DISORDERS OF COLLAGEN AND BONE

Kenneth Alonso, MD, FACP

Bone

- Mineral skeleton (hydroxyapatite or $Ca_5(PO4)_3(OH)$) provides the strength, stiffness, and rigidity characteristic of bone.
- Woven bone is found in areas of rapid bone formation and is present as a random weave.
- It is an abnormal finding in the adult.

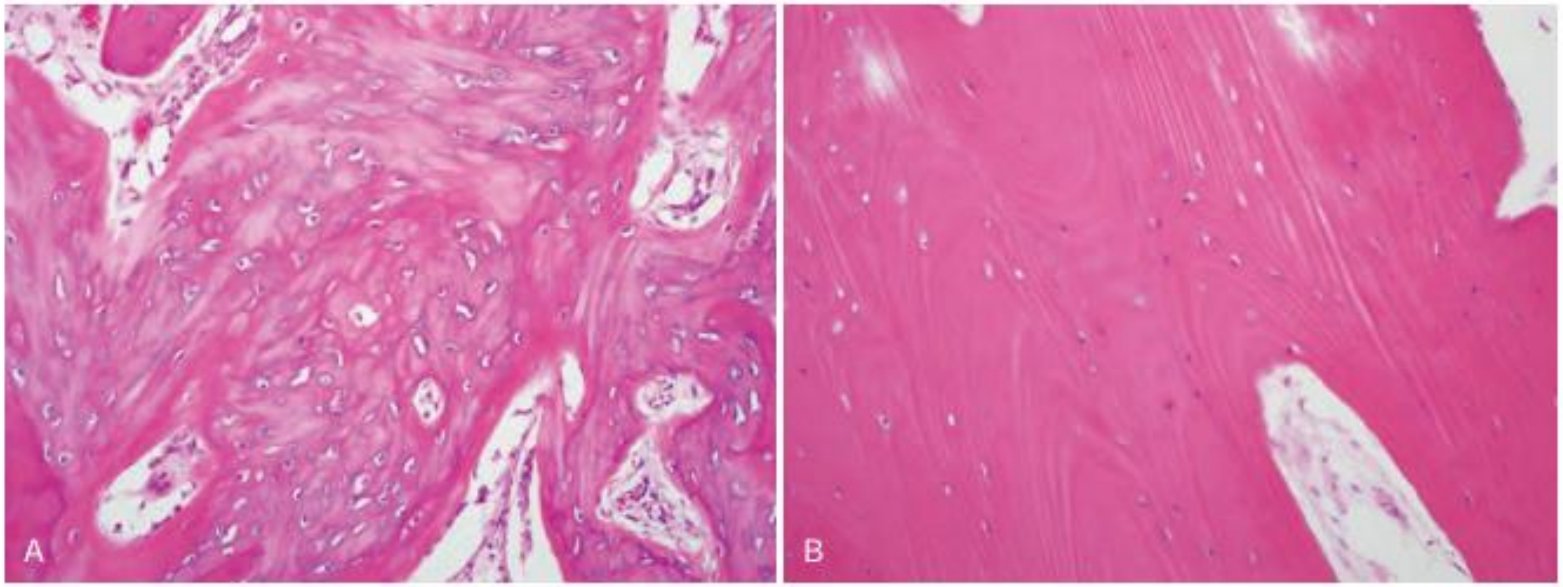


Figure 26-1 Woven bone **(A)** is more cellular and disorganized than lamellar bone **(B)**.

Table 26-1 Proteins of Bone Matrix

Osteoblast-Derived Proteins
Type I collagen
Calcium-binding proteins
Osteonectin, bone sialoprotein
Cell adhesion proteins
Osteopontin, fibronectin, thrombospondin
Cytokines
IL-1, IL-6, RANKL
Enzymes
Collagenase, alkaline phosphatase
Growth factors
IGF-1, TGF-β, PDGF
Proteins involved in mineralization
Osteocalcin
Proteins Concentrated from Serum
Albumin
β_2-microglobulin

IGF, linsulin-like growth factor; *TGF*, transforming growth factor; *PDGF*, platelet-derived growth factor; *IL*, interleukin; *RANKL*, receptor activator of nuclear factor-κB ligand.

Bone

- Protein component consists primarily of type I collagen
- Lends tensile strength and resiliency.
- Collagen is deposited in a lamellar fashion and strengthened by multiple crosslinks, both within and between the triple-helical collagen molecules.
- These crosslinks are pyridinolines that are resistant to degradation and are released during bone resorption, either as free or peptide forms.

Bone

- Non-collagen proteins include the calcium-binding proteins include osteocalcin (bone GLA protein) and matrix GLA protein
- Both contain gamma carboxyglutamic acid and are vitamin K-dependent
- These proteins may delay mineralization and allow bone matrix to mature.
- The periosteum, provides the vascular supply that plays an essential role in fracture healing.
- The periosteum in children is substantially thicker and more robust than in adults, accounting in part for the more rapid healing of pediatric fractures.

Osteoblasts

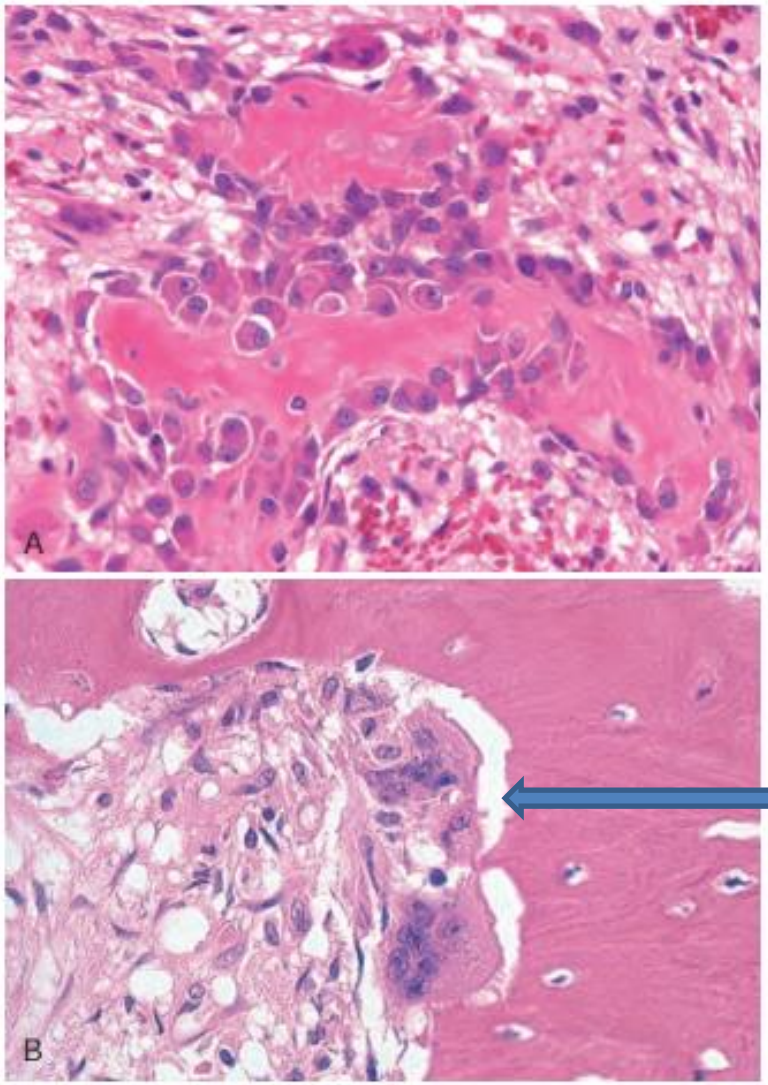
- Have receptors for factors that influence bone remodeling and they produce many regulators of bone growth.
- The receptors include those for PTH, calcitrol (1,25-dihydroxyvitamin D), glucocorticoids, sex hormones, growth hormone (GH) and thyroid hormone.
- Have receptors for and may also produce locally IL-1, TNF-α, prostaglandins, insulin-like growth factors, TGF-β, bone morphogenetic proteins (BMP), fibroblast growth factors (FGF), and platelet-derived growth factor (PDGF)

Osteoclasts

- Osteoclasts are often seen in groups, either on the surface to form Howship's lacunae or tunneling into cortical bone to produce Haversian canals.
- The life-span of an osteoclast may be as much as three to four weeks.
- Osteoclasts lose nuclei by apoptosis as they become inactive.
- Excessive osteoclastic resorption occurs in osteoporosis, Paget disease, hyperparathyroidism and inflammatory bone loss.
- Osteoclastic resorption is deficient in osteopetrosis.

Osteoclasts

- Osteoclasts are large, multinucleated cells that resorb bone by dissolving mineral and degrading matrix.
- Active osteoclasts usually have two to five nuclei, but may have more.
- They have abundant cytoplasm, multiple Golgi systems, and many mitochondria.
- Actively resorbing osteoclasts are firmly attached to bone by a zone of membrane that is relatively devoid of subcellular particles; this is called the "clear" zone, although a better term is the "sealing" zone.
- The zone surrounds an area of highly convoluted membrane, the "ruffled border", where resorption takes place.



Howship's lacunae

Figure 26-2 **A,** Active osteoblasts synthesizing bone matrix. The surrounding spindle cells represent osteoprogenitor cells. **B,** Two osteoclasts resorbing bone.

Endochondral ossification

- Most bones that form during embryogenesis develop from a cartilage mold via endochondral ossification.
- The cartilage mold (anlagen) is synthesized by mesenchymal precursor cells.
- A central medullary canal within the anlagen is created by chondroblasts at approximately 8 weeks of gestation.
- Simultaneously, osteoblasts begin to deposit the cortex beneath the nascent periosteum of the midshaft (diaphysis).
- This forms a primary center of ossification resulting in radial bone growth.

Endochondral ossification

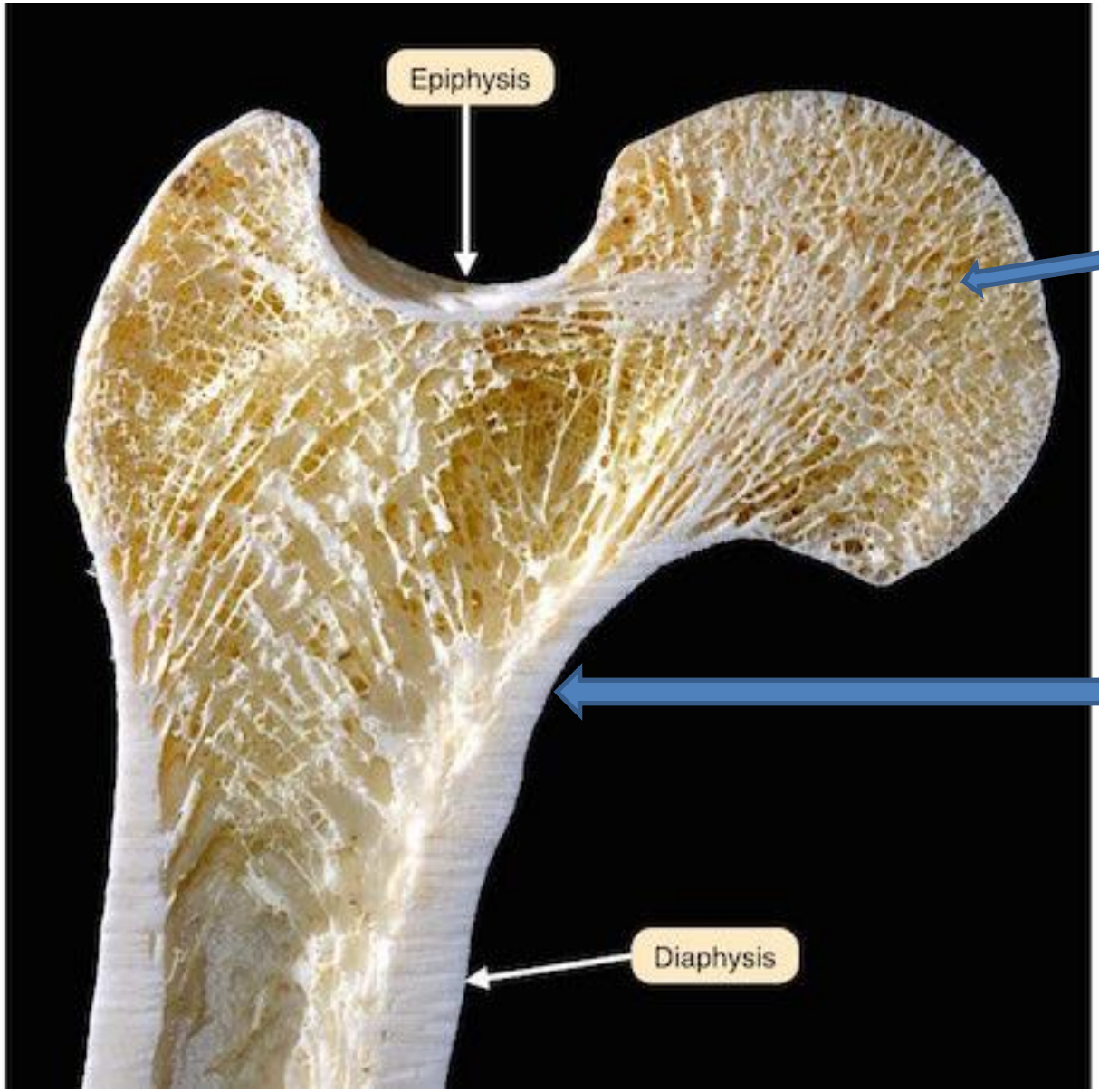
- At the longitudinal ends (epiphysis), endochondral ossification forms secondary centers of ossification.
- Eventually, plates of cartilage anlage become entrapped between the expanding centers of ossification forming physes or growth plates

Endochondral ossification

- Chondrocytes within the growth plates undergo sequential proliferation, hypertrophy, and apoptosis.
- Matrix mineralizes during apoptosis and is invaded by capillaries, providing the nutrients for activation of osteoblasts and osteoid synthesis.
- Most calcified cartilage matrix is ultimately resorbed leaving only strut-shaped remnants that serve as scaffolding for bone deposits known as primary spongiosa, the earliest bone trabeculae.
- Over time, this process produces longitudinal bone growth.

