first vertebrates had bony scales embedded in their skin - those around the mouth incidentally form the primitive basis of teeth. In some lines these scales fused to form bony carapaces. These carapaces are retained over our heads as skull vaults. Later the rest of the skeleton, vertebrae etc., which were cartilaginous also became bony. This explains the distribution and origins of membrane and cartilaginous bone. The surviving membrane bones, notably in the head and part of the clavicle (a later invention made up of 2 fused bones, one membranous one cartilaginous) are bits of dermal shield.
Whether in membrane or cartilage centres of ossification marked by the appearance of calcified matrix appear over a long period of time, some in embryonic life, others in fetal and yet others well into the postnatal growing period. Many bones ossify from one centre, others from a group, of which one, the primary centre of ossification, is usually central and early, and others, secondary centres, later and often peripheral.



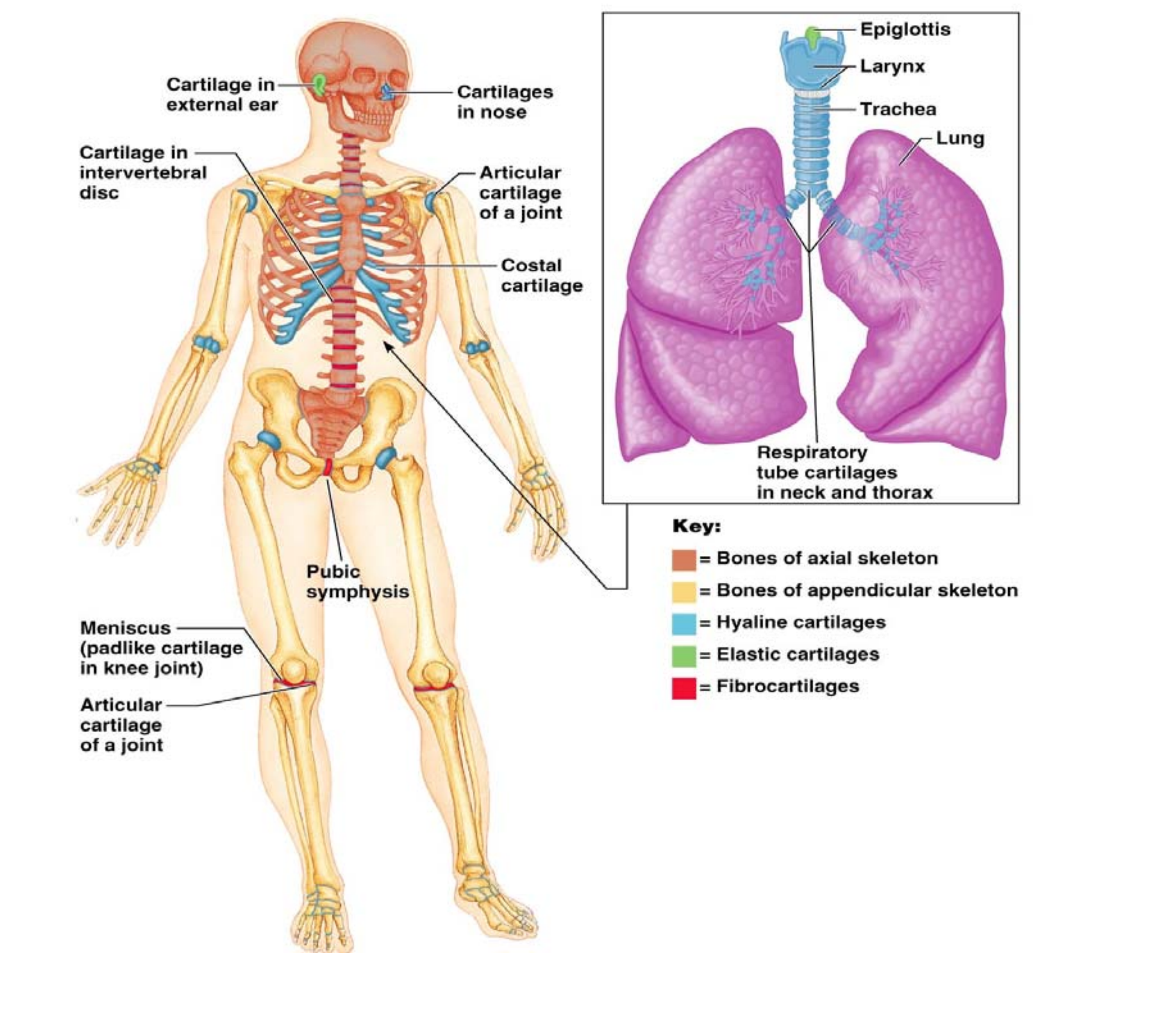
(a) Partially sectioned humerus (arm bone)

I/ Cartilage:

Semi-rigid matrix; virtually avascular (nutrients supplied by diffusion from vessels in perichondrium and synovial fluid); no lymphatic drainage or nerves.

- **is a specialised type of connective tissue.**
- consists, like other connective tissues, of cells and extracellular components.
- does, unlike other connective tissues, **not contain vessels or nerves.**
- is surrounded by a layer of dense connective tissue, the **perichondrium**.

- Cartilage is rather rare in the adult humans,
- very important during development because of its firmness and its ability to grow rapidly.
- In developing humans, most of the bones of the skeleton are preceded by a temporary cartilage "model".
- Cartilage is also formed very early during the repair of bone fractures.



CARTILAGE is an important part of the skeleton.

What type of cartilage is the most common type?

HYALINE CARTILAGE makes up most of the EMBRYONIC SKELETON, but eventually is replaced by bone during fetal and childhood development. HYALINE CARTILAGE is also found at the ends of long bones at joints, connects the ribs to the breastbone, and forms the end of the nose.

ELASTIC CARTILAGE gives shape to the outer ear.

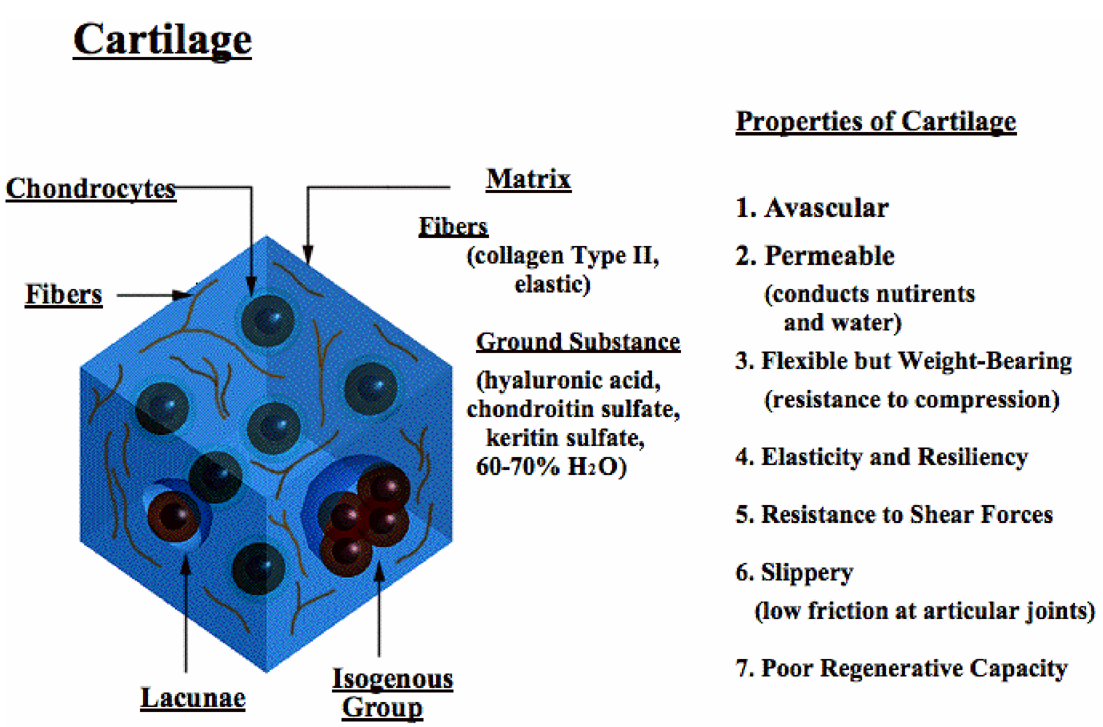
FIBROCARTILAGE forms the intervertebral discs, between the vertebrae.

CARTILAGE resists **compression** (pushing forces) & **tension** (pulling forces) due to its rubbery ground substance (**chondroitin sulfate**) and **collagen**.

Cartilage is also very **resilient**, able to spring back to its original shape following compression.

Unfortunately, cartilage is weak in resisting shear forces (twisting & bending).

Because of this weakness, torn cartilage is a common sports injury.



Skeletal Cartilage

- ***Contains no blood vessels or nerves***
- ***Surrounded by the perichondrium (dense irregular connective tissue) that resists outward expansion***
- ***Three types – hyaline, elastic, and fibrocartilage***

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**

Elastic Cartilage

- ***Similar to hyaline cartilage, but contains elastic fibers***
- ***Found in the external ear and the epiglottis***

Fibrocartilage

- ***Highly compressed with great tensile strength***
- ***Contains collagen fibers***
- ***Found in menisci of the knee and in intervertebral discs***

Types of Cartilage

a/ Hyaline Cartilage

b/ Elastic Cartilage

c/ Fibrous Cartilage

d/ Articular Cartilage

a/ Hyaline Cartilage

Hyaline cartilage develops, like other types of connective tissue, from mesenchymal cells.

From about the fifth foetal week precursor cells become rounded and form densely packed cellular masses, centres of chondrification.

The cartilage-forming cells, chondroblasts, begin to secrete the components of the extracellular matrix of cartilage.

The extracellular matrix consists of:

- ground substance
  - hyaluronan,
  - chondroitin sulfates
  - keratan sulfate
- tropocollagen, which polymerises extracellularly into fine collagen fibres.

Tropocollagen type II is the dominant form in collagen fibres of almost all types of cartilage.

As the amount of matrix increases the chondroblasts become separated from each other and are, from this time on, located isolated in small cavities within the matrix, the **lacunae.**

Concurrently the cells differentiate into mature cartilage cells, chondrocytes **.**

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)

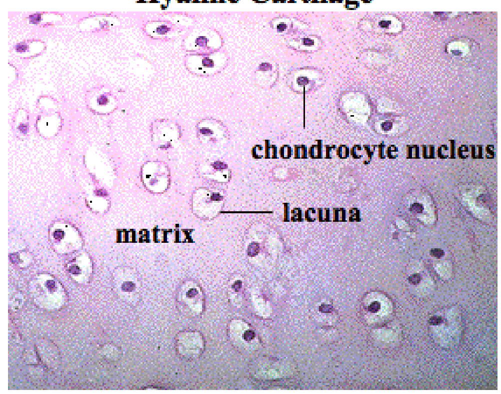
wall of trachea & bronchii

articular cartilage of bone

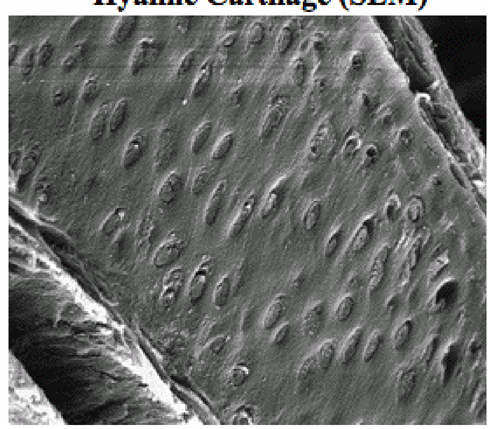
epiphyseal plate

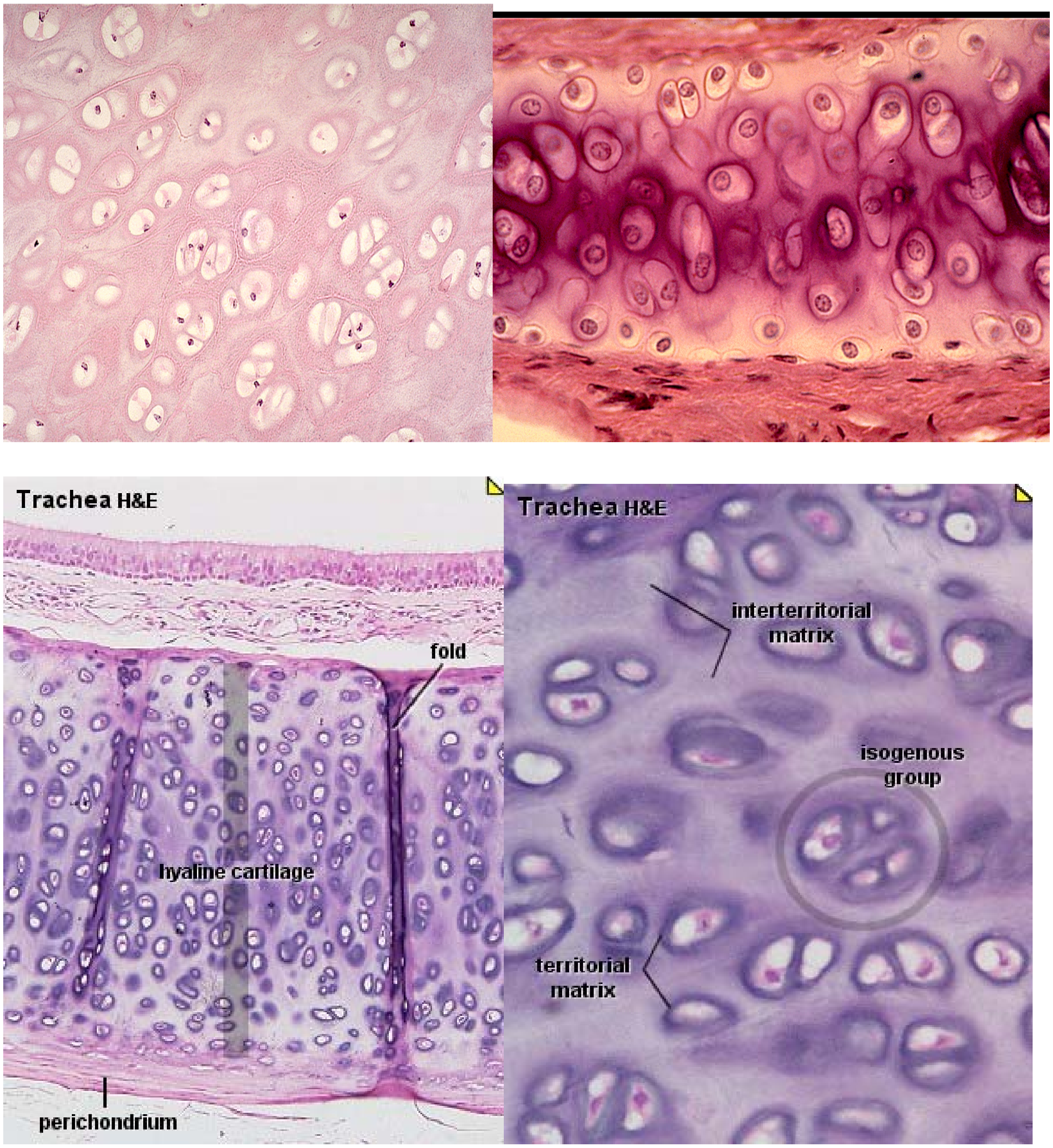
fetal axial skeleton

Hyaline Cartilage



Hyaline Cartilage (SEM)





Trachea, cat, H&E and Trachea, cat, van Gieson

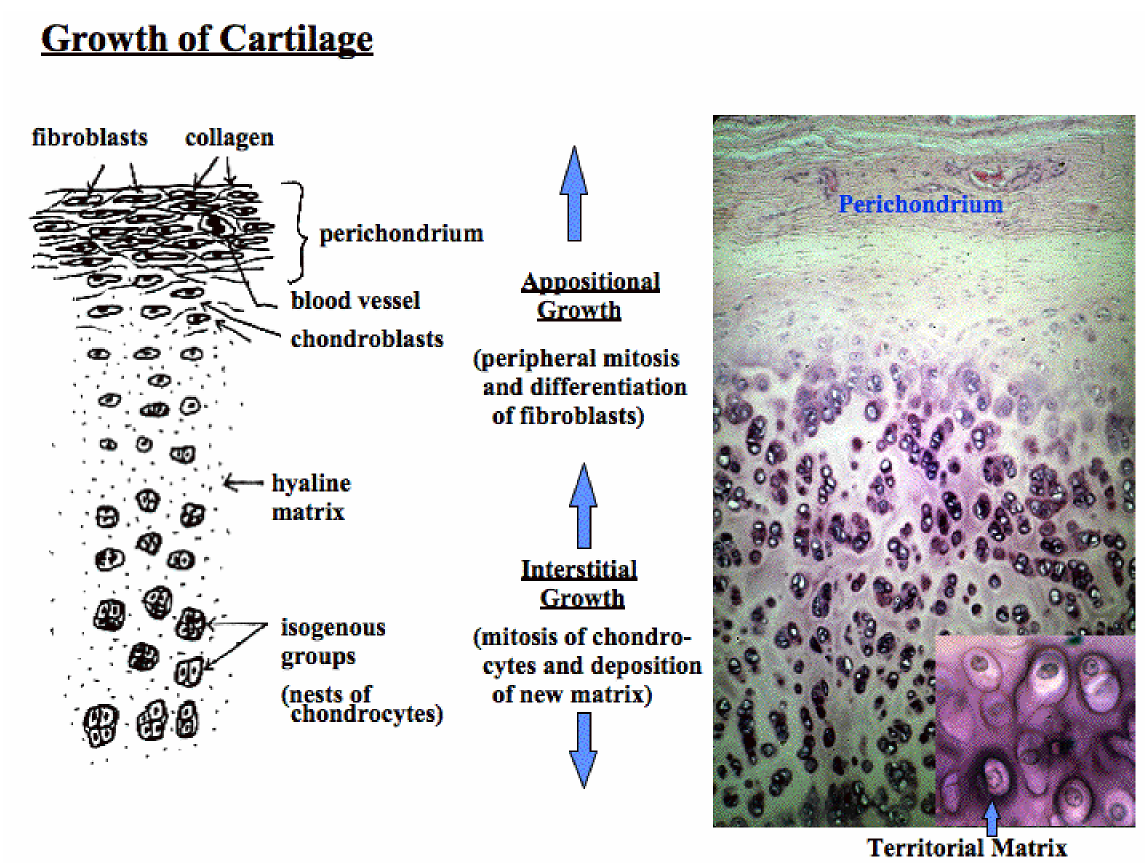
Growth occurs by two mechanisms

- **Interstitial growth** - Chondroblasts within the existing cartilage divide and form small groups of cells, isogenous groups, which produce matrix to become separated from each other by a thin partition of matrix. Interstitial growth occurs mainly in immature cartilage.

- **Appositional growth** - Mesenchymal cells surrounding the cartilage in the deep part of the perichondrium (or the chondrogenic layer) differentiate into chondroblasts. Appositional growth occurs also in mature cartilage.

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**



- Like all protein-producing cells, **chondroblasts contain plenty of rough endoplasmatic reticulum while they produce matrix.**
- The amount of rough endoplasmatic reticulum decreases as the chondroblasts mature into chondrocytes.
- Chondrocytes fill out the lacunae in the living cartilage.
- The matrix appears structureless because the collagen fibres are too fine to be resolved by light microscopy (~20nm), and because they have about the same refractive index as the ground substance. Collagen accounts for ~ 40% of the dry weight of the matrix.
- The matrix near the isogenous groups of chondrocytes contains larger amounts and different types of glycosaminoglycans than the matrix further away from the isogenous groups. This part of the matrix is also termed territorial matrix or capsule. In H&E stained sections the territorial matrix is more basophilic, i.e. it stains darker. The remainder of the matrix is called the interterritorial matrix.
- Fresh cartilage contains about 75% water which forms a gel with the components of the ground substance.
- Cartilage is nourished by diffusion of gases and nutrients through this gel.

Skeletal Cartilage: **Hyaline Cartilage**

A). articular cartilage

B). costal cartilage

C). nasal cartilage

b/ Elastic Cartilage

- occurs in the epiglottic cartilage, the corniculate and cuneiform cartilage of the larynx, the cartilage of the external ear and the auditory tube.
- corresponds histologically to hyaline cartilage, but, in addition, elastic cartilage contains a dense network of delicately branched elastic fibres.

Distribution of The Various Types Of Cartilage

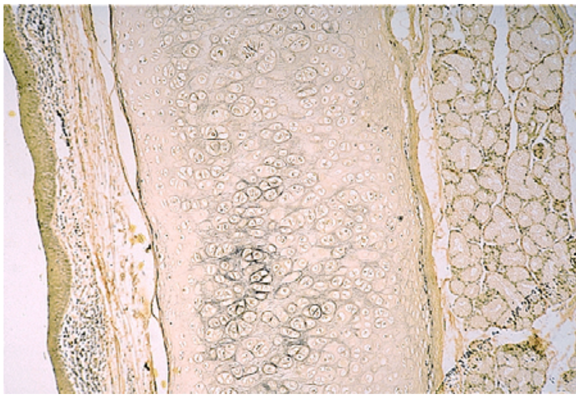
Hyaline Cartilage

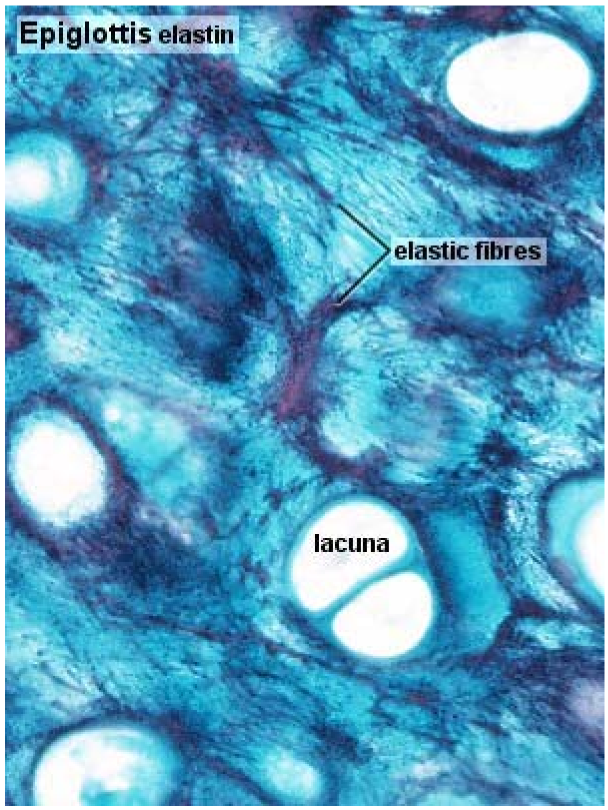
- Most bones of the embryonic skeleton
- Articular cartilage (synovial jt)
- Epiphyseal Plate
- Costal Cartilage
- Xiphoid process
- Nasal Cartilages
- Most Laryngeal Cartilages
- Tracheal Ring Cartilages
- Cartilage plates in large
- and medium bronchi

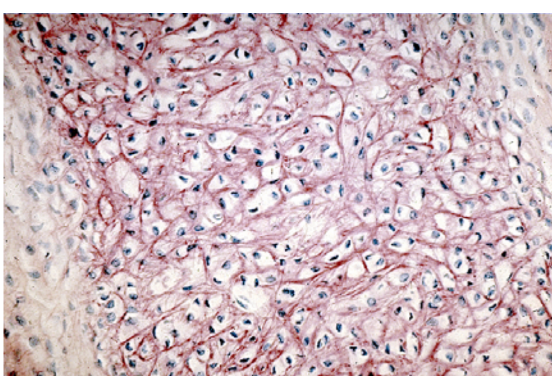
- **Elastic Cartilage**
  - Pinna
  - External Auditory tube
  - Eustachian Tube
  - Epiglottis
  - Laryngeal Cartilages (2)
  - Cartilage plates in small
  - bronchi
- **Fibrocartilage**
  - Symphyses
  - - Intervertebral disks
  - - Pubic symphysis
  - Menisci

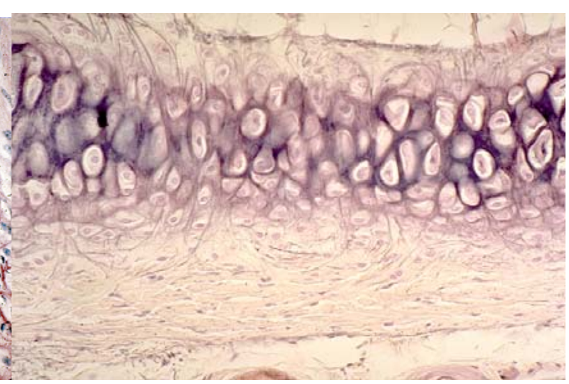
GENERAL CHARACTERISTICS OF CARTILAGE

• • Growth: appositional and interstitial
• • Perichondrium
– Two layers:
• • Outer fibrous (type 1 collagen)
• • Inner chondrogenic (appositional growth)
– Not found in articular cartilage and fibrocartilage
• • Cells = chondrogenic cells, chondroblasts, and chondrocytes
• • Matrix (ground substance and collagen)
– Territorial matrix, rich in GAG’s= basophilic, surrounds
• lacunae (also called “capsular” matrix)
– Interterritorial matrix, less basophilic
– Matrix binds water (negatively charged GAG’s attract Na+, H20
• follows); resistant to compression
• • Avascular (nourished by diffusion)




