MUSCULOSKELETAL BLOCK

PATHOLOGY

LECTURE 2:

CONGENITAL AND DEVELOPMENTAL BONE DISEASES

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Diseases of Bones

- Objectives
  - Be aware of some important congenital and developmental bone diseases and their principal pathological features
  - Be familiar with the terminology used in some important developmental and congenital disorders.
  - Understand the etiology, pathogenesis and clinical features of osteoporosis

Bone

- 206 bones
- organic matrix (35%) and inorganic elements (65%): calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]
- The bone-forming cells include osteoblasts and osteocytes, while cells of the bone-digesting lineage are osteoclasts
- is very dynamic and subject to constant breakdown and renewal: **remodeling**

Diseases of Bones

- Congenital
- Acquired
  - Metabolic
  - Infections
  - Traumatic
  - Tumors

Congenital Diseases of Bones

Localized or entire skeleton

- Dysostoses: e.g.
  - *aplasia*
  - extra bones
  - abnormal fusion of bones

Developmental anomalies resulting from localized problems in the migration of mesenchymal cells and the formation of condensations

- Dysplasias: e.g.
  - Osteogenesis imperfecta
  - Achondroplasia
  - Osteopetrosis

Mutations that interfere with bone or cartilage formation, growth, and/or maintenance of normal matrix components

Osteogenesis imperfecta

Congenital Diseases of Bones

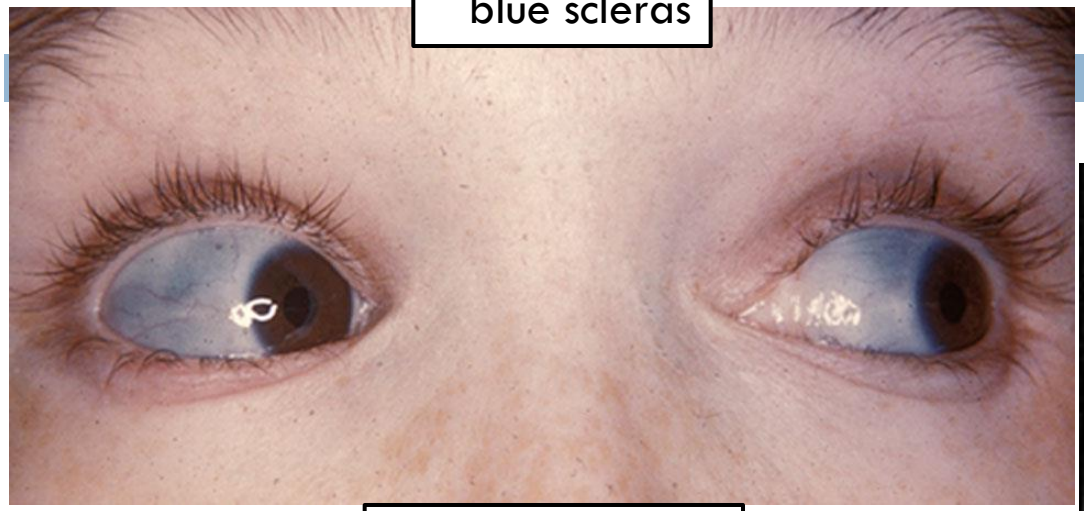
Osteogenesis imperfecta

(brittle bone disease)

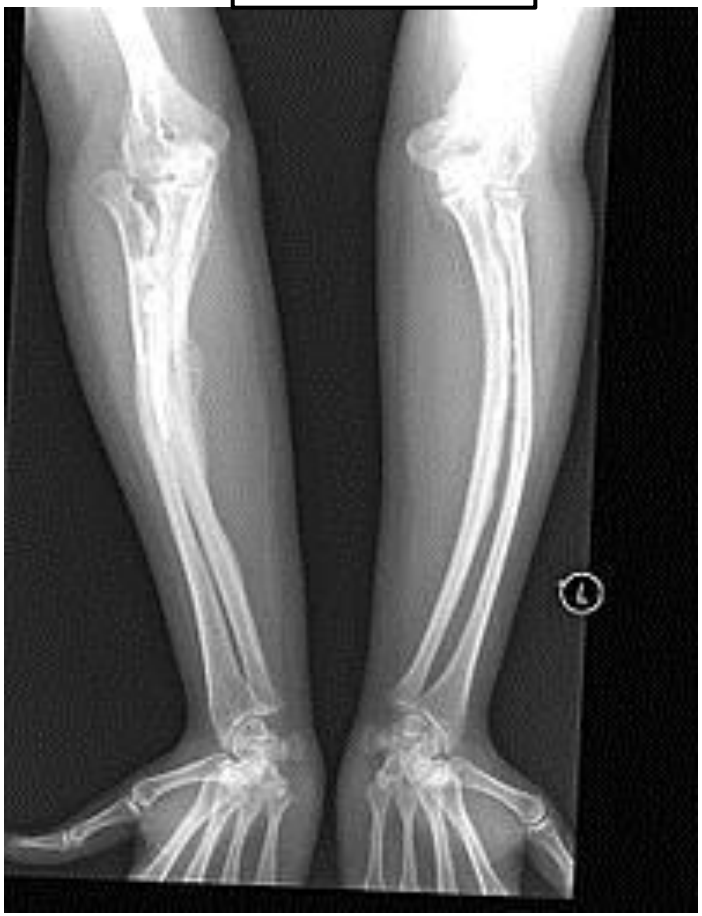
- Osteogenesis imperfecta is a group of inherited diseases characterized by brittle bones
- Defect in the synthesis of type I collagen leading to too little bone resulting in extreme skeletal fragility with susceptibility to fractures
- Four main types with different clinical manifestations classified according to the severity of bone fragility, the presence or absence of blue scleras, hearing loss, abnormal dentition, and the mode of inheritance, some are fatal.
  - Type 1: blue sclera in both eye, deformed teeth and hearing loss