Intramembranous ossification

- Flat bones, for example the cranium, are formed by intramembranous ossification, in which a dense layer of mesenchyme is directly ossified by osteoblasts without a cartilage anlagen.
- Bones enlarge by deposition of new bone on a preexisting surface, a process called appositional growth.



http://medcell.med.yale.edu/systems_cell_biology/bone_lab/images/bone.jpg
Accessed 05/10/2020

Bone

- Cortical bone is dense and compact.
- It constitutes the outer part of all skeletal structures.
- The lamellae may be extensive (circumferential) or tightly packed in concentric circles in osteons.
- Cortical bone comprises 80 percent of the skeleton.
- Its major function is to provide mechanical strength and protection, but it can participate in metabolic responses, particularly when there is severe or prolonged mineral deficit.

Bone

- Trabecular bone is found inside the long bones particularly at the ends, throughout the bodies of the vertebrae, and in the inner portions of the pelvis and other large flat bones.
- Trabecular bone is an important contributor to mechanical support, particularly in the vertebrae.
- It is also more metabolically active than cortical bone and provides the initial supplies of mineral in acute deficiency states.

Bone

- Growth of the skeleton and changes in bone shape are produced by modeling.
- Linear growth during childhood and adolescence occurs by growth of cartilage at the end plates, followed by endochondral bone formation.
- The width of the bones increases by periosteal apposition.
- During childhood, this is accompanied by endosteal resorption.
- The endosteal (inner) surface is in contact with the marrow; thus, endosteal resorption results in a concomitant enlargement of the marrow cavity.

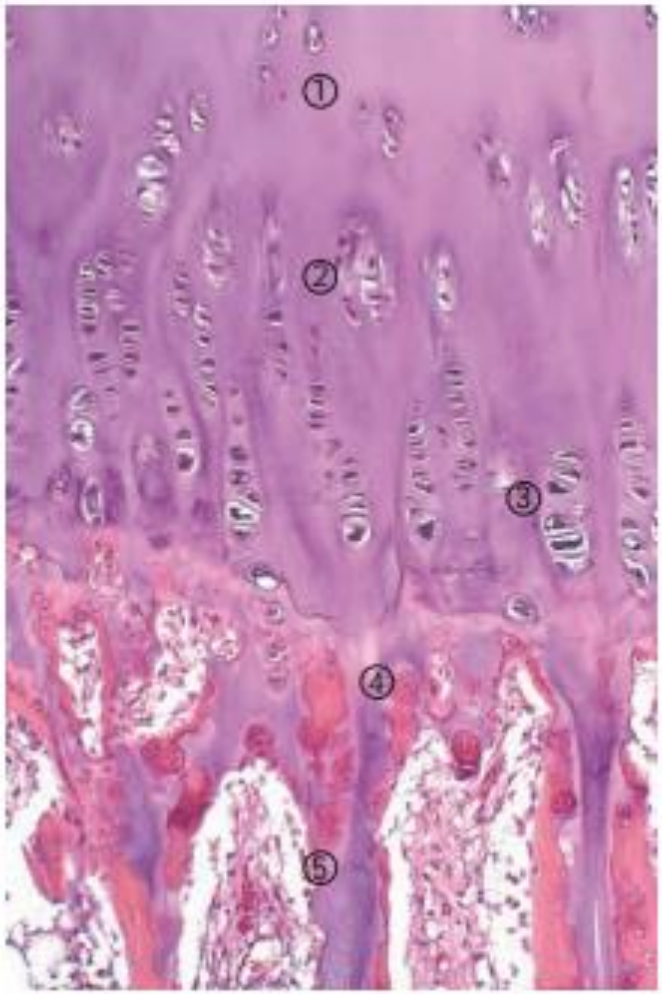


Figure 26-3 Active growth plate with ongoing enchondral ossification. 1, Reserve zone. 2, Zone of proliferation. 3, Zone of hypertrophy. 4, Zone of mineralization. 5, Primary spongiosa.

Bone

- During puberty and early adult life, endosteal apposition and trabecular thickening provide maximum skeletal mass and strength (peak bone mass).
- These processes are influenced by locally and systemically produced factors and mechanical forces.
- Peak bone mass is reached in early adulthood
- Set point determined by vitamin D and LRP5/6

Bone remodeling

- Endochondral remodeling in the primary and secondary spongiosa converts the relatively weak spicules of calcified cartilage into strong trabecular bone.
- On trabecular bone surfaces, the bone structural unit consists of irregular plates where resorption has produced scalloped indentations, Howship's lacunae, that are filled by new bone.

Bone remodeling

- Approximately 10% of the skeleton is replaced annually.
- This process can repair microdamage or change the shape of bones in response to structural and mechanical demands.
- Remodeling takes place at a microscopic locus known as the bone (or basic) multicellular unit (BMU), which consists of a unit of coupled osteoblast and osteoclast activity on the bone surface.
- Also known as the osteon

Bone remodeling

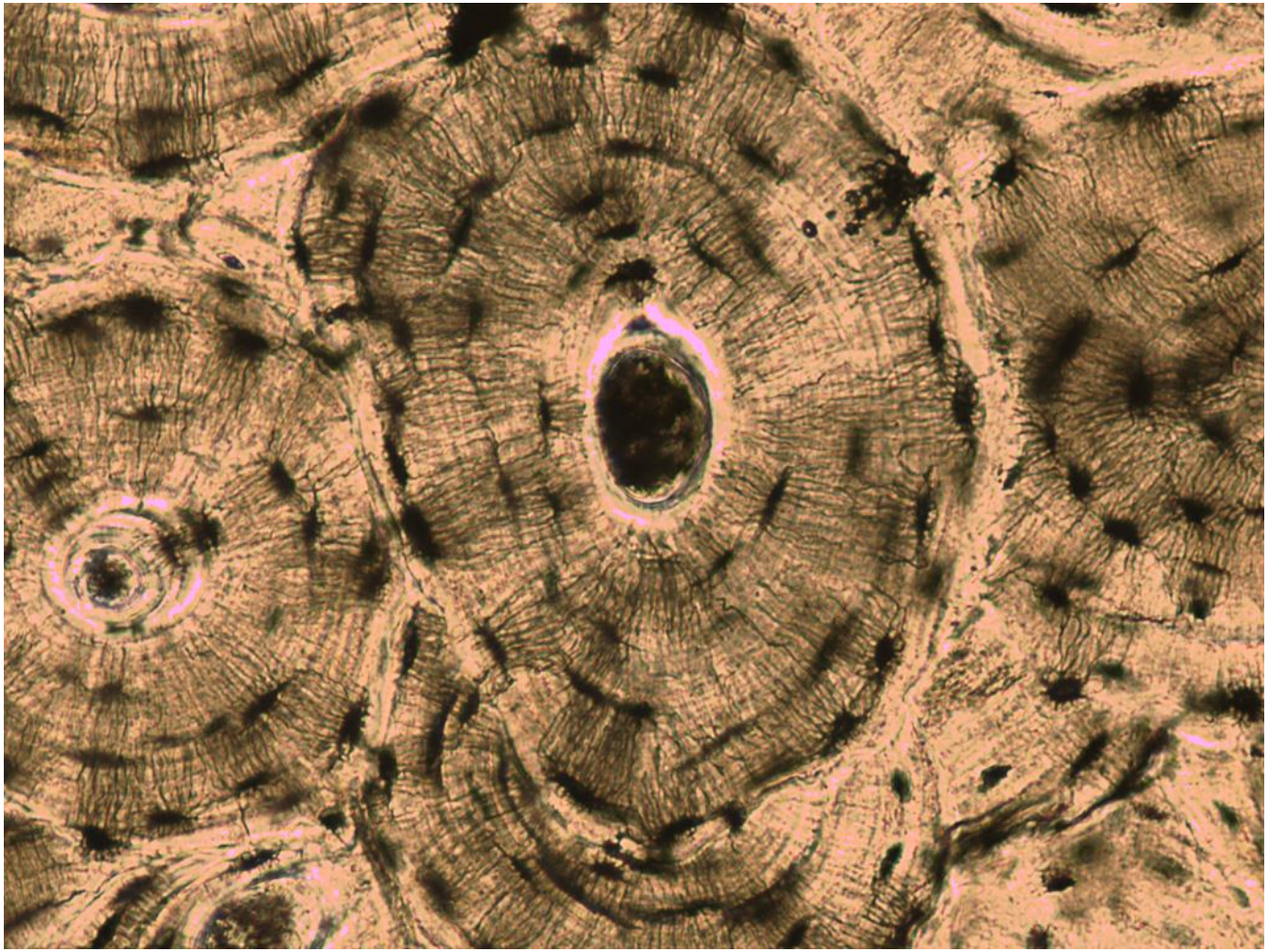
- Osteoclast attachment, bone resorption, osteoblast attachment and proliferation, and, finally, matrix synthesis occur sequentially at the BMU.
- Events at the BMU are regulated by cell-to-cell interactions and cytokines, and several signaling pathways

Bone remodeling

- The osteoblasts and osteocytes are connected to each other by many cell processes that lie in canaliculi within the bone.
- This syncytium of interconnected cells is probably critical for sensing mechanical forces. Loading of the skeleton results in shear stress along the canaliculi and around the lacunae in which the osteocytes are imbedded.
- Shear stress can stimulate the production of nitric oxide and prostaglandins, which may mediate the response to mechanical loading.

Bone remodeling

- Haversian remodeling in the cortex occurs in larger bones and may be necessary to maintain the viability of cells far from the bone surface.
- Haversian remodeling is probably also important in repairing fatigue damage to the skeleton.
- In cortical bone, the bone structural unit is the osteon, a cylinder of bone formed by osteoblasts after osteoclasts have tunneled into the cortex to form a Haversian canal.



Osteon with Haversian canal in center

http://medcell.med.yale.edu/histology/bone_lab/images/haversian_system.jpg

Accessed 05/10/2020

Systemic hormonal mediators

- Growth hormone (GH)
- Secreted by the anterior pituitary.
- It acts on resting chondrocytes to induce and maintain proliferation.
- Thyroid hormone (T3)
- Secreted by the thyroid gland
- Acts on proliferating chondrocytes to induce hypertrophy.

Paracrine hormonal mediators

- Indian hedgehog (Ihh)
- Locally secreted regulator (paracrine), made by prehypertrophic chondrocytes
- Coordinates chondrocyte proliferation and differentiation and osteoblast proliferation.
- Parathyroid hormone related protein (PTHrP)
- Local factor, expressed by perichondrial stromal cells and early proliferating chondrocytes that activates the PTH receptor and maintains proliferation of chondrocytes.

Paracrine hormonal mediators

- Wnt is a family of secreted factors that are expressed at highest levels in the proliferating zone and bind to the receptors
- Frizzled and LRP5/6
- Activate β-catenin signaling.
- They can promote both proliferation and maturation of chondrocytes.

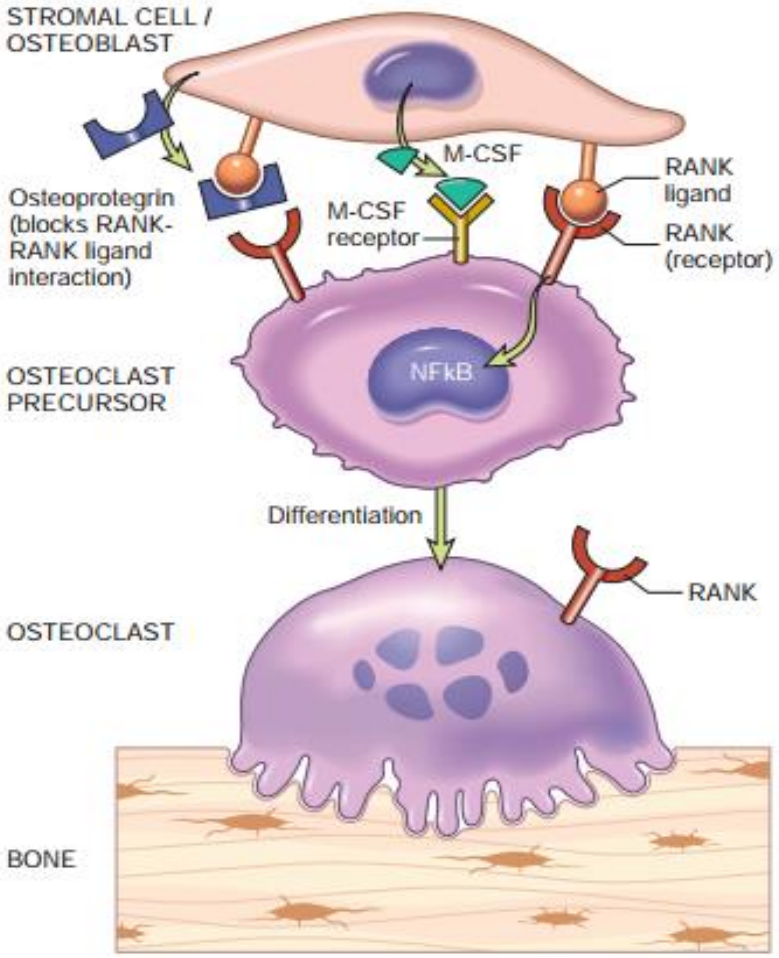


Figure 26-4 Paracrine molecular mechanisms that regulate osteoclast formation and function. Osteoclasts are derived from the same mononuclear cells that differentiate into macrophages. Osteoblast/stromal cell membrane-associated RANKL binds to its receptor RANK located on the cell surface of osteoclast precursors. This interaction in the background of macrophage colony-stimulating factor (M-CSF) causes the precursor cells to produce functional osteoclasts. Stromal cells also secrete osteoprotegerin (OPG), which acts as a "decoy" receptor for RANKL, preventing it from binding the RANK receptor on osteoclast precursors. Consequently, OPG prevents bone resorption by inhibiting osteoclast differentiation.

Homeostasis and remodeling

Homeostasis and bone remodeling

- RANK signaling
- (1) the transmembrane receptor RANK (receptor activator for
- NF-κB), which is expressed on osteoclast precursors;
- (2) RANK ligand, (RANKL) which is expressed on osteoblasts
- and marrow stromal cells;
- (3) osteoprotegerin (OPG), a secreted “decoy” receptor made by osteoblasts and several other types of cells that can bind RANKL and thus prevent its interaction with RANK.