Epiglottis elastin
elastic fibres
lacuna





Elastic Cartilage

Matrix

hyaluronic acid
chondroitin sulfate
kertatin sulfate

Fibers

elastic (elastin)

Typical Locations

external ear

walls of external auditory canal and eustachian tubes

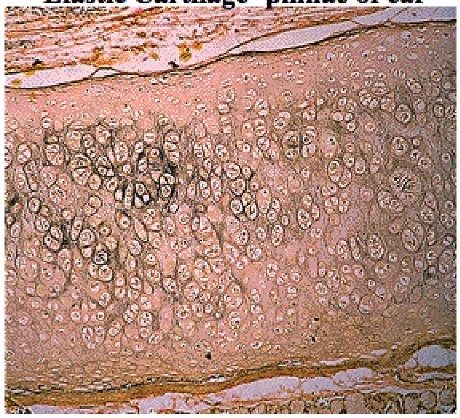
epiglottis & larynx

bridge of nose

Properties

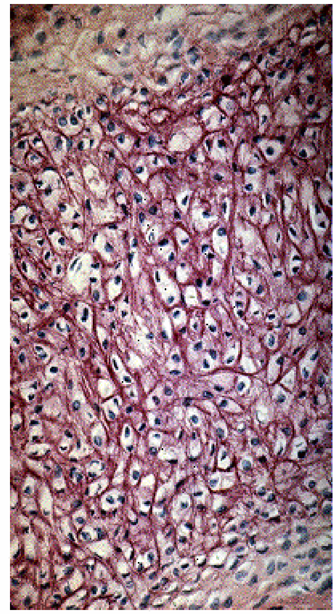
resiliency and pliability

Elastic Cartilage- pinnae of ear



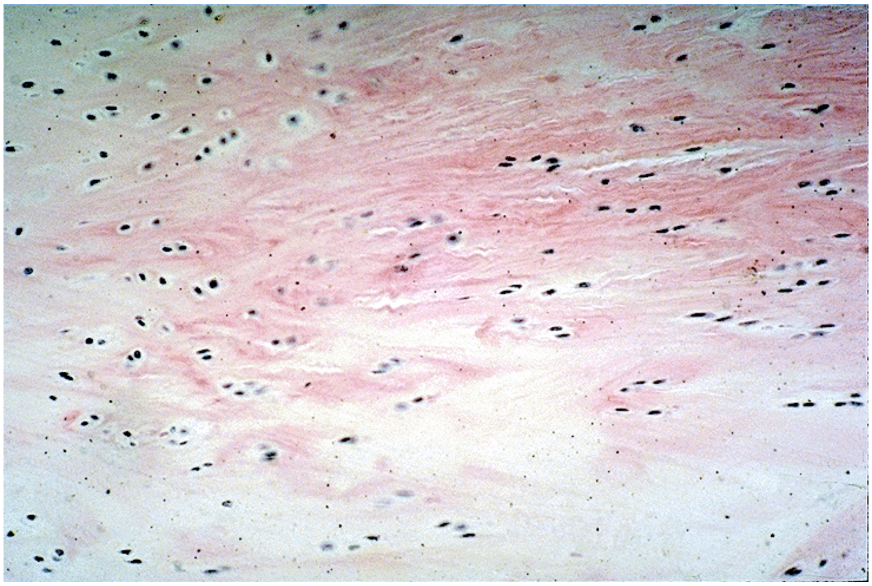
Elastic Fibers- silver stain

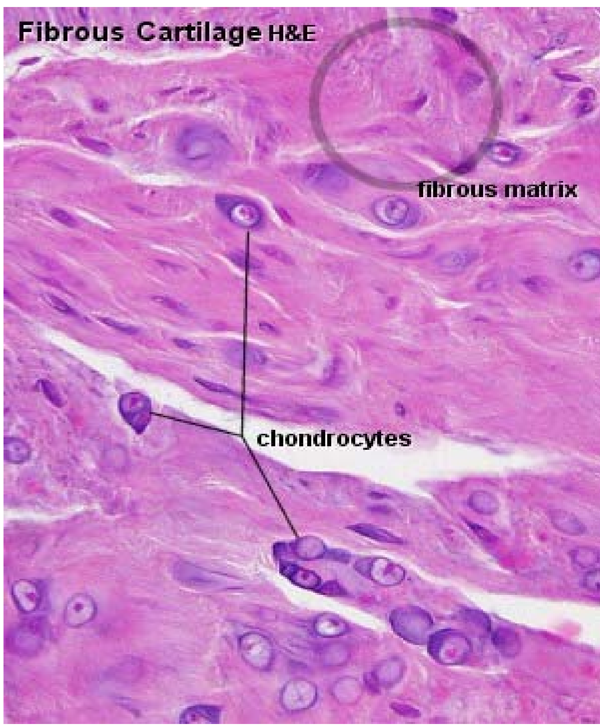
Elastic Fibers (resorcin-fuchsin stain)

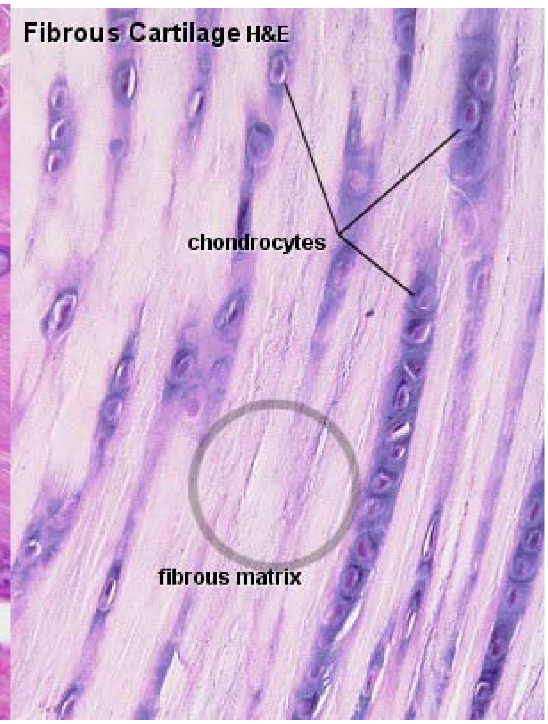


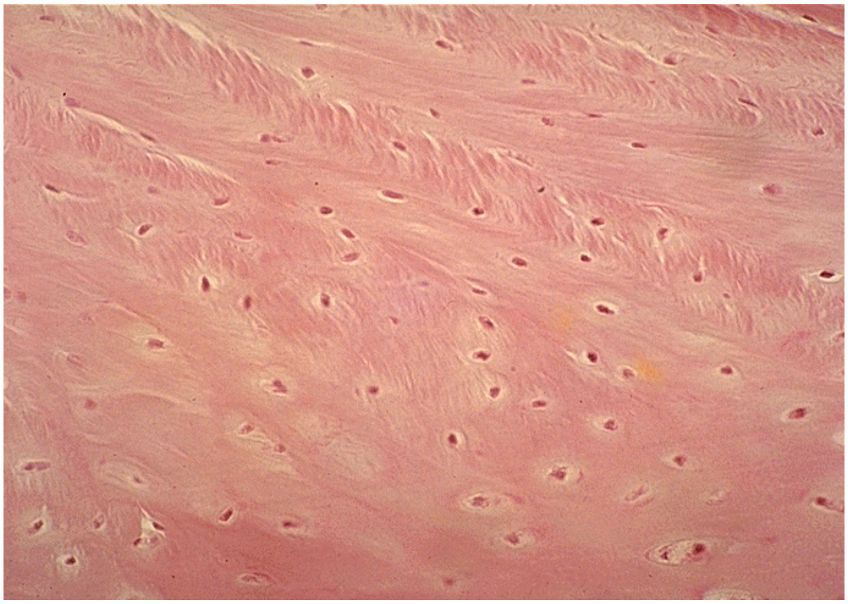
c/ Fibrous Cartilage

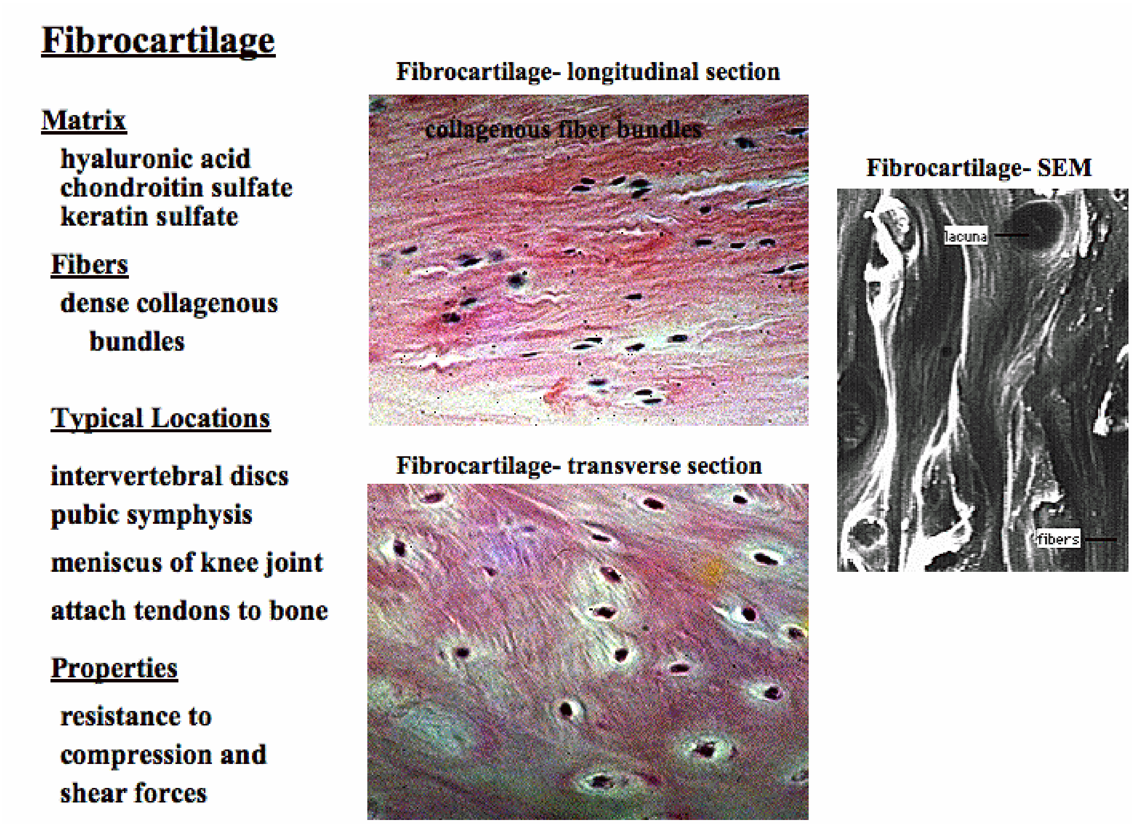
- is a form of connective tissue transitional between dense connective tissue and hyaline cartilage.
- Chondrocytes may lie singly or in pairs, but most often they form short rows between dense bundles of collagen fibres.
- **In contrast to other cartilage types, collagen type I is dominant in fibrous cartilage.**
- **is typically found in relation to joints (forming intra-articular lips, disks and menisci) and is the main component of the intervertebral disks.**
- merges imperceptibly into the neighbouring tissues, **typically tendons or articular hyaline cartilage.**
- It is difficult to define the perichondrium because of the fibrous appearance of the cartilage and the gradual transition to surrounding tissue types.




Fibrous Cartilage H&E
fibrous matrix
chondrocytes


Fibrous Cartilage H&E
chondrocytes
fibrous matrix

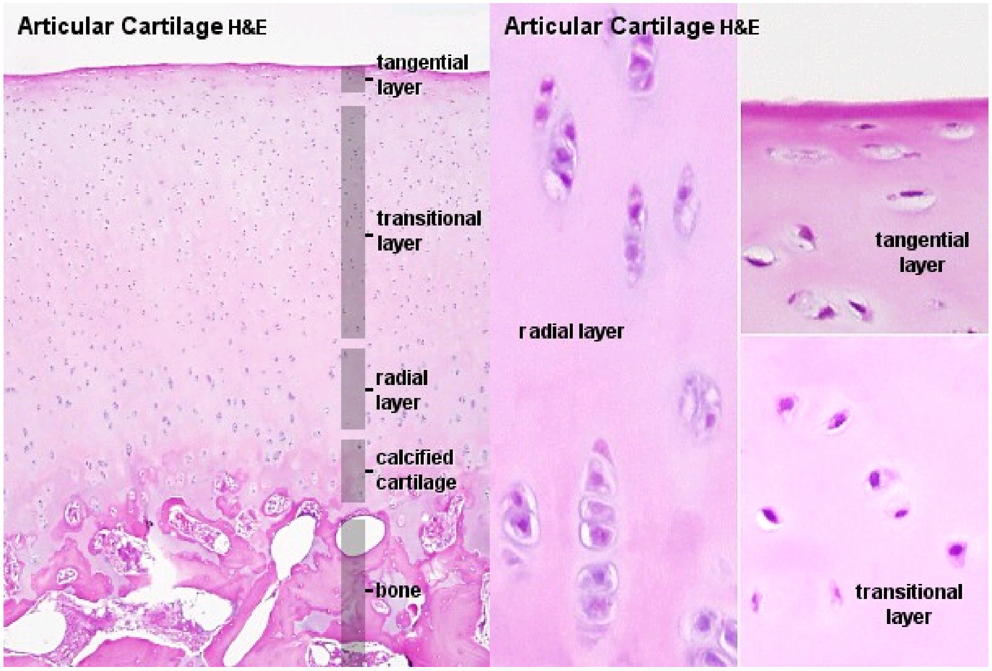




d/ Articular Cartilage

- 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:



1/ **<u>Tangential layer</u>**

- Chondrocytes are rather small and flattened parallel to the surface.
- The most superficial part (lamina splendens) is devoid of cells.
- Collagen fibres in the matrix of the tangential layer are very fine.
- They run parallel to the surface of the cartilage.
- Similar to the collagen fibres of the skin, the general orientation of collagen fibres in articular cartilage is determined by tensile and compressive forces at the articulating surfaces.

<u>2/ Transitional zone</u>

- The chondrocytes are slightly larger, are round and occur both singly and in isogenous groups.
- Collagen fibres take an oblique course through the matrix of the transitional zone.

<u>3/ Radial zone</u>

- Fairly large chondrocytes form radial columns, i.e. the stacks of cells are oriented perpendicular to the articulating surface.

- The course of the collagen fibres follows the orientation of the chondrocyte columns.

4/ Calcified cartilage layer

- It rests on the underlying cortex of the bone.
- The matrix of the calcified cartilage layer stains slightly darker (H&E) than the matrix of the other layers.
- The main source of nourishment for articular cartilage is the synovial fluid, which fills the joint cavity. Additional small amounts of nutrients are derived from blood vessels that course through the calcified cartilage close to the bone.

- Living chondrocytes have been found in small pieces of cartilage floating in the joint cavity after damage to the articular cartilage.

Osteoarthritis, the slow progressive degeneration of articular cartilage, is the most common joint disease. It may be caused by persistent and abnormally high loads on the joint surfaces, which initially result in the loss of proteoglycans and chondrocytes from the articulating surface of the cartilage. Subsequently, the cartilage may crack (fibrillate), erode and expose the underlying bone.

Degeneration and Regeneration of Cartilage

Due to the fairly poor access of nutrients to the chondrocytes they may atrophy in deep parts of thick cartilage. Water content decreases and small cavities arise in the matrix, which often leads to the calcification of the cartilage. This further compromises nutrition. The chondrocytes may eventually die, and the cartilage is gradually transformed to bone.

Chondrogenic activity of the perichondrium is limited to the period of active growth before adulthood. Although chondrocytes are able to produce matrix components throughout life, their production can not keep pace with the repair requirements after acute damage to hyaline or articular cartilage. If these cartilages are injured after the period of active growth, the defects are usually filled by connective tissue or fibrous cartilage. The extracellular matrix of these "repair tissues" is only poorly integrated with the matrix of the damaged cartilage.

Fortunately, cartilage is rather well suited for transplantation - the metabolism of the chondrocytes is rather slow, the antigenic power of cartilage is low, and it is difficult, if not impossible, for antibodies or cells of the immune system to diffuse through the matrix into the cartilage.

- **cartilage canals:** convey small vessels to other tissues but not cartilage; brought into center of cartilage mass where particularly thick (e.g., costal cartilage)

- **chondroblasts:** formed from stellate mesenchyme cells or embryonic fibroblasts; proliferate during growth; synthesize ground substance and fibrous ECM;

- **chondrocytes:** mature chondroblasts; maintain integrity of cartilage matrix; small nuclei with dispersed chromatin and basophilic, granular cytoplasm reflecting a well developed rER; space (shrinkage artifact) in ECM = **lacuna**; lg lipid droplets esp. in larger chondrocytes; separated by matrix;

- **isogenous clusters:** 2 or 4 with thin layer matrix; permits **interstitial growth** in embryonic cartilage

- **ground substance:** merges with perichondrium

  -inner (territorial or capsular) **zone** surrounds chondrocytes**:** rich in GAGs, poor in collagen; basophilic; chondrocytes in clusters appear to secrete fresh ECM; continuously turned over, dependent on viabiity of chondrocyte

  -outer (interterritorial) **zone :** pale-staining; contains numerous collagen fibrils
- **fibers**: collagen type II, with collagen type I and small amounts of other types, especially IX, X and XI; elastin in special cartilages
- **glycosaminoglycans** (GAGs): chains of **hyaluronic acid**; **chondroitin 4-sulfate, chondroitin 6-sulfate, keratan sulfate**

- **proteoglycans:** bottlebrushes with stems of core proteins and with bristles of sulfated glycosaminoglycans covalently linked to core proteins

- **proteoglycan aggregates** (up to 4 µm in length**):** proetoglycans noncovalently associated with hyaluronic acid via link protein and interacting with collagen

- **glycoprotein:** chondronectin (binds collagen type II and GAGs): adhesion chondrocytes to matrix
  -perichondrium:

  ***chondrogenic layer:** contains chondroblasts; provides **appositional growth**

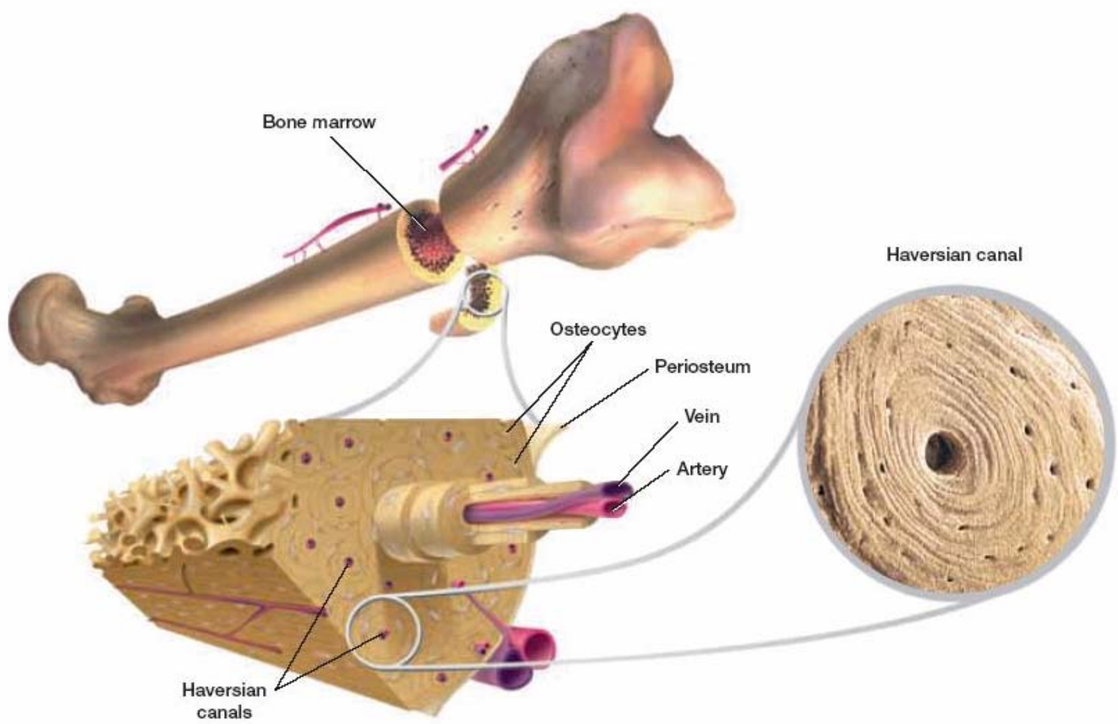
  ***fibrous layer:** dense regular ct; attachment sites; peripheral chondrocytes resemble fibroblasts; collagen type I

  - **hyaline cartilage**: small aggregates of chondrocytes (isogenous groups) embedded in matrix; perichondrium; growth both interstitial and appositional; type II collagen ; type I in articulate surfaces; perichondrium except at articulate surfaces

  - **fibrocartilage:** choanocytes within glycoprotein matrix in rows btwn layers of dense collagen bundles; no perichondrium; growth interstitional; bundles of type I collagen; no perichondrium

- **elastic (fibroelastic) cartilage:** perichondrium; growth both interstitial and appositional growth; type II collagen; perichondrium

II/ Bone



Bone is the main component of the skeleton in the adult human.

Like cartilage, bone is a specialised form of dense connective tissue.

Bone gives the skeleton the necessary rigidity to function as attachment and lever for muscles and supports the body against gravity.

Two types of bone can be distinguished macroscopically:

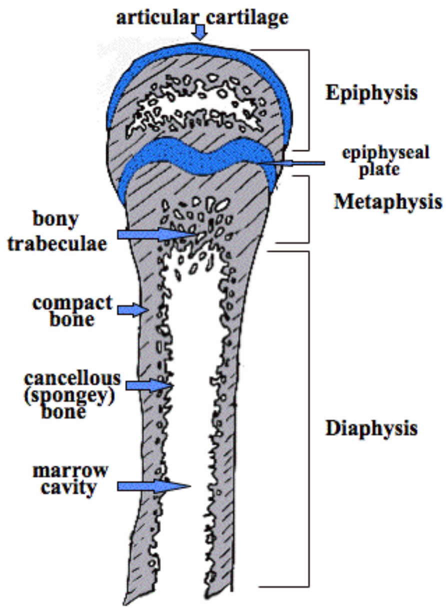
- Trabecular bone (also called cancellous or spongy bone) consists of delicate bars and sheets of bone, trabeculae, which branch and intersect to form a sponge like network. The ends of long bones (or epiphyses) consist mainly of trabecular bone.

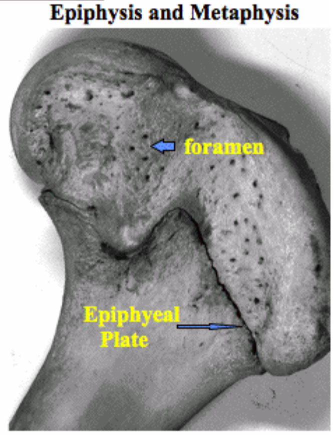
- Compact bone does not have any spaces or hollows in the bone matrix that are visible to the eye. Compact bone forms the thick-walled tube of the shaft (or diaphysis) of long bones, which surrounds the marrow cavity (or medullary cavity). A thin layer of compact bone also covers the epiphyses of long bones.

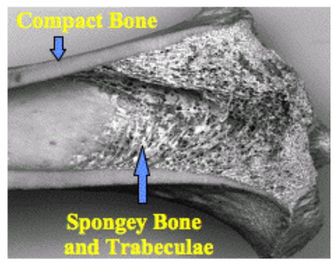
Bone is, again like cartilage, surrounded by a layer of dense connective tissue, the periosteum.
A thin layer of cell-rich connective tissue, the endosteum, lines the surface of the bone facing the marrow cavity.
Both the periosteum and the endosteum possess osteogenic potency.
Following injury, cells in these layers may differentiate into osteoblasts (bone forming cells) which become involved in the repair of damage to the bone.

