The first two pages are recap and explanations NOT in the slides
Black: slides (slightly modified/rearranged for better comprehension)
Blue: modified/notes/comments
Purple: extra information, NOT required, any photo labeled with a purple star is from an external source, added for context / feed personal curiosity, or for board exams (STEP 1)

Pathology of the MSS
Lectures 1&2:

Before we start let us recap some cell biology.

Main two bone cells

Osteoblasts: cells that synthesize the bone matrix, once these cells are buried in the bone matrix, they become **Osteocytes** (they control local calcium & phosphate levels)

Osteoclasts: specialized macrophages that are derived from circulating monocytes they secrete $\mathbf{H^+}$ & **proteases** thus dissolve bone matrix

The point is that our bones constantly undergo "remodeling" where osteoclasts break it down and osteoblasts remake it up it is NOT a *static* structure.
Osteoclasts' activity is modulated by signals from osteoblasts, some stimulatory and others limiting.

The **Bone Matrix**: extracellular material of the bone, synthesized by osteoblasts, made up of Type I collagen, hydroxyapatite.

It is made in the following steps:

1) Firstly, it is synthesized as **osteoid** which is non-mineralized bone matrix made mostly of proteins (by osteoblasts)
2) Then it's mineralized with calcium/phosphate → Relevant to bone disorders / tumors

Important signals and receptors:

-RANK (receptor activating nuclear factor κβ):
It is a receptor expressed on osteoclasts, when a ligand binds to this receptor it synthesizes NF-κβ (hence the name of the receptor) which stimulates the osteoclast.
-RANK-L (receptor activating nuclear factor κβ Ligand):
It binds RANK, expressed by osteoblasts.

So, when osteoblasts express more RANK-L they stimulate osteoclasts, this is one way in which osteoblasts can influence activity of osteoclasts, other ways include:

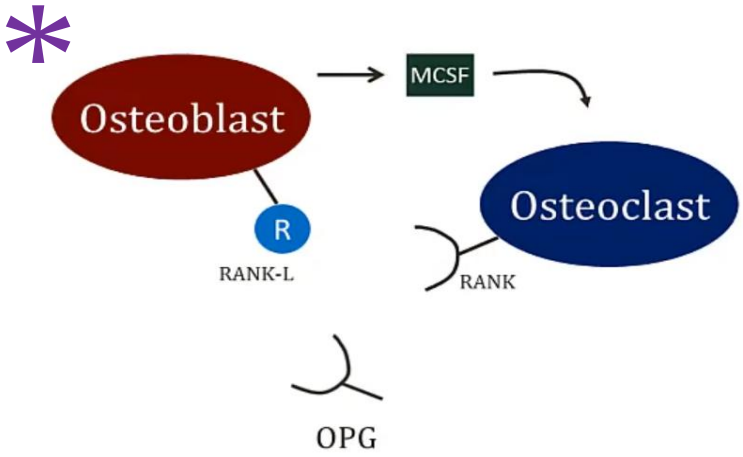
-Osteoprotegrin (OPG): it is made by osteoblasts and it is a decoy receptor, it binds to RANK-L thus prevents it from binding to RANK on osteoclasts (it competes with RANK in binding to the ligand)

-M-CSF (Macrophage colony stimulating factor): it is secreted by osteoblasts, stimulates osteoclasts.

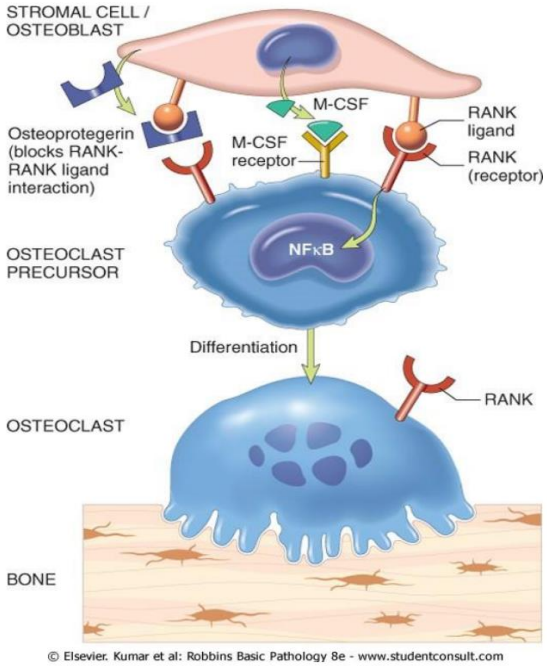
-**PTH**: directly stimulate osteoblasts, which indirectly activates the osteoclast (relevant to rickets and osteomalacia)