Homeostasis and remodeling

- When stimulated by RANKL, RANK signaling activates the transcription factor NF-κB, which is essential for the generation and survival of osteoclasts.
- Activation of the M-CSF receptor on osteoclast precursors stimulates a tyrosine kinase cascade that is also crucial for the generation of osteoclasts.
- WNT proteins produced by osteoprogenitor cells bind to the LRP5 and LRP6 receptors on osteoblasts and thereby trigger the activation of β-catenin and the production of OPG.
- Sclerostin, which is produced by osteocytes, inhibits the WNT/β-catenin pathway

Homeostasis and remodeling

- Parathyroid hormone, IL-1 and glucocorticoids promote osteoclast differentiation and bone turnover.
- Bone morphogenic proteins and sex hormones generally block osteoclast differentiation or activity by favoring OPG expression.
- Breakdown of matrix by osteoclasts liberates and activates matrix proteins, growth factors, cytokines, and enzymes (e.g., collagenase), including some that stimulate osteoblasts

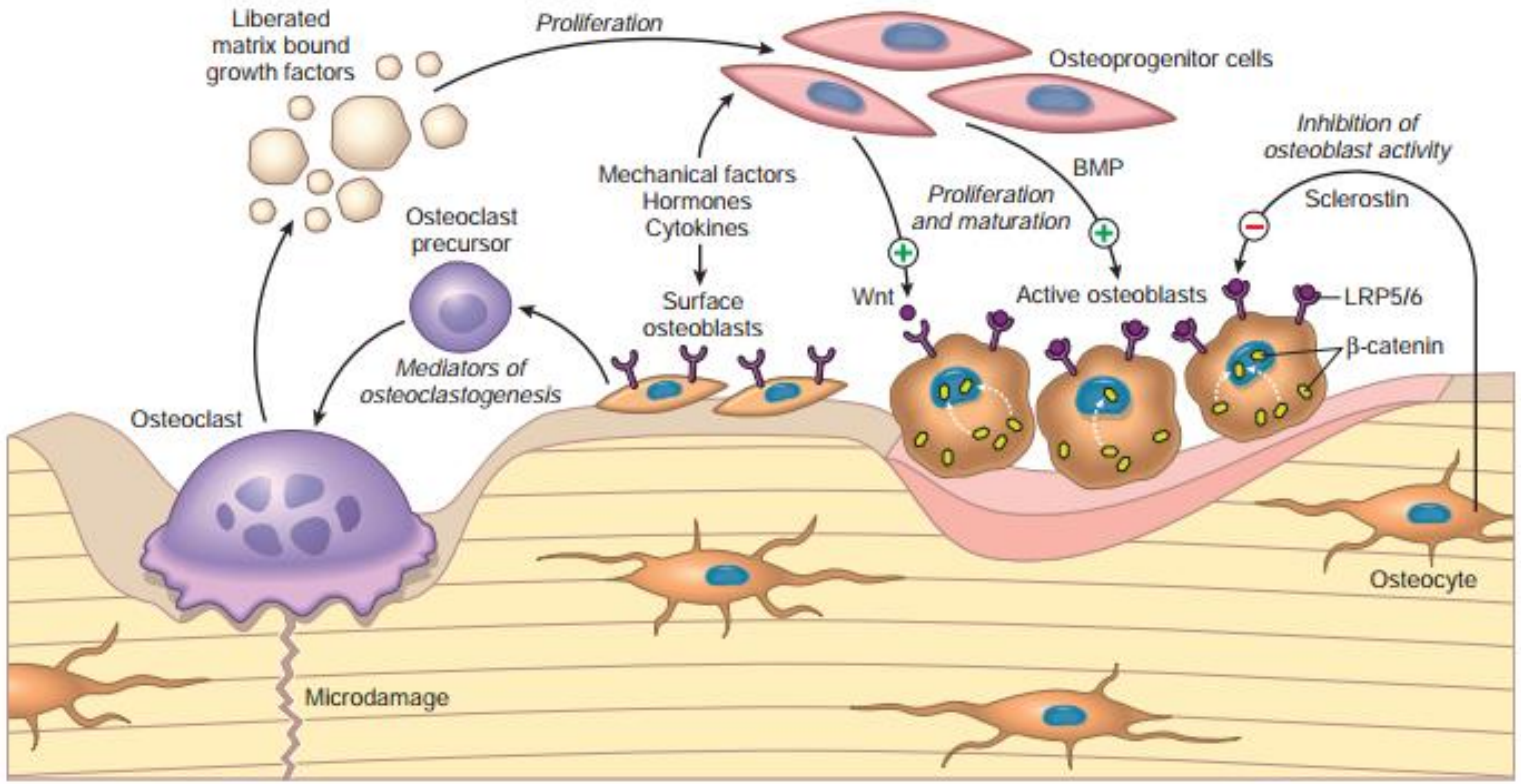


Figure 26-5 Bone cells and their interrelated activities. Hormones, cytokines, growth factors, and signal-transducing molecules are instrumental in their formation and maturation, and allow communication between osteoblasts and osteoclasts. Bone resorption and formation in remodeling are coupled processes that are controlled by systemic factors and local cytokines, some of which are deposited in the bone matrix. BMP, bone morphogenic protein; LRP5/6, LDL receptor related proteins 5 and 6.

Bone formation and repair

- Osteoblasts undergo shape changes and secrete and other enzymes that digest proteins on the bone surface.
- They also express receptor activator of NF-κB ligand (RANKL also called osteoclast differentiating factor). It is identical to TRANCE (tumor necrosis factor-related activation-induced cytokine), a factor that is involved in the interaction of T-cells and dendritic cells.
- Estrogen deficiency may increase bone resorption via upregulation of RANKL on bone marrow cells.

Bone formation and repair

- RANKL binding to RANK activates the receptor, induces binding of co-acitvators TRAF6 and c-SRC. These activate PI3K as well as NF-κB, JNK. MAPK pathways.
- The RANKL/RANK interaction results in activation, migration, differentiation, and fusion of hematopoietic cells of the osteoclast lineage to begin the process of resorption.
- $\alpha_v\beta_3$-integrin mediates adhesion of osteoclasts to bone surfaces. Also associated with angiogenesis.

Bone formation and repair

- Osteoclast precursors express RANK. RANKL binding results in differentiation and activation of mature osteoclasts.
- M-CSF produced by osteoblasts binds to its receptor on osteoclast precursors, resulting in generation of osteoclasts.
- Osteoclastic resorption per se may begin with the migration of partially-differentiated mononuclear pre-osteoblasts to the bone surface, which then coalesce to form the large, multinucleated osteoclasts that are required for bone resorption.

Bone formation and repair

- Osteoclasts remove mineral and matrix to a limited depth on the trabecular surface or within cortical bone.
- RANKL can bind to a protein produced by osteoblasts and other marrow cells (osteoprotegerin or osteoclastogenesis inhibitory factor). That protein serves as a decoy receptor, modulating the process.
- Cathepsin K is a lysosomal protease with collagenase activity expressed in osteoclasts. Deficiency is associated with osteoporosis.

Bone formation and repair

- After osteoclastic resorption is completed, there is a reversal phase in which monocyte/ macrophage cells appear on the bone surface And prepare the surface for new osteoblasts to begin bone formation.
- A layer of glycoprotein-rich material is laid down on the resorbed surface, the so-called "cement line", to which the new osteoblasts can adhere. Osteopontin may be a key protein in this process

Bone formation and repair

- The cells at the reversal site may also provide signals for osteoblast differentiation and migration.
- The formation phase follows with successive waves of osteoblasts laying down bone until the resorbed bone is completely replaced and a new bone structural unit is fully formed.
- When this phase is complete, the surface is covered with flattened lining cells, and there is a prolonged resting period with little cellular activity on the bone surface until a new remodeling cycle begins.

Bone formation and repair

- The stages of the remodeling cycle have different lengths.
- Resorption probably continues for about two weeks.
- The reversal phase may last up to four or five weeks, while formation can continue for four months until the new bone structural unit is fully formed.
- Bone resorption and bone formation are tightly coupled, so that the amount of bone formed in new bone unit equals the amount of bone resorbed.
- The size and shape of cortical bone unit, the osteon, is relatively uniform.

Bone formation and repair

- Osteoblasts have a reproducible temporal pattern of collagen and alkaline phosphatase synthesis followed by synthesis of osteocalcin
- Osteoblasts also express genes for specialized proteins such as osteopontin and bone sialoprotein.
- Osteoblastic metastatic deposits occur in areas of previous bone resorption.

Bone formation and repair

- Fully differentiated osteoblasts are oriented so that the collagen and noncollagen proteins are laid down on the bone surface in forms suitable for mineralization.
- Mineralization is delayed for several days, which allows time for collagen cross-linking and the development of large, strong fibers.
- As osteoblast production of collagen and non-collagen protein is completed, a few of the osteoblasts are buried in the matrix and become osteocytes.
- Lead (>10µg/dL) increases chondrogenesis and delays cartilage mineralization.

Matrix metallo-proteinases

- Zinc-proteases that can degrade the protein components of the extracellular matrix.
- Production of some matrix metallo-proteinases are strongly upregulated in malignant cells (e.g. type IV collagenase, urokinase plasminogen activator in breast cancer).
- May play an important role in tumor growth and metastasis.

Developmental anomalies

- Developmental anomalies can result from localized disruption of the migration and condensation of mesenchyme (dysostosis) or global disorganization of bone and/ or cartilage (dysplasia)
- Dysplasias arise from mutations in genes that control development or remodeling of the entire skeleton.

Developmental anomalies

- The most common forms include complete absence of a bone or entire digit (aplasia), extra bones or digits (supernumerary digit), and abnormal fusion of bones (e.g., syndactyly, craniosynostosis).
- Genetic alterations that affect genes encoding transcription factors (especially homeobox genes), cytokines, and cytokine receptors are especially common among dysostoses.

Table 26-2 Diseases of the Skeleton with Identified Genetic Defects

Disorder	Gene Symbol	Affected Molecule	Clinical Phenotype
Defects in transcription factors producing abnormalities in mesenchymal condensation and related cell differentiation			
Brachydactyly types D and E	*HOXD13*	Transcription factor	Short, broad terminal phalanges of first digits
Camptomelic dysplasia	*SOX9*	Transcription factor	Sex reversal, abnormal skeletal development
Cleidocranial dysplasia	*RUNX2*	Transcription factor	Abnormal clavicles, Wormian bones, supernumerary teeth
Holt-Oram syndrome	*TBX5*	Transcription factor	Congenital abnormalities, forelimb anomalies
Nail-patella syndrome	*LMX1B*	Transcription factor	Hypoplastic nails, hypoplastic or aplastic patellas, dislocated radial head, progressive nephropathy
Waardenburg syndrome types 1 and 3	*PAX3*	Transcription factor	Hearing loss, abnormal pigmentation, craniofacial abnormalities
Defects in hormones and signal transduction proteins producing abnormal proliferation or maturation of osteoblasts, osteoclasts or chondrocytes			
Achondroplasia	*FGFR3*	Receptor	Short stature, rhizomelic shortening of limbs, frontal bossing, midface deficiency
Hypochondroplasia	*FGFR3*	Receptor	Disproportionately short stature, micromelia, relative macrocephaly
Osteopetrosis, autosomal dominant	*LRP5*	Receptor	Increased bone density, hearing loss, skeletal fragility
Osteopetrosis, infantile form	*RANKL*	Receptor ligand	Increased bone density
Osteoporosis-pseudoglioma syndrome	*LRP5*	Receptor	Congenital or infant-onset loss of vision, skeletal fragility
Thanatophoric dysplasia	*FGFR3*	Receptor	Severe limb shortening and bowing, frontal bossing, depressed nasal bridge
Defects in extracellular structural proteins			
Achondrogenesis type 2	*COL2A1*	Type II collagen	Short trunk
Metaphyseal dysplasia, Schmid type	*COL10A1*	Type X collagen	Mildly short stature
Osteogenesis imperfecta types 1-4	*COL1A1, COL1A2*	Type I collagen	Bone fragility
Defects in metabolic enzymes and transporters			
Osteopetrosis with renal tubular acidosis	*CA2*	Carbonic anhydrase	Increased bone density, fragility, renal tubular acidosis
Osteopetrosis, late onset type 2	*CLCN7*	Chloride channel	Increased bone density, fragility

Modified from Mundlos S, Olsen BR: Heritable diseases of the skeleton. Part I: Molecular insights into skeletal development—transcription factors and signaling pathways. FASEB J 11:125-132, 1997; Mundlos S, Olsen BR: Heritable diseases of the skeleton. Part II: Molecular insights into skeletal development—matrix components and their homeostasis. FASEB J 11:227-233, 1997; Superti-Furga A, et al.: Molecular-pathogenetic classification of genetic disorders of the skeleton. Am J Med Genet 106:262-293, 2001; Krakow D, Rimoin DL: The skeletal dysplasias. Genet Med 2010:12(6):327-341.

Limb anomalies

- Amelia (absence of limb)
- Meromelia (loss of part of limb)
- Cleft hand
- Abnormal orientation of the hand.
- May result from congenital absence of the radius.
- Lobster claw deformity
- Absence of central digits.
- Failure of digital rays to form.
- Congenital dislocation of the hip
- Results from joint laxity or underdevelopment of the acetabulum.

Limb anomalies

- Brachydactyly.
- Short digits.
- Often associated short stature.
- Polydactyly.
- Extra digit usually medial or lateral on limb.
- Syndactyly.
- Webbing (cutaneous) or fusion (osseus) of adjacent digits.
- Clubfoot.
- Abnormal orientation of the foot that prevents normal weight bearing. (Talus abnormality).
- May correct with serial casting to return to normal orientation.

Developmental anomalies

- Brachydactyly types D and E are caused by mutations in the homeobox HOXD13 gene and are characterized by shortening of the terminal phalanges of the thumb and big toe, respectively.
- Loss-of-function mutations in RUNX2 result in cleidocranial dysplasia, an autosomal dominant disorder characterized by patent fontanelles, delayed closure of cranial sutures, Wormian bones (extra bones that occur within a cranial suture), delayed eruption of secondary teeth, primitive clavicles, and short stature.