Osteogenesis imperfecta, type 1

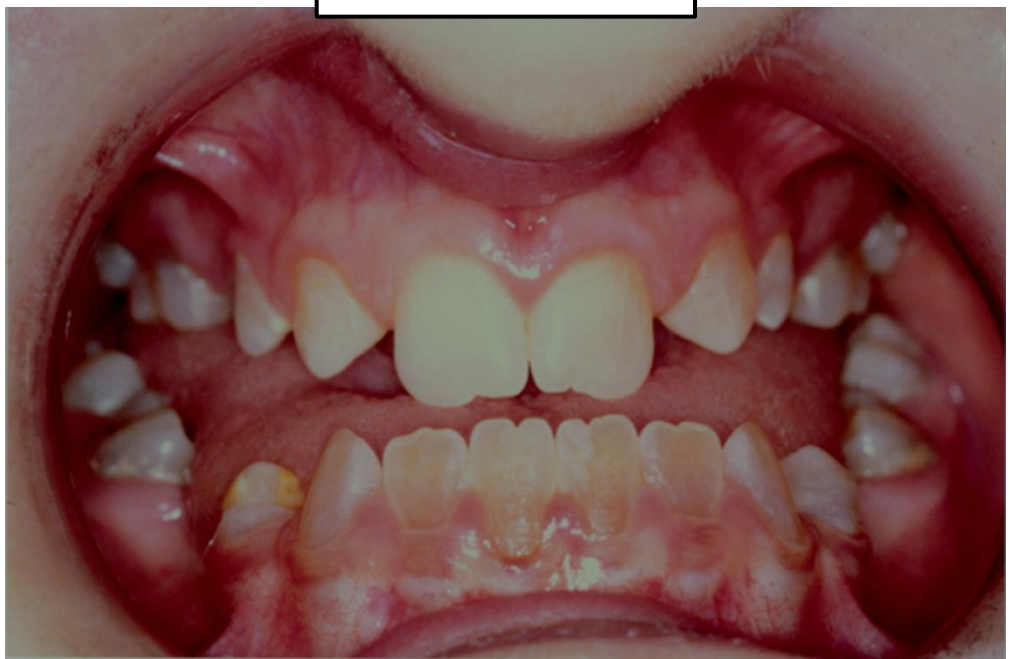
blue scleras



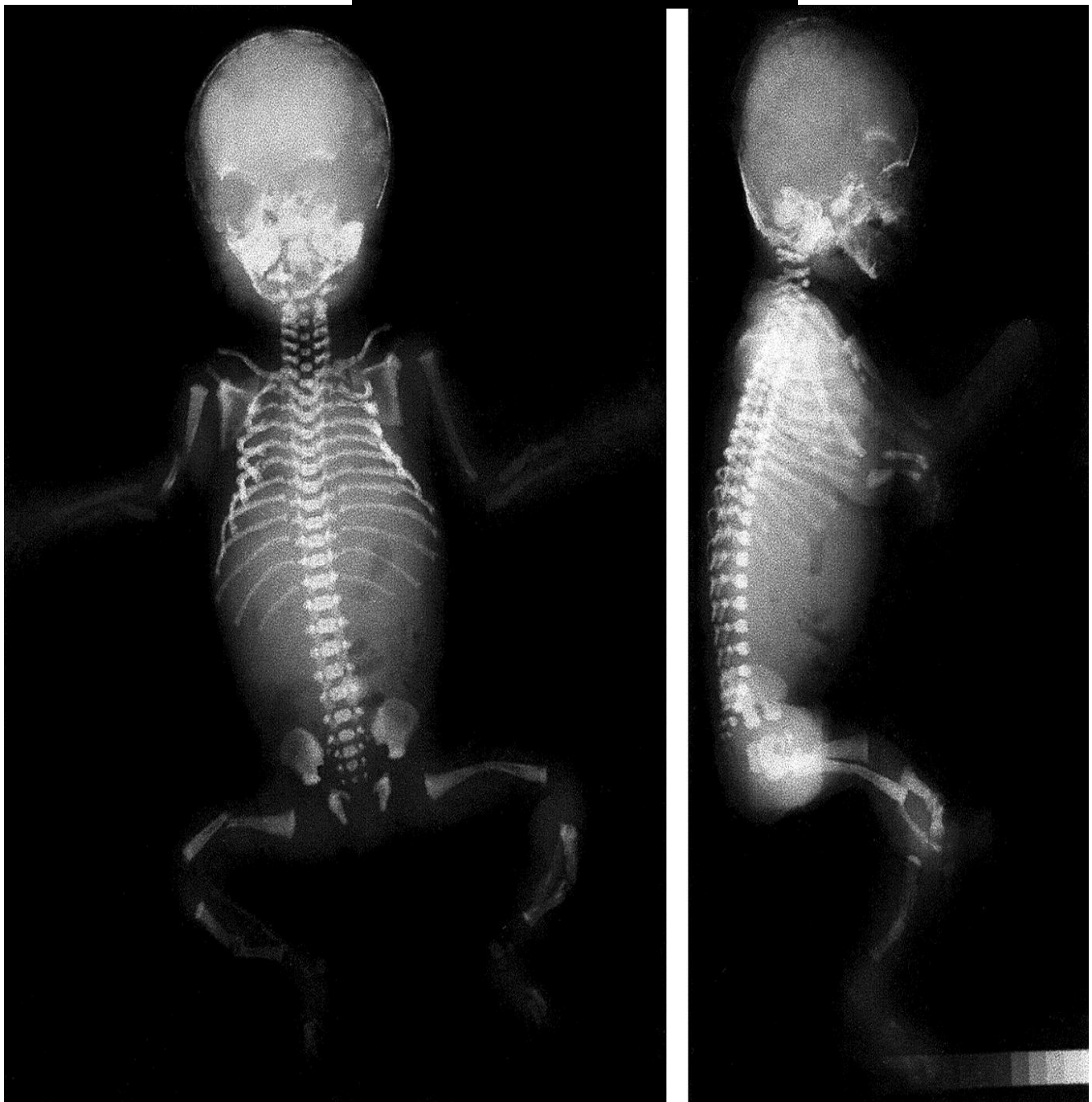
brittle bones



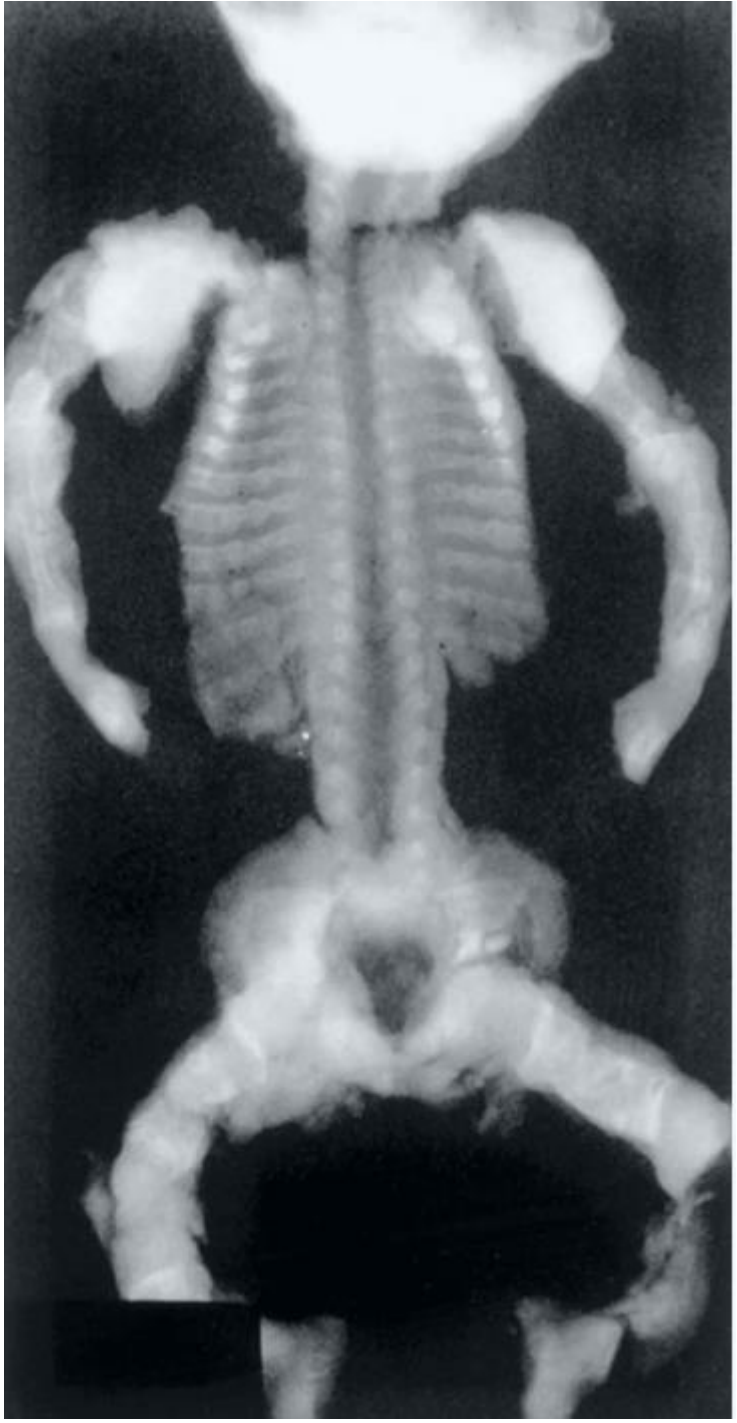
deformed teeth



Osteogenesis imperfecta



Skeletal radiograph of a fetus with lethal type 2 osteogenesis imperfecta



Achondroplasia

Achondroplasia is the most common skeletal dysplasia and a major cause of dwarfism.

Congenital Diseases of Bones

Achondroplasia

- Is transmitted as an autosomal dominant trait resulting from:
  - Defect in the cartilage synthesis at growth plates due to gain-of-function mutations in the FGF receptor 3 (FGFR3).
  - Normally, FGF-mediated activation of FGFR3 inhibits endochondral growth. Therefore gain-of-function mutation lead to inhibition of chondrocytes proliferation.
- It is characterized by failure of cartilage cell proliferation at the epiphysial plates of the long bones, resulting in failure of longitudinal bone growth and subsequent short limbs.
- Membranous ossification is not affected, so that the skull, facial bones, and axial skeleton develop normally.

Bones Congenital Diseases of **Achondroplasia**

- Known as Dwarfism
- Affected individuals have shortened proximal extremities, a trunk of relatively normal length, and an enlarged head with bulging forehead and conspicuous depression of the root of the nose.
- General health, intelligence, or reproductive status are not affected, and life expectancy is normal

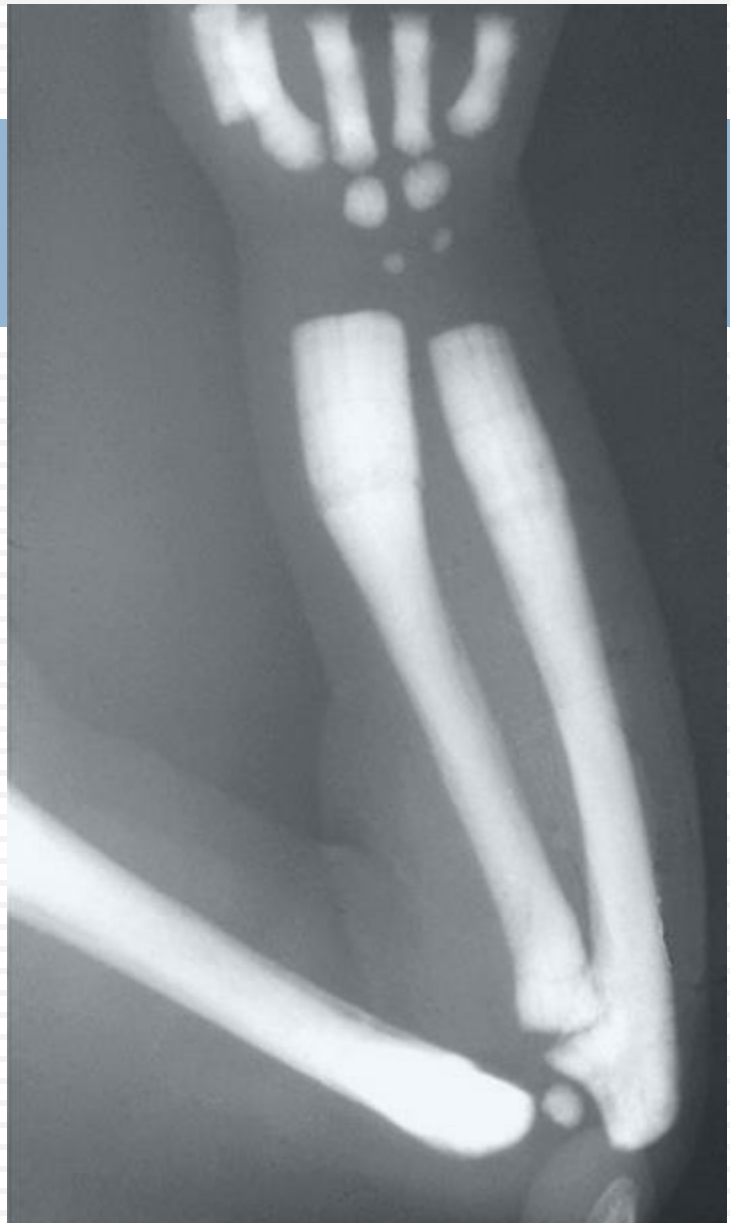

Achondroplasia
Autosomal Dominant

Achondroplasia

- Approximately 90% of cases stem from new mutations (sporadic mutation), almost all of which occur in the paternal allele (associated with advanced paternal age).