-**Estrogen**: close growth plate at puberty, ↑bone density (relevant to post-menopause) (induces osteoclast apoptosis, inhibits osteoblast apoptosis, ↓RANKL production, promote OPG expression)

Here's a picture that summarizes it nicely:



And this pic from the slides:

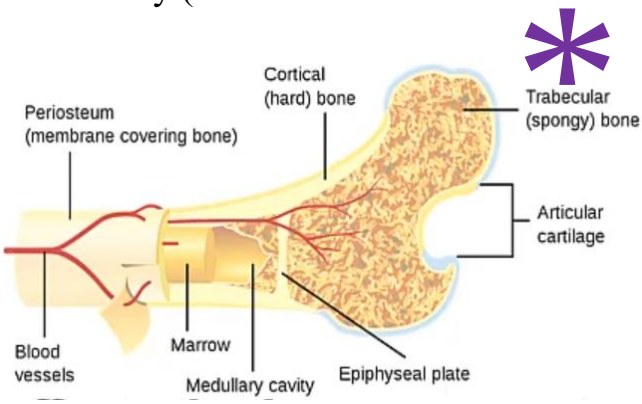


More RANK-L/M-CSF: more osteoclast activity
More OPG: less osteoclast activity

Bone is formed by:

1) **Endochondral ossification** (in long bones which develop from hyaline cartilage that is secreted from chondroblasts/cytes → creates "mold" which grows → chondrocytes die when mold grows → blood delivers osteoblasts) (diaphysis (primary center of ossification), epiphysis (2ry center of ossification), metaphysis, forms epiphyseal plate)

2) **Membranous ossification** (in flat bones, formed directly (not from cartilage) by osteoblasts which lay down **woven** bone (primary type of bone found in children/new born, it is weak) which is then remodeled to **lamellar** (layered, organized & strong bone)

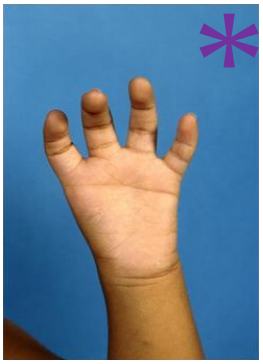


Alkaline environment is good for bone formation.
Acidosis is bad for bone formation (stimulates osteoclasts, may cause hypercalcemia, osteoporosis or reduced mineral density relevant in osteopetrosis)

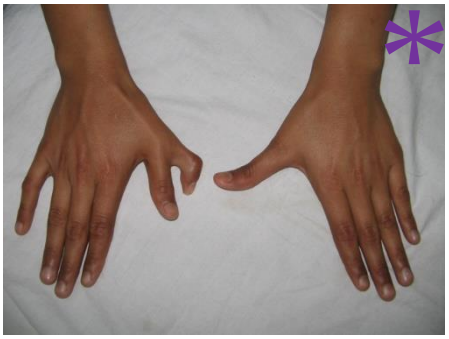
Congenital disorders of the bone:

▪ **1) Dysostosis** خلل العظم: localized abnormal bone formation
▪ Failure of migration and condensation of mesenchyme (something went wrong during growth and development of mesenchyme) which is the embryonic connective tissue that give rise to many tissues including bones.
▪ Examples:

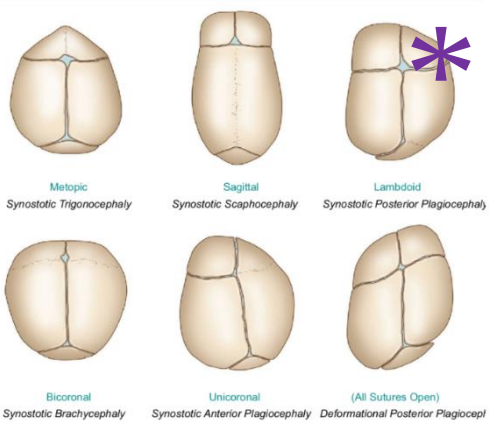
1) Aplasia: absence of bone or digit (missing finger for example (4 instead of 5))
2) Supernumerary digits or ribs (an additional finger or toe)
3) Craniosynostosis & Syndactyly: abnormal fusion of bones
   Craniosynostosis: an abnormality in the sutures of the skull that affects the brain growth.
   Syndactyly: Fusion of the fingers