Achondroplasia

- Most common skeletal dysplasia
- 90% stem from paternal line gain of function mutations in FGFR3
- Retarded cartilage growth
- Shortened proximal extremities with normal trunk length
- Enlarged head with bulging forehead and depression at the root of the nose
- No cognitive defect

Thanatophoric dysplasia

- Most common lethal form of dwarfism
- Micromelic limb shortening, frontal bossing with relative macrocephaly, a small thorax, and a bell-shaped abdomen
- Die of pulmonary insufficiency
- Disorganization of zone of proliferation
- Diminished proliferation of chondrocytes
- FGFR3 gain of function mutation

Inheritance of collagen disorders

Osteogenesis imperfecta	Autosomal dominant
Ehlers-Danlos syndrome types I-IV	Autosomal dominant
Ehlers-Danlos syndrome types VI	Autosomal recessive
Ehlers-Danlos syndrome types VIIa, VIIb	Autosomal dominant
Ehlers-Danlos syndrome types VIIc	Autosomal recessive
Alport's syndrome	Autosomal recessive OR X-linked recessive
Epidermolysis bullosa dystrophica	Autosomal dominant OR autosomal recessive
Menke's syndrome	X-linked recessive

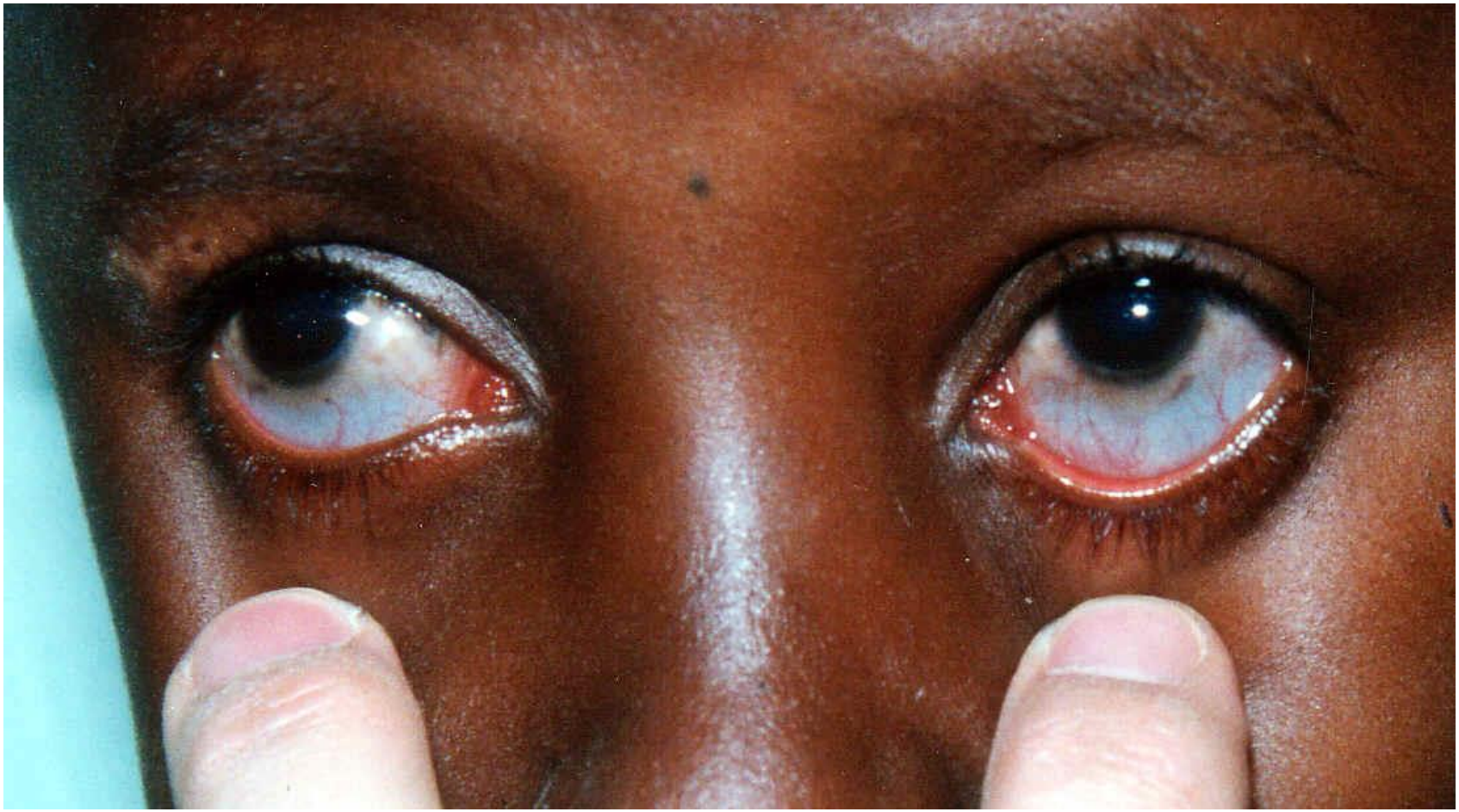
Table 26-3 Subtypes of Osteogenesis Imperfecta

Subtype	Collagen Defect	Inheritance	Major Clinical Features	Prognosis
I	Decreased synthesis of pro-α1(1) chain Abnormal pro-α1(1) or pro-α2(1) chains	Autosomal dominant	Postnatal fractures, blue sclera Normal stature Skeletal fragility Dentinogenesis imperfecta Hearing impairment Joint laxity Blue sclerae	Compatible with survival
II	Abnormally short pro-α1(1) chain Unstable triple helix Abnormal or insufficient pro-α2(1)	Most autosomal recessive Some autosomal dominant New mutations	Death in utero or within days of birth Skeletal deformity with excessive fragility and multiple fractures Blue sclera	Perinatal lethal
III	Altered structure of pro-peptides of pro-α2(1) Impaired formation of triple helix	Autosomal dominant (75%) Autosomal recessive (25%)	Compatible with survival Growth retardation Multiple fractures Progressive kyphoscoliosis Blue sclera at birth that become white Hearing impairment Dentinogenesis imperfecta	Progressive, deforming
IV	Short pro-α2(1) chain Unstable triple helix	Autosomal dominant	Postnatal fractures, normal sclerae Moderate skeletal fragility Short stature Sometimes dentinogenesis imperfecta	Compatible with survival

OI, Osteogenesis imperfecta.

Osteogenesis imperfecta

- Bones lack density.
- Hearing loss.
- Blue sclerae due to translucency of connective tissue over choroid.
- Type I collagen defect.
- Collagen is highly-modified triple-helix. Glycosylated; hydroxylated; cross-linked.
- Multiple helices form fibrils.
- Helical region has glycine every third residue.
- Inside helix, packing requires small side chain. Substitutions in glycine position disrupt fibril formation.



Osteogenesis imperfecta

- Group of 19 related disorders characterized by abnormal bone fragility.
- Type I.
- Most common, mildest.
- Normal stature.
- COL1A1 mutation at 17q21.33
- Type II.
- Most severe, often lethal in perinatal period.
- Both COL1A1 and COL1A2 mutation at 7q21.33
- Mutations substitute bulky amino acids for glycine.
- Types III, IV.
- Intermediate in severity.
- Mutations substitute bulky amino acids for glycine.

Alport's syndrome

- Characterized by progressive renal failure and deafness.
- Second most common cause of inherited kidney disease.
- Affects type IV collagen (basement membrane of kidney and of cochlea). Several different mutations with varying clinical manifestations.
- 80% mutation at COL 4A5 (Xq22.3)
- 20% mutation at COL 4A3-4A6 (2q36.3)
- Most patients develop renal failure in early adult life.

Ehlers-Danlos syndrome

- Group of 11 inherited disorders characterized by hyperextensibility of skin and hypermobility of joints.
- Abnormal type V collagen.
- Classical (Types I and II).
- Most common.
- COL5A1 at 9q34.3 or COL5A2 at 2q32.2
- Type III.
- Mildest form.
- Hypermobility
- Mutation TNXB gene at 6p21.32-33
- Tenascin-X

Ehlers-Danlos syndrome

- Abnormal Type III collagen
- Type IV
- Most severe.
- Rupture of arteries and bowel.
- COL3A1 at 2q32.2

- Deficiency of lysyl hydroxylase.
- Type VI
- Kyphoscoliosis.
- Collagen lacks normal structural stability.

Ehlers-Danlos syndrome

- Types VIIa and VIIb
- Arthrochalasia
- Autosomal dominant associated with COLA1 at gene 17q21.33 and COLA2 gene at 7q21.3 abnormalities (encode the α_1 and α_2 chains of collagen).
- Type VIIc
- Dermatosparaxis
- Deficiency of procollagen N-proteinase leads to impaired conversion of procollagen to collagen.

Osteopetrosis

- Albers-Schönberg or marble bone disease
- The bones lack a medullary canal and the ends of the long bones are deformed (Erlenmeyer flask deformity).
- Deficient osteoclast activity.
- Primary spongiosa remains, leaving little room for the marrow, and prevents formation of mature trabeculae. Neural foramina are small and compress exiting nerves.

Osteopetrosis

- 60 percent of patients with severe autosomal recessive osteopetrosis have a defect in the osteoclast-specific proton-pump subunit (TCIRG1 at 11q13.2), preventing acidification and solubilization of hydroxyapatite.
- Other clinically significant mutations have been identified in CLCN7 at 16p13.3, a gene that encodes an osteoclast-specific chloride channel at the ruffled membrane (preventing acidification and solubilization of hydroxyapatite);
- CAII at 8q21.2, the carbonic anhydrase II gene (preventing acidification and solubilization of hydroxyapatite);

Osteopetrosis

- OSTM-1 at 6q21 involved in ubiquination of G-proteins.
- Abnormal in severe, infantile form.
- Optic atrophy, deafness, facial paralysis, leukopenia
- These mutations are associated with normal or elevated numbers of abnormally functioning osteoclasts.
- In contrast, mutations in RANKL result in an osteoclast poor form of osteopetrosis.
- Hematopoietic stem cell transplantation provides osteoclasts

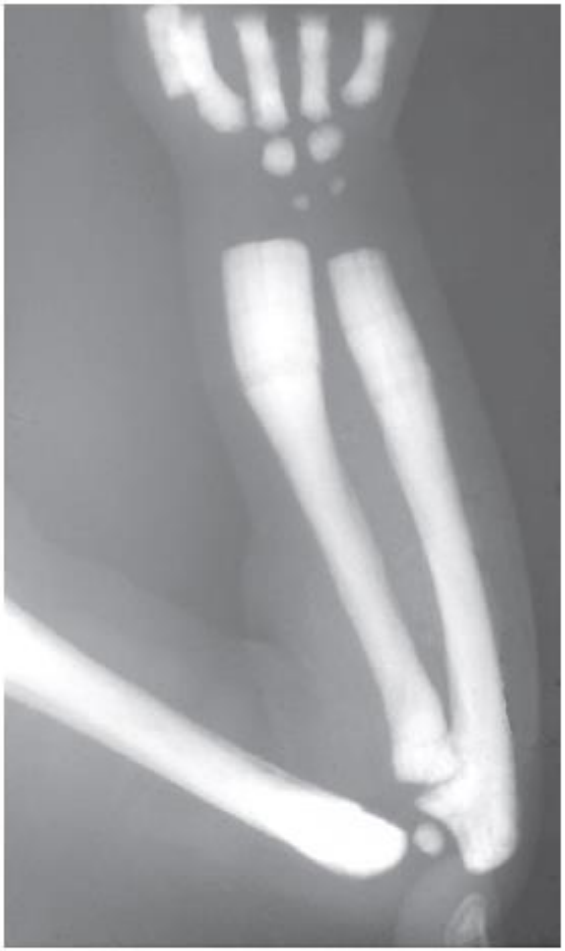


Figure 26-7 Radiograph of the upper extremity in an individual with osteopetrosis. The bones are diffusely sclerotic, and the distal metaphyses of the ulna and radius are poorly formed.

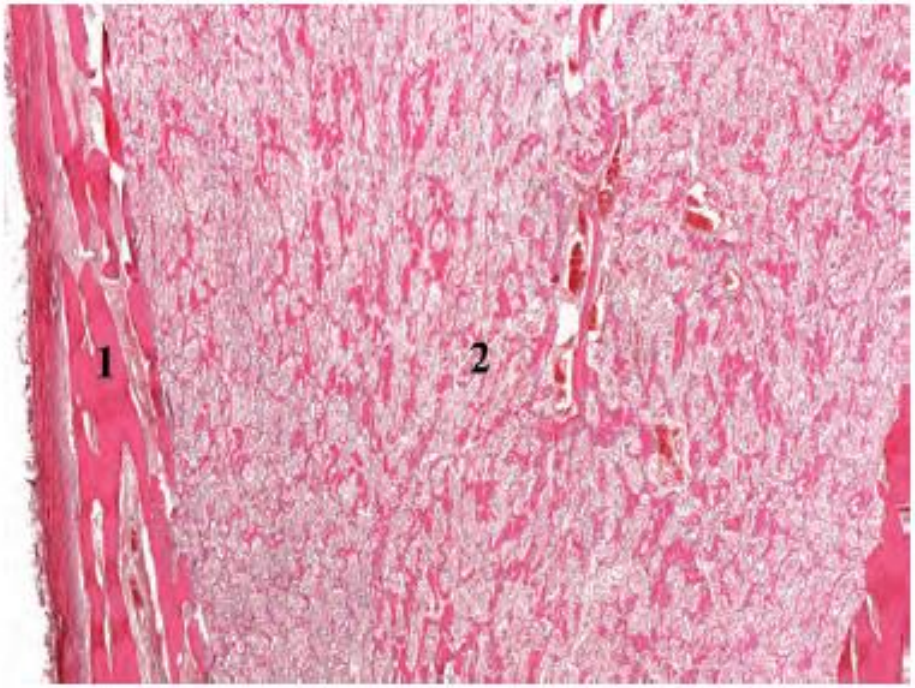


Figure 26-8 Section of proximal tibial diaphysis from a fetus with osteopetrosis. The cortex (1) is present, but the medullary cavity (2) is filled with primary spongiosa, which replaces the hematopoietic elements.

Elastin disorders

- Supravalvular aortic stenosis.
- Deletion in elastin gene (ELN) at 7q11.23
- Lack of elasticity in large arteries leads to (relative) contraction.
- Williams syndrome.
- Deletion of 26-28 genes on chromosome 7
- Affects central nervous system and connective tissue.
- May see supravalvular aortic stenosis
- Scleroderma characterized by loss of elastin.

Dystrophic epidermolysis bullosa

- Characterized by blisters and breaks in the skin.
- COL7A1 at 3p21.31
- Defective Type VII collagen.
- Cannot form anchoring fibrils that keep layers of skin together.

Collagen disorders

- Menke’s disease
- Lysine hydroxylase deficiency
- Regulate copper absorption and transport in Golgi
- ATP7 gene at Xq21.1

Collagen disorders

- Severe chondrodysplasia
- Deficiency in Type II collagen
- COL 2A1 at 12q13.11
- Schmid metaphyseal chondrodysplasia
- Type X collagen is a product of hypertrophic chondrocytes and has been localized to presumptive mineralization zones of hyaline cartilage.
- COL10A1 at 6q22.1

Osteoporosis

- The prevalence of osteoporosis in women of European origin ranges from 15% in the sixth decade to 40% in the eighth decade; the prevalence in the 9th decade of life is 70%.
- The lifetime risk for hip fracture is approximately 20% in white women.
- For women of sub-Saharan origin more than 50 years old, the prevalence of osteoporosis is 12%.
- Women of Asian origin as well as men older than 70 and those on long-term steroid therapy (six weeks or more) are also at risk.