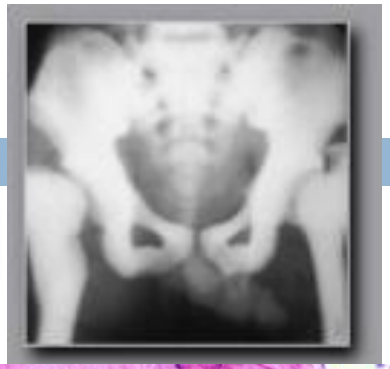
Osteopetrosis

Marble bone disease



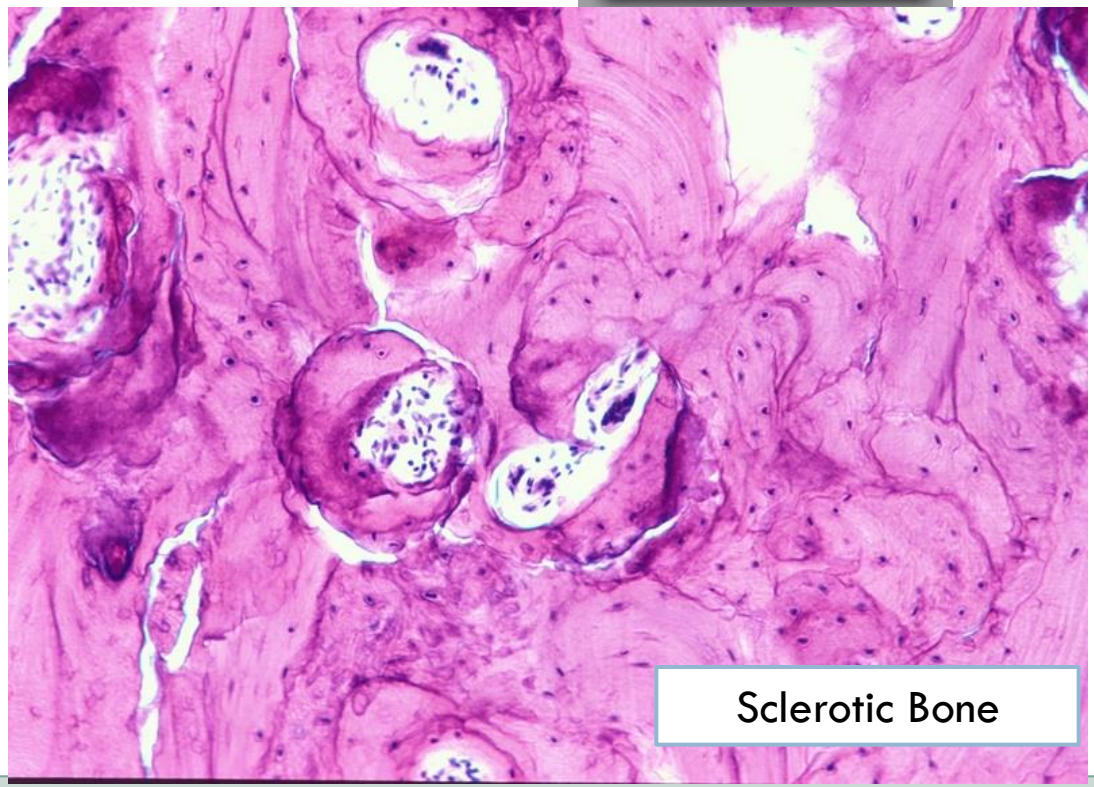
Congenital Diseases of Bones

Osteopetrosis



Sclerotic Bone

- Rare diseases
- failure of normal bone resorption by osteoclasts results in uniformly thickened, dense bones
- due to abnormal function of osteoclasts (deficiency of carbonic anhydrase leads to an abnormal environment around the osteoclast, resulting in defective bone resorption)



Sclerotic Bone

- increased tendency to fractures and osteomyelitis
- anemia and extramedullary hematopoiesis

METABOLIC BONE DISESES

Metabolic bone disease

comprises four fairly common conditions in which there is an imbalance between osteoblastic (bone forming) and osteoclastic (bone destroying) activity:

- **Osteoporosis**
- **Osteomalacia**
- **Paget's disease of bone**
- **Hyperparathyroidism**

OSTEOPOROSIS

OSTEOPOROSIS

Osteoporosis is an acquired condition characterized by reduced bone mass, leading to bone fragility and susceptibility to fractures.

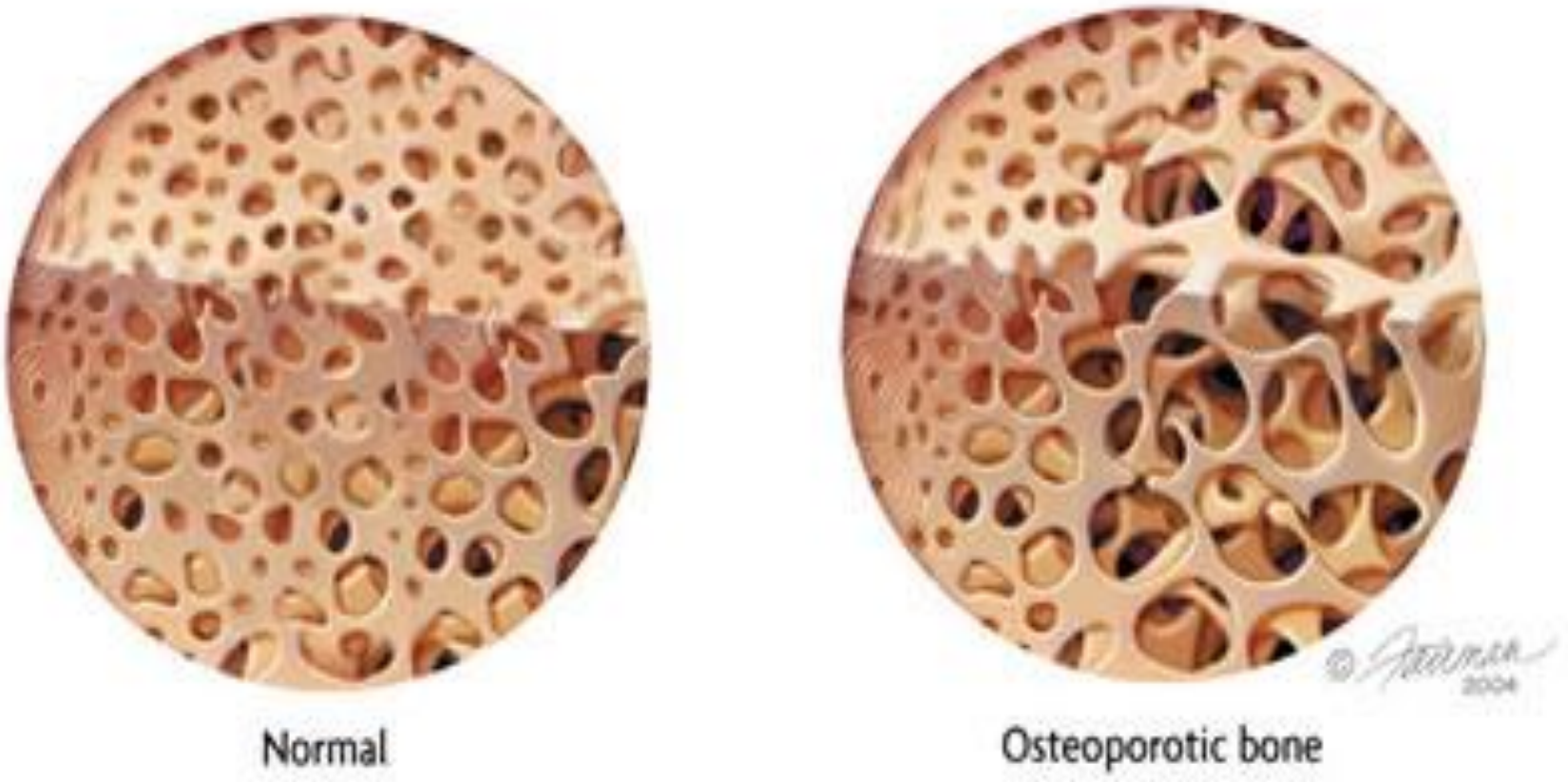
- There is a slowly progressive increase in bone erosion
- The cortical bone is thinned, and the bone trabeculae are thinned and reduced in number

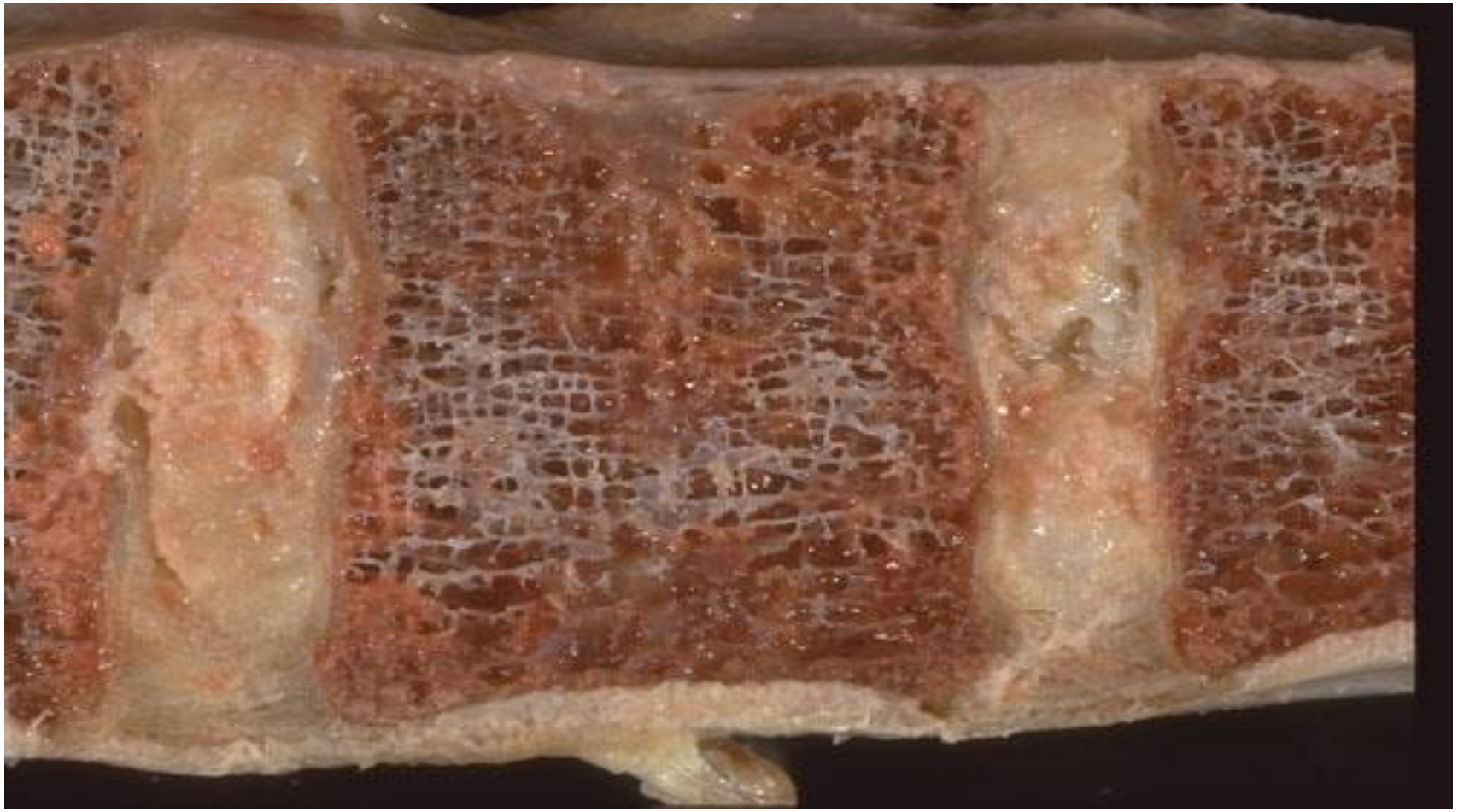
→ increased porosity of the skeleton leading to reduction in the bone mass but without distortion of architecture.

- It may be localized → disuse osteoporosis of a limb.

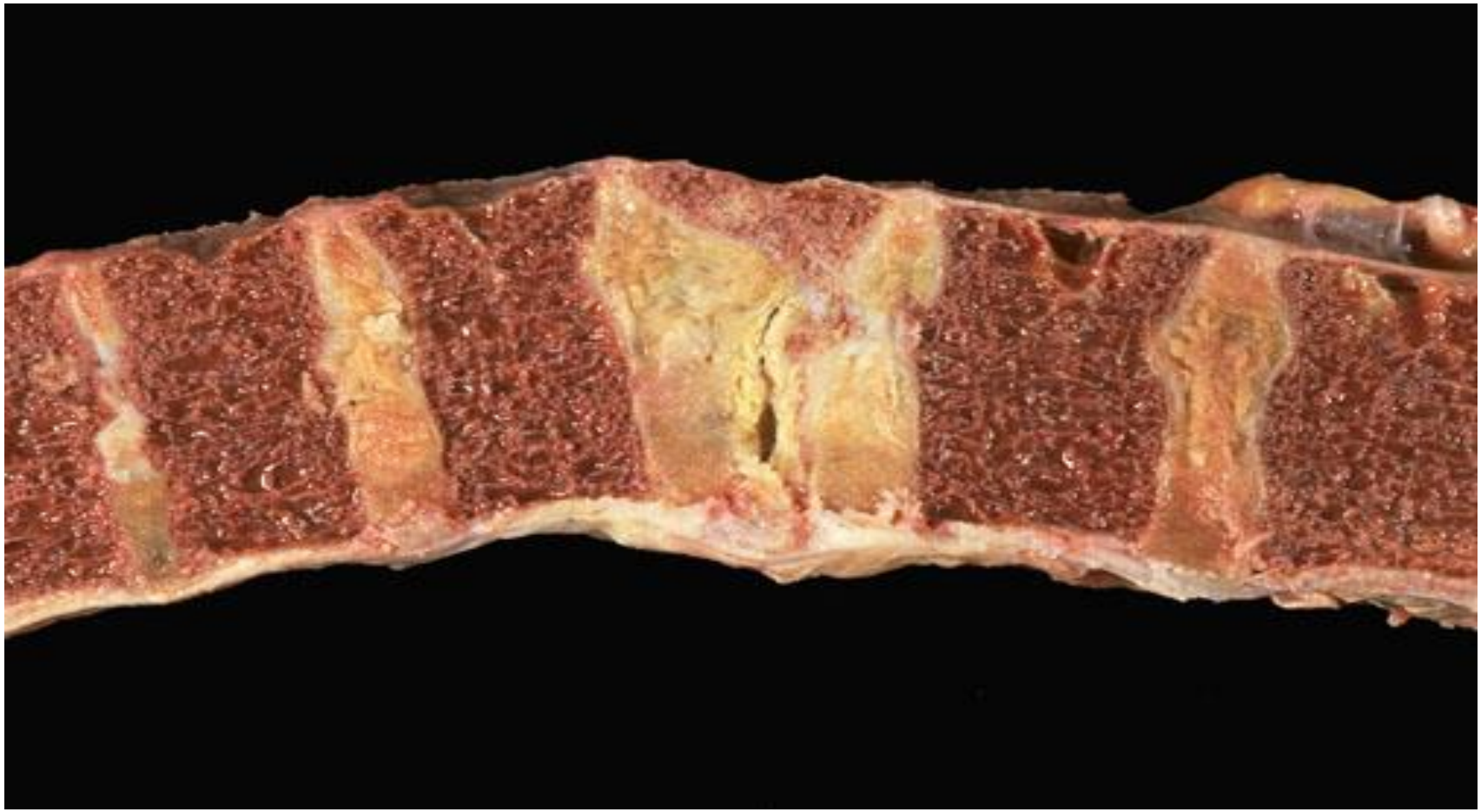
  or

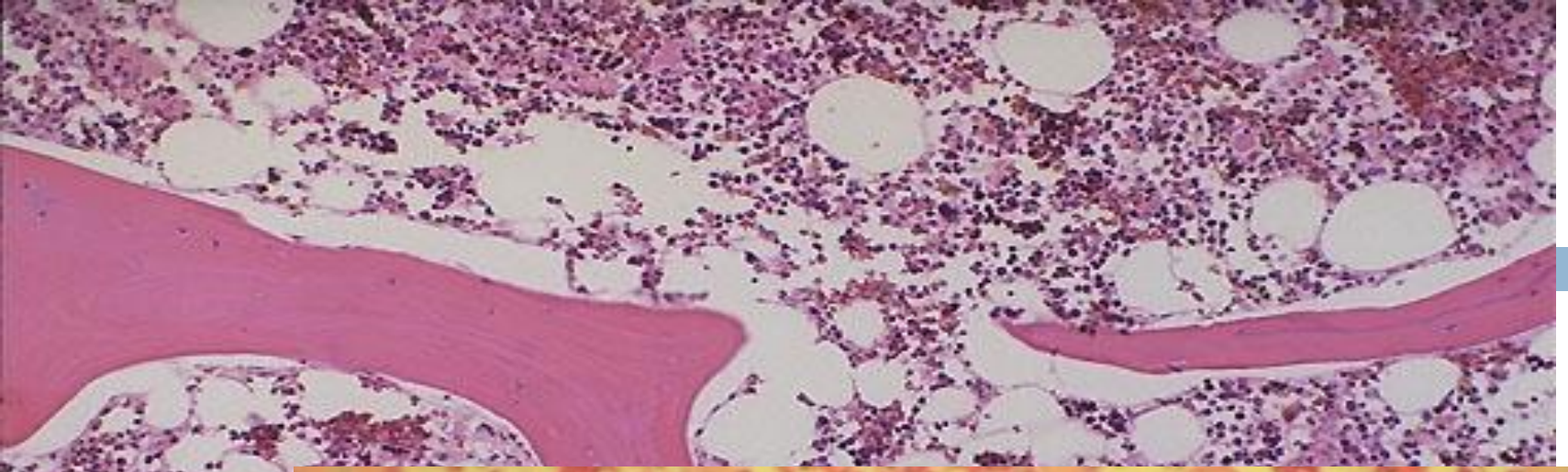
  may involve the entire skeleton, as a metabolic bone disease.

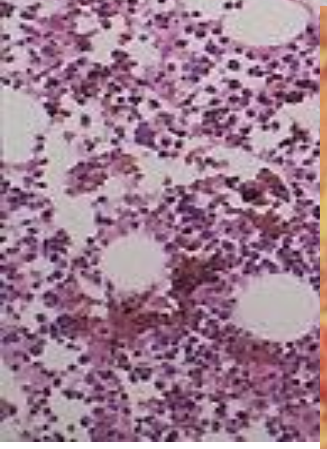

Normal
Osteoporotic bone

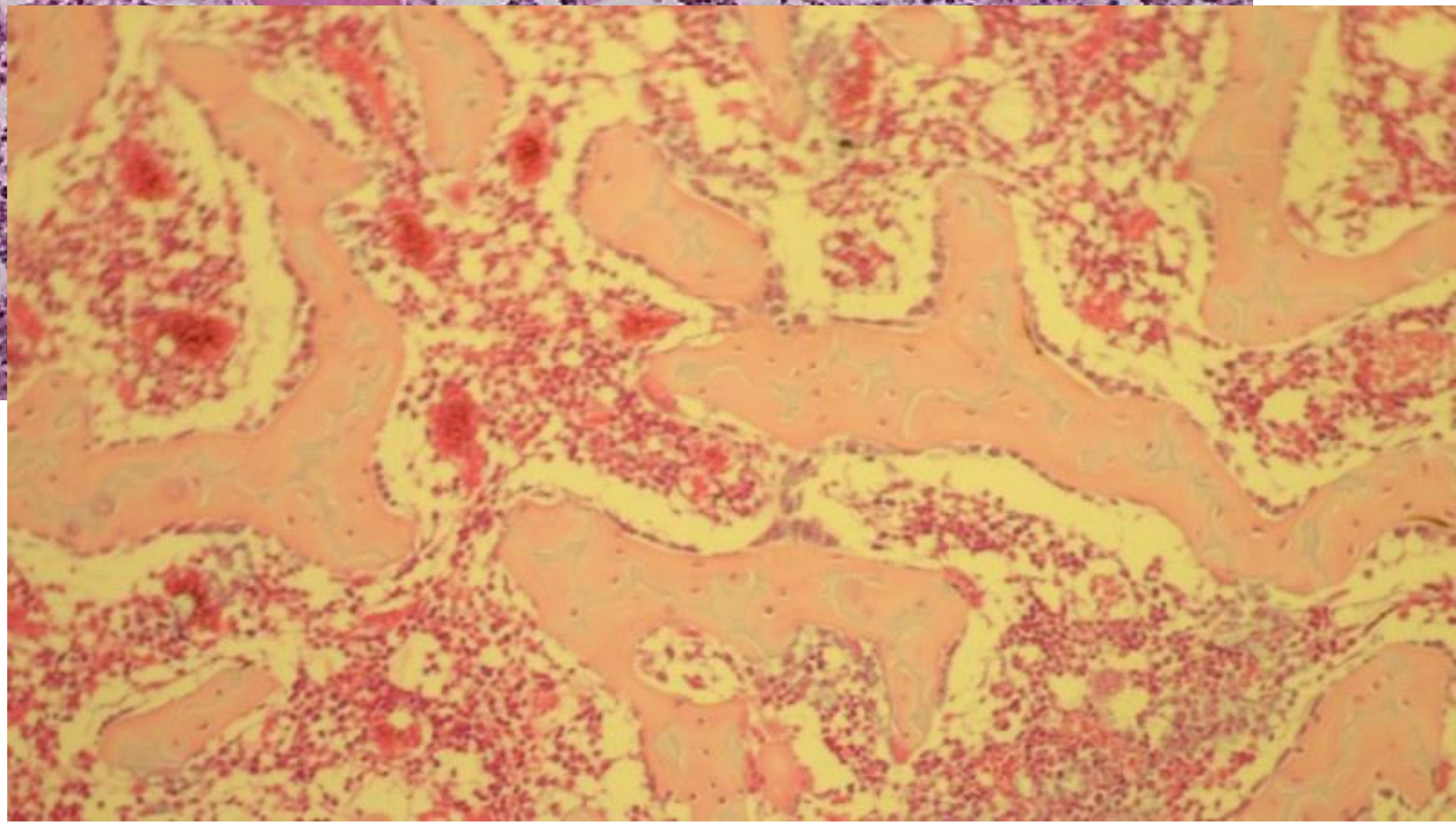


Vertebral bone with osteoporosis and a compression fracture









OSTEOPOROSIS

Categories of Generalized Osteoporosis

- Primary
- Secondary

OSTEOPOROSIS

PRIMARY:

- Idiopathic
- Post menopausal probably a consequence of declining levels of estrogen
- Senile

Environmental factors may play a role in osteoporosis in the elderly: decreased physical activity and nutritional protein or vitamin deficiency (1,25-dihydroxycholecalciferol)

Post menopausal Osteoporosis

- In the decade after menopause, yearly reductions in bone mass may reach up to 2% of cortical bone and 9% of cancellous bone. Women may lose as much as 35% of their cortical bone and 50% of their cancellous bone by 30 to 40 years after menopause.

OSTEOPOROSIS

such as Addison disease, DM type1, hypo or hyperthyroidism, and acromegaly.

- Secondary:
  - Endocrine Disorders
  - Gastrointestinal disorders
  - Neoplasia
  - Drugs
  - Others (Smoking, Immobilization, Anemia, Pulmonary disease)

Malnutrition
Malabsorption
Hepatic insufficiency
Vitamin C, D deficiencies

Drugs:
Anticoagulants
Chemotherapy
Corticosteroids
Anticonvulsants
Alcohol

Neoplasia:
Multiple myeloma
Carcinomatosis

OSTEOPOROSIS

- **The most common forms of osteoporosis are the senile and postmenopausal types.**

OSTEOPOROSIS

Pathophysiology:

- Occur when the balance between bone formation and resorption tilts in favor of resorption

OSTEOPOROSIS

- **Pathophysiology:**
  - Genetic factors
  - Nutritional effects
  - Physical activity
  - Aging
  - Menopause

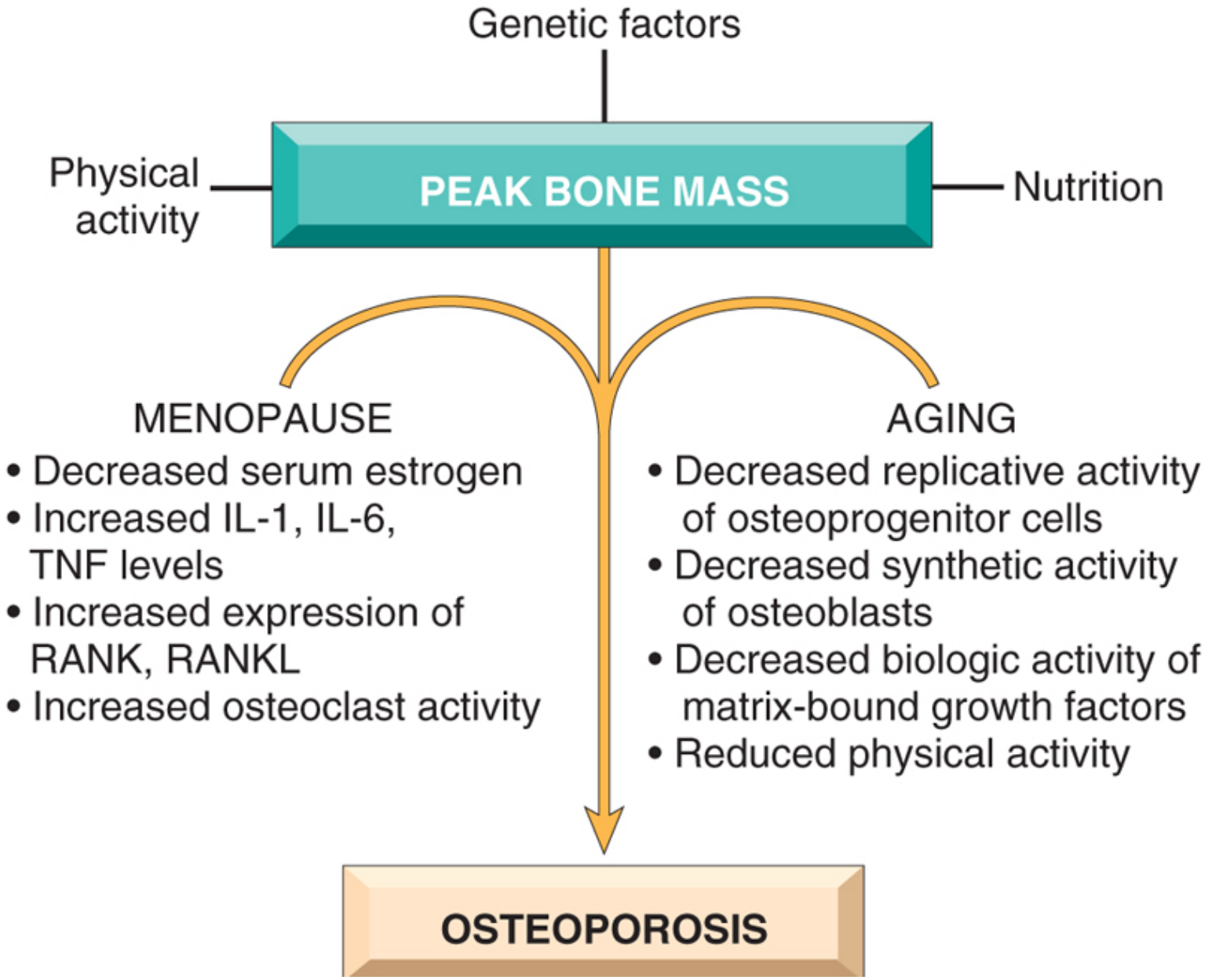
Vitamin D receptor polymorphisms

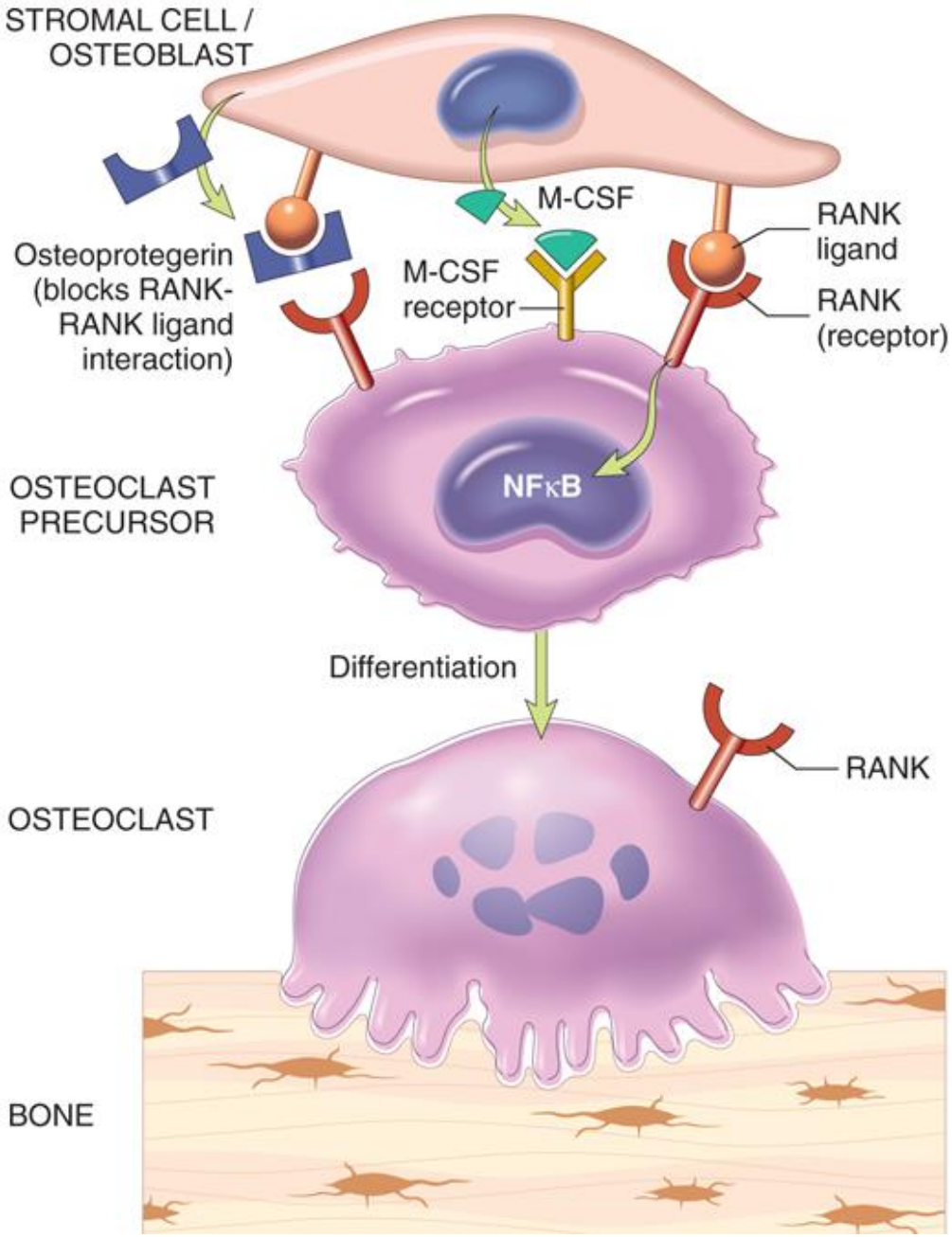
A majority of adolescent girls (but not boys) have insufficient dietary calcium.

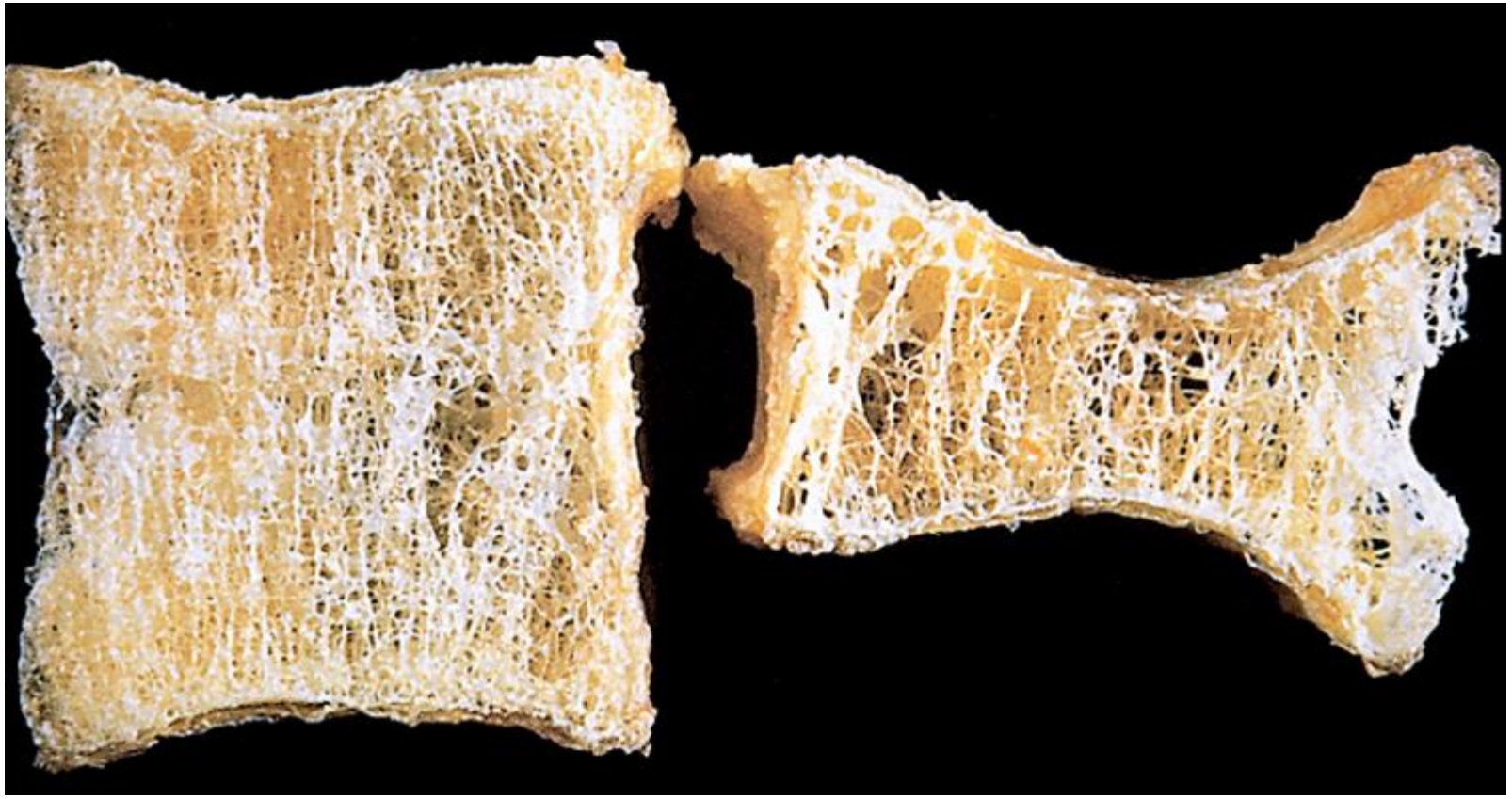
reduced physical activity increases bone loss.

Bone mass peaks during young adulthood; the greater the peak bone mass, the greater the delay in onset of osteoporosis. In both men and women, beginning in the third or fourth decade of life, bone resorption begins to outpace bone formation.
The bone loss, averaging 0.5% per year

The postmenopausal drop in estrogen leads to increased cytokine production (especially IL-1, IL-6, and TNF), presumably from cells in the bone. These stimulate RANK-RANK ligand activity and suppress OPG production

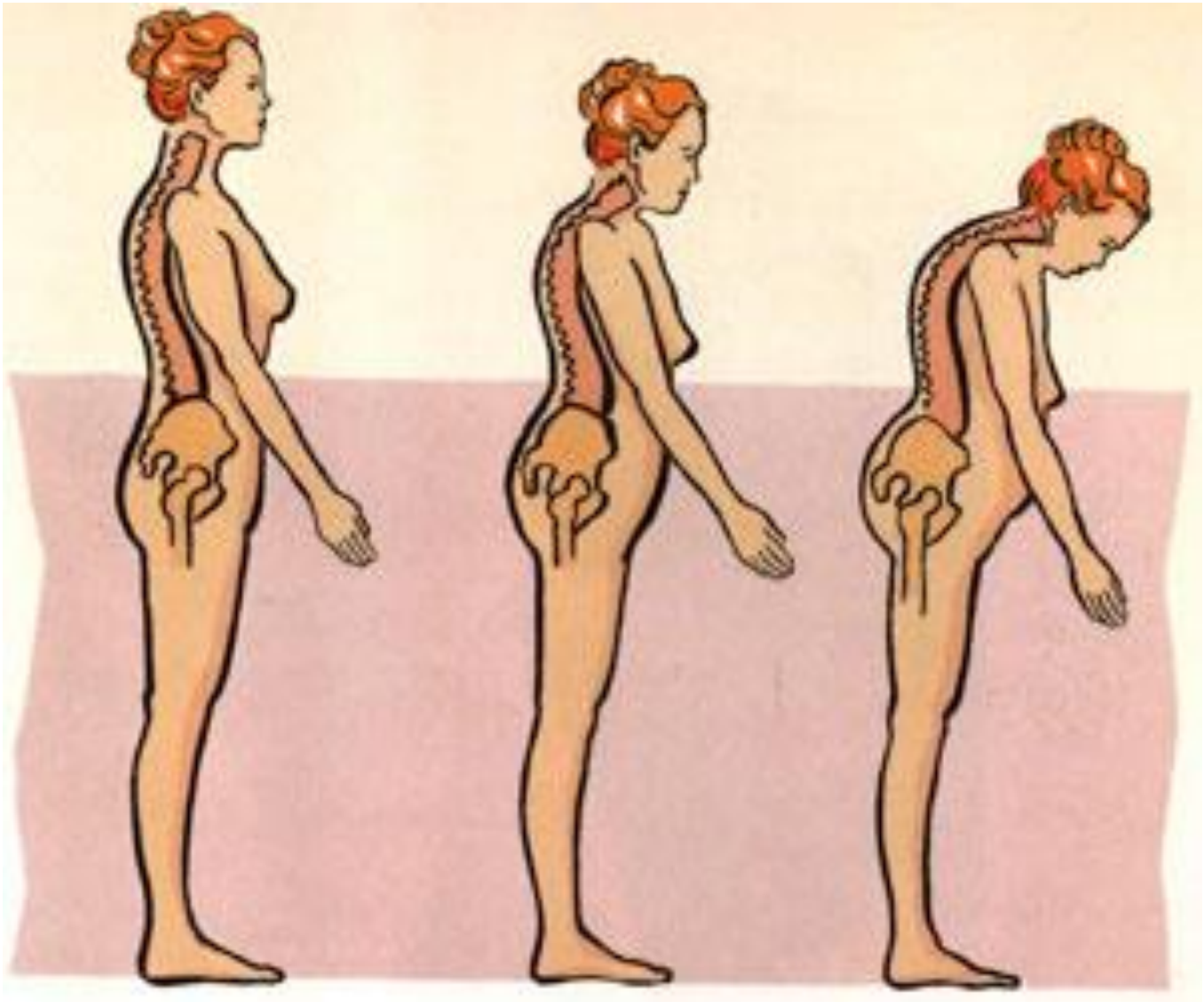

Genetic factors
Physical activity
PEAK BONE MASS
Nutrition
MENOPAUSE
• Decreased serum estrogen
• Increased IL-1, IL-6, TNF levels
• Increased expression of RANK, RANKL
• Increased osteoclast activity
AGING
• Decreased replicative activity of osteoprogenitor cells
• Decreased synthetic activity of osteoblasts
• Decreased biologic activity of matrix-bound growth factors
• Reduced physical activity
OSTEOPOROSIS


STROMAL CELL /
OSTEOBLAST
M-CSF
RANK
ligand
Osteoprotegerin
(blocks RANK-
RANK ligand
interaction)
M-CSF
receptor
RANK
(receptor)
OSTEOCLAST
PRECURSOR
NFκB
Differentiation
RANK
OSTEOCLAST
BONE

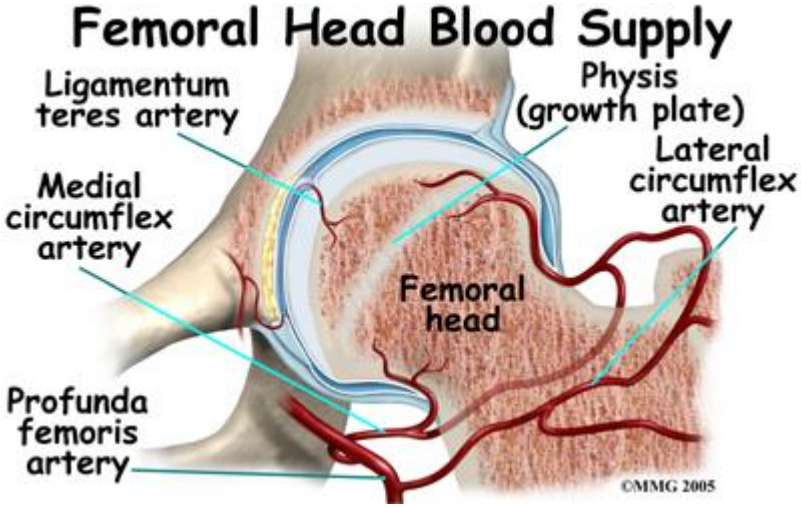


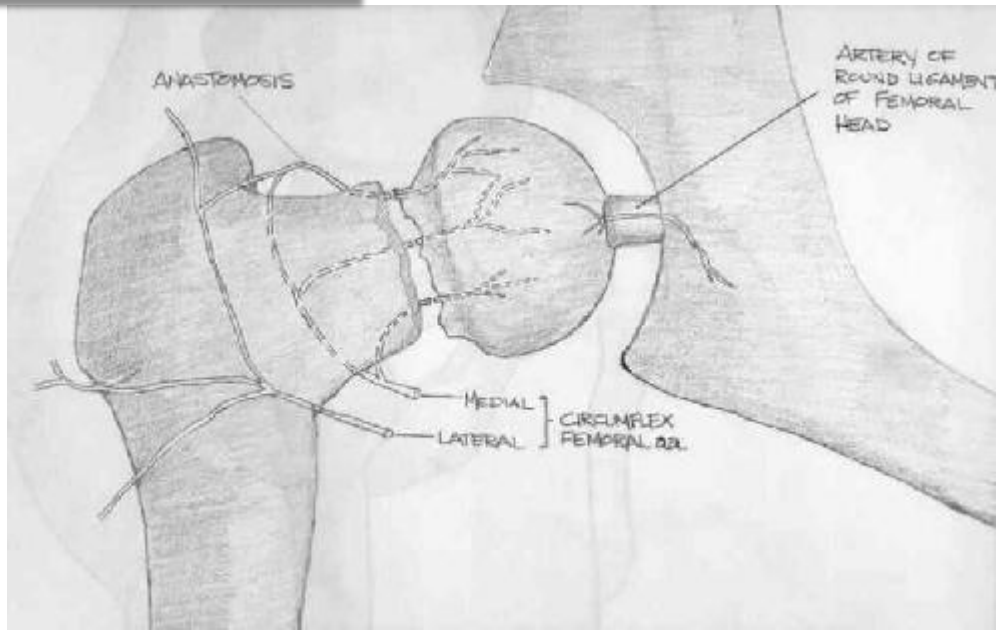
OSTEOPOROSIS

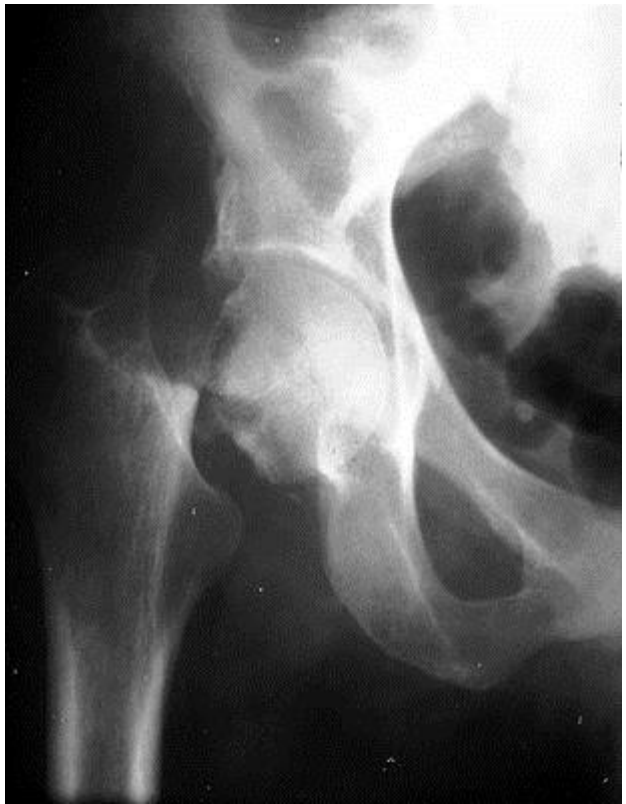
- Clinical features
  - Difficult to diagnose
  - Remain asymptomatic ----fracture
  - Fractures
    - Vertebrae
    - Femoral neck
  - Patients with osteoporosis have normal serum levels of calcium, phosphate, and alkaline phosphatase

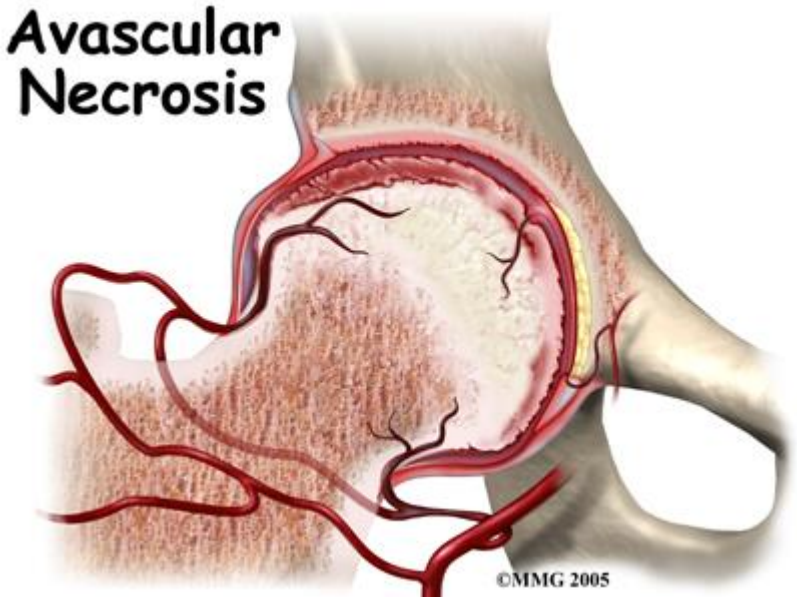


Complication of fracture





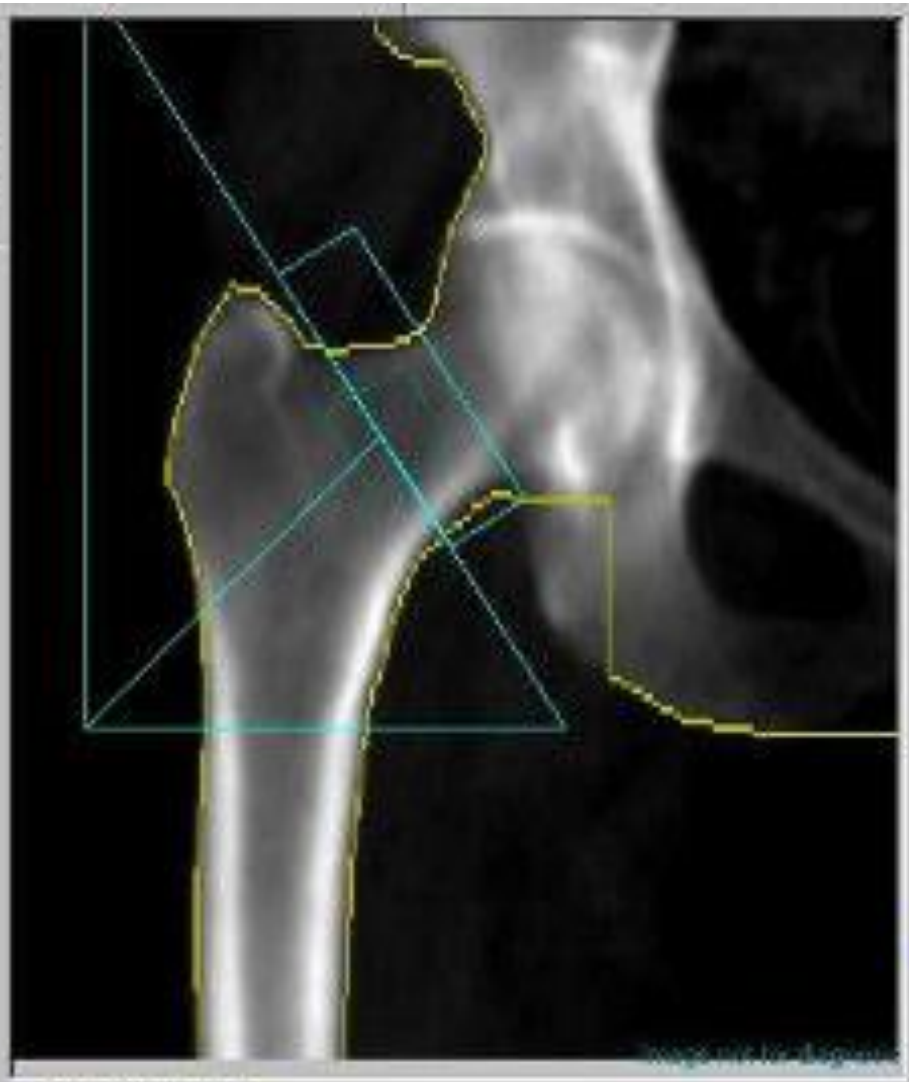




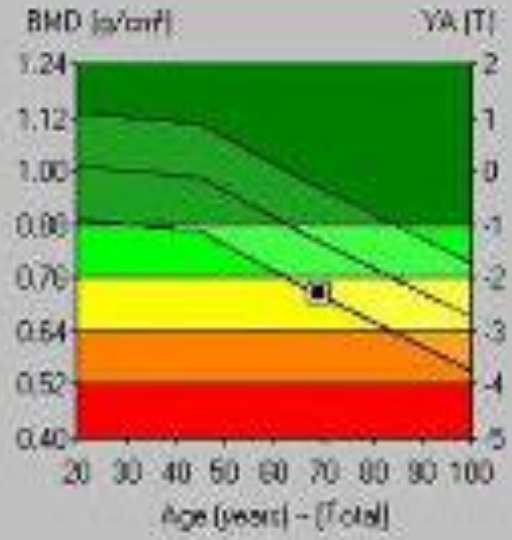
Diagnosis
Bone density by radiographic measures

- Plain X ray: cannot detect osteoporosis until 30% to 40% of bone mass has already disappeared.
- Dual-emission X-ray absorptiometry (DXA scan): is used primarily to evaluate bone mineral density, to diagnose and follow up pt. with osteoporosis.

DXA scan



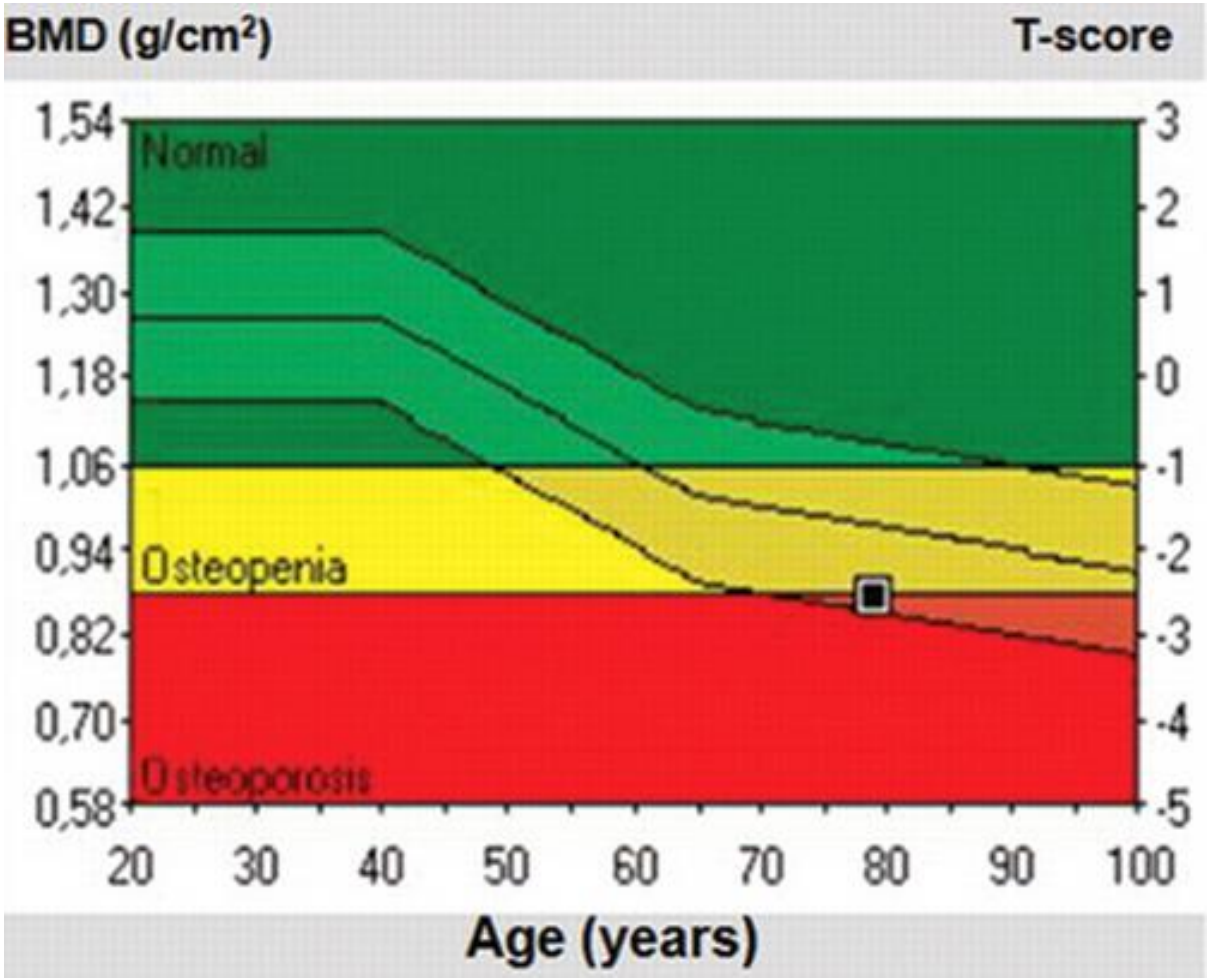
Densitometry | Reference | Trend | Information



Region	BMD [g/cm²]	YA [T]	AM [Z]
Neck	0.615	3.0	1.5
Wards	0.459	-3.5	-1.3
Troch	0.552	-2.2	-1.3
Shaft	0.926	-	-
Total	0.725	-2.3	-1.0

Standard Results
Select region: up/down arrows
Change results tab: left/right arrows

116, BLO
Born 12/10/1929 67.0 in. 120.0 lbs. White Female
51


BMD (g/cm²)
T-score
1,54
1,42
1,30
1,18
1,06
0,94
0,82
0,70
0,58
3
2
1
0
-1
-2
-3
-4
-5
Normal
Osteopenia
Osteoporosis
20
30
40
50
60
70
80
90
100
Age (years)

Prognosis

- Osteoporosis is rarely lethal.
- Patients have an increased mortality rate due to the complications of fracture.

    e.g. hip fractures can lead to decreased mobility and an additional risk of numerous complications: deep vein thrombosis, pulmonary embolism and pneumonia

OSTEOPOROSIS

Prevention Strategies

- The best long-term approach to osteoporosis is prevention.
- children and young adults, particularly women, with a good diet (with enough calcium and vitamin D) and get plenty of exercise, will build up and maintain bone mass.
- This will provide a good reserve against bone loss later in life. Exercise places stress on bones that builds up bone mass

International Osteoporosis Foundation

LOVE YOUR BONES

embrace an active lifestyle

embrace calcium rich foods

embrace vitamin D

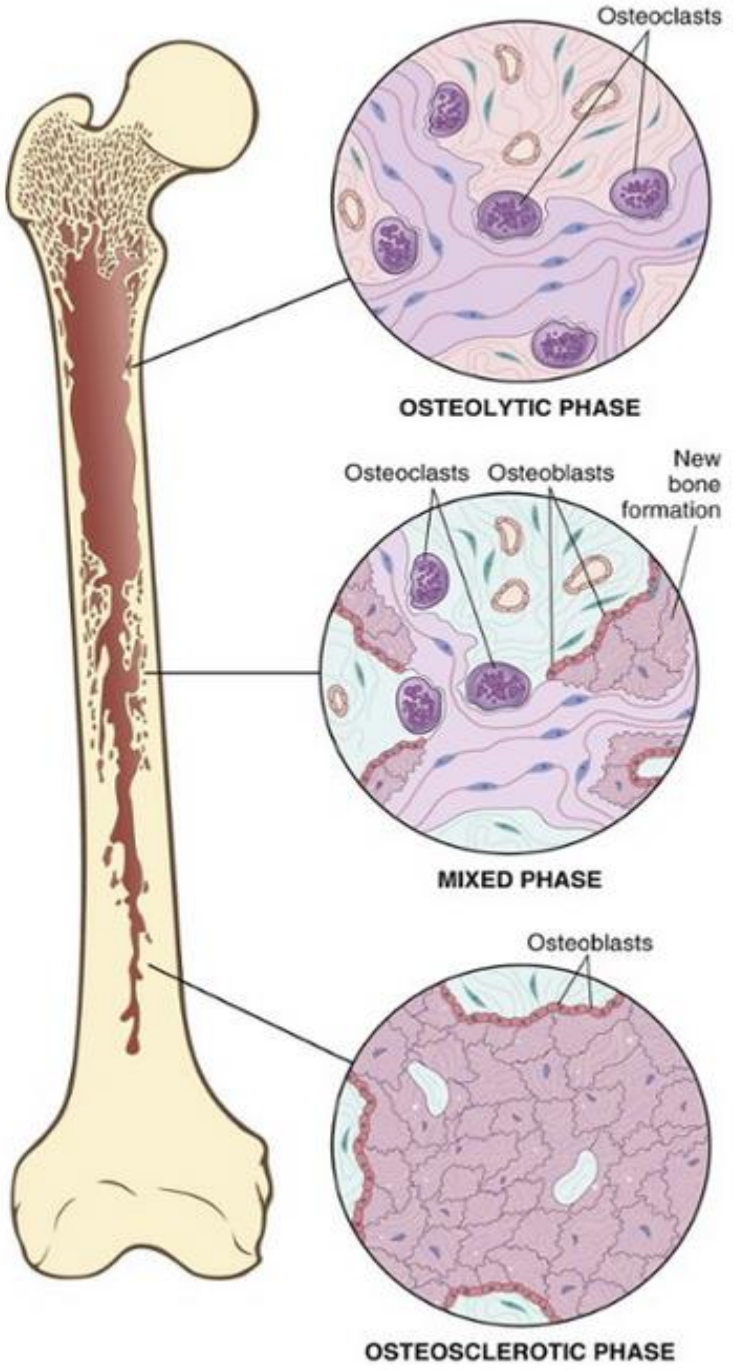
World Osteoporosis Day & Unbreakable Embrace

Metabolic bone disease

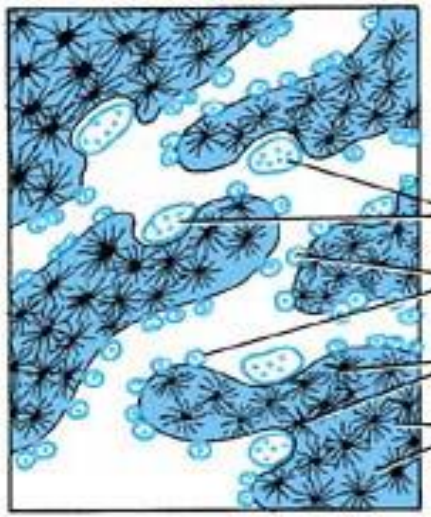
- In **osteomalacia and Rickets,** osteoblastic production of bone collagen is normal but mineralization is inadequate. It is a manifestations of vitamin D deficiency
- In **Paget's disease of bone** there is excessive uncontrolled destruction of bone by abnormally large and active osteoclasts, with concurrent inadequate attempts at haphazard new bone formation by osteoblasts, producing physically weak woven bone. It may result from a paramyxovirus infection in genetically susceptible persons.
- In **hyperparathyroidism,** excessive secretion of PTH produces increased osteoclastic activity. There is excessive destruction of cortical and trabecular bone, with inadequate compensatory osteoblastic activity.

Paget disease of bone

The three phases in the evolution of the disease



Metabolic bone disease



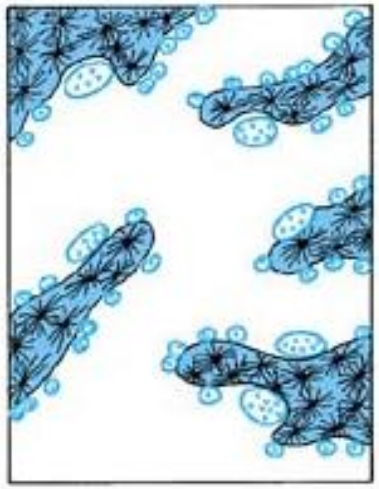
Normal
Normal trabeculae and calcification

Osteoclasts

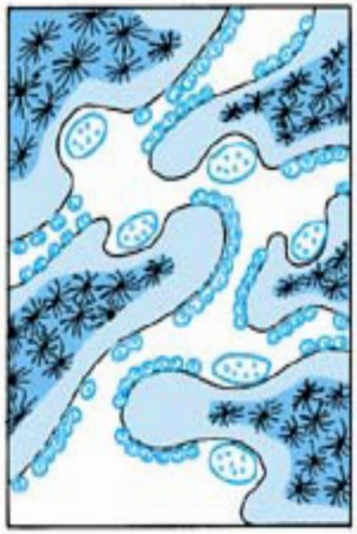
Osteoblasts

Osteocytes

Lamellae



Osteoporosis
- Thin, sparse trabeculae
- Calcification normal
- Normal osteoblasts, osteoclasts
- Results:
  - Weakness
  - Fractures



Osteomalacia
- Trabeculae normal in size but only partially calcified
- Surface shows "seams" of uncalcified osteoid
- Often increased osteoblasts
- Results:
  - Soft bones
  - Weakness
  - Deformity
  - Fracture

Hyperparathyroidism
- Increased osteoclasts erode bone
- Compensatory increase in osteoblasts insufficient to restore trabeculae
- Normal calcification of residual bone
- Fibrosis of marrow spaces with giant cells

Laboratory Findings in Metabolic Bone Disease

	Serum Calcium	Serum Phosphorus	Alkaline Phosphatase	Parathyroid Hormone (PTH)
Osteoporosis				
Osteomalacia (rickets)				
Primary hyperparathyroid bone disease				
Bone disease in renal failure—with secondary hyperparathyroidism				
Lytic bone neoplasms				
Paget's disease of bone				

Laboratory Findings in Metabolic Bone Disease

	Serum Calcium	Serum Phosphorus	Alkaline Phosphatase	Parathyroid Hormone (PTH)
Osteoporosis	N	N	N	N
Osteomalacia (rickets)	↓	↓(↑)[1]	↑	N(↑)
Primary hyperparathyroid bone disease	↑	↓	N↑	↑
Bone disease in renal failure—with secondary hyperparathyroidism	N↓	↑	↑	↑
Lytic bone neoplasms	N↑	N↑	N↑	N
Paget's disease of bone	N	N	↑	N