Aplasia



Supernumerary digits



Different types of Craniosynostosis

Syndactyly

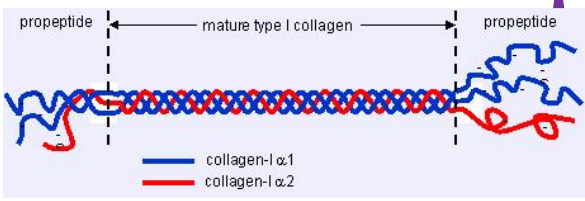
▪ Dysostosis results from mutations in homeobox genes, cytokines or cytokine-receptors genes.

2) Bone Dysplasia: (does NOT mean pre-neoplastic/pre-malignant as we took last semester) instead it means abnormal pattern of growth
▪ Generalized abnormality affecting the whole skeleton
▪ Basic pathology of the disorder is: disorganization of bone and/or cartilage
▪ Mutation occurs in genes that control development or remodeling of the entire skeleton (usually a point mutation)

Examples of bone dysplasia:

1) Osteogenesis imperfecta:

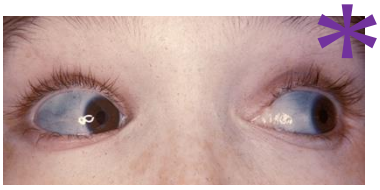
Recall structure of collagen *



- Most common inherited disorder of connective tissue
- Mutation in type I collagen gene, protein becomes defective & is prematurely degraded
- Different types of mutations, each variable in severity, may affect α1/α2 subunits
- Bone matrix amount is too little, results in bone fragility, deformity

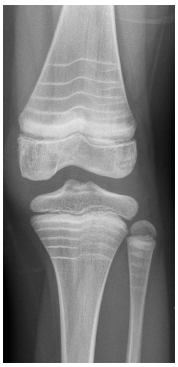
Symptoms:

- Skeletal deformity
- Repeated fractures
- Skin, joints & eyes are affected (blue sclera)
- Hearing loss (conduction defects in the middle and inner bones)
- Small misshapen teeth are a result of dentin deficiency
- Type I: most common, normal life expectancy
- Type II: severest, death early in life or in utero (severe fractures)



Blue sclera (blue tint in eyes) -an osteogenesis imperfecta manifestation (Why?? due to exposure of the choroidal veins *a high yield board question)

"cyclical bisphosphonate therapy"
Radiological sign → Metaphyseal lines of increased density "Zebra lines"



2) Achondroplasia:

- Most common skeletal dysplasia
- Major cause of dwarfism
- Autosomal dominant transmission (this means only 1 copy of the genes is required for disease)
- 90% of cases represent new acquired mutation, mostly from the paternal side

Pathogenesis:

- Point mutation in the **FGFR3** (fibroblast growth factor receptor 3) that results in permanent activation of the receptor
- Activated FGFR3 inhibits chondrocyte proliferation (defective **endochondoral ossification**); as a result, the normal epiphyseal growth plate of long bones is suppressed
- Patients have normal head and trunk (recall these are mostly flat bones that form by **membranous ossification** so they're not affected) but short bowing limbs (long bones)
- Normal life expectancy and mental function

Similar pathogenesis is seen in:
Hunter's and Hurler's syndromes:
The body is unable to metabolize heparan & dermatan sulfate which leads to the accumulation of mucopolysaccharides leading to the death of chondrocytes

3) Thanatrophic dysplasia:

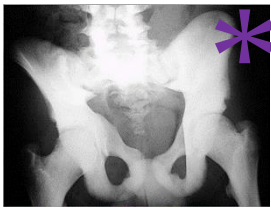
- A lethal form of dwarfism
- FGFR3 mutation, but MORE increase in signaling activity
- Short limbs, frontal bone bossing (an unusually prominent forehead), microcephaly, small chest, belly-like abdomen
- Die at birth or shortly after