Osteoporosis

- Bone density is largely genetically determined (BMP-2 gene at 20p12.3 secretes ligand for TGF-β).
- BMI <25 is the single best finding for detecting women with osteoporosis (positive likelihood ratio, LR+, 4.5).
- Kyphosis is specific for osteoporosis but has low sensitivity. Screening questionnaires offer little additional information.
- Historical height loss (> 4cm) in an osteoporotic woman is compatible with vertebral fracture (LR+ 4.6).

Osteoporosis

- Reduced physical activity increases rate of bone loss.
- Resistance training (increase load bearing) is effective therapy.
- Calcium deficiency, vitamin D deficiency, and increased PTH may contribute to age related bone loss.
- Estrogen levels post-menopause increase both bone resorption and formation; however, new bone does not keep pace with bone resorption. (High turnover osteoporosis).
- Inflammatory cytokines increase osteoclast recruitment.

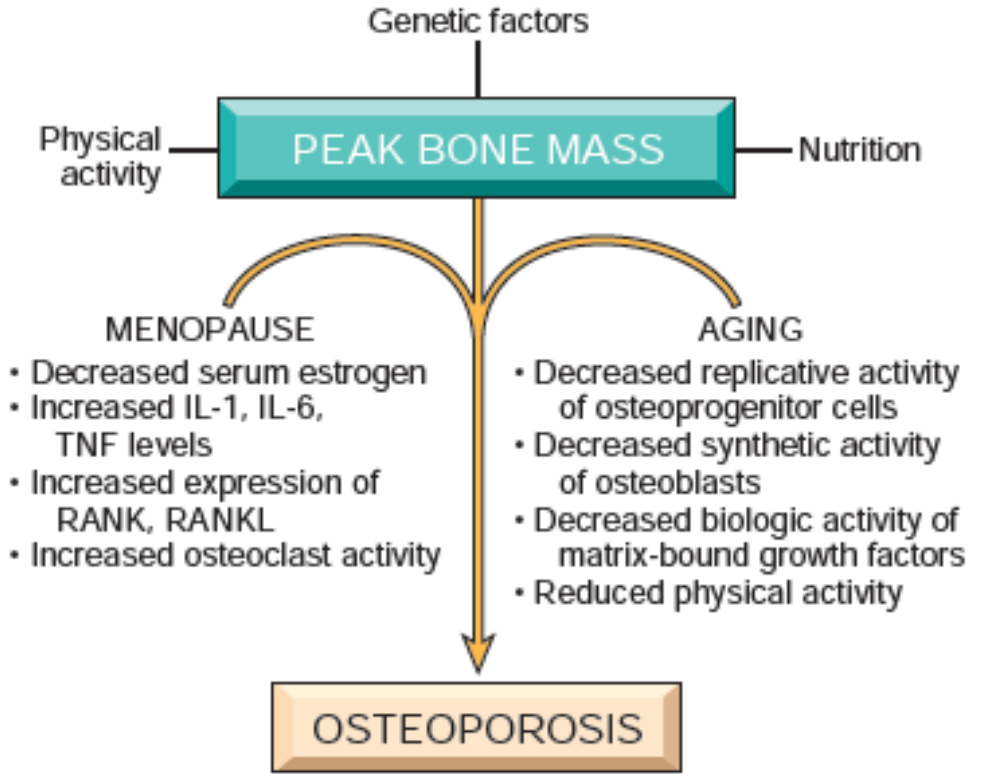


Figure 26-9 Pathophysiology of postmenopausal and senile osteoporosis

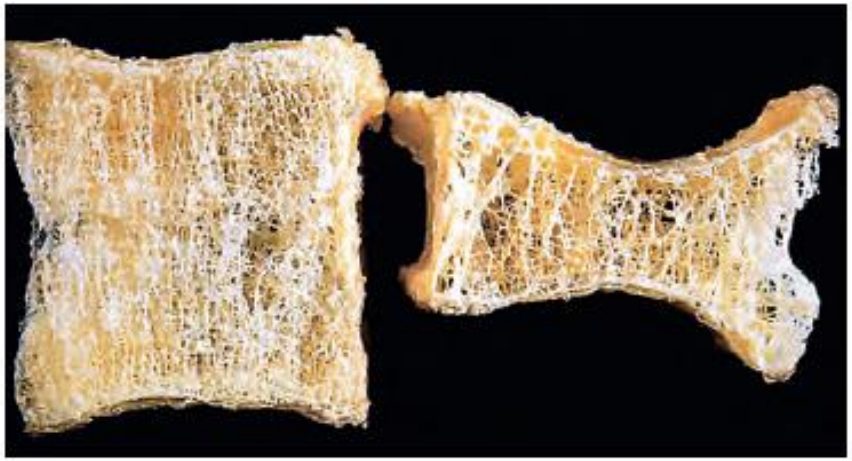


Figure 26-10 Osteoporotic vertebral body *(right)* shortened by compression fractures compared with a normal vertebral body *(left)*. Note that the osteoporotic vertebra has a characteristic loss of horizontal trabeculae and thickened vertical trabeculae.

Osteoporosis

- 40% of bone must be lost for it to be noted on plain x-ray.
- Medicare pays for DXA screening.
- There is no evidence that early therapy limits later fracture.
- DXA scan does not change significantly with therapy.
- Do not repeat more frequently than every 2 years while on therapy.

Osteoporosis therapy

- Begin calcium replacement whenever a patient will be on corticosteroid for more than 60 days.
- Osteoporosis therapy instituted if bone density (DXA) T-score is below 3 standard deviations from the “normal”.
- Fracture risk increases two to three times for each standard deviation below the mean.

Osteoporosis therapy

- Daily intake of Calcium, vitamin D may retard osteoporosis. Associated with elevated cardiovascular risk and development of prostate cancer.
- Boron cross-links fibrous matrix on which Calcium deposited; fracture risk decreases with daily intake.
- Back and leg strengthening exercises helpful.

Osteoporosis therapy

- Hormone replacement therapy increases risk of breast and uterine cancer. Limited beneficial effect on cardiovascular system after menopause.
- Biphosphonates bind to matrix proteins. Inhibit osteoclast activity and promote apoptosis. Biphosphonates IV twice yearly maintain bone density.
- Bone pain a side-effect.
- Denosumab binds RANKL. More effective than biphosphonates.

Osteoporosis therapy

- If progression on biphosphonates, calcitonin instituted.
- Calcitonin (nasal administration) associated with 30% increase in bone density; many side effects. Often associated with disabling local symptoms.
- Daily teriparatide injections (synthetic parathormone) if calcitonin fails. Teriapatide associated with 60% increase in bone density particularly if used in conjunction with hormone replacement.
- Odanacatib inhibits cathepsin K.

Paget's disease of bone

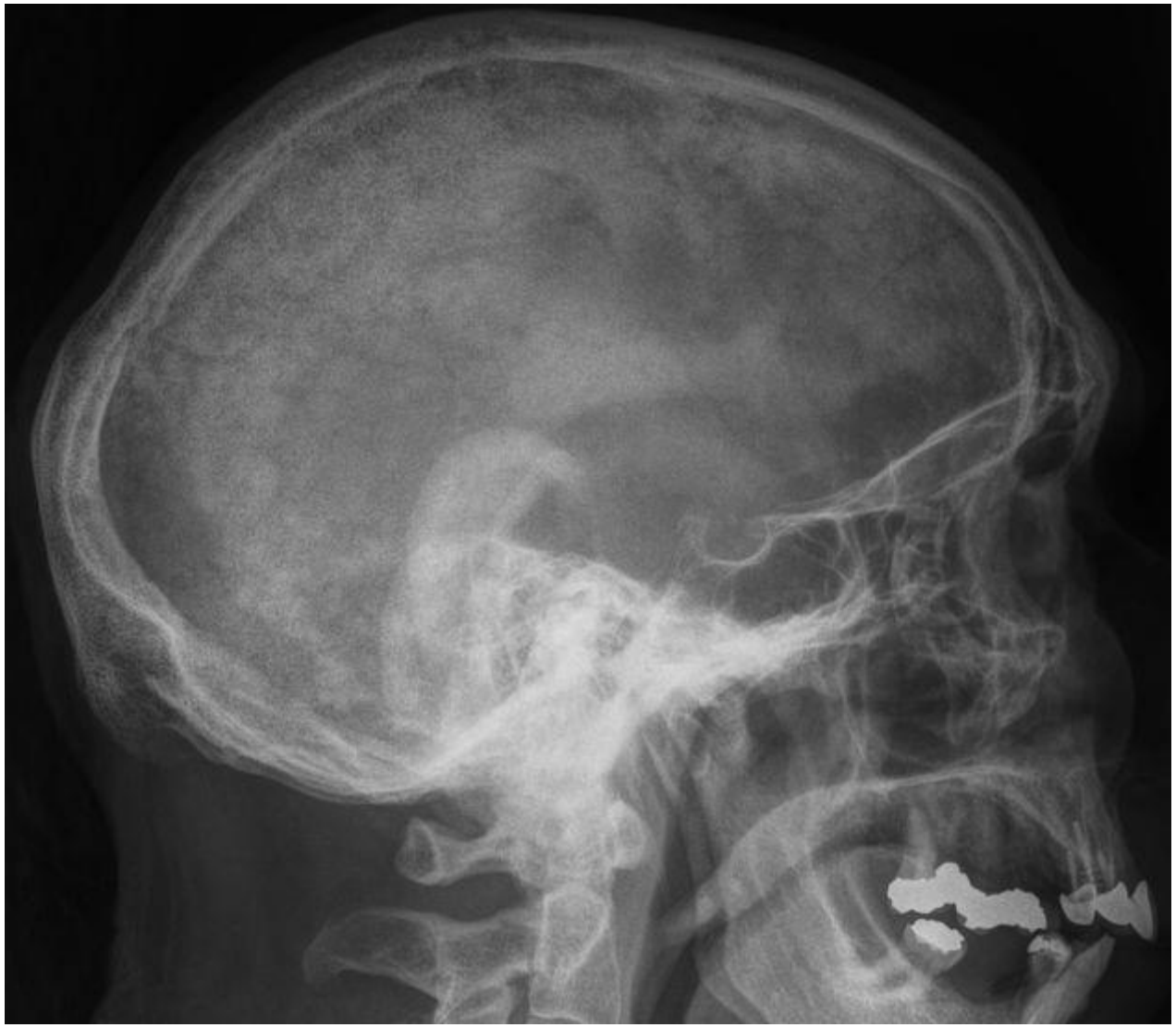
- Average age at diagnosis is 70 years old.
- May be asymptomatic.
- Patients may have bone pain, headache, skeletal deformities, neurologic compression symptoms.
- Caused by microfractures or by bone overgrowth
- Leonine facies if craniofacial bones involved
- Platybasia as a result of weakened bone; may compress the posterior fossa
- Anterior bowing of femur because of weakened bone may lead to chalk stick-type fracture

Paget's disease of bone

- Osteolytic, mixed osteolytic-osteoblastic, and osteosclerotic stages.
- Monostotic in up to 15% of cases.
- Axial skeleton involved in 80% of cases (ribs, fibula, and small bones of the hands and feet are usually uninvolved by the disease process).
- Thickening of the skull, indistinct bone edges, and a "cotton wool" appearance to bone can be seen on skull x-ray.
- Serum alkaline phosphatase and urinary proline levels elevated.

Paget's disease of bone

- The lesion is hypervascular. In polyostotic disease may lead to high output cardiac failure.
- SOSTM1 mutation at 5q35.33 in 50% of familial cases. Protein p62 enhances NF-κB activation by RANK signaling.
- Mosaic pattern of lamellar bone in sclerotic phase is pathognomonic.
- Giant cell tumor may develop.
- Up to 10% of those with severe polyostotic disease may develop sarcoma.
- In severe cases, biphosphonates or calcitonin employed in therapy.



https://radiopaedia.org/articles/paget-disease-bone?lang=us

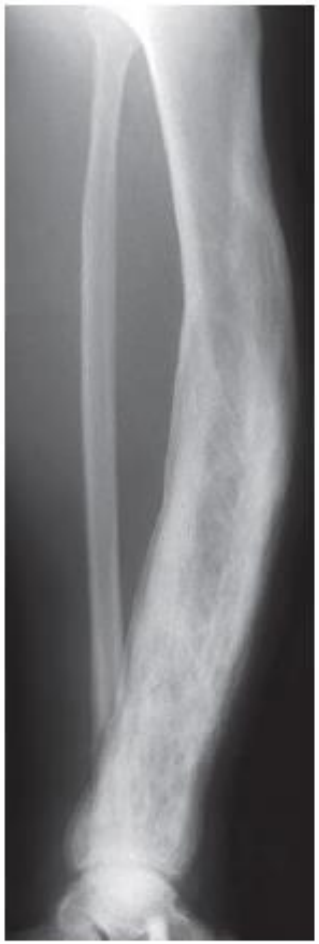


Figure 26-14 Severe Paget disease. The tibia is bowed and the affected portion is enlarged, sclerotic, and exhibits irregular thickening of both the cortical and cancellous bone.