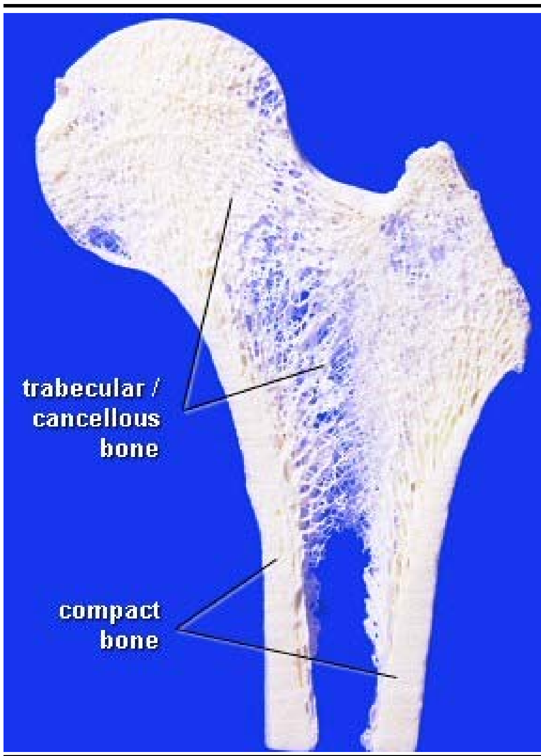
BONE ANATOMY

Epiphysis and Metaphysis



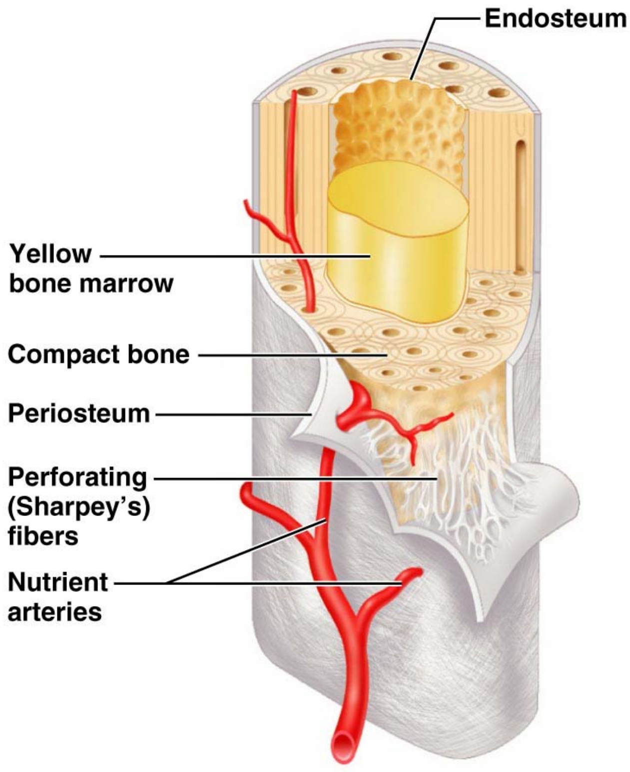






Compact Bone

- ***Osteocytes – mature bone cells***
- ***Lacunae – small cavities in bone that contain osteocytes***
- ***Canaliculi – hairlike canals that connect lacunae to each other and the central canal***
- ***Haversian system, or osteon – the structural unit of compact bone***
  - **Lamella – weight-bearing, column-like matrix tubes composed mainly of collagen**
  - **Haversian, or central canal – central channel containing blood vessels and nerves**
  - **Volkmann's canals – channels lying at right angles to the central canal, connecting blood and nerve supply of the periosteum to that of the Haversian canal**



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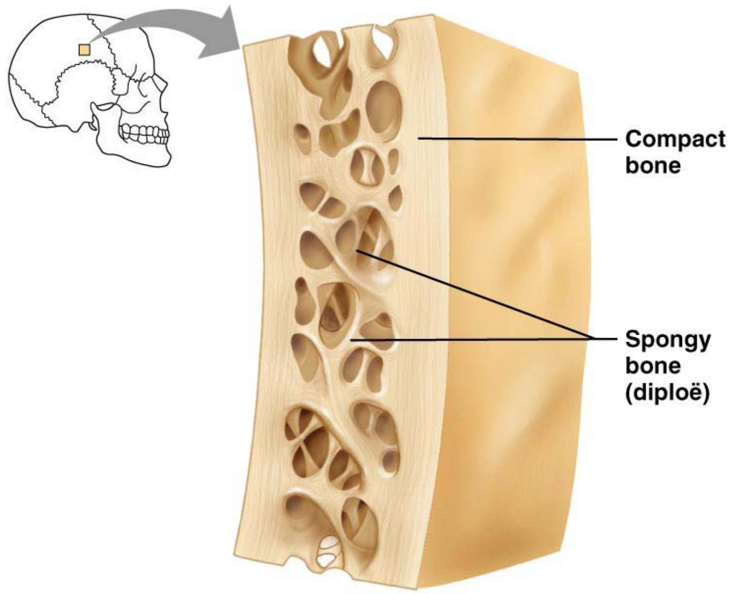
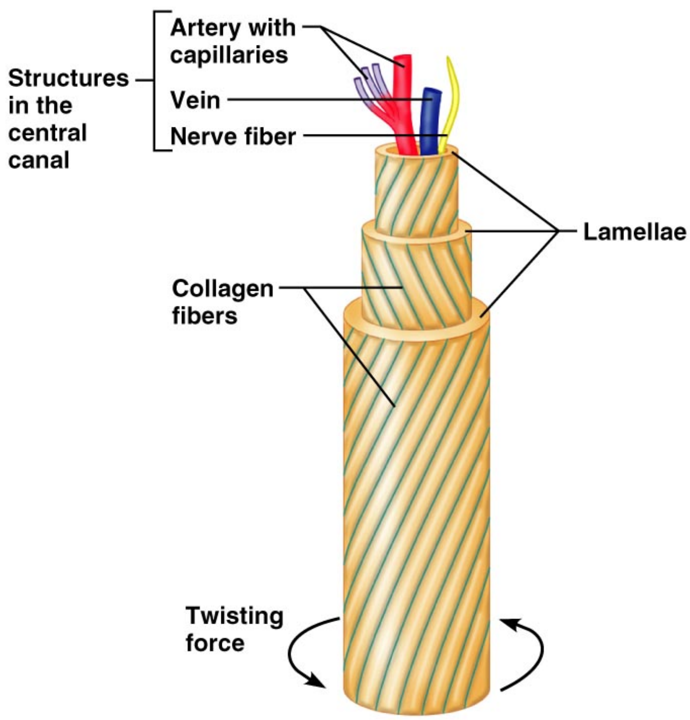




Function of Bones

- ***Support – form the framework that supports the body and cradles soft organs***
- ***Protection – provide a protective case for the brain, spinal cord, and vital organs***
- ***Movement – provide levers for muscles***

- ***Mineral storage – reservoir for minerals, especially calcium and phosphorus***
- ***Blood cell formation – hematopoiesis occurs within the marrow cavities of bones***

Bone Markings

- ***Bulges, depressions, and holes that serve as:***
  - **Sites of attachment for muscles, ligaments, and tendons**
  - **Joint surfaces**
  - **Conduits for blood vessels and nerves**

<u>Mechanical Loads on the Human Body</u>

1. Types of loading

- **Compression:** pressing or squeezing force directed axially through a body
- **Tension:** pulling or stretching force directed axially through a body
- **Shear:** force directed parallel to a surface
- **Bending:** asymmetric loading that produces tension on one side of a body's longitudinal axis and compression on the other
- **Torsion:** load causing twisting of a body around its longitudinal axis
- **Combined loading:** combination of different types of loading

2. Effects of loading

- **deformation:** change in shape
- **acute vs. repetitive:** likelihood of injury: load magnitude vs. frequency

3. Mechanical Stress and Strain

- **Mechanical stress**: distribution of force inside of a solid body (lumbar vs. thoracic vertabrae)
- **strain:** deformation due to stress
- **load-deformation curve (stress-strain curve)**

  - yield point (elastic limit): permanent deformation
  - failure point: loss of mechanical continuity

PROPERTIES OF BONE

Bone Cells: Osteocytes, osteoblasts, osteoclasts, osteoprogenitor cells

Organic Matrix:

Ground Substance:

complex polysaccharides and glycoproteins

Collagen: Type I

Mineral:

calcium phosphate
hydroxyapitite

Physical Properties:

Strength- resistance to compression, shear and tensile strength (protects vital organs and provides for motion due to muscle contraction)

Mobilizable reservoir of calcium

Adapts to growth and weight changes by remodeling

Self repair

Site of hematopoeisis

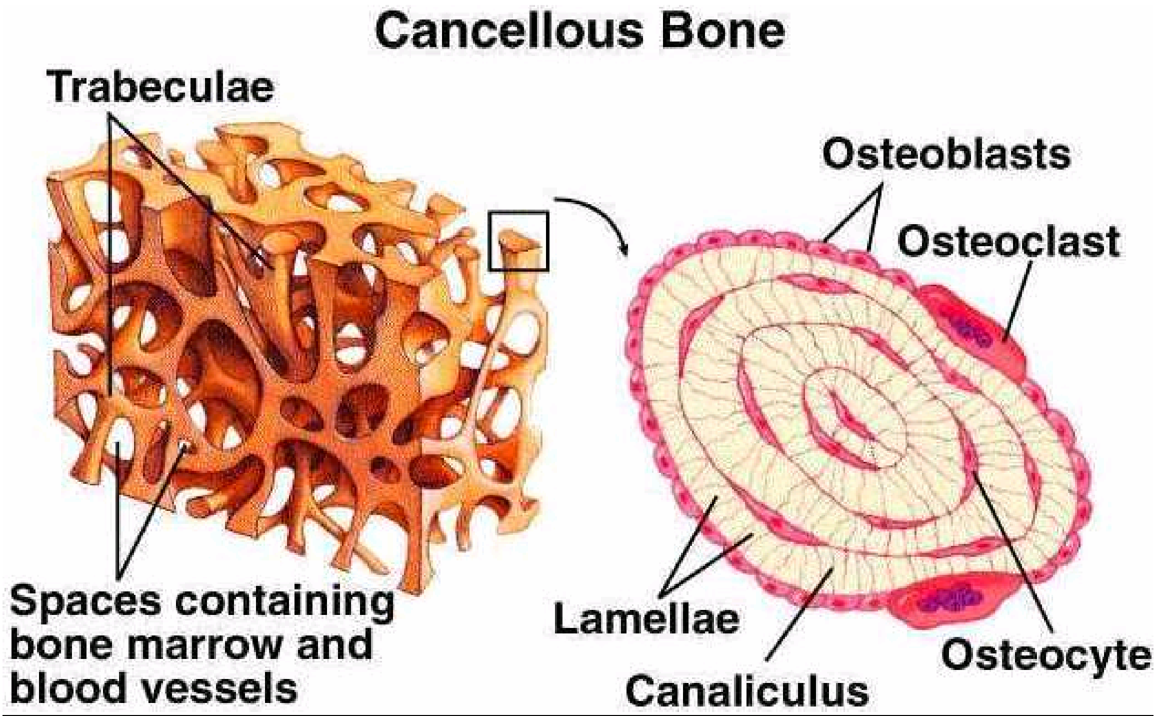
Composition and Structure of Bone

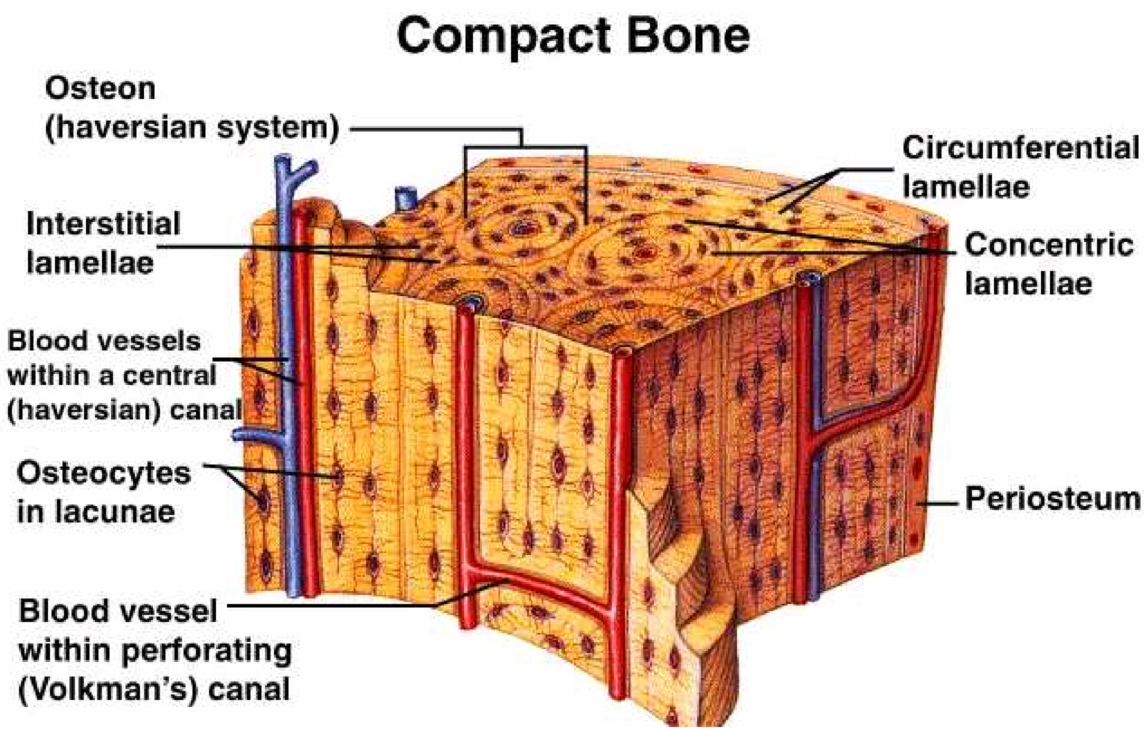
- **Stiffness -** ratio of stress to strain in a loaded material (stress divided by the relative amount of change in structure's shape)

- **Compressive strength -** ability to resist pressing or squeezing force

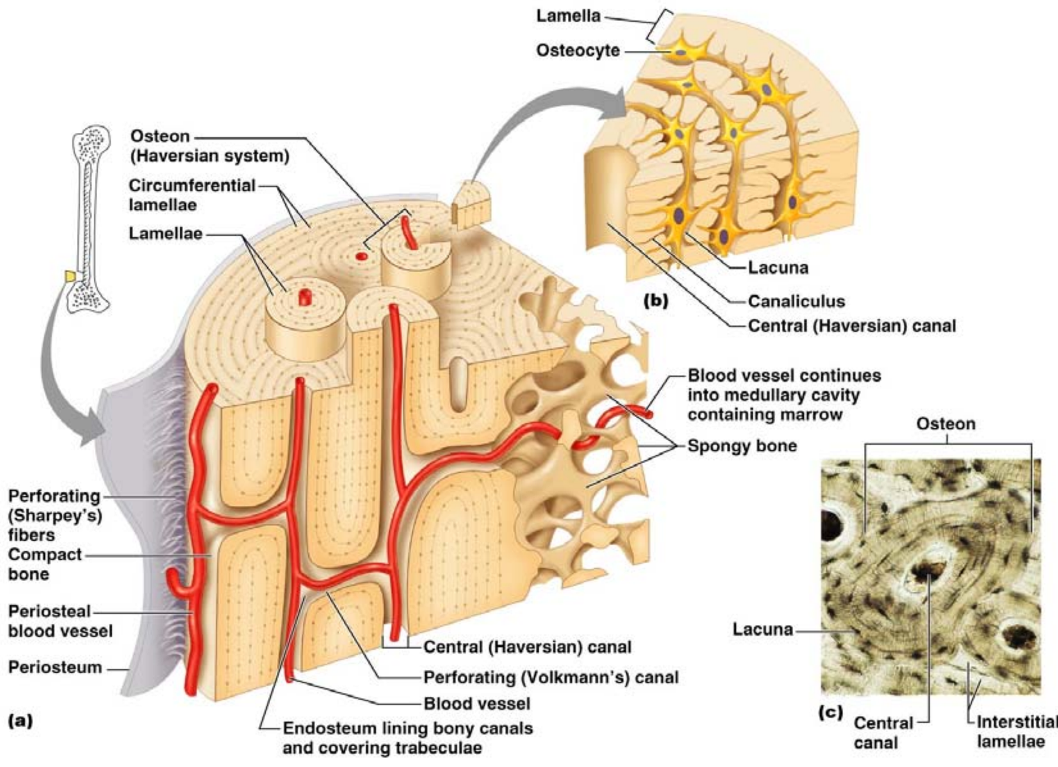
- ***Building Blocks of Bone***
    - Minerals (calcium carbonate and calcium phosphate ~ 60-70% of bone weight)
        - source of stiffness and compressive strength
    - Collagen (protein) ~ 10%
        - source of flexibility and tensile strength
        - aging causes decrease in collagen and, as a result, increase in fragility
    - Water ~ 25-30%
        - important contributor to bone strength

- **Cortical Bone** (compact mineralized tissue with low porosity) vs. **Trabecular Bone** (less compact with high porosity)





Histological Organisation of Bone

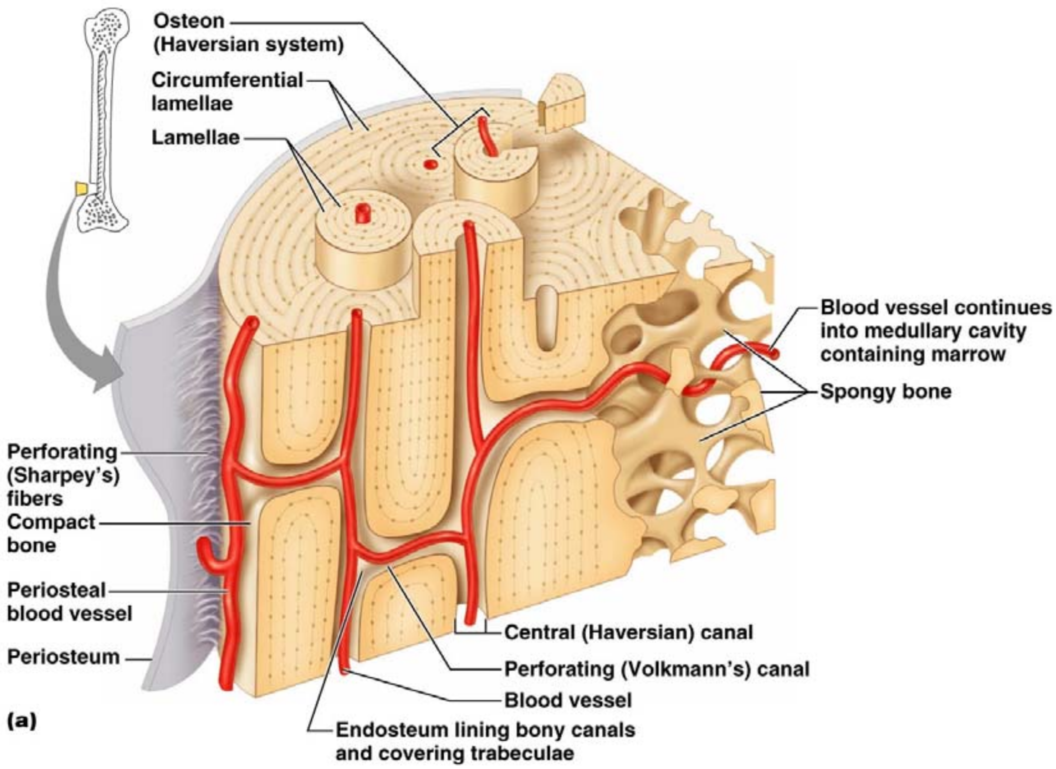


Compact Bone

- Compact bone consists almost entirely of extracellular substance, the matrix.
- Osteoblasts deposit the matrix in the form of thin sheets which are called lamellae.
- Lamellae are microscopical structures. Collagen fibres within each lamella run parallel to each other.
- Collagen fibres which belong to adjacent lamellae run at oblique angles to each other.
- Fibre density seems lower at the border between adjacent lamellae, which gives rise to the lamellar appearance of the tissue.
- Bone which is composed by lamellae when viewed under the microscope is also called lamellar bone.
- In the process of the deposition of the matrix, osteoblasts become encased in small hollows within the matrix, the lacunae.
- Unlike chondrocytes, osteocytes have several thin processes, which extend from the lacunae into small channels within the bone matrix , the canaliculi. Canaliculi arising from one lacuna may anastomose with those of other lacunae and, eventually, with larger, vessel-containing canals within the bone.

- Canaliculi provide the means for the osteocytes to communicate with each other and to exchange substances by diffusion.
- In mature compact bone most of the individual lamellae form concentric rings around larger longitudinal canals (approx. 50 µm in diameter) within the bone tissue. These canals are called Haversian canals.
- Haversian canals typically run parallel to the surface and along the long axis of the bone.

- The canals and the surrounding lamellae (8-15) are called a **Haversian system or an osteon**. A Haversian canal generally contains one or two capillaries and nerve fibres.
- Irregular areas of interstitial lamellae, which apparently do not belong to any Haversian system, are found in between the **Haversian systems.**
- Immediately beneath the periosteum and endosteum a few lamella are found which run parallel to the inner and outer surfaces of the bone. They are the circumferential lamellae and endosteal lamellae.
- A second system of canals, called **Volkmann's canals**, penetrates the bone more or less perpendicular to its surface.
- These canals establish connections of the Haversian canals with the inner and outer surfaces of the bone.
- Vessels in Volkmann's canals communicate with vessels in the Haversian canals on the one hand and vessels in the endosteum on the other.
- A few communications also exist with vessels in the periosteum.



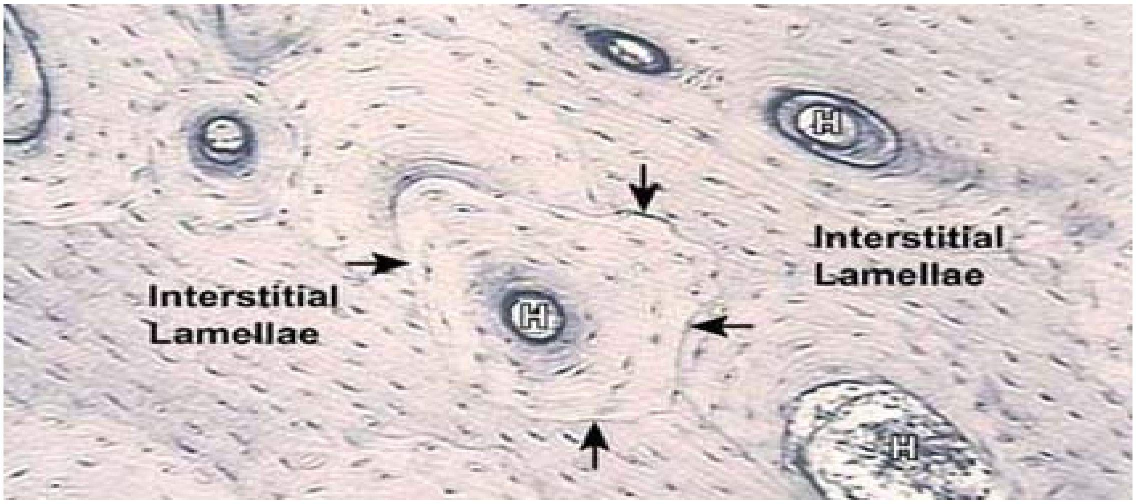
MICROANATOMY OF AN OSTEON
– **Haversian canal**
• Blood vessels and nerves
• Lined by endosteum - osteoprogenitor cells

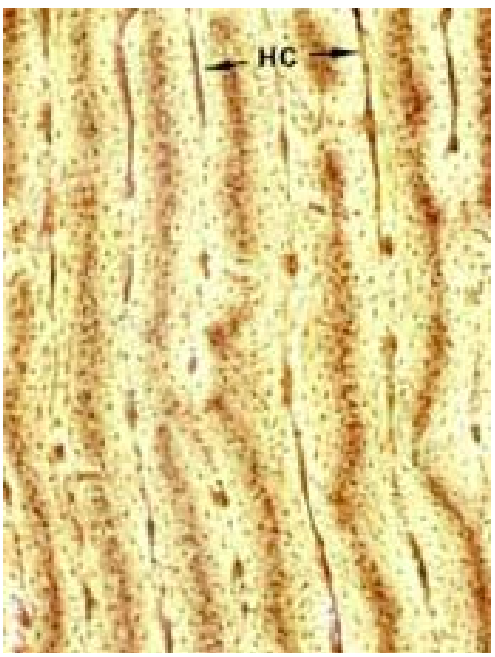
– **Cement line**
• Outermost boundary of osteon
• Area lacking canaliculi

– **Concentric lamellae**
• Oldest = closest to cement line
• Lacunae containing osteocytes
• Canaliculi containing osteocyte processes (gap junctions)

– **Osteons grow in osteoclast resorption tunnel**
• **Growth from outer wall of tunnel toward the middle**

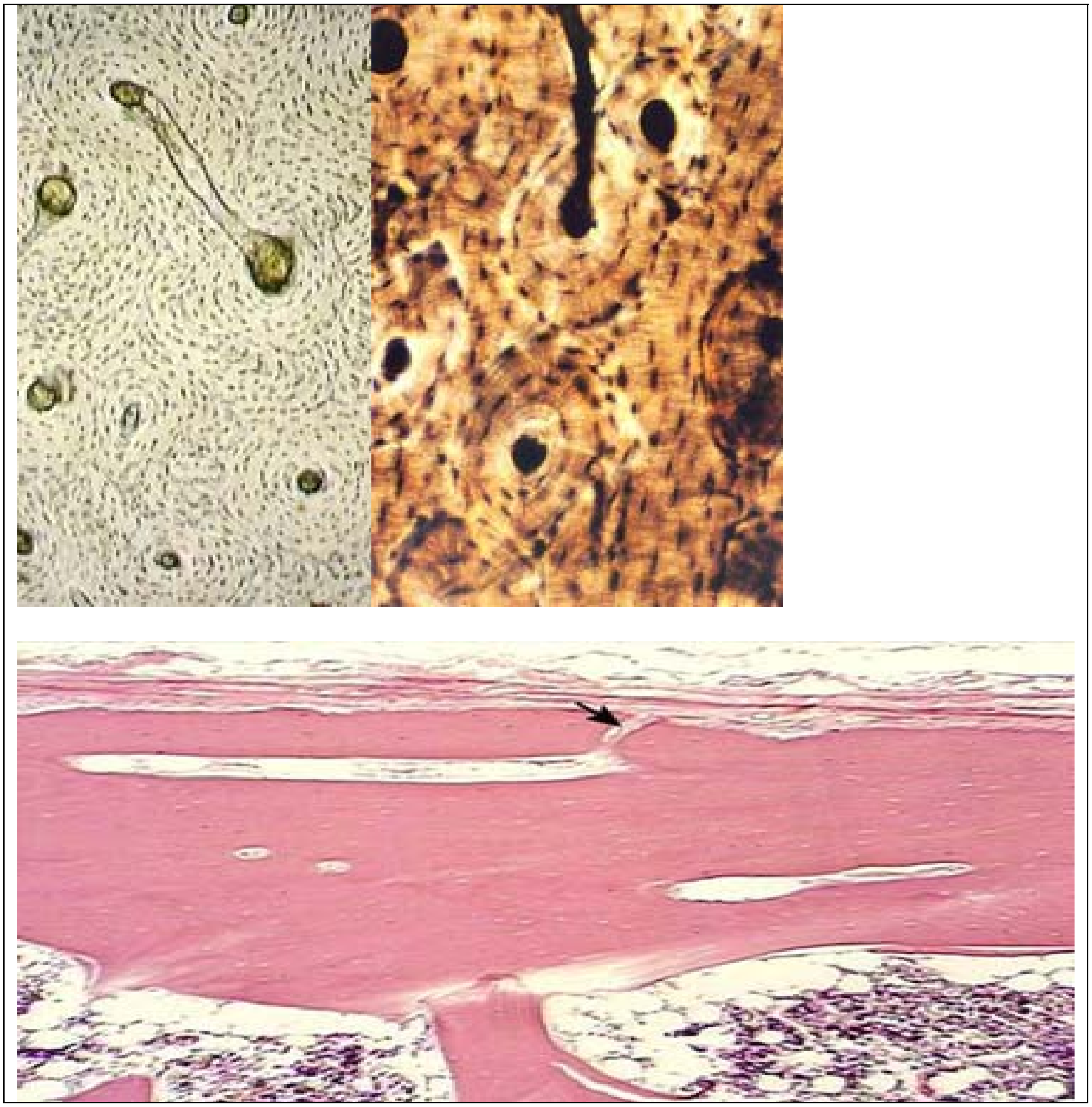
(Opposite to tree growth process)

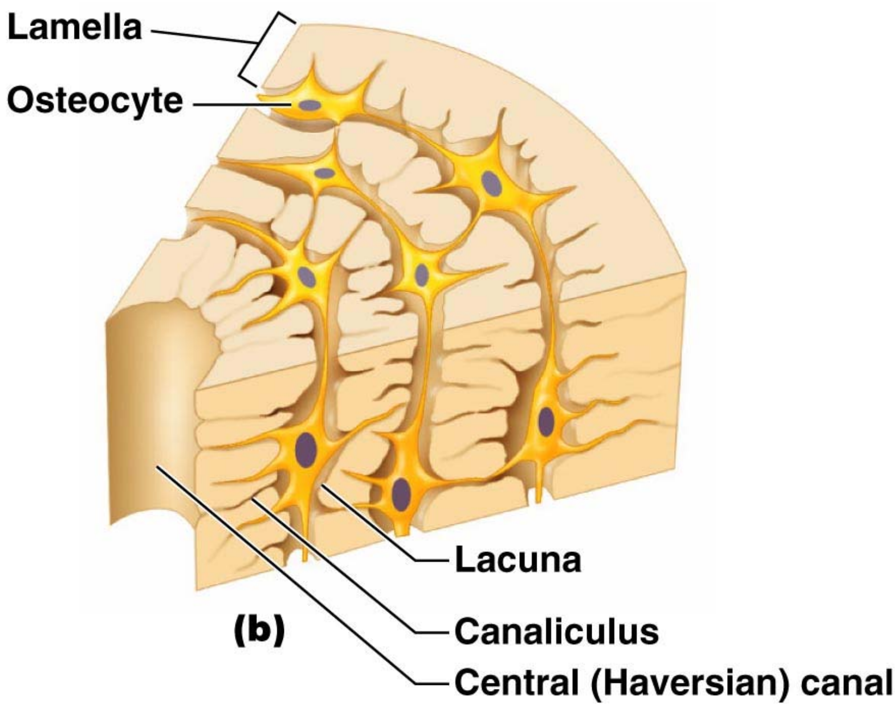




VOLKMANN’S CANAL

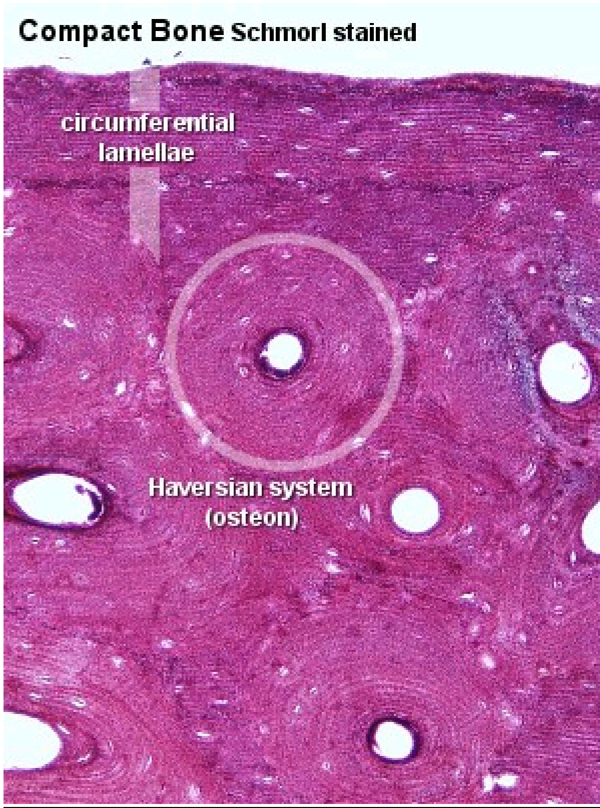
(CROSS SECTION)

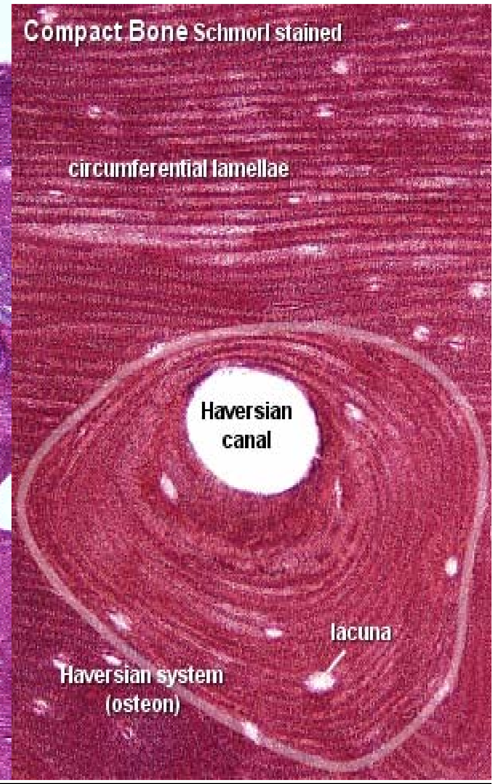


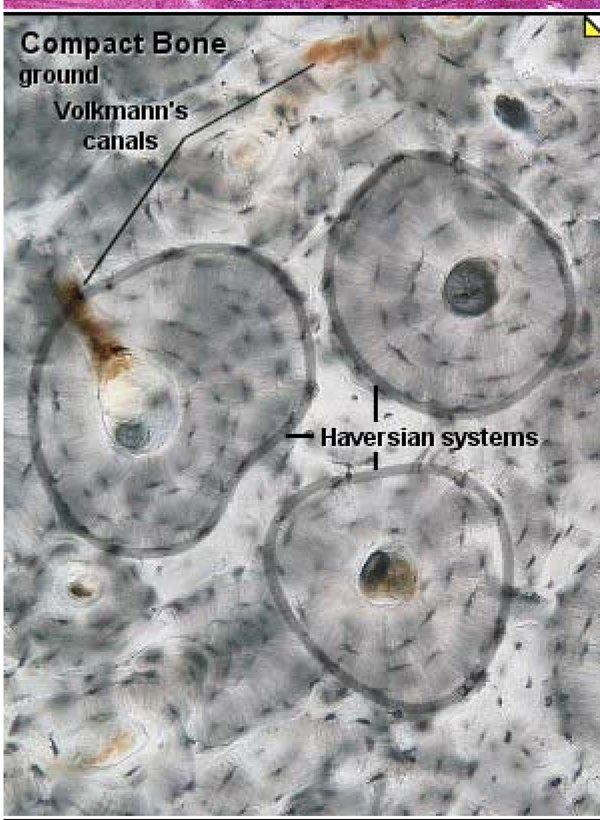


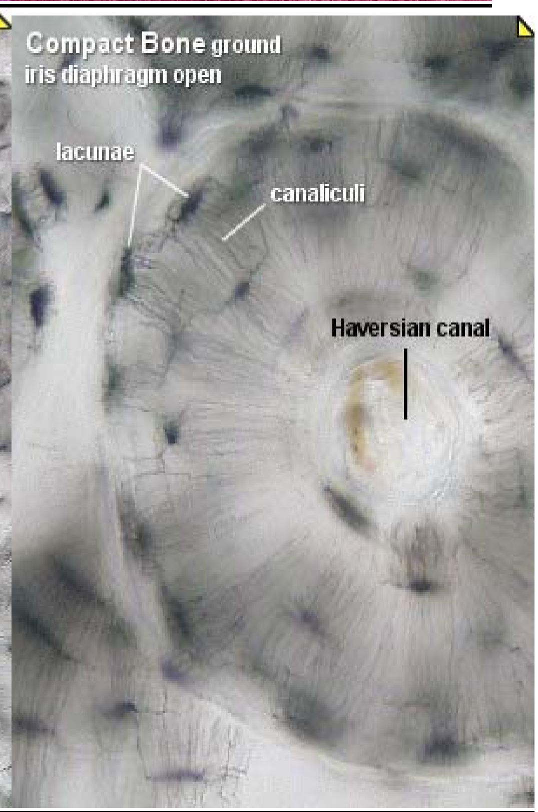
Trabecular Bone

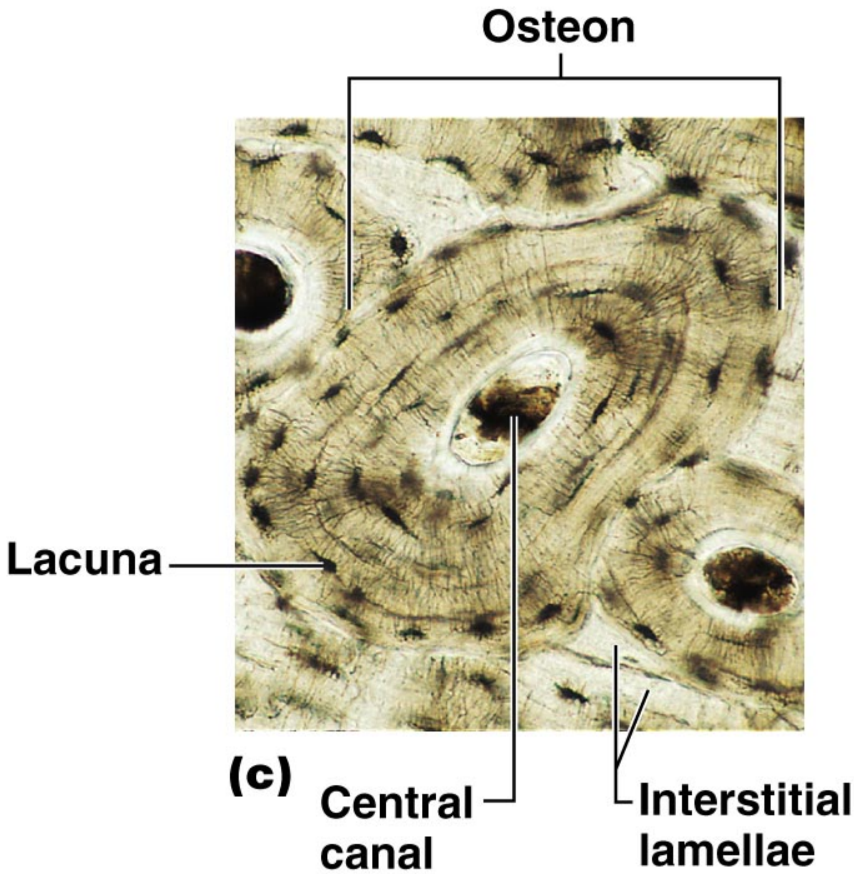
- The matrix of trabecular bone is also deposited in the form of lamellae. In mature bones, trabecular bone will also be lamellar bone.
- However, lamellae in trabecular bone do not form Haversian systems.
- Lamellae of trabecular bone are deposited on preexisting trabeculae depending on the local demands on bone rigidity.
- Osteocytes, lacunae and canaliculi in trabecular bone resemble those in compact bone.

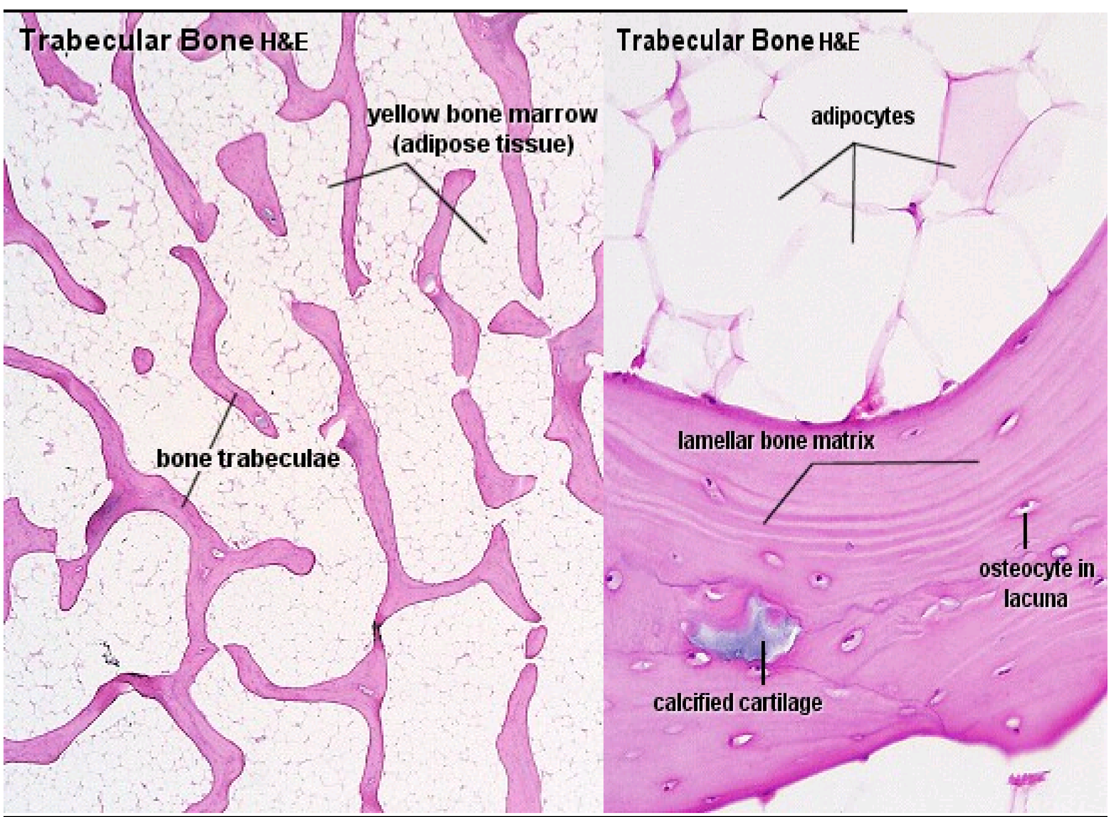

Compact Bone Schmorl stained
circumferential lamellae
Haversian system (osteon)


Compact Bone Schmorl stained
circumferential lamellae
Haversian canal
lacuna
Haversian system (osteon)

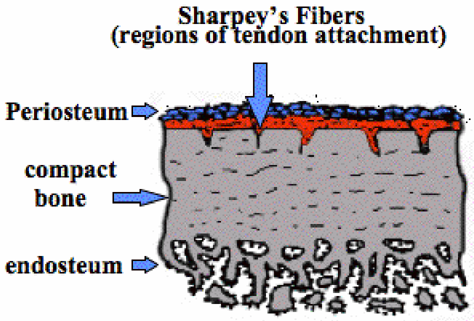

Compact Bone ground
Volkmann's canals
Haversian systems

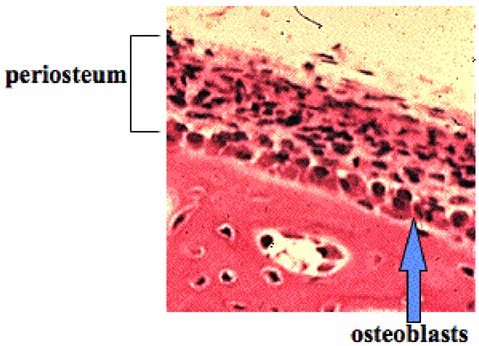

Compact Bone ground iris diaphragm open
lacunae
canaliculi
Haversian canal


Osteon
Lacuna
(c)
Central canal
Interstitial lamellae

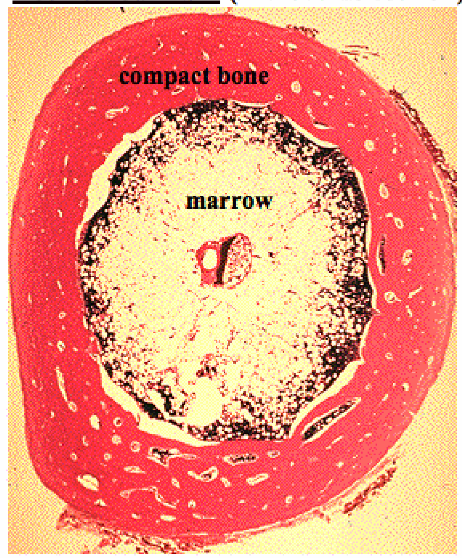

Trabecular Bone H&E
yellow bone marrow (adipose tissue)
bone trabeculae
Trabecular Bone H&E
adipocytes
lamellar bone matrix
osteocyte in lacuna
calcified cartilage

PERIOSTEUM

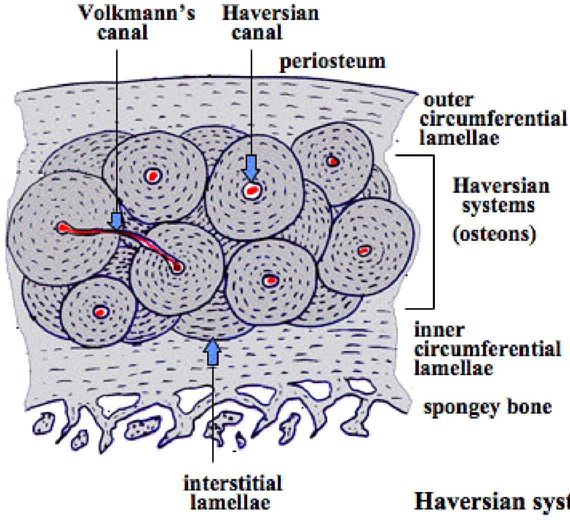




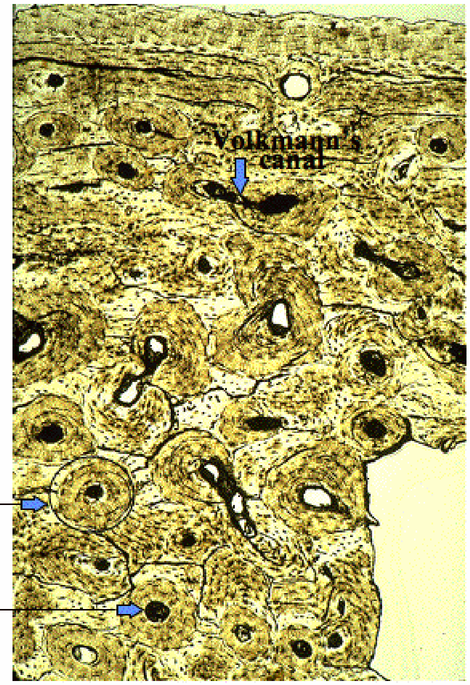
Decalcified Tibia (transverse section)



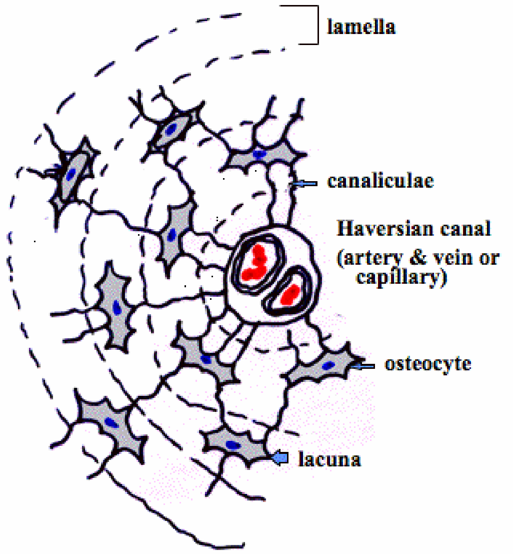
COMPACT BONE



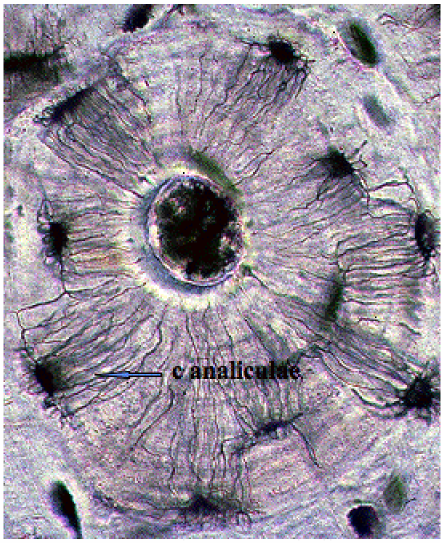
Ground Bone



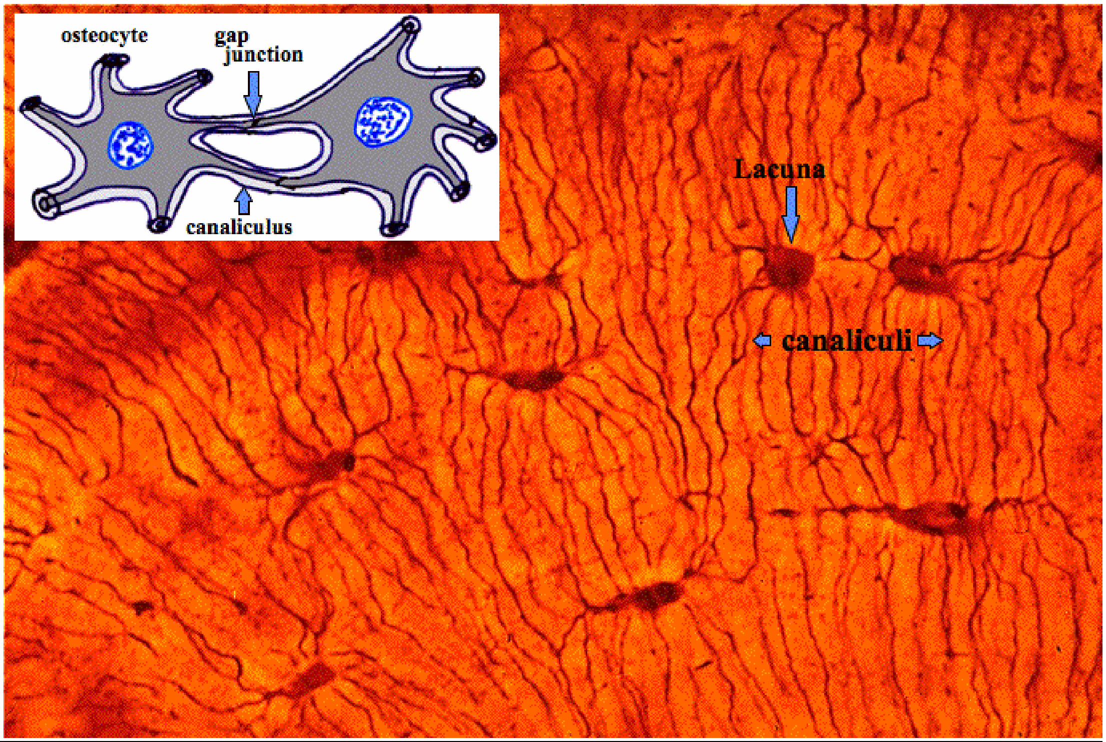
HAVERSIAN SYSTEMS



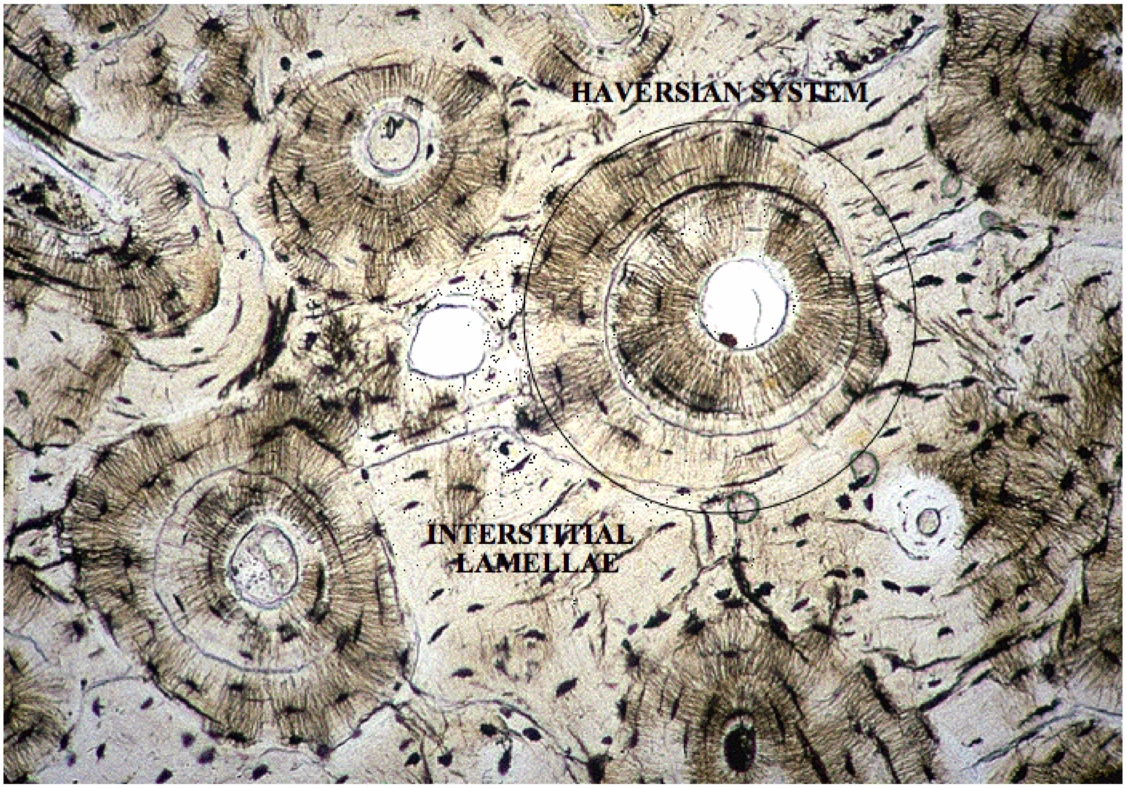
Ground Bone



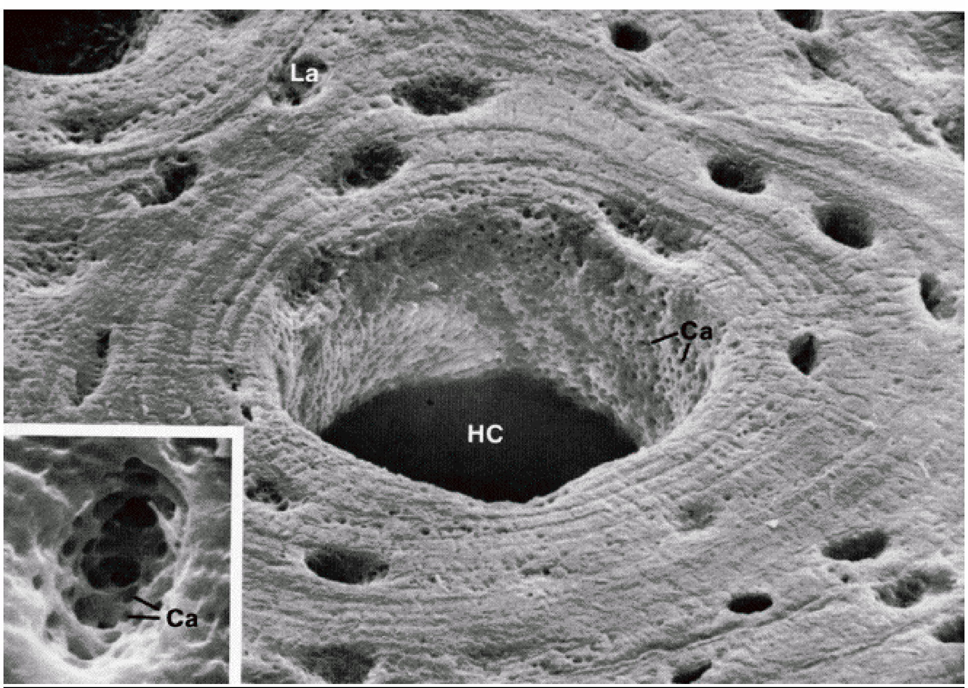
LACUNAE AND CANALICULI



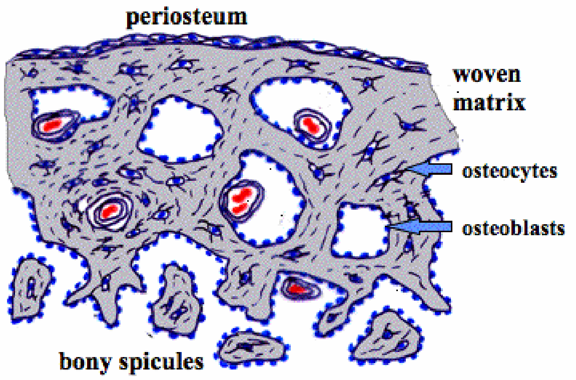
HAVERSIAN SYSTEMS AND INTERSTITIAL LAMELLAE

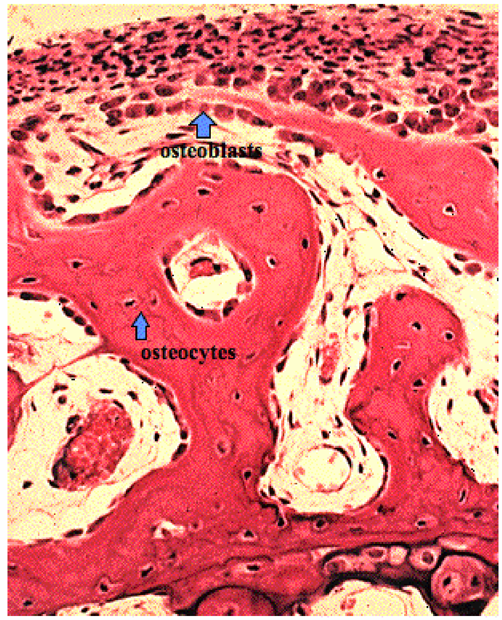


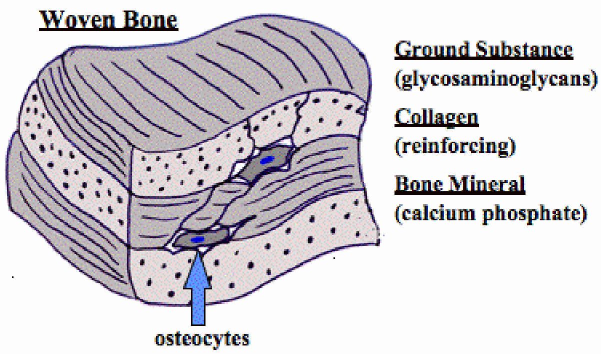
HAVERSIAN SYSTEM SEM



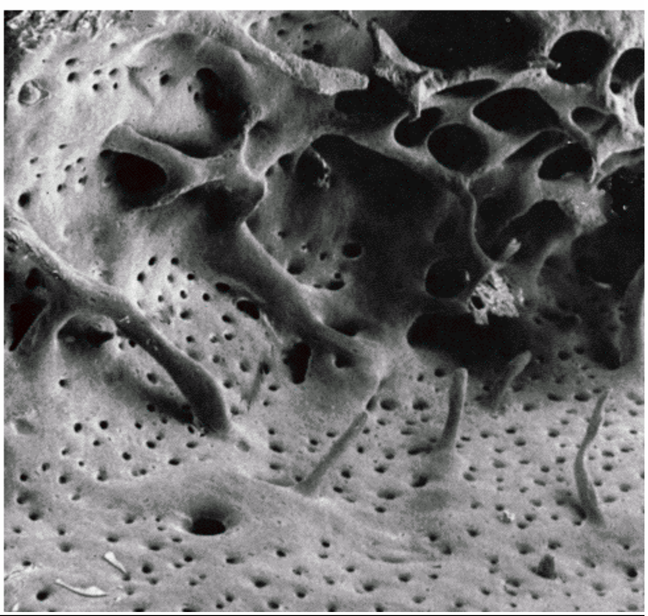
CANCELLOUS (SPONGEY) BONE







SPONGEY BONE



Bone Matrix and Bone Cells

a/ Bone Matrix

BONE MATRIX PROTEINS
(NON-COLLAGENOUS)
• **osteocalcin**
– binds calcium (hydroxyapatite)
– attracts osteoclasts
– levels in urine can increase in disease, (e.g., Paget's, hyperparathyroidism & renal osteodystrophy)
• **osteopontin**
– cell-binding protein (binds integrins)
– anchors osteoclasts to mineralized matrix (hydroxyapatite)
• **osteonectin**
– binds calcium
– regulation of mineralization
– anchors mineral components of bone to collagen
• **sialoprotein**
– important in cell attachment to matrix
• **thrombospondin**
– binds calcium & important in cell attachment
• **serum proteins**
– in same concentrations as in serum except albumin, which is increased

Bone matrix consists of :

- **<u>collagen fibres</u>** (about 90% of the organic substance) and ground substance.
    - **Collagen type I** is the dominant collagen form in bone.
- The hardness of the matrix is due to its content of inorganic salts (**hydroxyapatite; about 75% of the dry weight of bone**), which become deposited between collagen fibres.

Calcification begins a few days after the deposition of organic **bone substance (or osteoid)** by the **osteoblasts**.

Osteoblasts are capable of producing high local concentration of calcium phosphate in the extracellular space, which precipitates on the collagen molecules.

About 75% of the hydroxyapatite is deposited in the first few days of the process, but complete calcification may take several months.

b/ Bone Cells

- ***Osteoblasts – bone-forming cells***
- ***Osteocytes – mature bone cells***
- ***Osteoclasts – large cells that resorb or break down bone matrix***
- ***Osteoid – unmineralized bone matrix composed of proteoglycans, glycoproteins, and collagen***

OSTEOBLASTS
Derived from:

Mesenchymal **precursor cells / stem cells in bone marrow / osteoprogenitor cells of periosteum**
(mesenchymal cells can also differentiate into fat cells, fibroblasts, chondrocytes or muscle cells)
Characteristics:
- stellate (cytoplasmic processes unlike chondroblasts)
- prominent Golgi and RER = basophilic

Functions:
1. Make and mineralize bone extracellular matrix.
2. Produce matrix proteins:
Type 1 collagen (90% of the protein in bone)
osteocalcin
osteopontin
osteonectin
proteoglycans
alkaline phosphatase

3. Deposit osteoid on pre-existing mineralized or calcified surfaces only (= the mineralization front) Requires vitamin C.

4. Become trapped in lacunae within the Matrix of bone as o*steocytes (appositional growth).*
5. Produce factors that stimulate osteoclasts.

• large amt. RER
• prominent golgi
– contains collagen precursors
• secretes osteoid

SECRETORY AREA
• collagen fibrils in osteoid
• process becoming trapped in bone

OSTEOCYTES
Derived from:
- osteoblasts, mesenchymal origin

Characteristics:
- represent inactive osteoblasts trapped in lacunae
- cytoplasmic processes in canaliculi
- communicate via gap junctions
- surrounded by extracellular fluid in lacunae and canaliculi (periosteocytic space, site of calcium resorption)
- small golgi and RER (relatively quiescent)
- nondividing (NO interstitial bone growth)

Functions:
- osteocytic osteolysis role in calcium regulation via plasma [Ca++]
- assist in nutrition of bone

- mechanotransduction (regulate bone response to the mechanical environment via release of factors that recruit preosteoblasts)

OSTEOCLASTS

Derived from:
- ***Hematopoetic stem cells*** **in bone marrow (GM-CFU) that undergo endoreduplication (old theory = fusion of monocytes)**

Characteristics:
-large, motile, *multinucleated,* acidophilic cells
-some features of *macrophages*
-located on bone surfaces in Howship's lacuna
-ruffled border of the cell membrane
- cytosolic organelle-free region, or 'clear zone' (actin ring), seal
-adhere to the bone surface via integrins (specialized cell surface low-affinity receptors)
-many mitochondria, golgi, vesicles (lysosomes), RER
- nondividing

Function:
-Resorption of bone matrix:
initially involves mineral dissolution, followed by degradation of the organic components (collagen)

MINERAL DISSOLUTION:
• Occurs beneath ruffled boarder
• Depends on lysosomal enzyme secretion AND acid environment
pH gradient across the ruffled membrane established by:
- active transport mechanisms (e.g. Na+/H+ exchange)
-ATP-dependent proton pumps
- the enzyme *carbonic anhydrase* catalyzes production of carbonic acid (H2CO3) which dissociates into H+ ions

COLLAGEN DEGRADATION:
• Osteoclast lysosomal enzymes required:
- tartrate resistant isoenzyme of acid phosphatase (TRAP)
(used as a marker of the osteoclast phenotype),
- cysteine-proteinases such as the cathepsins that are capable of degrading collagen

<u>Osteoprogenitor cells (or stem cells of bone)</u>

- **are located in the periosteum and endosteum**.
- They are very difficult to distinguish from the surrounding connective tissue cells.
- They differentiate into:

<u>Osteoblasts (or bone forming cells).</u>

Osteoblasts may form a low columnar **"epitheloid layer"** at sites of bone deposition.

They contain plenty of rough endoplasmatic reticulum (collagen synthesis) and a **large Golgi apparatus**.

As they become trapped in the forming bone they differentiate into

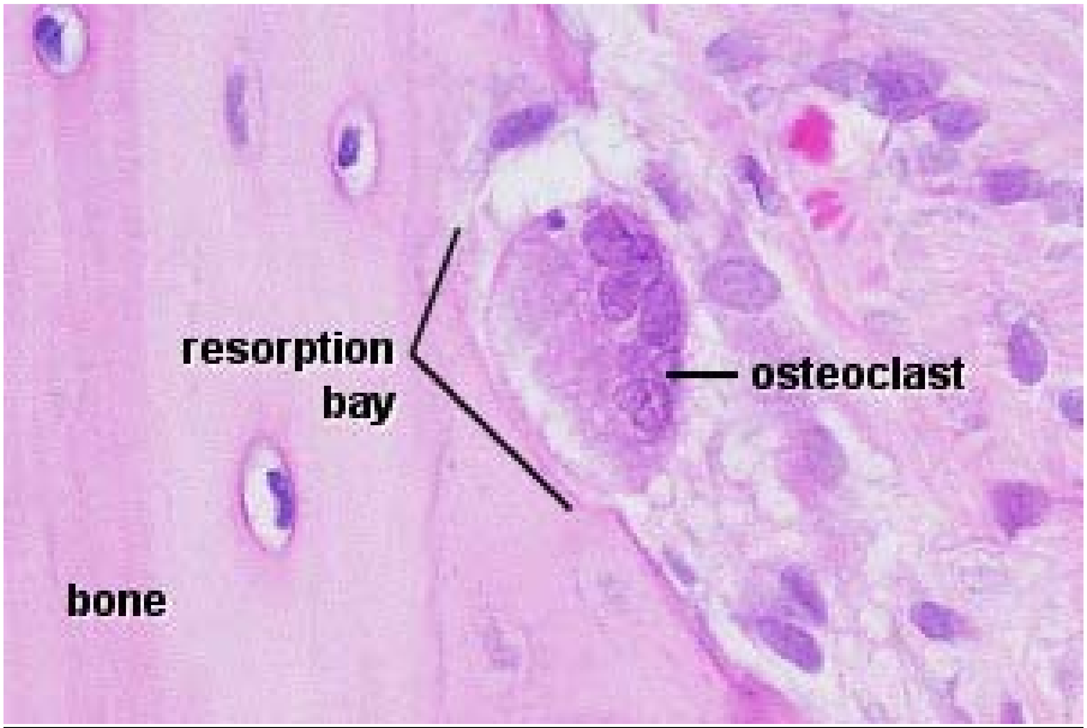
Osteocytes.

Osteocytes contain less endoplasmatic reticulum and are somewhat smaller than osteoblasts.

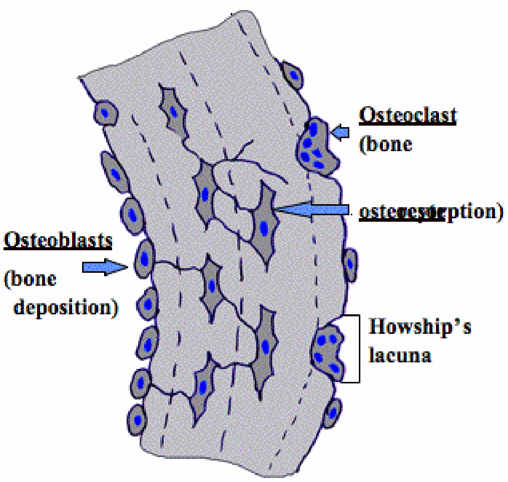
Osteoclasts

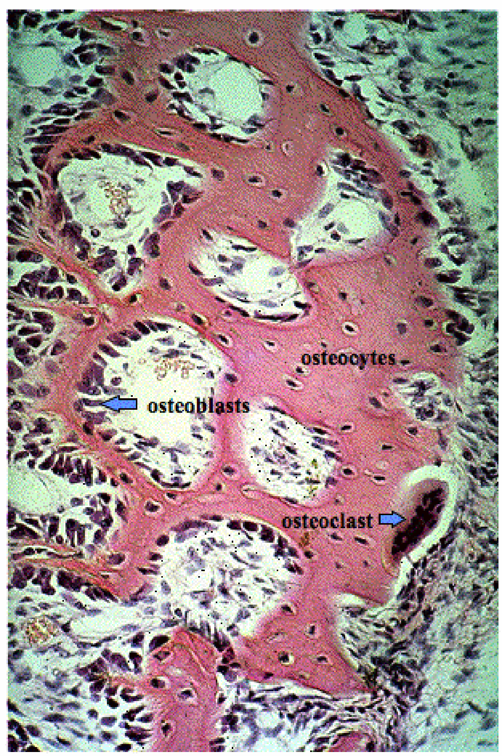
- are very large (up to 100 µm), multi-nucleated (about 5-10 visible in a histological section, but up to 50 in the actual cell) **bone-resorbing cells.**
- **They arise by the fusion of monocytes (macrophage precursors in the blood) or macrophages**.
- Osteoclasts attach themselves to the bone matrix and form a tight seal at the rim of the attachment site.
- The cell membrane opposite the matrix has deep invaginations forming a ruffled border.
- Osteoclasts empty the contents of lysosomes into the extracellular space between the ruffled border and the bone matrix.
- The released enzymes break down the collagen fibres of the matrix.
- **Osteoclasts are stimulated by parathyroid hormone (produced by the parathyroid gland) and inhibited by calcitonin (produced by specialised cells of the thyroid gland).**
- **Osteoclasts are often seen within the indentations of the bone matrix that are formed by their activity (resorption bays or Howship's lacunae).**

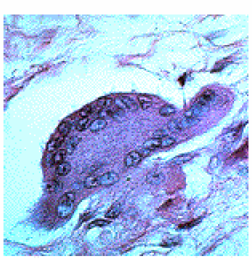
REGULATION OF OSTEOCLAST ACTIVITY	
STIMULATORS **(lead to increased serum calcium)**	**INHIBITORS** **(lead to decreased serum calcium)**
Parathyroid hormone (PTH) **-made in parathyroid gland** **-acts through osteoBLAST derived factors below:** **Osteoprotegrin ligand (OPGL)** **-osteoblast derived factor in response to PTH** **-preosteoclasts to osteoclasts** **Osteoclast stimulating factor** **-osteoblast derived factor in response to PTH** **IL-1, IL-6,TNF, CSF-1** **-induces osteoclast production**	**Calcitonin (calcium stays in bone)** **-made in thyroid gland** **-reduces osteoclast motility** **- retracts cytoplasmic extensions** **- reduces size of ruffled border** **Osteoprotegrin, TGF, Interferon** **-stops differentiation** **Bisphosphonates (Fosamax)** **- exogenous, synthetic analogue of pyrophosphate** **-causes osteoclast apoptosis** **-used to treat osteoporosis**



BONE CELLS

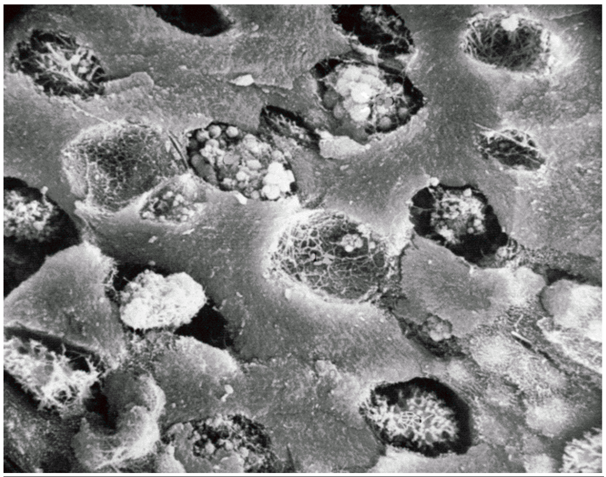






Osteoclast

OSTEOCLASTS AND HOWSHIP'S LACUNAE



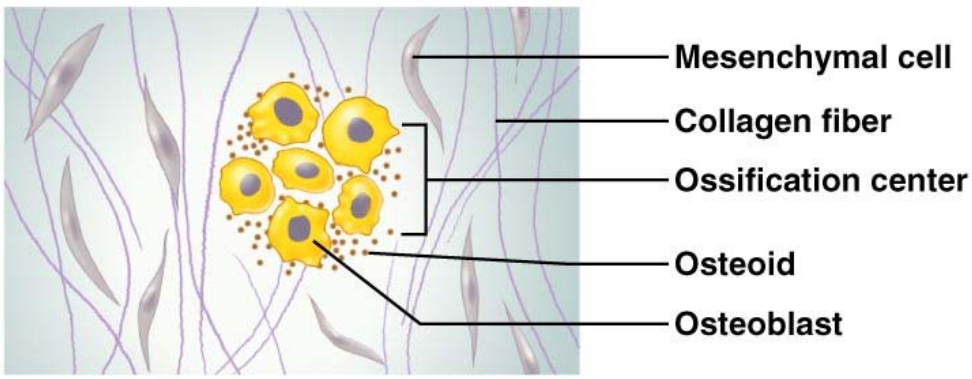
Formation of Bone

Bones are formed by two mechanisms:

- **intramembranous ossification (bones of the skull, part of the mandible and clavicle) or endochondral ossification.**

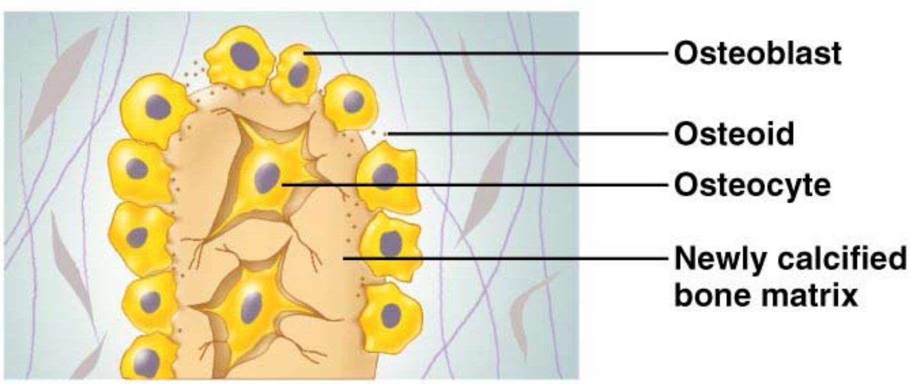
Stages of Intramembranous Ossification

- *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*



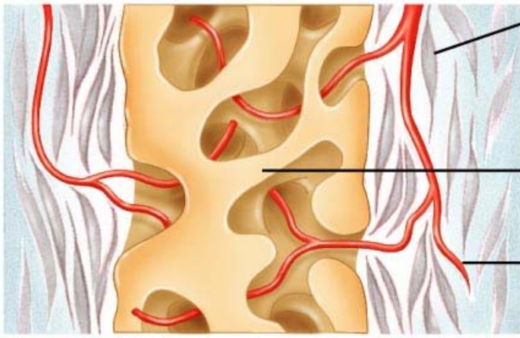
① **An ossification center appears in the fibrous connective tissue membrane.**

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



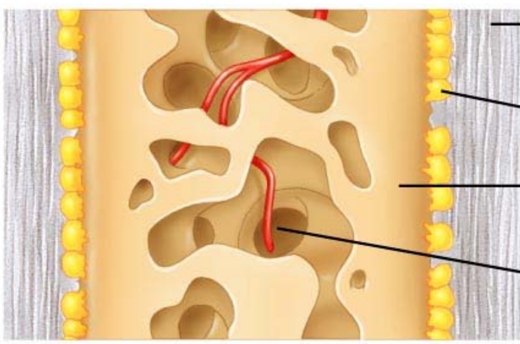
② **Bone matrix (osteoid) is secreted within the fibrous membrane.**

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



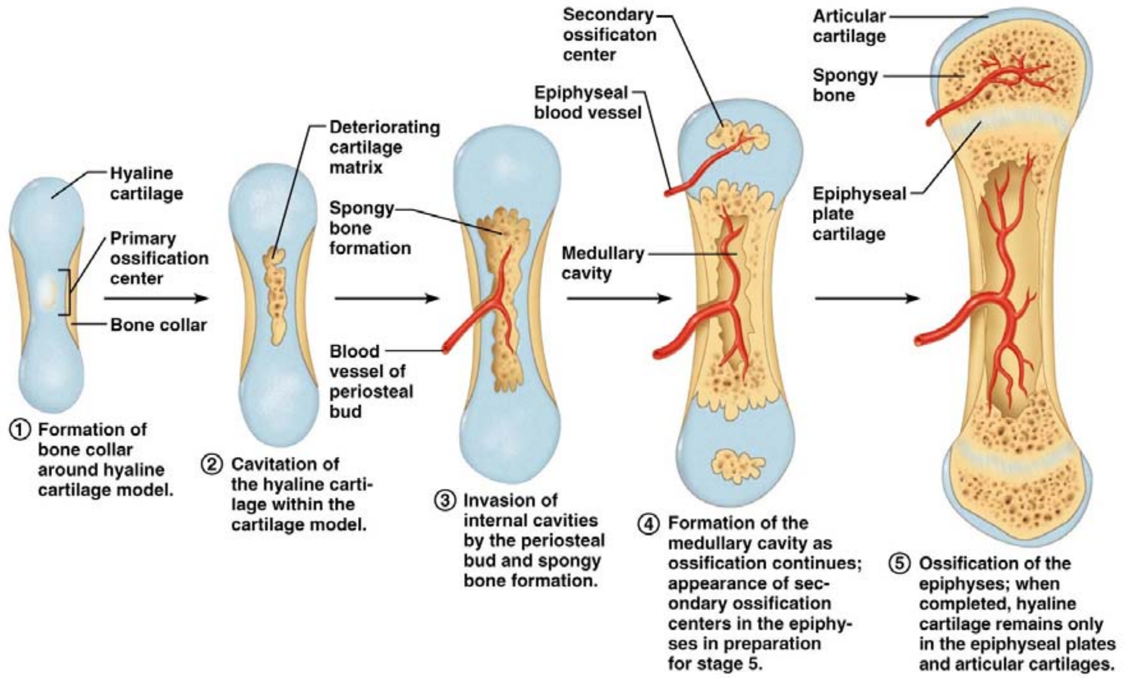
③ **Woven bone and periosteum form.**

- 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.



MINERAL DISSOLUTION:
• Occurs beneath ruffled boarder
• Depends on lysosomal enzyme secretion AND acid environment
pH gradient across the ruffled membrane established by:
- active transport mechanisms (e.g. Na+/H+ exchange)
-ATP-dependent proton pumps
- the enzyme *carbonic anhydrase* catalyzes production of carbonic acid (H2CO3) which dissociates into H+ ions

COLLAGEN DEGRADATION:
• Osteoclast lysosomal enzymes required:
- tartrate resistant isoenzyme of acid phosphatase (TRAP) (used as a marker of the osteoclast phenotype),
- cysteine-proteinases such as the cathepsins that are capable of degrading collagen

Intramembranous Ossification

- Intramembranous ossification occurs within a membranous, condensed plate of mesenchymal cells.
- At the initial site of ossification (ossification centre) mesenchymal cells (osteoprogenitor cells) differentiate into osteoblasts.
- The osteoblasts begin to deposit the organic bone matrix, the osteoid.
- The matrix separates osteoblasts, which, from now on, are located in lacunae within the matrix.
- The collagen fibres of the osteoid form a woven network without a preferred orientation, and lamellae are not present at this stage.
- Because of the lack of a preferred orientation of the collagen fibres in the matrix, this type of bone is also called woven bone.

- The osteoid calcifies leading to the formation of primitive trabecular bone.
- Further deposition and calcification of osteoid at sites where compact bone is needed leads to the formation of primitive compact bone.

? Note the distinction between macroscopic and microscopic appearance when the bone is named. We again have the two macroscopically different forms of bone - trabecular bone and compact bone - but their early developmental ("primitive") forms consist of woven bone.

Through subsequent reorganisation the primitive compact and trabecular bone is converted into mature compact and trabecular bone.

During reorganisation and growth, woven bone will, in time, be replaced by lamellar bone.

Intramembranous ossification does not require the existence of a cartilage bone model.

Endochondral Ossification

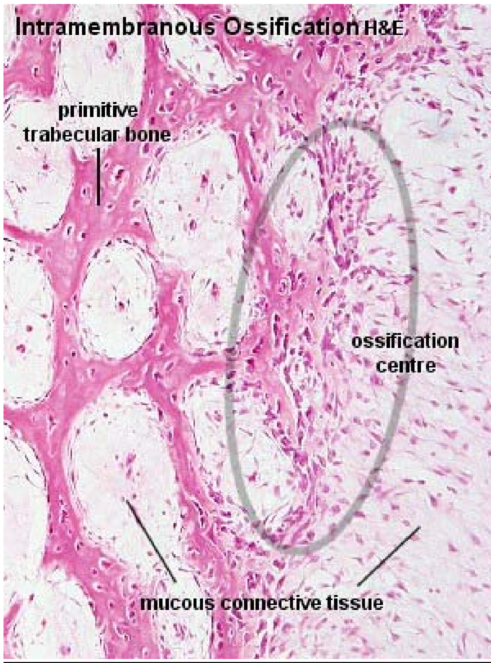
- ***Begins in the second month of development***
- ***Uses hyaline cartilage "bones" as models for bone construction***
- ***Requires breakdown of hyaline cartilage prior to ossification***

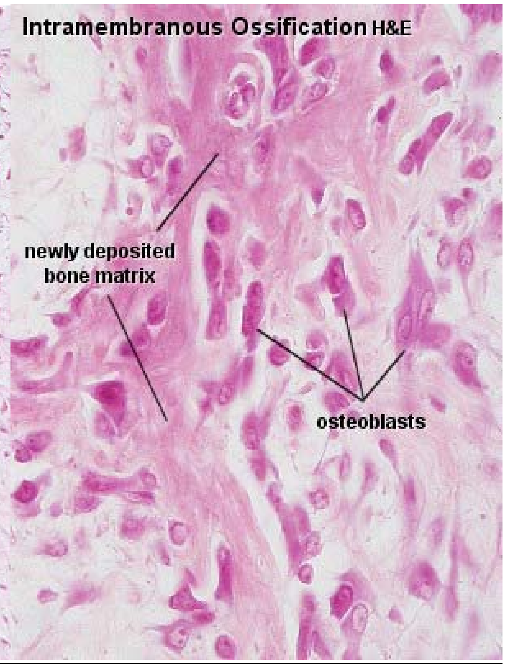
Stages of Endochondral Ossification

- ***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***

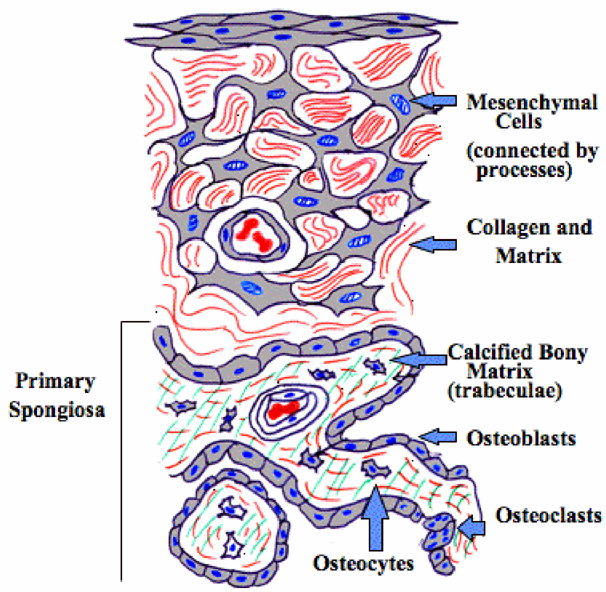
Postnatal Bone Growth

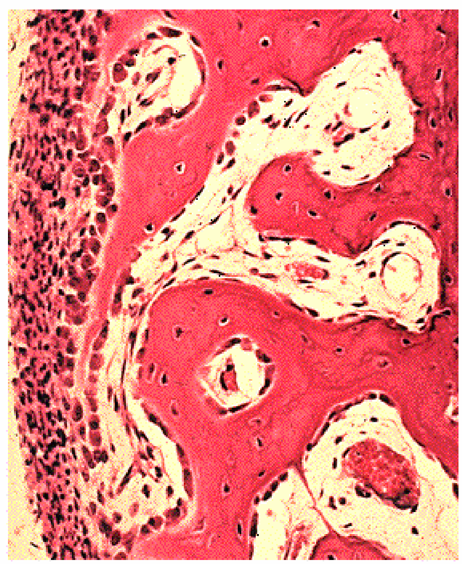
- ***Growth in length of long bones***
  - **Cartilage on the side of the epiphyseal plate closest to the epiphysis is relatively inactive**
  - **Cartilage abutting the shaft of the bone organizes into a pattern that allows fast, efficient growth**
  - **Cells of the epiphyseal plate proximal to the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





INTRAMEMBRANOUS OSSIFICATION





posteoprogentor cells → osteoblasts → osteocytes

monocytes → osteoclasts

Intramembranous Ossification

Skull- frontal, parietal, occipital temporal bones
mandible- jaw

Endochondral Ossification

- **Most bones are formed by the transformation of cartilage "bone models", a process called endochondral ossification.**
- A periosteal bud invades the cartilage model and allows osteoprogenitor cells to enter the cartilage.
- At these sites, the cartilage is in a state of hypertrophy (very large lacunae and chondrocytes) and partial calcification, which eventually leads to the death of the chondrocytes.

- Invading osteoprogenitor cells mature into osteoblasts, which use the framework of calcified cartilage to deposit new bone.
- The bone deposited onto the cartilage scaffold is lamellar bone.
- The initial site of bone deposition is called a primary ossification centre.
- Secondary ossification centres occur in the future epiphyses of the bone.

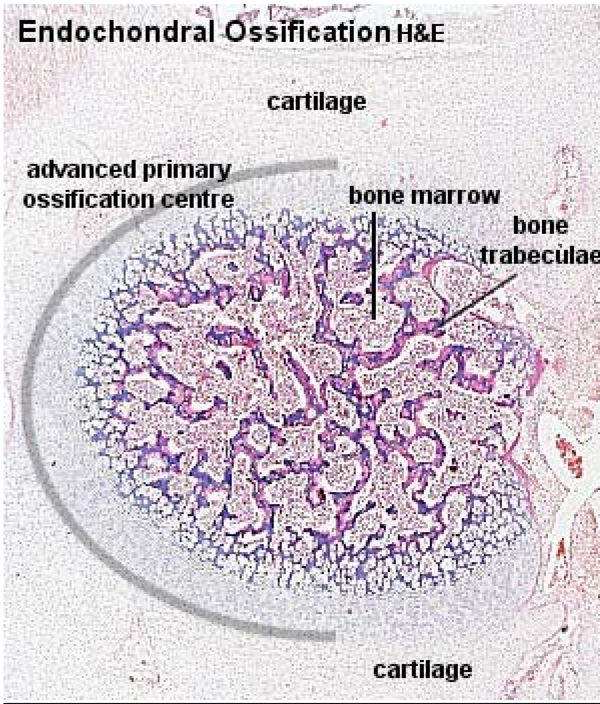
- A thin sheet of bone, the periosteal collar, is deposited around the shaft of the cartilage model. The periosteal collar consists of woven bone.

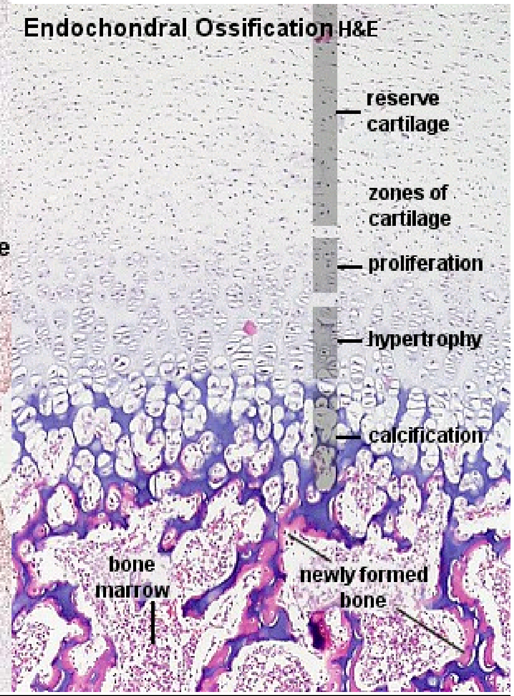
Close to the zone of ossification, the cartilage can usually be divided into a number of distinct zones :

1. Reserve cartilage, furthest away from the zone of ossification, looks like immature hyaline cartilage.
2. A zone of chondrocyte proliferation contains longitudinal columns of mitotically active chondrocytes, which grow in size in
3. the zone of cartilage maturation and hypertrophy.
4. A zone of cartilage calcification forms the border between cartilage and the zone of bone deposition.

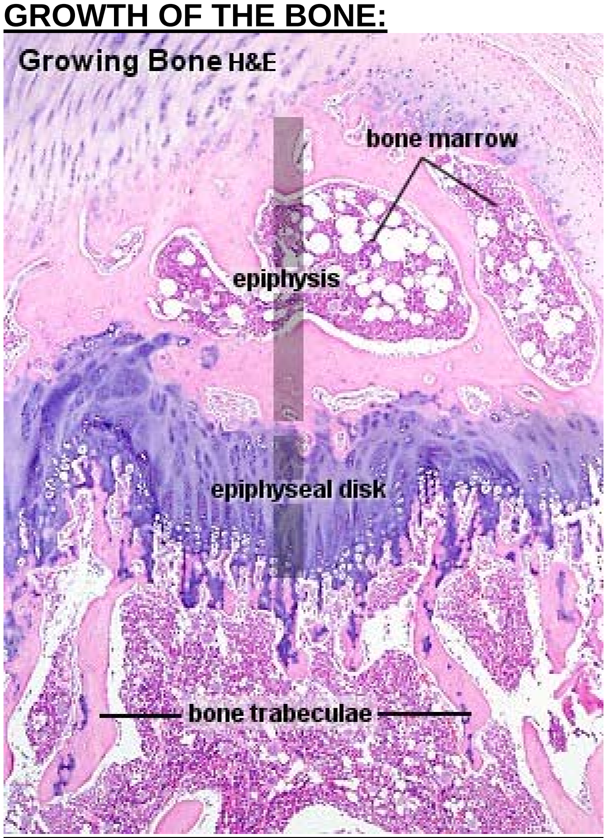
- Primary and secondary ossification centres do not merge before adulthood.
- Between the diaphysis and the epiphyses a thin sheet of cartilage, the epiphyseal plate, is maintained until adulthood.
- By continuing cartilage production, the epiphyseal plate provides the basis for rapid growth in the length of the bone.
- Cartilage production gradually ceases in the epiphyseal plate as maturity is approached.
- The epiphyseal plate is finally removed by the continued production of bone from the diaphyseal side.
- Bone formation and bone resorption go hand in hand during the growth of bone.
- This first deposited trabecular bone is removed as the zone of ossification moves in the direction of the future epiphyses.
- This process creates the marrow cavity of the bones.
- Simultaneously, bone is removed from the endosteal surface and deposited on the periosteal surface of the compact bone which forms the diaphysis.

This results in a growth of the diameter of the bone.

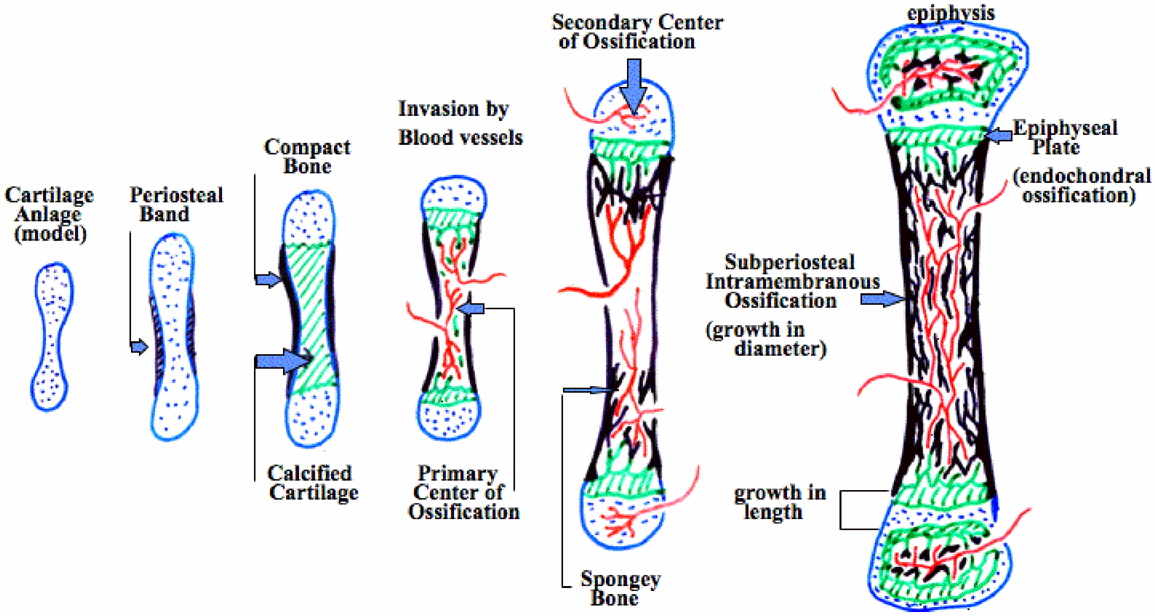




GROWTH OF THE BONE:

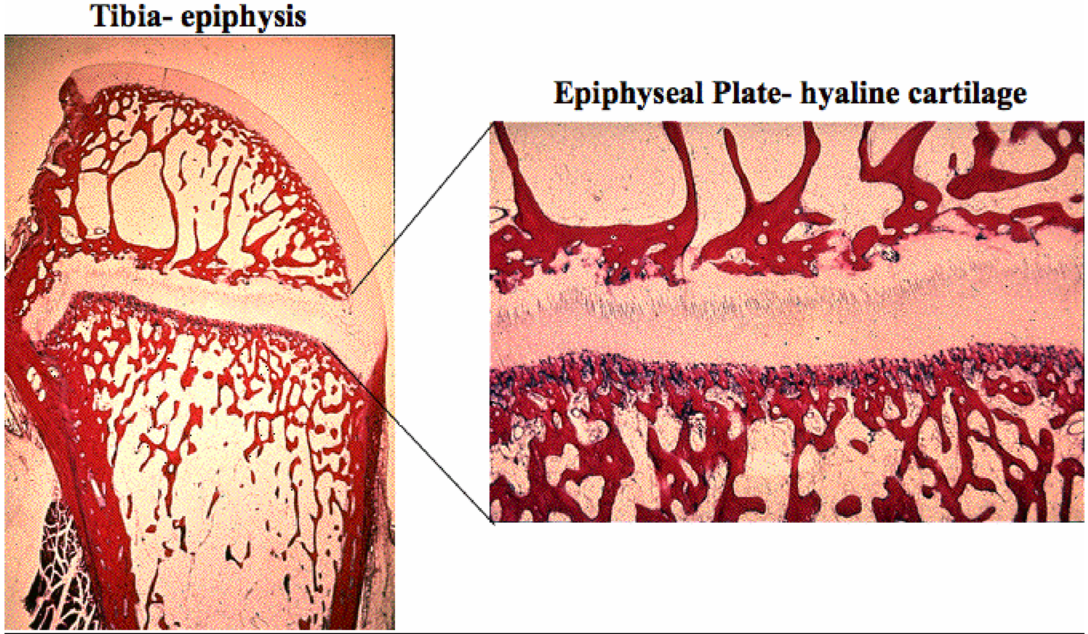


GROWTH OF LONG BONES



EPIPHYSEAL PLATE

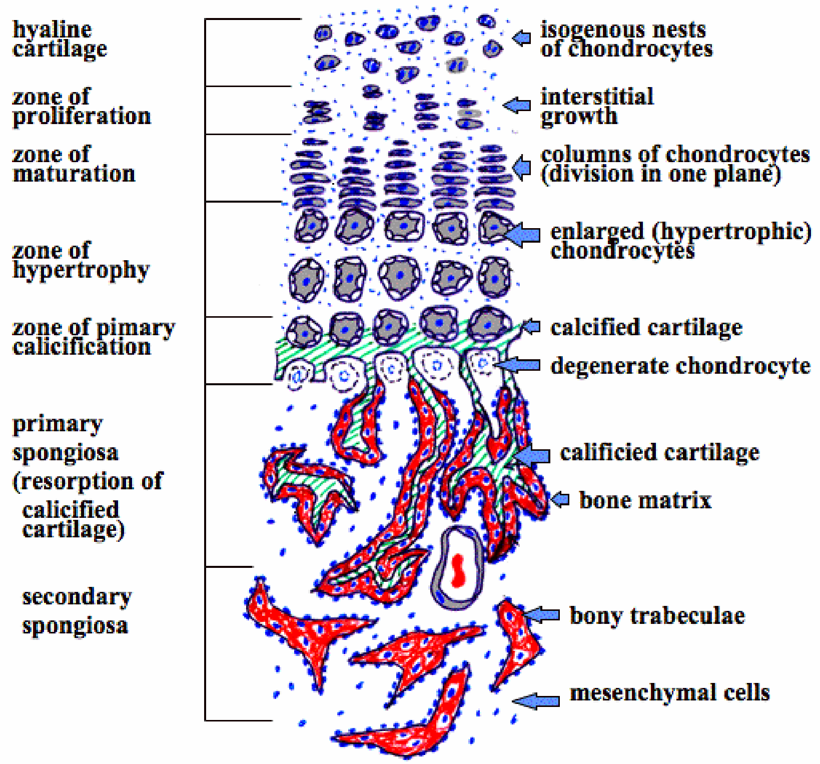
Tibia- epiphysis

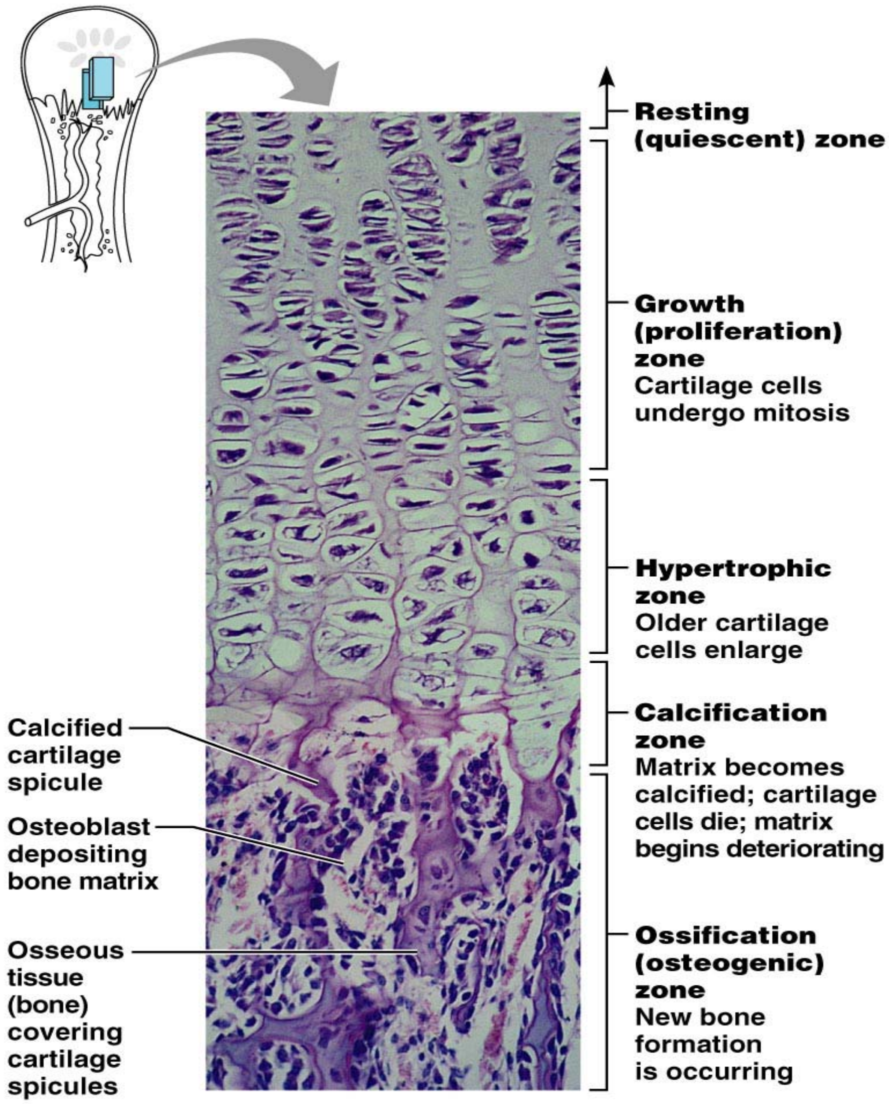


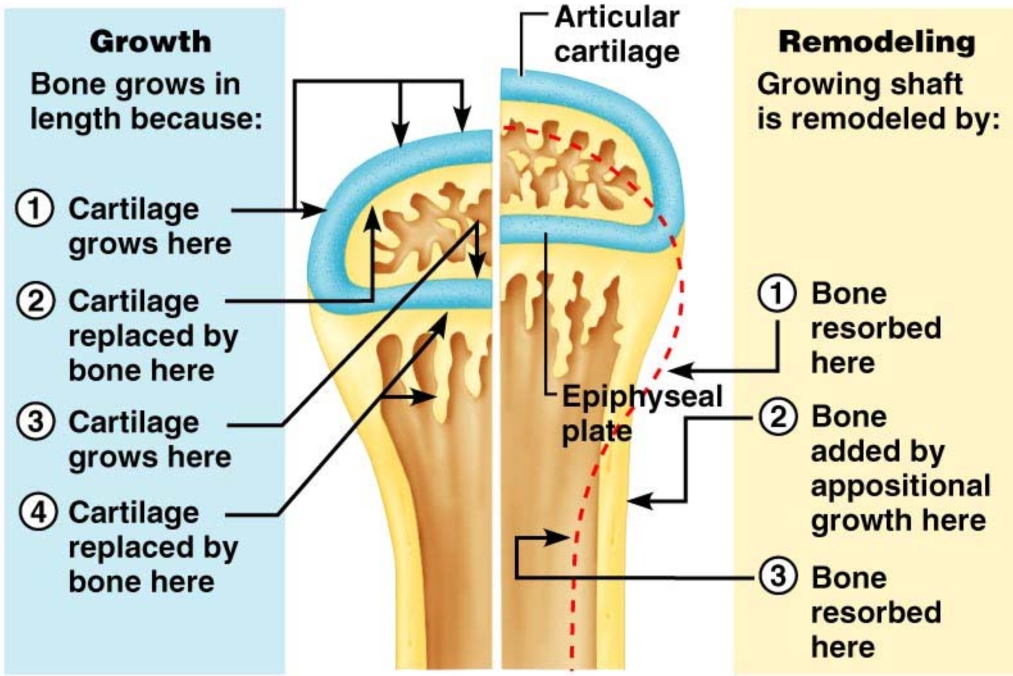
Epiphyseal Plate- hyaline cartilage

ENDOCHONDRAL OSSIFICATION

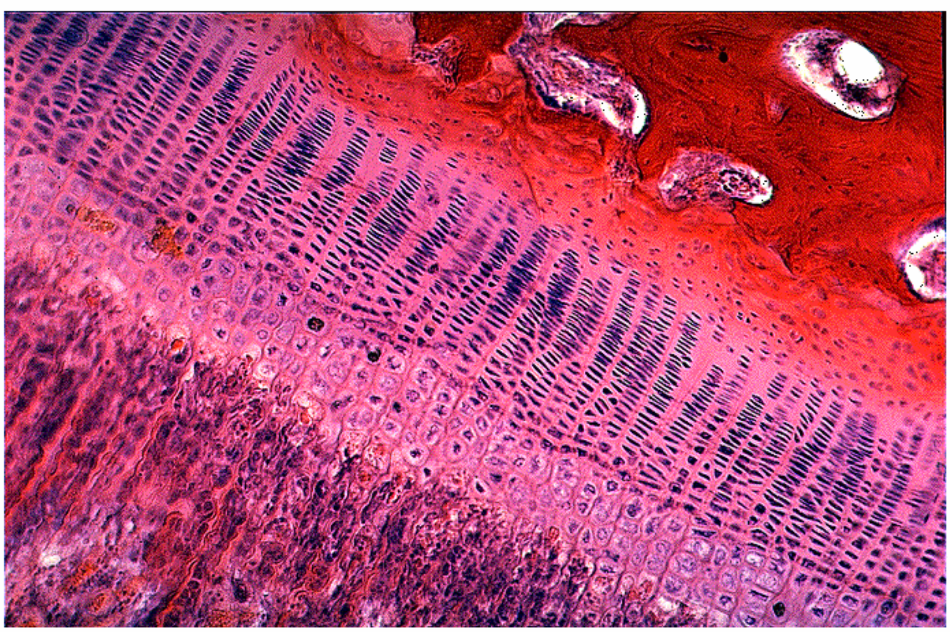
(base of skull, vertebral column, bones of extremities, long bones)



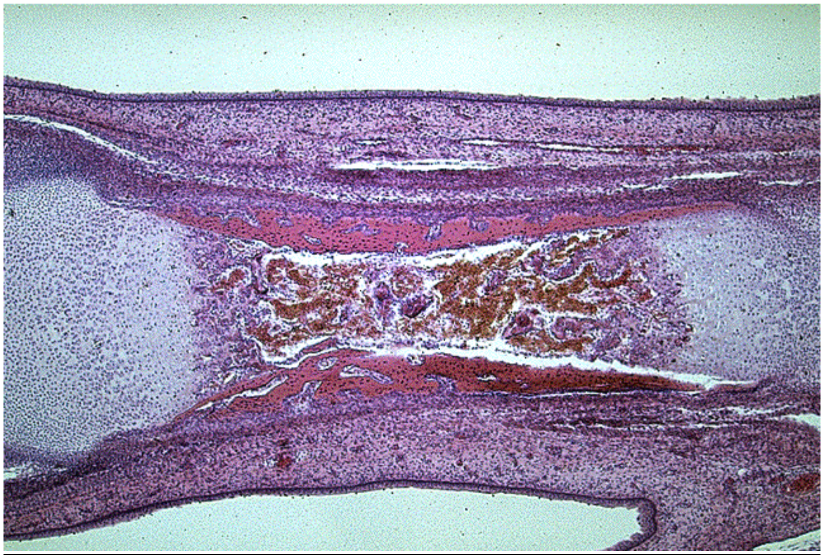

Resting
(quiescent) zone
Growth
(proliferation)
zone
Cartilage cells
undergo mitosis
Hypertrophic
zone
Older cartilage
cells enlarge
Calcification
zone
Matrix becomes
calcified; cartilage
cells die; matrix
begins deteriorating
Ossification
(osteogenic)
zone
New bone
formation
is occurring
Calcified
cartilage
spicule
Osteoblast
depositing
bone matrix
Osseous
tissue
(bone)
covering
cartilage
spicules



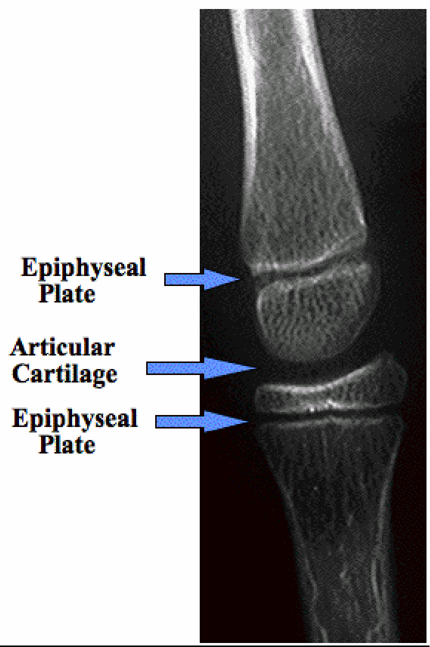
EPIPHYSEAL PLATE



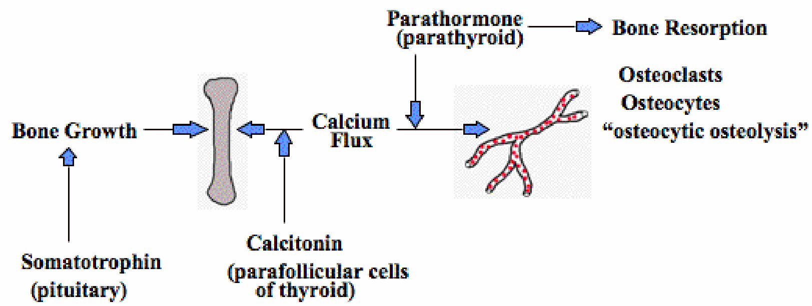
FETAL DIGIT BONE DEVELOPMENT



HAND X-RAY



BONE AND CALCIUM REGULATORY FACTORS



giantism dwarfism
(prior to closure of epiphyseal plate)
acromegely
(after closure of epiphyseal plate)

Nutritional Factors:

Calcium & Vitamin D Deficiency

Child- Ricketts
Adult- osteomalacia

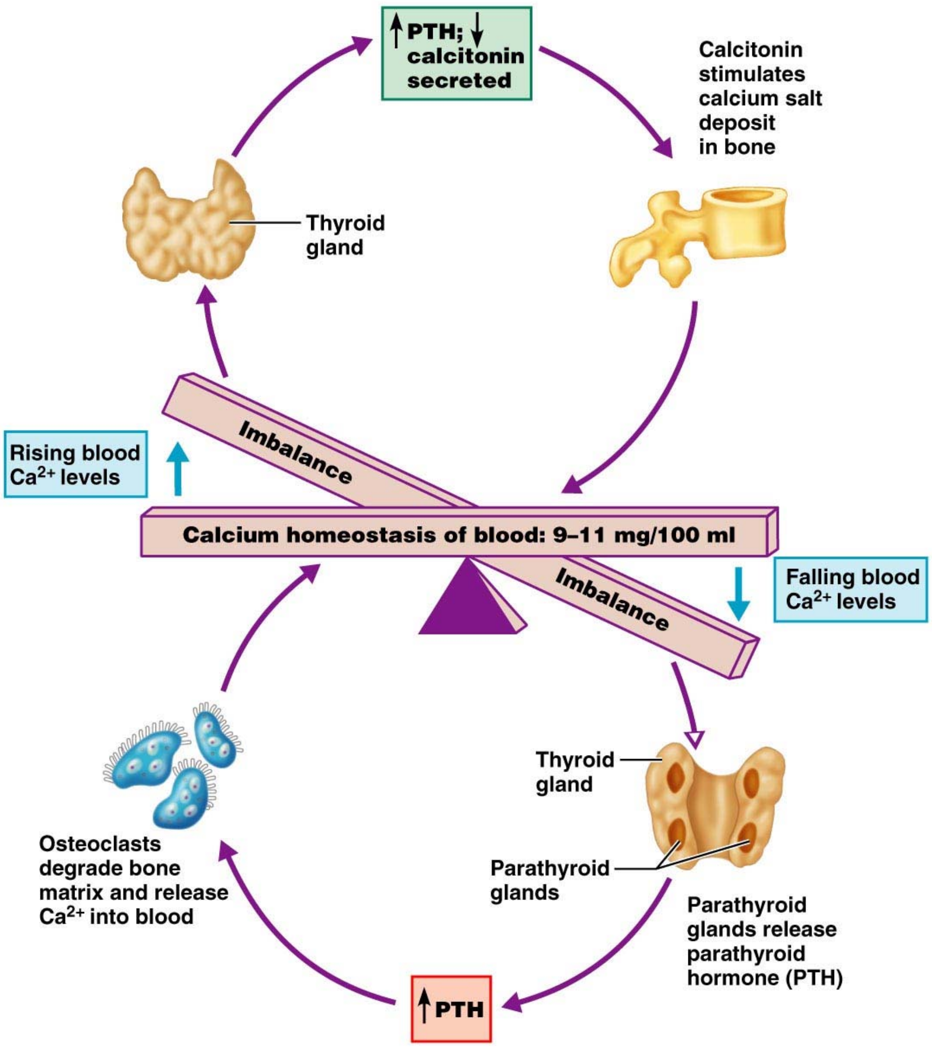
Vitamin C Deficiency

Scurvy- matrix not calicifiable

Chemical Composition of Bone: Inorganic

- ***Hydroxyapatites, or mineral salts***
  - **Sixty-five percent of bone by mass**
  - **Mainly calcium phosphates**

Responsible for bone hardness and its resistance to compression



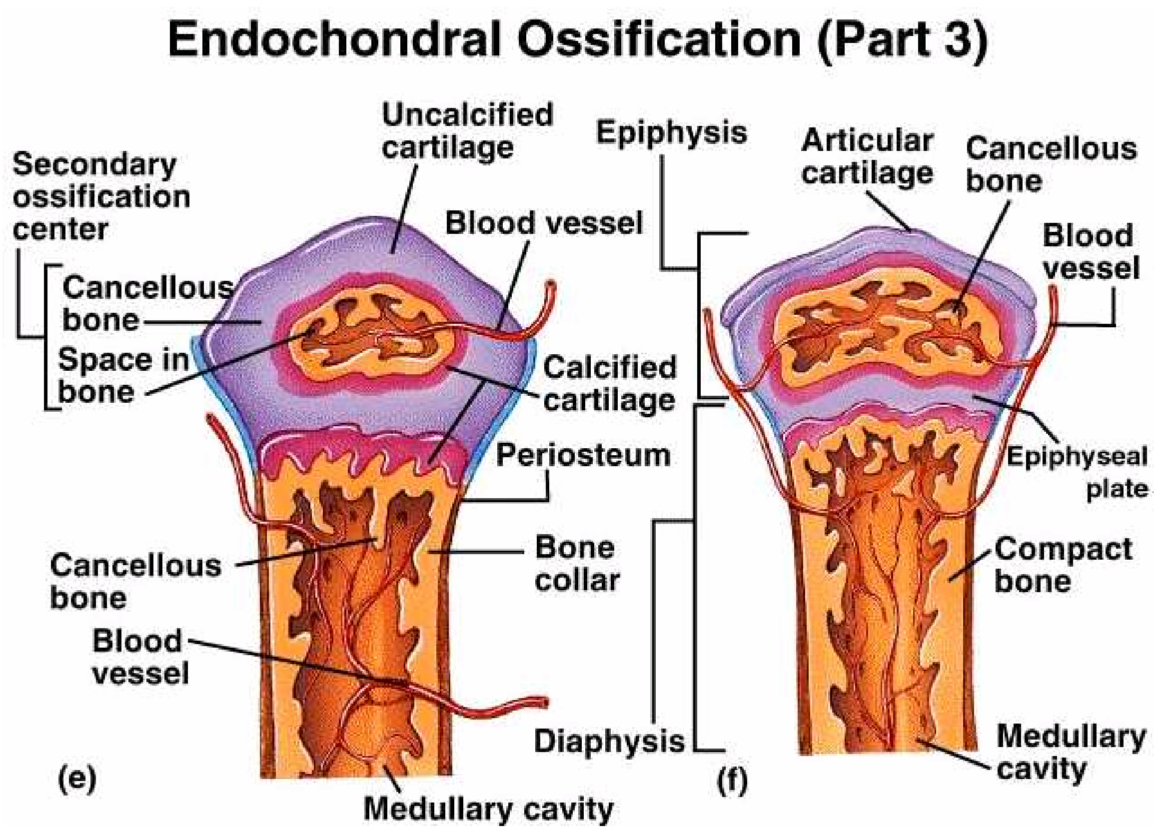
Reorganisation and Restoration of Bone

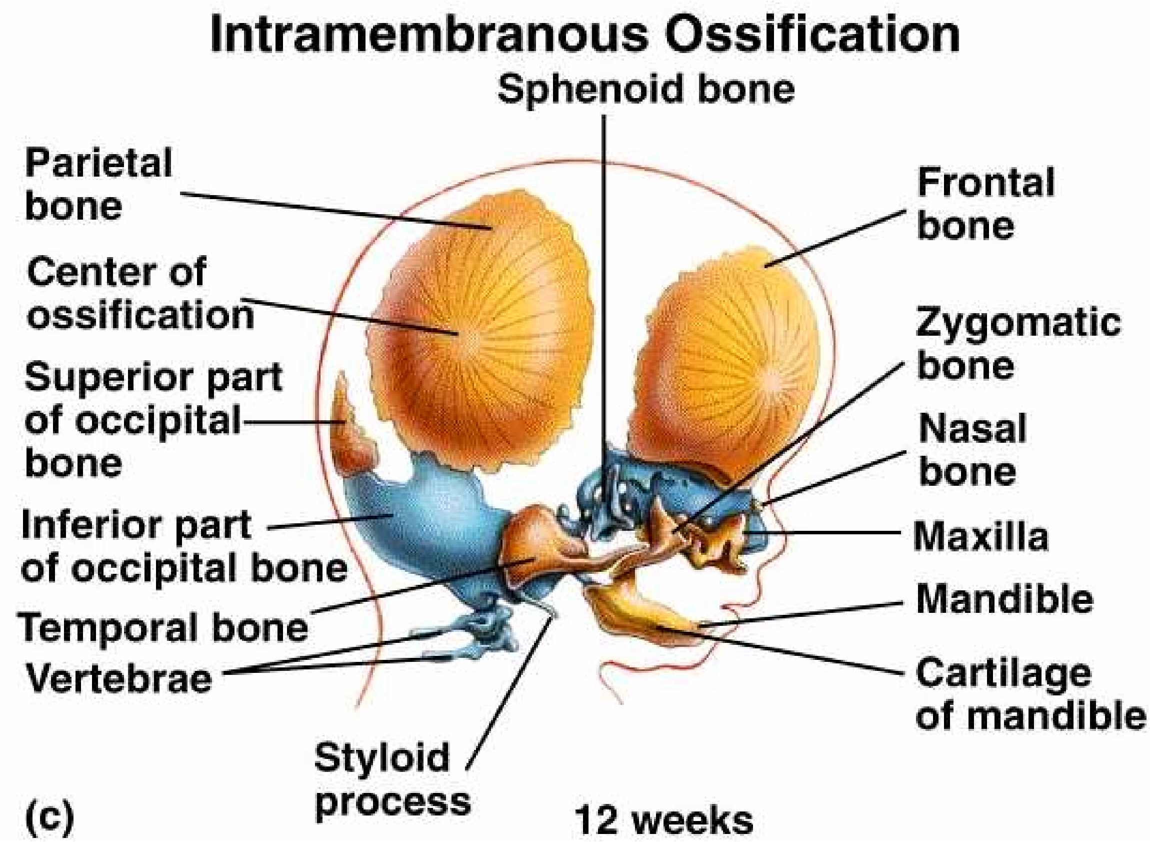
Changes in the size and shape of bones during the period of growth imply some bone reorganisation.

- Osteoblast and osteoclast constantly deposit and remove bone to adjust its properties to growth-related demands on size and/or changes of tensile and compressive forces.

compact bone remodelling

- Although the reorganisation of bone may not result in macroscopically visible changes of bone structure, it continues throughout life to mend damage to bone (e.g. microfractures) and to counteract the wear and tear occurring in bone.
- Osteoclasts and osteoblasts remain the key players in this process. Osteoclasts "drill" more or less circular tunnels within existing bone matrix.
- Osteoblasts deposit new lamellae of bone matrix on the walls of these tunnels resulting in the formation of a new Haversian system within the matrix of compact bone.
- Parts of older Haversian systems, which may remain between the new ones, represent the interstitial lamellae in mature bone. Capillaries and nerves sprout into new Haversian canals.
- Restorative activity continues in aged humans (about 2% of the Haversian systems seen in an 84 year old individual contained lamellae that had been formed within 2 weeks prior to death!).
- However, the Haversian systems tend to be smaller in older individuals and the canals are larger because of slower bone deposition. If these age-related changes in the appearance of the Haversian systems are pronounced they are termed osteopenia or senile osteoporosis.
- The reduced strength of bone affected by osteoporosis will increase the likelihood of fractures





Responses to Stress

- Bone is **Ansiotropic** (exhibits different mechanical properties in response to loads from different directions)

- **Wolff's Law (1892):**
  - "Bone elements place or displace themselves in the direction of functional forces."
    - bone - alive and reacts to mechanical stress
    - increase in functional force on bone = increase in bone strength
    - increase in functional force = increase in bone mass
    - bone density (function off magnitude and direction of the mechanical stresses)

- **Modeling** (increase in bone mass) **and Remodeling** (bone mass maintains with new bone cells)
  - Endochondral ossification (length) vs. Intramembranous ossification (diameter)
  - Osteoblasts, osteoclasts, and osteocytes

- **Hypertrophy** (increase in bone mass)
  - in response to regular physical activity
  - function of the intensity of the activity
  - transfer effects - "regular exercise seems to increase bone density, not only in the regions that are particularly stressed, but throughout the skeletal system"

- **Atrophy** (decrease in bone mass, strength, and bone resistance))

- calcium loss
- **Osteoporosis** - bone mineral density below -2.5 SD of the young adult mean
- **Osteopenia** - bone mineral density between -1 and -2.5 SD of the young adult mean
- **Female Athlete Triad** - combination of disordered eating, amenorrhea, and osteoporosis in female athletes

Normal bone

Bone in osteoporosis

Dowager's hump

Effects of Osteoporosis

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***

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***

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**

Formation of the Bony Skeleton

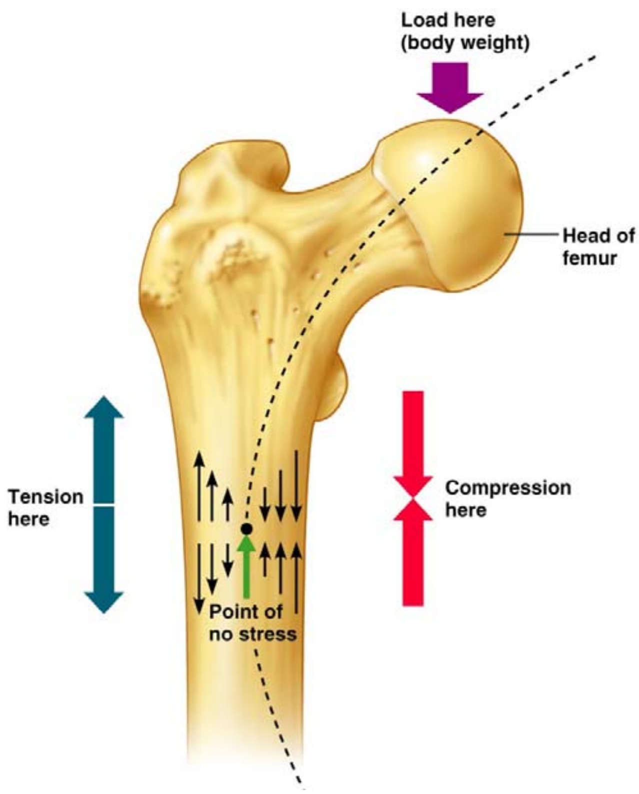
- ***Begins at week 8 of embryo development***
- ***Intramembranous ossification – bone develops from a fibrous membrane***
- ***Endochondral ossification – bone forms by replacing hyaline cartilage***

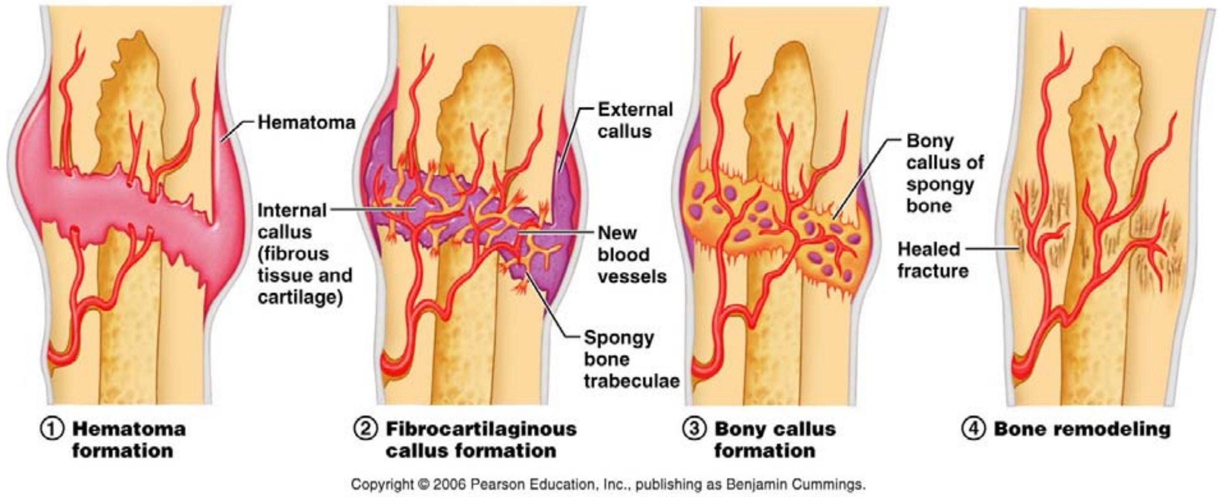
Intramembranous Ossification

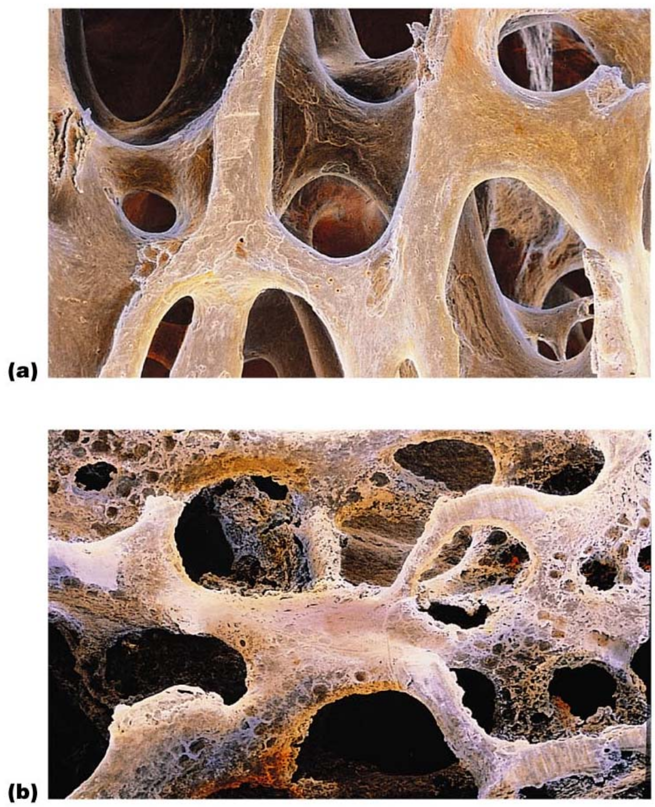
- ***Formation of most of the flat bones of the skull and the clavicles***
- ***Fibrous connective tissue membranes are formed by mesenchymal cells***

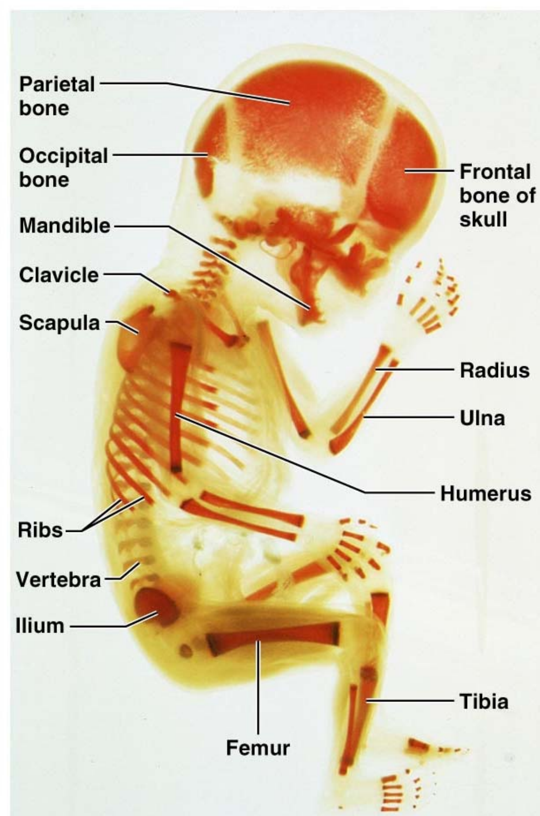
Location of Hematopoietic Tissue
(Red Marrow)

- ***In infants***
  - **Found in the medullary cavity and all areas of spongy bone**
- ***In adults***
  - **Found in the diploë of flat bones, and the head of the femur and humerus**









To resume

Bone: ECM mineralized (**hydroxyapatite)** ground substance; fibrous matrix; collagen type I (banded), dynamic state of growth & resorption. **Endosteum** and **periosteum** line internal cavities and cover external surface; osteoclasts resorb mineralized bone.

two main developmental varieties (and stages of development)**:**

primary, immature or **woven:** immature; random weave of coarse collagen fibers; first bone to develop; remodelled into lamellar bone; first bone laid down at site of fracture

secondary, mature or **lamellar:** most mature skeleton; successive layers with organized infrastructure [note: lamellar bone is either circumferential at edge of bone or concentric in osteons]

Dynamics: *development & growth:* formation and replacement woven bone by lamellar bone; controlled by growth, thyroid (calcitonin), parathyroid and sex hormones.

- **osteoprogenitor cells:** derived from periosteum and endosteum

- **osteoblasts:** synthesize and secrete **osteoid** = organic (matrix) components of ECM before mineralization; mineralized to form bone;

- **osteocytes:** bone-entrapped osteoblast; maintains matrix; connected via gap junctions; secretion Ca^{2+} controlled by local concentrations, parathormone and calcitonin; also respond to piezo-electric currents induced by deformation;

- **monocyte-macrophage** derived **osteoclasts:** multinucleated; bone resorption associated with continuous remodeling; in **resorption lacuna** (Howships lacuna); fine microvilli form **ruffled border** that secretes organic acids capable of dissolving mineral component of bone; lysosomal proteolytic enzymes destroy organic matrix.

Osteogenesis: note: bone always replaces some other connective tissue: endochondral ossification: bone follows cartilage; inttamembranous ossification: bone follows mesenchym.

Endochondral ossification: long bones, vertebrae, pelvis and bones of base of skull; **preceded by cartilage model**

- **diaphysis** (two growing points)**:** bony collar formed appositionally around shaft of cartilagenous model

- **epiphysis** (upon the growing point): originally hyaline cartilage at end of shaft

- **growth of epiphysial plate**: hyaline cartilage plate at junction of diaphysis and epiphysis (5 zones)

  zone of reserve cartilage: typical hyaline cartilage

  zone of proliferation: columns of chondrocytes formed by successive mitotic divisions; matrix deeply stained (rich in proteoglycan)

  zone of hypertrophy ([enlarging or swelling] hypertrophying cells and lacunae) = (zone of maturation: end division; increase in size of lacunae)

  zone of calcification (calcifying cartilage): matrix calcified around enlarged spaces = (zone of cartilage degeneration: degeneration chondrocytes; invasion calcified cartilage by osteogenic cells in wake of vasculature) zone of erosion and ossification (osteogenic zone: osteogenic cells) differentiate into ostebolasts; commence formation woven bone on surface of spicules of calcified cartilage; followed by extensive remodelling to produce mature compact and spongy bone

- **metaphysis** (change in growth): junction of shaft with growth plate

  primary ossification: between ends of original cartilage model
  secondary ossification: conversion of central epiphysial cartilage to bone

at maturity: endochondral ossification ceases; fusion of diaphysis with epiphysis resulting in obliteration of growth plates

fracture repair: blood clot initially; replaced by highly vascular collagenous tissue = granulation tissue; becomes more fibrous; mesenchymal cells differentiate into chondroblasts; replace fibrous granulation tissue with hyaline cartilage = provisional callus; strengthened by deposition of calcium salts within cartilage matrix; osteoprogenitor cells lay down meshwork of woven bone within and around provisional callus which becomes bony callus; fracture site is bridged by woven bone in bony union; remodelled to mature lamellar bone

Intramembranous ossification: bones of vault of skull, maxilla and most of mandible; deposition bone within primitive mesenchymal tissue; direct replacement mesenchyme by bone; membranous bone
mesenchyme begins synthesis of osteoid at several centers of ossification; osteoprogenitor cells at surface undergo mitosis; produce further osteoblasts; lay down more bone; adjacent centers fuse; bone spongy in gross appearance; progressive remodelling by osteoclastic resorption and osteoblastic deposition; forms mature compact or spongy bone;

TABLE 6.2 Common Types of Fractures

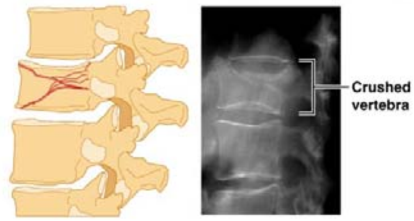
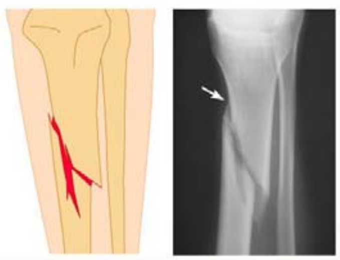
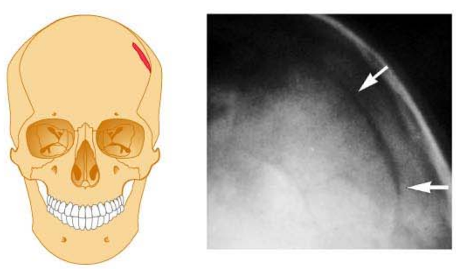
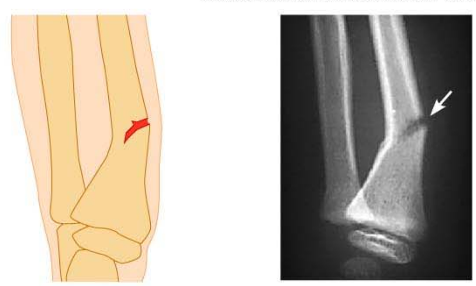
FRACTURE TYPE	DESCRIPTION AND COMMENTS	FRACTURE TYPE	DESCRIPTION AND COMMENTS
Comminuted	Bone fragments into three or more pieces Particularly common in the aged, whose bones are more brittle 	***Compression***	Bone is crushed Common in porous bones (i.e., osteoporotic bones) subjected to extreme trauma, as in a fall 
Spiral	Ragged break occurs when excessive twisting forces are applied to a bone Common sports fracture 	***Epiphyseal***	Epiphysis separates from the diaphysis along the epiphyseal plate Tends to occur where cartilage cells are dying and calcification of the matrix is occurring 

TABLE 6.2 Common Types of Fractures

FRACTURE TYPE	DESCRIPTION AND COMMENTS	FRACTURE TYPE	DESCRIPTION AND COMMENTS
Depressed	Broken bone portion is pressed inward Typical of skull fracture 	***Greenstick***	Bone breaks incompletely, much in the way a green twig breaks. Only one side of the shaft breaks; the other side bends Common in children, whose bones have relatively more organic matrix and are more flexible than those of adults 

Importance of Ionic Calcium in the Body

- ***Calcium is necessary for:***
  - **Transmission of nerve impulses**
  - **Muscle contraction**
  - **Blood coagulation**
  - **Secretion by glands and nerve cells**
  - **Cell division**

Control of Remodeling

- ***Two control loops regulate bone remodeling***
  - **Hormonal mechanism maintains calcium homeostasis in the blood**
  - **Mechanical and gravitational forces acting on the skeleton**

Hormonal Mechanism

- ***Rising blood Ca^{2+} levels trigger the thyroid to release calcitonin***
- ***Calcitonin stimulates calcium salt deposit in bone***
- ***Falling blood Ca^{2+} levels signal the parathyroid glands to release PTH***
- ***PTH signals osteoclasts to degrade bone matrix and release Ca^{2+} into the blood***

Response to Mechanical Stress

- ***Wolff's law – a bone grows or remodels in response to the forces or demands placed upon it***
- ***Observations supporting Wolff's law include***
  - **Long bones are thickest midway along the shaft (where bending stress is greatest)**
  - **Curved bones are thickest where they are most likely to buckle**

Response to Mechanical Stress

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

Bone Fractures (Breaks)

- ***Bone fractures are classified by:***
  - **The position of the bone ends after fracture**
  - **The completeness of the break**
  - **The orientation of the bone to the long axis**
  - **Whether or not the bones ends penetrate the skin**

Types of Bone Fractures

- ***Nondisplaced – bone ends retain their normal position***
- ***Displaced – bone ends are out of normal alignment***
- ***Complete – bone is broken all the way through***
- ***Incomplete – bone is not broken all the way through***
- ***Linear – the fracture is parallel to the long axis of the bone***
- ***Transverse – the fracture is perpendicular to the long axis of the bone***
- ***Compound (open) – bone ends penetrate the skin***
- ***Simple (closed) – bone ends do not penetrate the skin***

Common Types of Fractures

- ***Comminuted – bone fragments into three or more pieces; common in the elderly***
- ***Spiral – ragged break when bone is excessively twisted; common sports injury***
- ***Depressed – broken bone portion pressed inward; typical skull fracture***

- ***Compression – bone is crushed; common in porous bones***
- ***Epiphyseal – epiphysis separates from diaphysis along epiphyseal line; occurs where cartilage cells are dying***
- ***Greenstick – incomplete fracture where one side of the bone breaks and the other side bends; common in children***

Stages in the Healing of a Bone Fracture

- ***Hematoma formation***
  - **Torn blood vessels hemorrhage**
  - **A mass of clotted blood (hematoma) forms at the fracture site**
  - **Site becomes swollen, painful, and inflamed**
- ***Fibrocartilaginous callus forms***
- ***Granulation tissue (soft callus) forms a few days after the fracture***
- ***Capillaries grow into the tissue and phagocytic cells begin cleaning debris***
- ***The fibrocartilaginous callus forms when:***
  - **Osteoblasts and fibroblasts migrate to the fracture and begin reconstructing the bone**
  - **Fibroblasts secrete collagen fibers that connect broken bone ends**
  - **Osteoblasts begin forming spongy bone**
  - **Osteoblasts furthest from capillaries secrete an externally bulging cartilaginous matrix that later calcifies**
- ***Bony callus formation***
  - **New bone trabeculae appear in the fibrocartilaginous callus**
  - **Fibrocartilaginous callus converts into a bony (hard) callus**
  - **Bone callus begins 3-4 weeks after injury, and continues until firm union is formed 2-3 months later**
- ***Bone remodeling***
  - **Excess material on the bone shaft exterior and in the medullary canal is removed**
  - **Compact bone is laid down to reconstruct shaft walls**

Homeostatic Imbalances

- ***Osteomalacia***
  - **Bones are inadequately mineralized causing softened, weakened bones**
  - **Main symptom is pain when weight is put on the affected bone**
  - **Caused by insufficient calcium in the diet, or by vitamin D deficiency**

Homeostatic Imbalances

- ***Rickets***
  - **Bones of children are inadequately mineralized causing softened, weakened bones**
  - **Bowed legs and deformities of the pelvis, skull, and rib cage are common**
  - **Caused by insufficient calcium in the diet, or by vitamin D deficiency**

Isolated Cases of Rickets

- ***Rickets has been essentially eliminated in the US***
- ***Only isolated cases appear***
- ***Example: Infants of breastfeeding mothers deficient in Vitamin D will also be Vitamin D deficient and develop rickets***

Homeostatic Imbalances

- ***Osteoporosis***
  - **Group of diseases in which bone reabsorption outpaces bone deposit**
  - **Spongy bone of the spine is most vulnerable**
  - **Occurs most often in postmenopausal women**
  - **Bones become so fragile that sneezing or stepping off a curb can cause fractures**

Osteoporosis: Treatment

- ***Calcium and vitamin D supplements***
- ***Increased weight-bearing exercise***
- ***Hormone (estrogen) replacement therapy (HRT) slows bone loss***
- ***Natural progesterone cream prompts new bone growth***
- ***Statins increase bone mineral density***

Paget's Disease

- ***Characterized by excessive bone formation and breakdown***
- ***Pagetic bone with an excessively high ratio of woven to compact bone is formed***
- ***Pagetic bone, along with reduced mineralization, causes spotty weakening of bone***
- ***Osteoclast activity wanes, but osteoblast activity continues to work***

Paget's Disease

- ***Usually localized in the spine, pelvis, femur, and skull***
- ***Unknown cause (possibly viral)***
- ***Treatment includes the drugs Didronate and Fosamax***

Fetal Primary Ossification Centers

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)***
- ***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***

• Nutrient artery/vein

  - **Enters the bone through nutrient foramen**
  - **Supplies inner part of compact bone tissue and red marrow up to the epiphyseal plate**

• Metaphyseal arteries/veins

  - **Supplies the red bone marrow and bone tissue of the metaphysic**

• Epiphyseal arteries/veins

– Supplies the red bone marrow and bone tissue of the epiphysis

Nerve supply to bone
• Accompany the blood vessels that supply bone tissue
• Periosteum is rich in sensory nerves

– Is the reason for the extreme pain when you break a bone

“CARTILAGE AND BONE.”

“Generalities.”		
	“Bone.”	**“Cartilage.”**
Definition.	➢ Is a dynamic, living tissue that is constantly turning over. ➢ Is a mineralized connective tissue.	➢ Is a semirigid supporting tissue that: • Is strong but • Slightly flexible. ➢ Cannot regenerate itself if : • Damaged or • Diseased.
Role.	➢ Provide: • Support. • Protection. • Locomotion (with muscles). ➢ Acts as: • Repository for hemopoeitic tissues • A storage facility for calcium and phosphorus.	➢ Articular cartilage acts as a shock absorber. ➢ Cartilage makes an excellent skeletal tissue for the fetus. ➢ Provide : • Flexible support • Protection. ➢ A key role in the development and growth of long bones.
Characteristics.	➢ Older bone is resorbed and continously replaced by deposition of new bone. ➢ Compositionof bone: • 25% organic matrix, mostly collagen type I and non-collagenous proteins. • 65% inorganic matrix. • 10% water.	➢ Contains cells: • fibroblasts • chonroblasts • chondrocytes ➢ Fibers: • collagen • elastin. ➢ Amorphous ground substance: • chondroitin sulfate • hyaluronate. ➢ Have no capillaries.

“Different types of cartilage.”			
	“ Hyalin.”	“ Elastic.”	“Fibrocartilage.”
Morphology.	➢ Glass-like appearance. ➢ Has a bluish, opalescent color.	➢ Yellow in color. ➢ Contains: • Many chondrocytes. • Elastic fibers composed of elastin and collagen.	➢ White in color. ➢ Strong bundles of collagens. ➢ Smaller amount of amorphous matrix.
Location.	➢ Articular surface of synovial joints. ➢ Costal and respiratory cartilage: • Trachea. • Bronchi ➢ Epiphyseal growth plates.	➢ External ear (pinna). ➢ Epiglittis. ➢ Auditory tube. ➢ Parts of the larynx.	➢ Annulus fibrosus of intervertebral disks. ➢ Link between tendon and bone. ➢ Menisci of the knee joint.
Characteristics	➢ Most abundant type of cartilage in adult. ➢ Articular hyalin: the hyaluronic acid-protein complexes give the cartilage a : • Viscous • Slippery property • A very low coefficient of friction ideal for joint surfaces. ➢ Hyalin cartilage is: • Avascular • Lacks nerves. ➢ In light microscope: discrete masses of tissue surrounded by a dense connective tissue	➢ Exhibit great: • Flexibility • Elasticity ➢ Extracellular matrix is metachromatic due to high concentration of glycosaminoglycans.	➢ Fibrocartilage is not found alone. ➢ It blends with adjacent tissues, therefore: • Has no definite perichondrium. • Looks like intermediate tissue between tendon and cartilage. ➢ Extracellular matix is less metachromatic, because it contains: • Fewer glycosaminoglycan. ➢ More collagen fibers.

	layer called the perichondrium.		

“ **Cartilage formation.”**	
Chondroblast.	➢ Derives from embryonic mesenchymal cells. ➢ Mitotic division gives rise to packed chondroblasts, which start the synthesis of: • Ground substance • Fibrous extracellular material. ➢ The secretion of the extracellular material traps each chondroblast within the matrix. ➢ This allows the packed chondroblast to separate from each other. ➢ Then, each chondroblast goes under mitotic division and become chondrocytes separated by only a small amount of extracellular material.
Chondrocyte.	➢ Mature cartilage cell. ➢ The cell has small cytoplasmic extensions, which mediate the interaction with the matrix. ➢ It has a prominent RER, a well developed Golgi apparatus and glycogen granules. ➢ Chondrocytes maintain the integrity of the cartilage matrix.
Growth of cartilage.	➢ At the center of a mass growing cartilage: • Maturation of chondrocytes is more prominent ➢ At the periphery: • Chondroblasts are seen at earlier stages of differentiation. • A zone of condensed supporting tissue called “perichondrium”. ➢ Growth of cartilage occurs by: • Interstitial growth in the center and • Appositional at the periphery.

“Bone.”	
Definition.	➢ Specialized supporting tissue in which extracellular components are mineralized.

STRUCTURE.	➢ **Adult bone is composed of three types of cells and an organic extracellular matrix called "osteoid".** ➢ **<u>Cells are:</u>** • **Osteoblasts** • **Osteocytes** • **Osteoclasts.** ➢ **<u>Extracellular matrix or osteoid, before mineralization occurs, is formed of:</u>** • **A fibrous component, type I collagen.** • **Proteoglycan ground substance (glycosaminoglycan gel).** ➢ **<u>After mineralization, the organic matrix contain:</u>** • **Inorganic salt, calcium hydroxyapatite crystals.** • **Phosphate.** ➢ **Osteoid becomes calcified right after deposition.** ➢ **Extracellular matrix before mineralization is called → osteoid.** ➢ **Extracellular matrix after mineralization is the final → bone matrix.**

"<u>Osteoblast.</u>"	"<u>Osteocyte.</u>"	"<u>Osteoclast</u>."
➢ **Derives from mesenchymal cells called "osteoprogenitors cells".** ➢ **Synthesize and secrete the organic extracellular matrix of bone "osteoid".** ➢ **Control mineralization of bone.** ➢ **Are large cells with basophilic cytoplasm and a large Golgi apparatus.**	➢ **Is a modification of osteoblasts into osteocytes.** ➢ **Osteoblast becomes trapped within the bone as osteocyte.** ➢ **Is responsible for maintenance of the matrix.** ➢ **Have fine cytoplasmic process called "canaliculi" which, link osteocytes to each other.**	➢ **Is a multinucleated cell, derived from the macrophage-monocyte system.** ➢ **Resorb bone in remodeling process.** ➢ **Characterized by fine microvilli forming "a ruffled border".** ➢ **Ruffled border secretes organic acids, which are responsible for dissolving the mineral components.** ➢ **Participate in long-term maintenance of blood calcium by responding to:** • **Parathyroid hormone and** • **Calcitonin.**

<u>Types.</u>	➢ **Two types of bones:** • **Woven** • **Lamellar bone.**

	" <u>Woven bone."</u>	" <u>Lamellar bone."</u>
<u>State.</u>	➢ **Is the immature form of bone.**	➢ **Is the mature form of bone.**

	<u>Organization.</u>	➢ **Characterized by a random (woven) organization of its collagen.**	➢ **Characterized by a successive layers of collagen organized into sheets (lamellae).** ➢ **May be formed as:** • **A solid mass and called "<u>compact or cortical bone</u>"** • **Disposed as a sponge and called "<u>cancellous or trabecular bone".</u>**
	<u>Development.</u>	➢ **Is the first bone produced during skeletal development.**	➢ **Constitutes most of the mature skeletal bone in adult.**
	<u>Strength.</u>	➢ **Mechanically weak bone.**	➢ **Mechanically strong bone.**