Osteopetrosis: تصخر العظم

- Marble-like bone
- Rare genetic disorders characterized by reduced osteoclast-mediated bone resorption and therefore defective bone remodeling
- Bone shows diffuse symmetric sclerosis, yet can fracture easily (even tho it's abnormally thick and heavy)

Inheritance:

- Multiple variants based on both the mode of inheritance & severity of symptoms
- All variants share a problem in the acidification process of osteoclasts that is responsible for bone resorption
- Autosomal dominant variant is the mildest (makes sense)
- Repetitive fractures
- Cranial nerve deficits (due to thickening of foramen magnum, or due to hydrocephaly)
- Anemia
- Erlenmeyer-Flask deformity of long bones

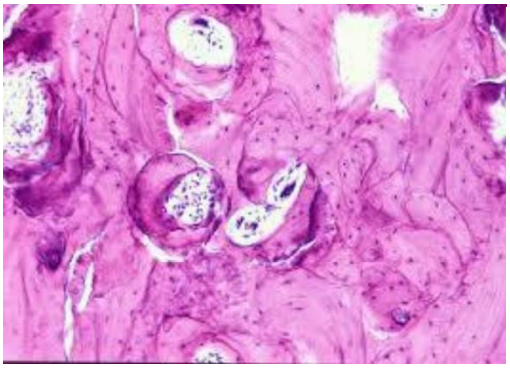


Very thick bone (white x-ray no black spaces)

Severe Infantile Osteopetrosis:

- Autosomal recessive
- Severe symptoms that appear early in life
- Leukopenia (a decrease in the total number of white blood cells)
- Hepatosplenomegaly (extramedullary hematopoiesis)
- Fatal

-Extra:
Treatment: bone marrow transplant



Osteopetrosis: markedly thickened bone trabeculae, marrow spaces are minimal.

(Doctor said it's hard to spot alone, it should be compared with normal bone histology image)

Osteopenia & Osteoporosis:
▪ Osteopenia: decreased bone mass
▪ Osteoporosis (OP): severe osteopenia that predisposes fracture.

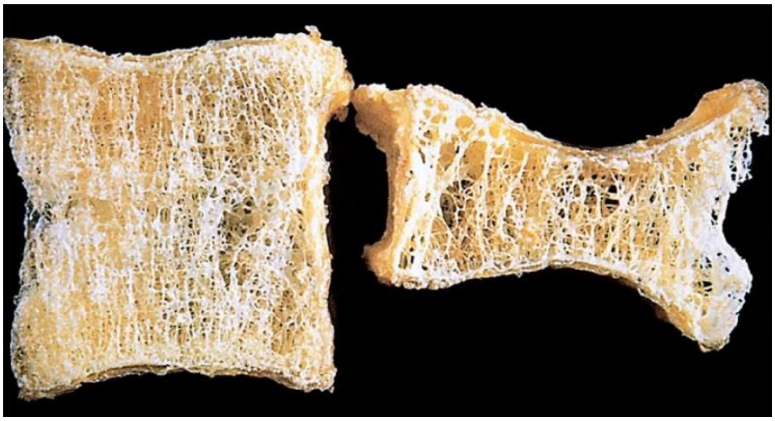
Radiologically:
▪ Osteopenia: bone mass is 1-2.5 standard deviation below mean normal
▪ Osteoporosis: <2.5 S.D. of normal bone mass
▪ Normally, maximum bone density is reached in second decade of life, then an annual loss of 0.7% of mass takes place
▪ Maximum mass depends on genetic factors, diet & exercise

Clinical types of Osteoporosis:
▪ Might be localized to certain bones (disuse of limbs)
▪ Generalized OP is mostly primary, seen in two settings:
A) Senile (aging)
B) Post-menopausal (estrogen drop)
▪ Secondary OP is rare, associated with:
A) Endocrine diseases (hyperthyroidism)
B) Gastrointestinal diseases (malnutrition)
C) Exposure to drugs (corticosteroid, heparin (which prevent thrombosis))