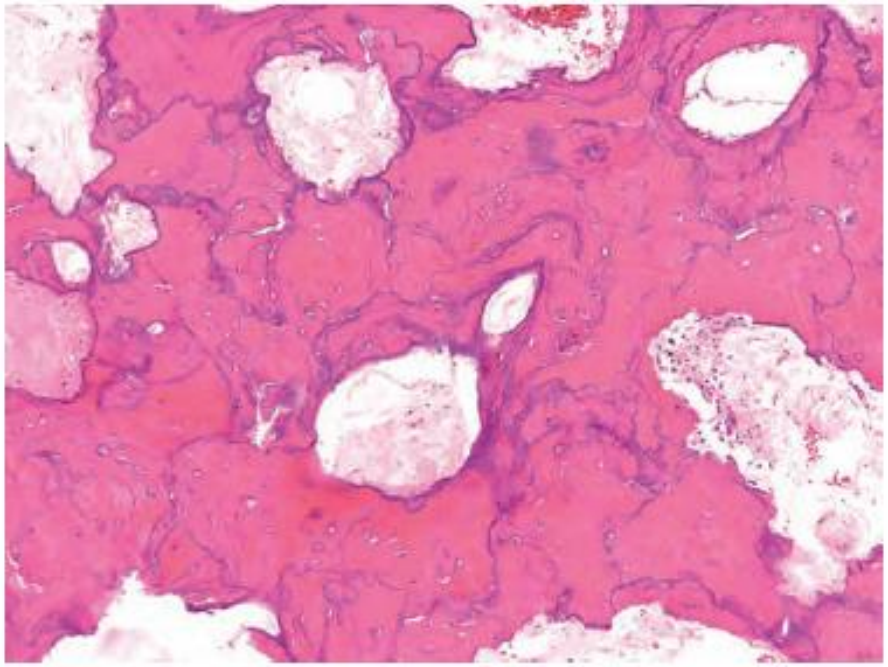


Figure 26-13 Mosaic pattern of lamellar bone pathognomonic of Paget disease.

Hyperparathyroidism

- The increased osteoclast activity in hyperparathyroidism is most prominent in cortical bone (subperiosteal and endosteal surfaces) but medullary bone is not spared.
- Osteoclasts may tunnel into and dissect centrally along the length of the trabeculae, creating the appearance of railroad tracks and producing what is known as dissecting osteitis.
- Marrow spaces around the affected surfaces are replaced by fibrovascular tissue.

Hyperparathyroidism

- The bone loss predisposes to microfractures and secondary hemorrhages that elicit an influx of macrophages and an ingrowth of reparative fibrous tissue, creating a mass of reactive tissue, known as a brown tumor **.**
- The brown color is the result of the vascularity, hemorrhage, and hemosiderin deposition, and it is not uncommon for the lesions to undergo cystic degeneration.
- Severe hyperparathyroidism is known as generalized osteitis fibrosa cystica (von Recklinghausen disease of bone).

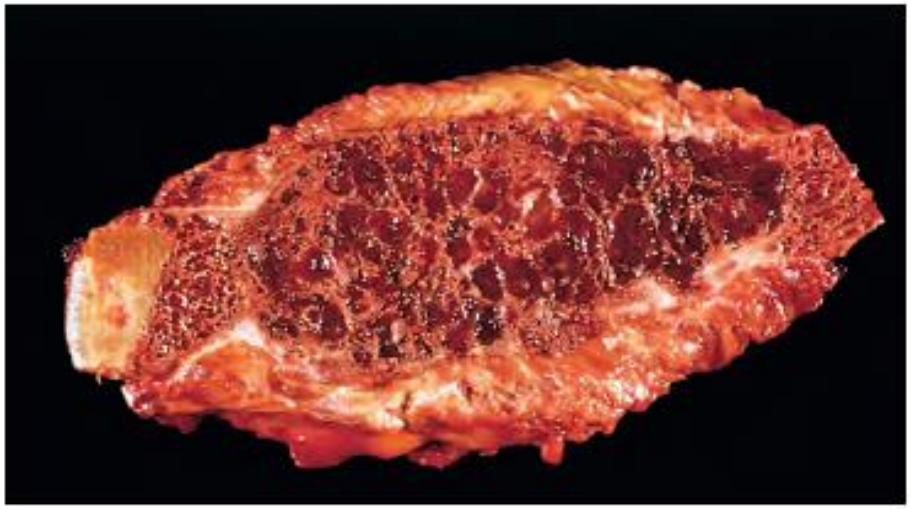


Figure 26-16 Resected rib, harboring an expansile brown tumor adjacent to the costal cartilage.

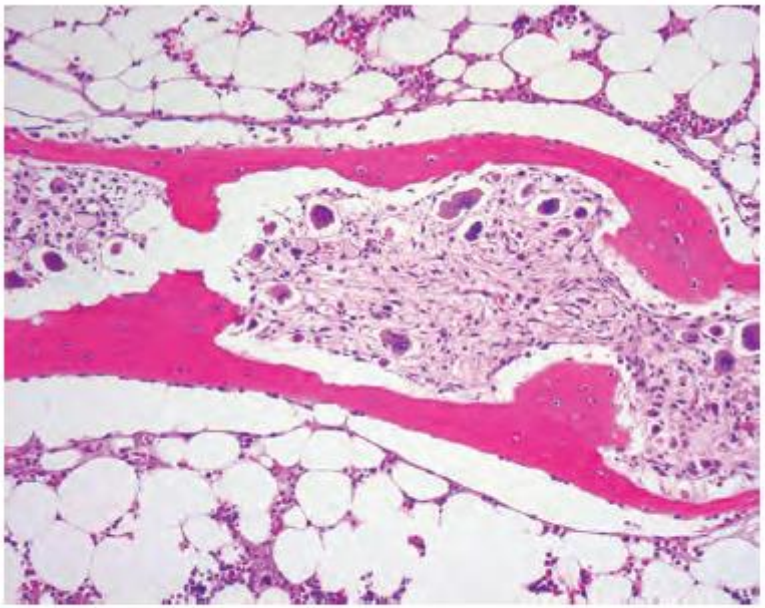


Figure 26-15 Hyperparathyroidism with osteoclasts boring into the center of the trabeculum (dissecting osteitis).

Osteodystrophy

- High-turnover osteodystrophy is characterized by increased bone resorption and bone formation, with the former predominating.
- Low-turnover or aplastic disease is manifested by adynamic bone (little osteoclastic and osteoblastic activity) and, less commonly, osteomalacia.
- Mixed pattern of disease with areas of high turnover and low turnover.

Renal osteodystrophy

- Osteopenia and osteomalacia may be seen as well in chronic renal failure
- Metabolic acidosis leads to demineralization of hydroxyapatite
- Renal tubular dysfunction as well as diminished glomerular filtration leads to hyperphosphatemia and hypocalcemia.
- Levels of PTH are elevated (secondary)
- Inadequate vitamin D conversion to active form as α_1-hydroxylase depressed. Diminished calcium absorption from intestinal tract results as well as depressing RANKL on osteoblasts.

Osteodystrophy

- BMP-7, produced by renal renal tubular cells, induces osteoblast differentiation and proliferation, whereas FGF-23, made by osteocytes, acts on the kidney to regulate phosphate homeostasis and vitamin D production, which are dependent on production of membrane bound Klotho in the kidney.

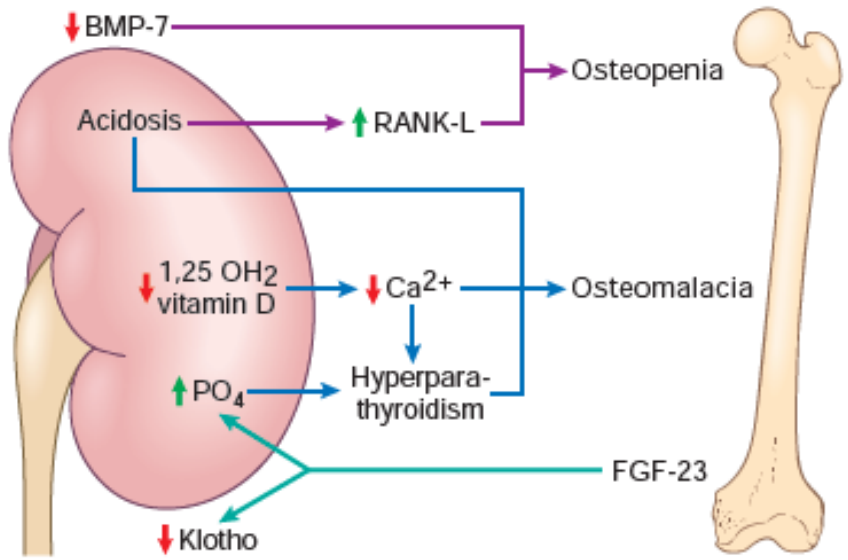
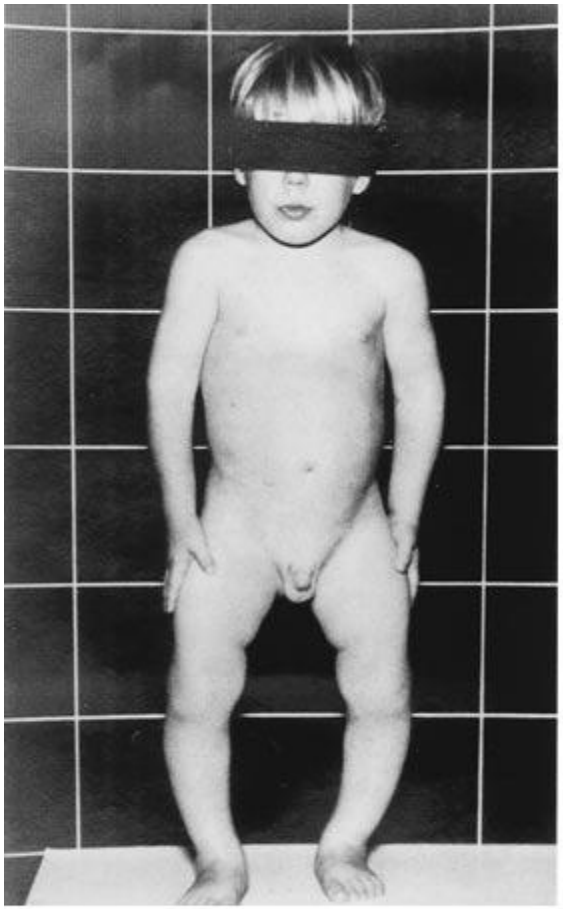


Figure 26-17 Mechanisms of renal osteodystrophy involves electrolyte levels and endocrine signaling between bone and kidney.

Rickets

- Inadequate levels of Vitamin D.
- Impaired Calcium absorption.
- In children, the impairment of mineralization is noted most at the growth plate.
- Poor bone formation.
- Unable to cope with stress on bones; bowing.
- In the adult, this is called osteomalacia.

Rickets



(Photograph courtesy of Dr. Sara Arnaud.)

Fig. 9-28 Accessed 07/01/2010

Osteonecrosis

- Most cases of bone necrosis stem from fractures or corticosteroid administration.
- Medullary infarcts are geographic and involve the trabecular bone and marrow.
- The cortex is usually not affected because of its collateral blood flow.
- In subchondral infarcts, a triangular or wedge-shaped segment of tissue that has the subchondral bone plate as its base undergoes necrosis.
- The overlying articular cartilage remains viable, as it can access nutrients that are present in synovial fluid.

Osteonecrosis

- Subchondral infarcts cause pain that is initially associated only with activity but then becomes constant as secondary changes supervene.
- Subchondral infarcts often collapse and may lead to severe, secondary osteoarthritis.
- Medullary infarcts are usually small and clinically silent
- Exceptions: Gaucher disease, dysbarism ("bends"), and sickle cell anemia.

Table 26-5 Conditions Associated with Osteonecrosis

Alcohol abuse
Bisphosphonate therapy (especially jawbones)
Connective tissue disorders
Corticosteroid administration
Chronic pancreatitis
Dysbarism (the "bends")
Gaucher disease
Infection
Pregnancy
Radiation therapy
Sickle cell crisis (Chapter 14)
Trauma
Tumors

Osteonecrosis

- Microscopically, dead bone is recognized by empty lacunae surrounded by necrotic adipocytes that frequently rupture and form insoluble calcium soaps that may persist.
- In the healing response, osteoclasts resorb the necrotic trabeculae. Trabeculae that remain act as scaffolding for the deposition of new bone (creeping substitution).
- In subchondral infarcts the pace of this substitution is too slow to be effective, so there is collapse of the necrotic bone and distortion, fracture, and even sloughing of the articular cartilage.

Figure 26-19 Femoral head with a subchondral, wedge-shaped pale yellow area of osteonecrosis. The space between the overlying articular cartilage and bone is caused by trabecular compression fractures without repair.

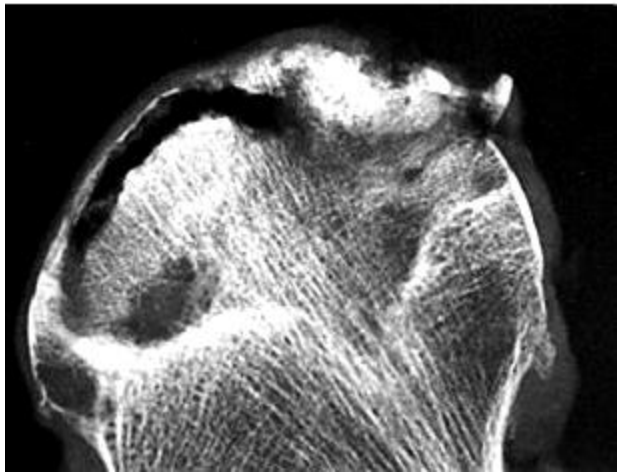
Avascular necrosis

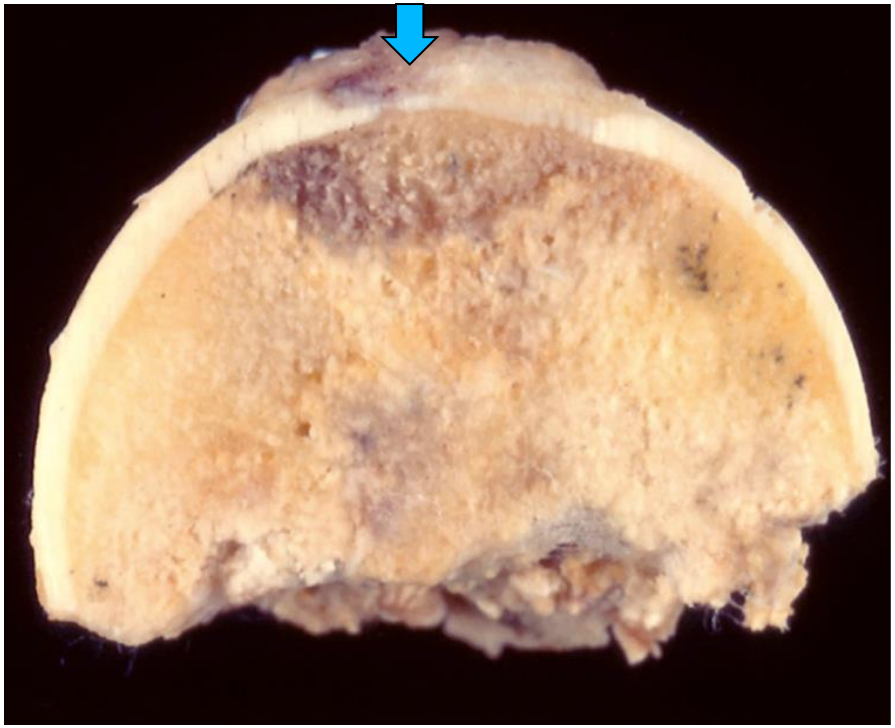
- Osteonecrosis
- Affects any bone
- Tibial tuberosity (Osgood-Schlatter's disease)
- Proximal femoral epiphysis (Legg-Calve'-Perthes disease)
- > 50% of cases are multifocal
- Causes 10% of joint replacements
- Significant cause of arthritis due to fractures through articular surface of hip, knee and other major joints
- Also due to collapse of necrotic bone segment, detachment of cartilage and secondary degenerative joint disease

Avascular necrosis

- Pathophysiology:
- Initially necrosis of epiphysis, with variable necrosis of adjacent cartilage
- Dead bone is resorbed. Dead trabeculae that are not resorbed by osteoclasts serve as scaffolds for deposition of new living bone (creeping substitution)
- New bone is soft, may flatten and cause degenerative joint disease

Dead bone





http://www.pathologyoutlines.com/topic/boneasepticbonenecrosis.html

Osteomyelitis

- Inflammation of bone and marrow secondary to infection
- Arise from:
- (1) Hematogenous spread
- (2) Extension from a contiguous site
- (3) Direct implantation
- Usually pyogenic

Osteomyelitis

- Hematogenous osteomyelitis may manifests as an acute systemic illness
- Malaise, fever, chills, leukocytosis
- Marked-to-intense throbbing pain over the affected region.
- Else, there may be only unexplained fever (most often in infants) or localized pain (most often in adults).

Osteomyelitis

- Usually long tubular bones of children
- Involvement of flat bones is more common in adults
- In elderly, vertebral column
- In diabetics, the small bones of the feet
- 80% of cases with known organisms are due to Staphylococcus aureus
- Produces receptors to bone matrix components

Osteomyelitis

- Sickle cell patients may have infections by Salmonella species
- Neonates are prone to Treponema (periostitis), gram negative rods, Group B Streptococci, Hemophilus influenzae and Listeria species
- Post-traumatic cases are usually Pseudomonas

Osteomyelitis

- Escherischia coli, Pseudomonas aeruginosa, and Klebsiella species isolates in those with genitourinary infections or with venous access.
- In neonates, Hemophilus B and Streptococcus pneumoniae are common.
- Salmonella is generally found in those with sickle cell disease.

Osteomyelitis

- In the neonate the metaphyseal vessels penetrate the growth plate, resulting in frequent infection of the metaphysis, epiphysis, or both.
- In children, localization of microorganisms in the metaphysis is typical.
- After growth plate closure, the metaphyseal vessels reunite with their epiphyseal counterparts and provide a route for the bacteria to seed the epiphyses and subchondral regions.

Osteomyelitis

- In the acute phase, bacteria proliferate and induce a neutrophilic inflammatory reaction.
- Necrosis of bone cells and marrow ensues within the first 48 hours.
- The bacteria and inflammation spread longitudinally and may percolate throughout the Haversian systems to reach the periosteum.
- In children the periosteum is loosely attached to the cortex. May separate.

Osteomyelitis

- Lifting of the periosteum further impairs the blood supply to the affected region, contributing to the necrosis.
- Leads to "sequestrum"
- Rupture of the periosteum leads to a soft tissue abscess which can channel to the skin as a draining sinus.
- If the sequestrum crumbles, fragments are released that pass through the sinus tract.

Osteomyelitis

- After the first week, chronic inflammatory cells release cytokines that stimulates osteoclastic bone resorption, ingrowth of fibrous tissue, and the deposition of reactive bone at the periphery.
- The newly deposited bone can form a shell of living tissue, ("involucrum"), around the segment of devitalized infected bone.
- Sclerosing osteomyelitis of Garré typically develops in the jaw and is associated with extensive new bone formation that obscures much of the underlying osseous structure.

Chronic osteomyelitis

- Sequestrum
- Dead piece of bone gradually separated from living bone by granulation tissue
- May pass through sinus tract
- Avascular and dense on X-ray
- Involucrum
- Sleeve of living tissue created by periosteum which is deposited around sequestrum
- Chronic osteomyelitis develops in 15-30%
- Usually inadequate therapy or surgery

Osteomyelitis

- In infants, epiphyseal infection spreads through the articular surface or along capsular and tendo-ligamentous insertions into a joint, producing septic or suppurative arthritis, which can cause destruction of the articular cartilage and permanent disability.
- In the vertebrae, the hyaline cartilage end plate and intervertebral disc are destroyed

Osteomyelitis

- Brodie abscess:
- Small intraosseous abscess in cortex, walled off by reactive bone with no periosteal reaction
- Cavity may contain infectious organisms or be sterile
- May have late recrudescence
- May develop sinus tract lined by squamous epithelium that forms large epidermal inclusion cyst within bone
- Rarely transforms to well differentiated squamous cell carcinoma

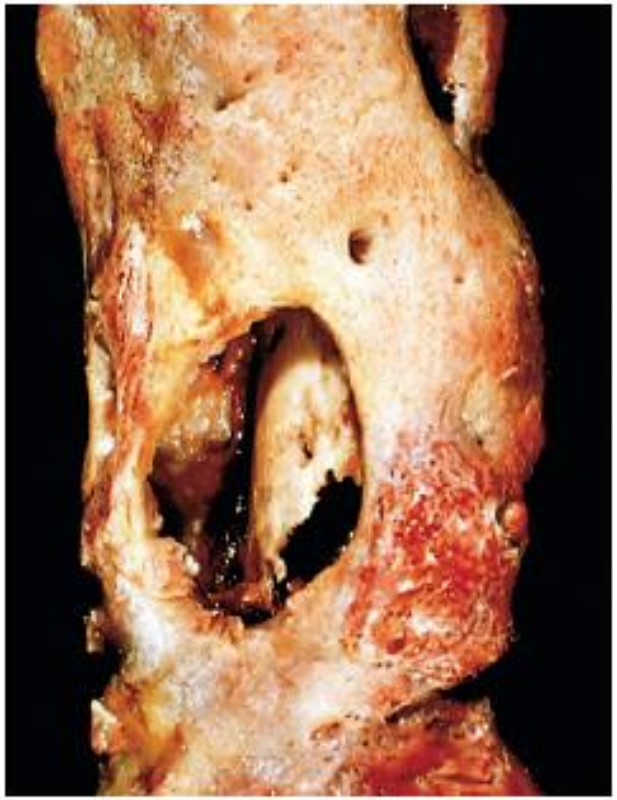
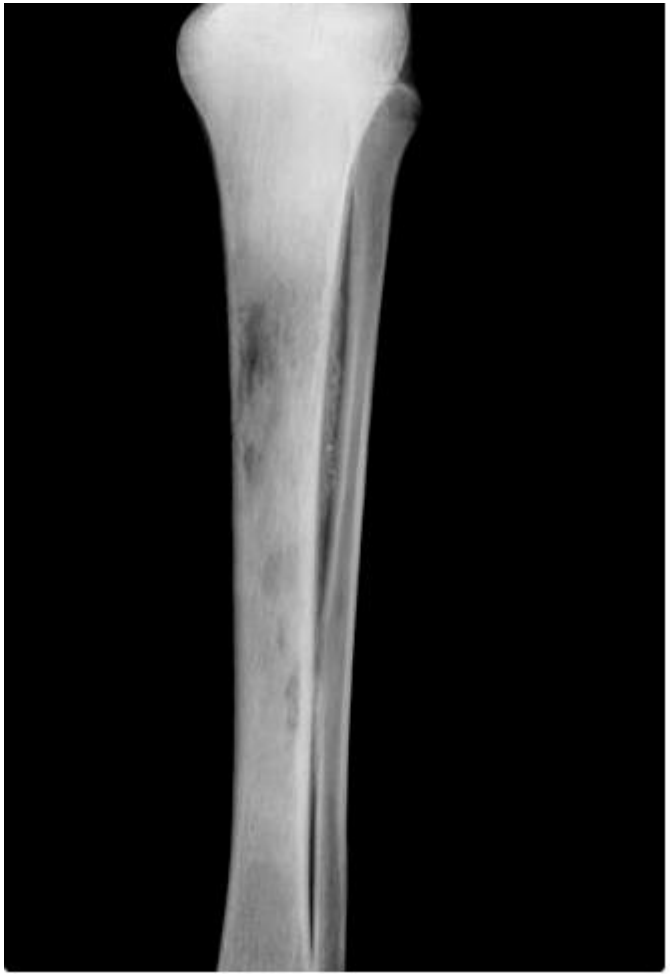
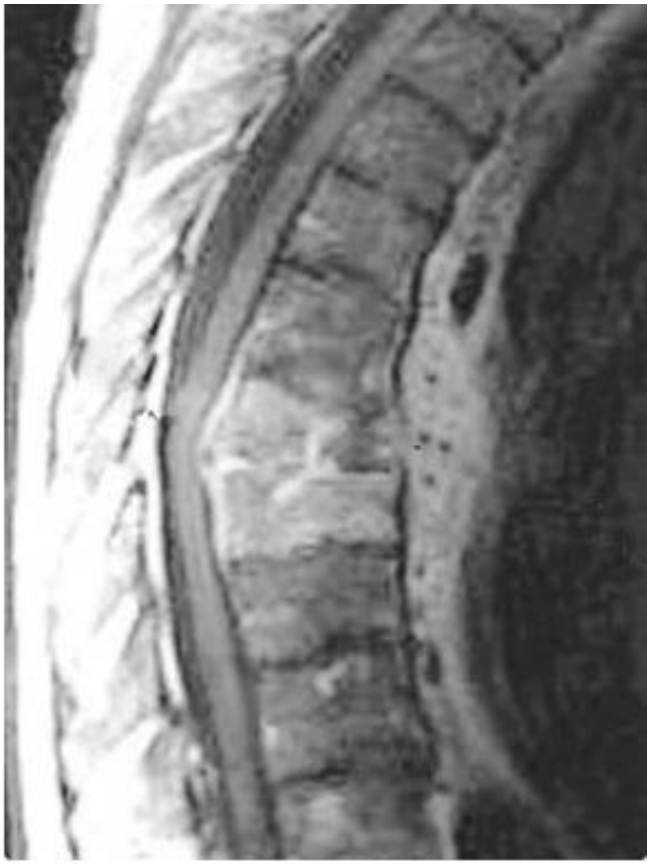


Figure 26-20 Resected femur in a person with draining osteomyelitis. The drainage tract in the subperiosteal shell of viable new bone (involucrum) reveals the inner native necrotic cortex (sequestrum).

Osteomyelitis

- 5% to 25% of cases persist as chronic infection.
- Spontaneous flare-ups
- Pathologic fracture
- Secondary amyloidosis as sequel
- May develop squamous carcinoma in draining sinus.





http://www.pathologyoutlines.com/topic/bonebacterialosteomyelitis.html

Mycobacterial osteomyelitis

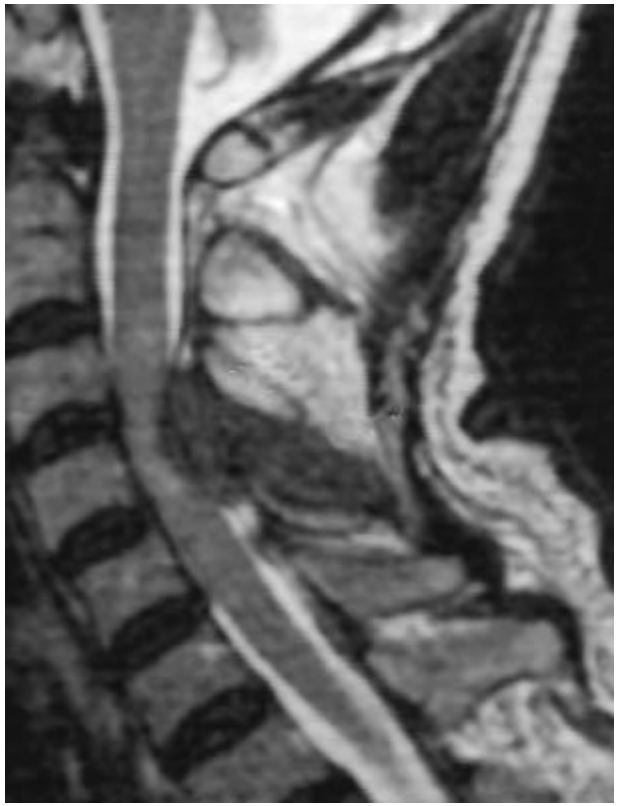
- Usually young adults or children
- Usually from focus of acute visceral disease, direct extension or lymphatics
- Thoracic or lumbar vertebrae, hip, knee, ankle, elbow, wrist
- Usually involves synovium, epiphysis or metaphysis
- Associated with fusion of joint, denudation of cartilage, sequestra of medullary cavity
- Advanced cases are associated with cutaneous sinuses

Mycobacterial osteomyelitis

- Pott's disease
- The spine is involved in 40% of cases.
- The infection breaks through intervertebral discs to affect multiple vertebrae and extends into the soft tissues.
- Destruction of discs and vertebrae frequently results in permanent compression fractures that produce scoliosis or kyphosis and neurologic deficits secondary to spinal cord and nerve compression.

Mycobacterial osteomyelitis

- May present with pain on hip flexion (psoas abscess).
- Rarely causes inguinal mass
- Caseating granuloma found

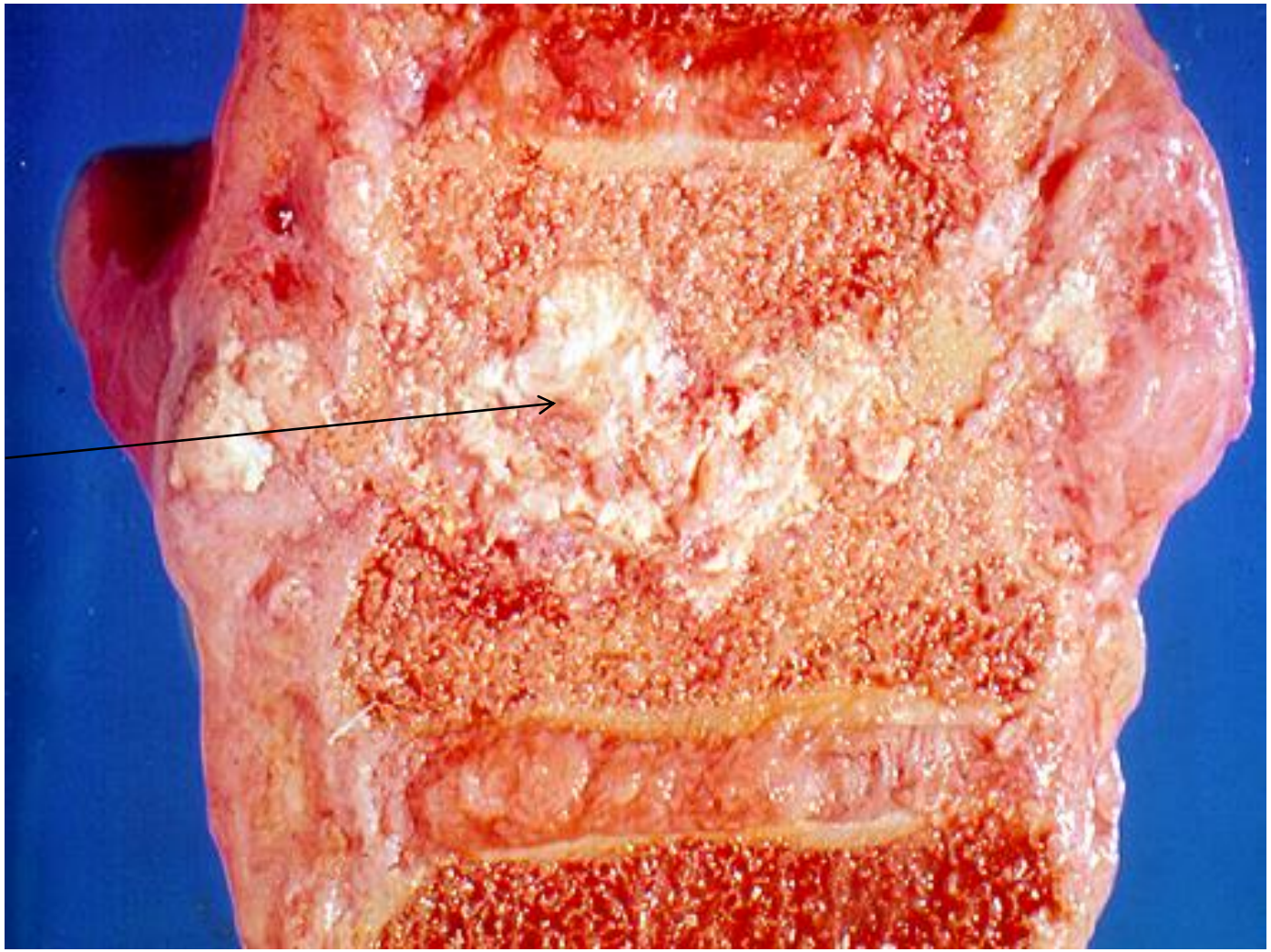


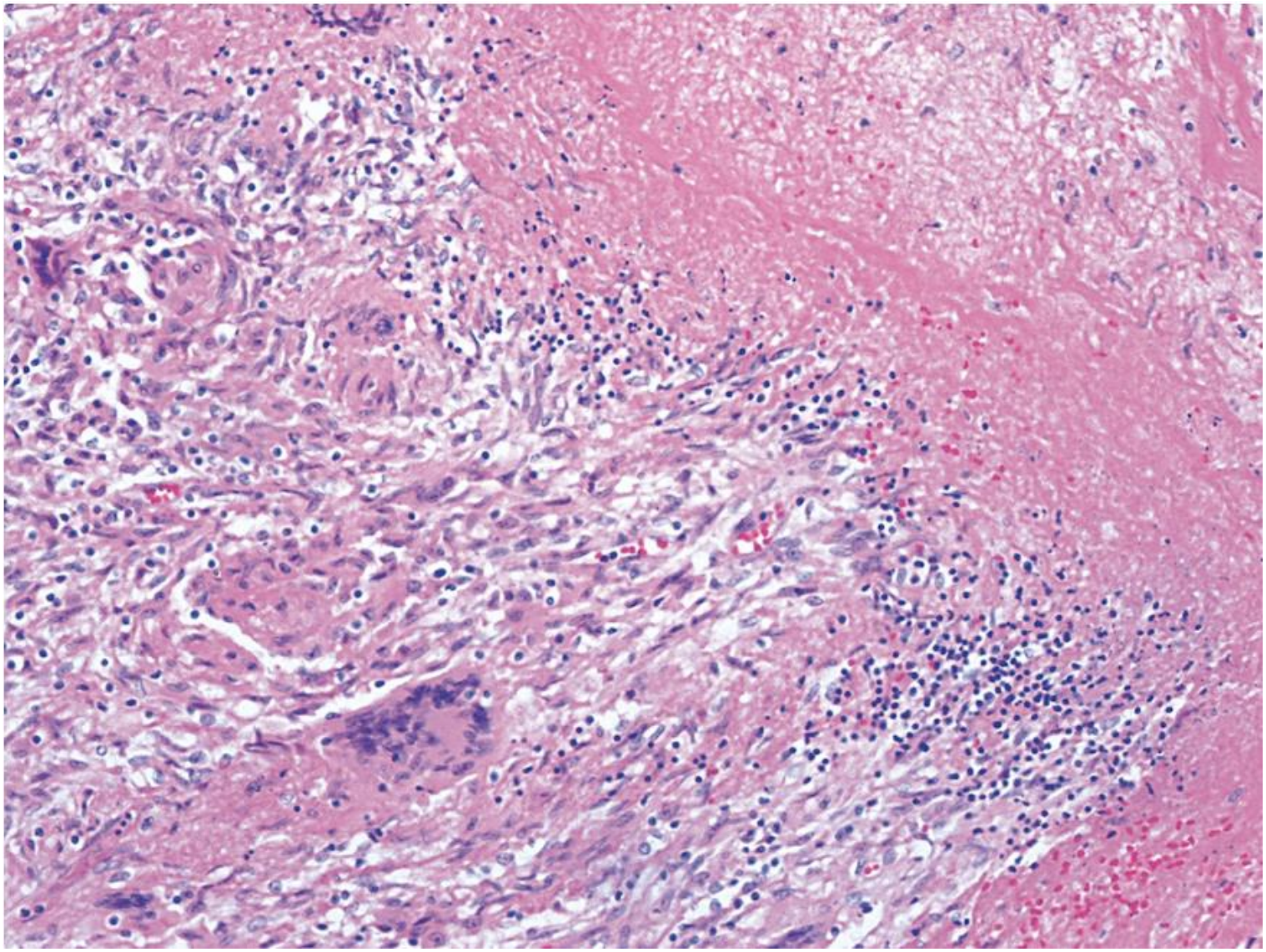
Cervical vertebrae
Paraspinal tuberculous abscess
MRI

http://www.pathologyoutlines.com/wick/bone%20cervical%20vertebrae%20paraspinal%20tuberculous%20abscess%20mri.jpg

Tuberculosis

Caseous necrosis





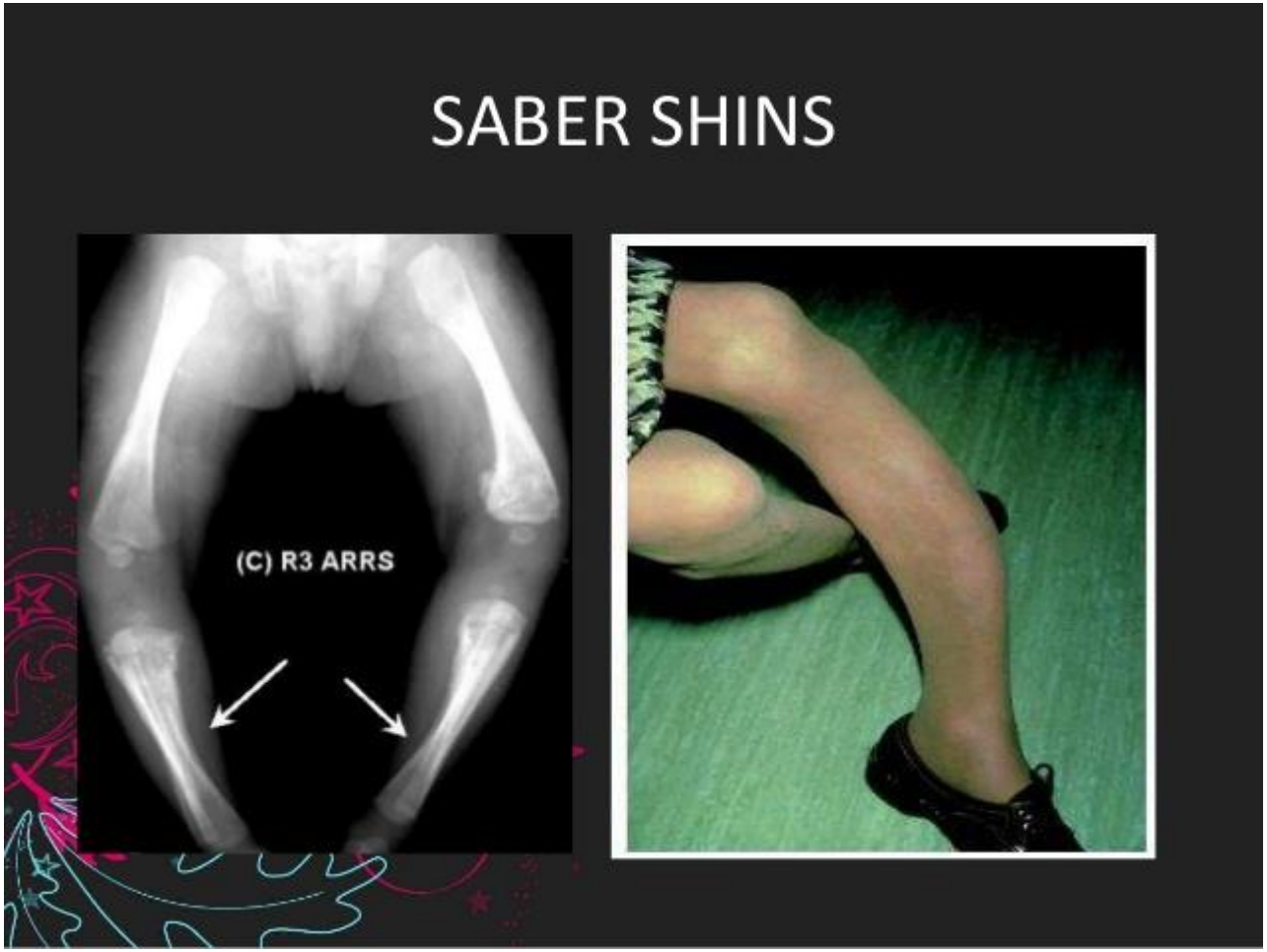
http://www.pathologyoutlines.com/topic/boneTBosteo.html

Treponemal osteomyelitis

- Syphilis and Yaws
- In congenital syphilis, the bone lesions appear about the fifth month of gestation and are fully developed at birth.
- The spirochetes tend to localize in areas of active enchondral ossification (osteochondritis) and in the periosteum (periostitis).

Treponemal osteomyelitis

- The syphilitic saber shin is produced by massive reactive periosteal bone deposition on the medial and anterior surfaces of the tibia.
- Nose, palate, skull, and extremities, especially the long tubular bones, are involved in acquired syphilis (tertiary).



https://image.slidesharecdn.com/syphilis-160905101330/95/syphilis-31-638.jpg?cb=1473070522

Treponemal osteomyelitis

- Syphilitic bone infection is characterized by edematous granulation tissue containing numerous plasma cells and necrotic bone.
- The spirochetes can be demonstrated in the inflammatory tissue with silver histochemical stains or immunohistochemistry.
- Typical gummas may also form in both congenital and acquired syphilis

Mucopolysaccharidoses

- Enzyme deficiency is generalized.
- Autosomal recessive except for Hunter's (X-linked).
- Most are not apparent at birth. May present in both severe and mild forms (mildest is Scheie).
- Some result in corneal clouding (Hurler, Scheie, Sly).

Mucopolysaccharidoses

- Defects in the degradation of keratan sulfate and dermatan sulfate cause skeletal deformities and other connective tissue abnormalities.
- Only defects in heparan sulfate degradation cause mental retardation and neurological degeneration.
- Chondroitin sulfate and hyaluronic acid do not accumulate because they have an alternative pathway of degradation.

Mucopolysaccharidoses

- Hurler's syndrome. MPS I H.
- Allelic with Scheie's syndrome. MPS I S.
- Both are autosomal recessive.
- α-L-iduronidase deficiency. Affects degradation of heparan sulfate and dermatan sulfate.
- Dwarfism. Mental retardation. Corneal clouding. Deposition of mucopolysaccharide in coronary arteries leads to ischemia and death before age 10.
- Scheie's syndrome presents with corneal clouding, aortic valve disease. Normal intelligence. Normal life span.

Mucopolysaccharidoses

- Hunter's syndrome. MPS II.
- X-linked recessive.
- Iduronate sulfatase deficiency. Affects degradation of heparan sulfate and dermatan sulfate.
- Mental retardation. No corneal clouding. Death by 15 years of age.
- Sly's syndrome. MPS VII.
- Autosomal recessive.
- β-glucoronidase deficiency. Affects degradation of heparan sulfate and dermatan sulfate.
- Hepatosplenomegaly.

Mucopolysaccharidoses

- Sanfillipo's syndrome. MPS III.
- Autosomal recessive.
- Four enzymatic steps required to remove N-sulfated or N-acetylated glucosamine residues from heparan sulfate. Heparan sulfate affected.
- Type A. Heparan sulfase deficiency.
- Type C. N-acetyltransferase deficiency.
- Type B. N-acetylglucosaminodase deficiency.
- Type D. N-acetylglucosamine deficiency.
- Mental retardation. Severe nervous system disorders.

Mucopolysaccharidoses

- Morquio syndrome. Type IV.
- Autosomal recessive.
- Type A. Galactose-6-sulfatase deficiency.
- Type B. β-galactosidase deficiency.
- Keratan sulfate affected.
- Skeletal deformities, corneal clouding, normal intelligence.

Mucopolysaccharidoses

- Maroteaux-Lamy. Type VI.
- Autosomal recessive.
- N-acetylgalactosamine-4-sulfatase deficiency. Dermatan sulfate affected.
- Skeletal deformities, corneal clouding, normal intelligence.