Senile OP: (low-turnover OP)
▪ Occurs due to:
1) Age-related cellular changes (low replication rate of cells, less biosynthesis)
2) Reduced physical activity (resistance training like weight lifting is better for bone health, but as people age they become more inclined to avoid such exercises and instead prefer endurance training such as walking "cardio")
3) Genetic factors: polymorphism in RANK, RANK-L, OPG, HLA & estrogen receptors
4) Calcium deficiency in adolescence (especially in girls) and vitamin D deficiency are risk factors for senile OP

Post-menopausal OP: (high-turnover OP)
▪ In normal conditions, estrogen: (reverse effects in post-menopausal as estrogen **DROPS**)
1) Inhibits osteoblast apoptosis 2) Increase osteoclast apoptosis
3) Inhibits RANKL (by suppressing cytokines)
▪ The rate of bone loss in postmenopausal women is 2% annually (compared to the normal 0.7%)
▪ For unknown reasons, estrogen deficiency causes increase in serum cytokines (IL-1, IL-6, TNF) which all activate RANKL

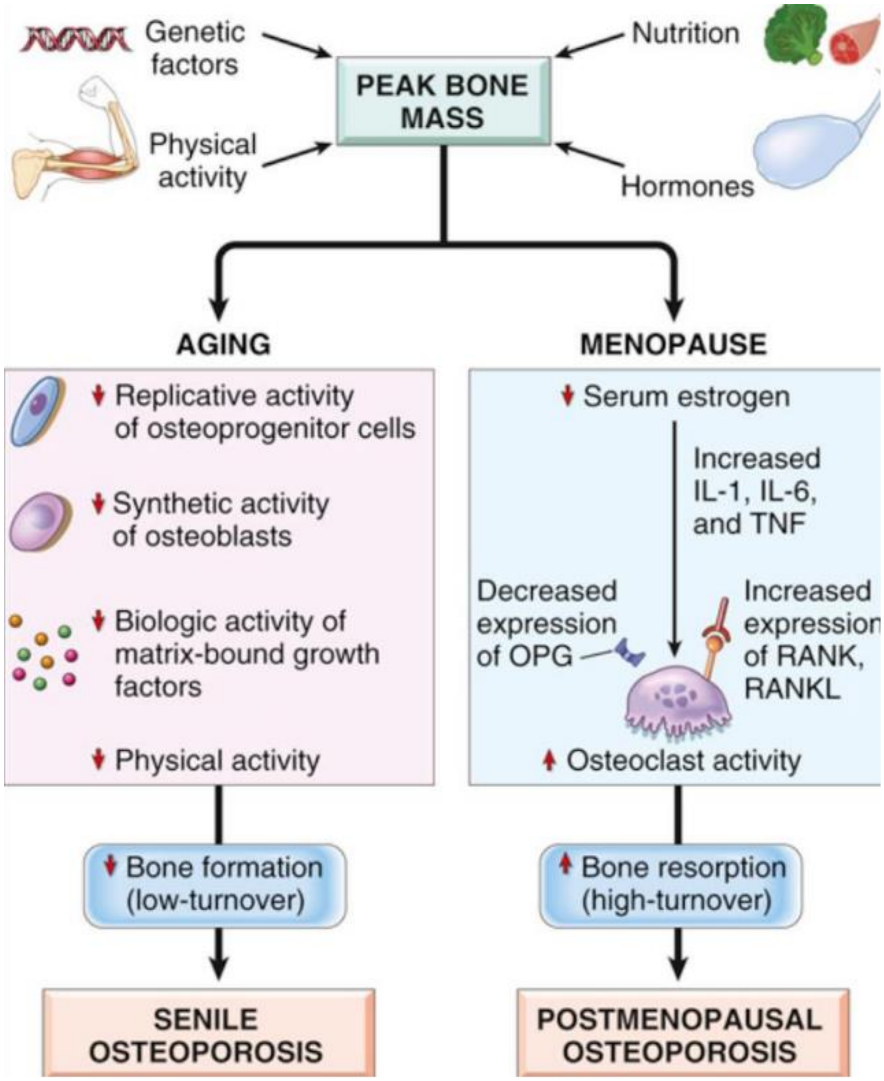
Morphology: Gross



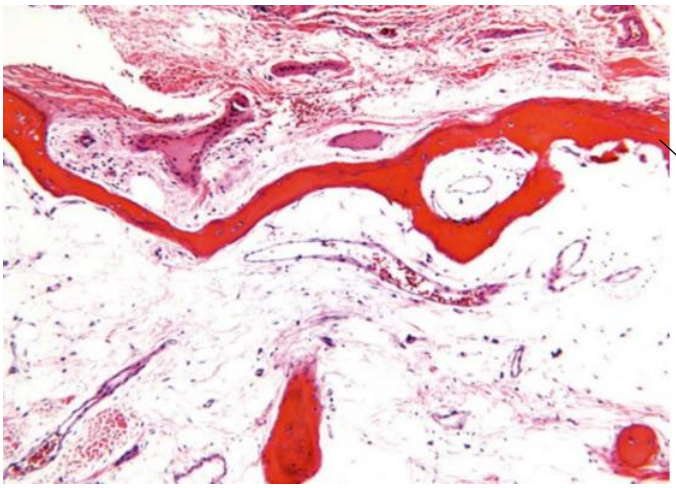
▪ Grossly: decreases interconnections, more porous

▪ Most prominent regions: cancellous bone of vertebrae, femur neck

An amazing summary pic from the slides:

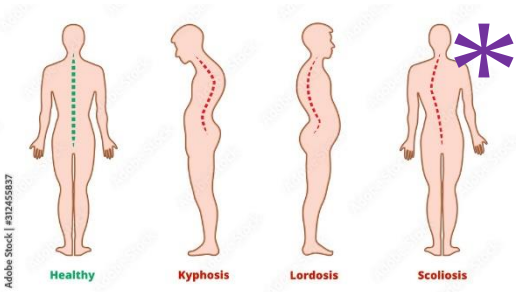


Morphology: Microscopic (histology)



▪ Normal morphology but less tissue

▪ Bone trabeculae becomes thin



Clinical complications:

▪ Fracture is painful, causes significant morbidity
▪ Fracture of spine causes deformity, lordosis, kyphoscoliosis
▪ Fracture of femur neck or pelvis may cause fat embolism, pneumonia
▪ A few patients are asymptomatic.

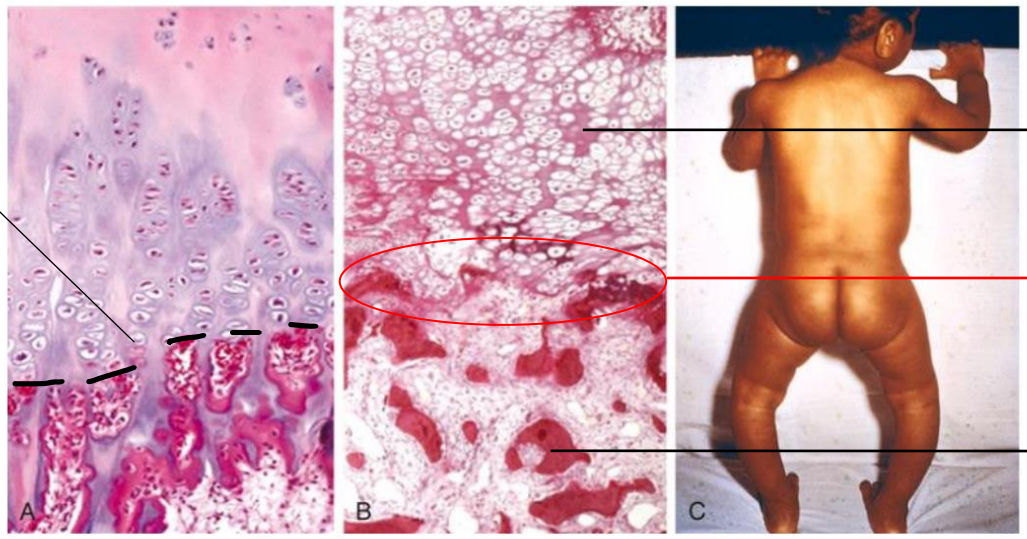
Rickets & Osteomalacia:

▪ Bone diseases secondary to vitamin D deficiency or its abnormal metabolism
▪ **Rickets**: occurs in children, abnormal deposition of bone in the growth plates
▪ **Osteomalacia**: occurs in adults, bone has less minerals, prone to fractures
▪ Vitamin D deficiency is caused by:
1) Limited sun exposure
2) Inadequate dietary vitamin D
3) Malabsorption disease
4) Renal disease (no or reduced conversion of vitamin D to its active form: 1,25-dihydroxyvitamin D)
▪ Vitamin D deficiency results in hypocalcemia which activates secretion of parathyroid hormone, aggravating bone resorption

*We mentioned this in the beginning (recap)

Rickets:

- Growth of long tubular bones occur through endochondoral ossification
- The cartilage of epiphyseal plate is provisionally mineralized, then reabsorbed and replaced by osteoid matrix, which undergo mineralization to create bone.
- In rickets, epiphyseal cartilage appears large & distorted due to inadequate calcification & failure of maturation, may protrude into bone marrow cavity.
- There is a disposition of osteoid matrix on this cartilage, but the replacement is disordered, and show lateral expansion of the osteochondral junction



- Rickets. (A) Normal costochondral junction of a young child. Note cartilage palisade formation and orderly transition from cartilage to new bone. (B) Rachitic costochondral junction in which the palisade of cartilage is absent. Darker trabeculae are well-formed bone; paler trabeculae consist of uncalcified osteoid. (C) Note bowing of legs as a consequence of the formation of poorly mineralized bone in a child with rickets.

Morphologic changes of Rickets:

Infants:

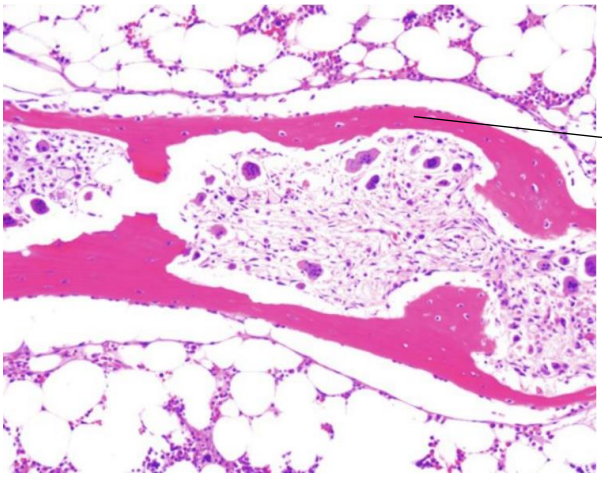
- Craniotabes: flattened soft skull bone
- Frontal bossing
- Chest deformity: Large costochondral junction appears as nodules. Inward bending of ribs due to pull of respiratory muscles and diaphragm (Harrison groove)

Toddlers:
▪ Deformity of pelvis, spines (lordosis)
▪ Bowing of lower limbs

Morphology of Osteomalacia:
▪ Grossly, bone has normal contour, but fragile
▪ Histologically: abundant osteoid matrix deposition, but appears eosinophilic (not mineralized), in contrast to normal basophilic osteoid (well-mineralized)

Hyperparathyroidism:
▪ PTH causes osteoclast activation, through increased RANKL expression on osteoblasts
▪ Increased reabsorption of calcium by renal tubules
▪ Increased urinary excretion of phosphates
▪ Increased synthesis of active vitamin D
▪ End result: generalized bone osteopenia, hypercalcemia & hypophosphatemia
▪ Small bones of phalanges, vertebra & proximal femur show the most prominent changes

Etiology:
▪ Mostly secondary to parathyroid gland adenoma (→ "primary hyperparathyroidism")
▪ Most cases are sporadic (in middle-aged adults)
▪ Sometimes syndromic (multiple endocrine neoplasia syndrome), appears in early life
▪ Secondary hyperparathyroidism: seen in patients with renal failure
(no active vitamin D → hypocalcemia → increased PTH)



Microscopic changes (histology):

▪Thin bone trabeculae (similar to **osteoporosis**)
▪ **Dissecting osteitis** (railroad appearance)
▪ **Brown tumor**: due to repeated microfractures, the bone marrow is replaced by macrophages. Fibroblasts, blood vessels & hemorrhage. Hemosiderin appears brown in color.
▪ **Osteitis fibrosa cystica**: an advanced stage where cysts & cavities develop.

Paget disease:

▪ Also called Osteitis Deformans

▪ Characterized by increase bone formation, that is disordered & abnormal

▪ Divided into 3 stages:

1) **Osteolytic stage**: repetitive episodes of severe, regional osteoclastic activity & bone resorption

2) **Mixed osteoclastic-osteoblastic stage**: exuberant bone formation

3) **Osteosclerotic stage**: apparent exhaustion of cellular activity
(exhausted osteoclast activity, continued osteoblast activity)

▪ The net effect of this process is gain in bone mass; however, the newly formed bone is disordered and lacks strength

▪ Does not occur until mid-adulthood but becomes progressively more common thereafter

▪ Most common in white populations (especially the British)

Pathogenesis:

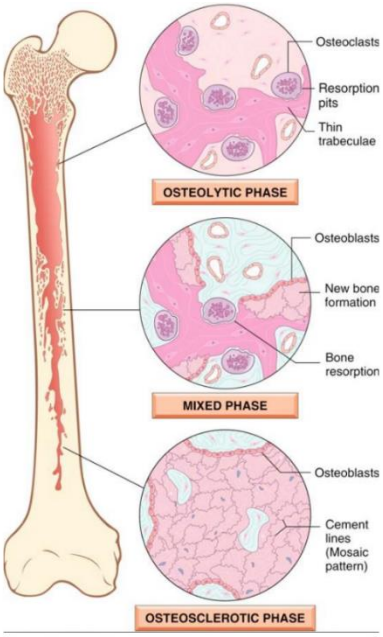
▪ Familial cases of Paget are present

▪ Sequestosome-1 mutation (SQSTM1) occurs in 50% of familial cases & 10% of sporadic cases

▪ It activates NF-κβ, which activates osteoclasts

▪ Activating mutations in RANK gene and inactivating mutations in OPG result in juvenile-onset Paget disease

▪ Environmental factors: osteoclasts precursors are infected by measles, paramyxovirus

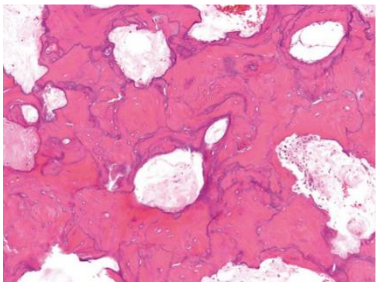


Microscopic findings:

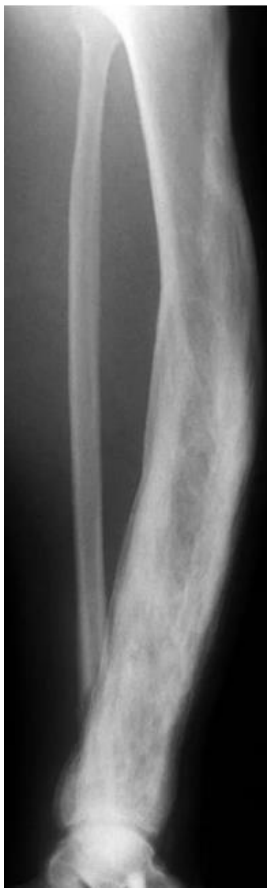
▪ Initial lytic phase: numerous large osteoclasts, some have >100 nuclei

▪Mixed phase: osteoclasts persist, osteoblasts increase in number

▪ Sclerotic phase: mosaic pattern & jigsaw-puzzle of lamellar bone



▪ Severe Paget disease.
The tibia is bowed.
The affected portion is
enlarged and sclerotic,
and it exhibits irregular thickening
of cortical and cancellous bone.



Clinical findings

▪ 85% are polyostotic, 15% monostotic
▪ Spine and proximal femur are involved in 80% of cases
▪ Most cases are asymptomatic (usually found by mistake, ex: x-ray for another reason)
▪ Localized pain is the most common symptom (microfracture, nerve compression)
▪ Leontiasis ossea (lion face): enlargement of craniofacial bones, heavy skull
▪ Platybasia: base of skull is flattened and compress against posterior fossa
▪ Bowing of femur and tibia, Secondary osteoarthritis
▪ Kyphosis, spinal cord injury
▪ Increased vascularity in bone: warm skin heart failure
(Can hear heart beats in bone due to increase vascularity)
▪ Secondary osteosarcoma

Leontiasis ossea: