MSS

Sheet no.2

Pathology

Writer: Hala Masadeh

Corrector: Joud Abu Khass

Doctor: Mousa Alabbadi

Congenital disorders: (not common)

Divided into two major groups:

1- **Dysostosis** (dys: abnormal … ostosis: bone).
2- **Dysplasia** (doesn't mean preneoplastic).

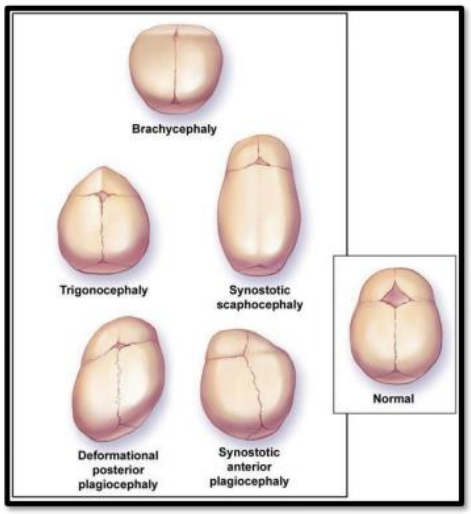
❖Dysostosis:

These group of diseases are characterized by:

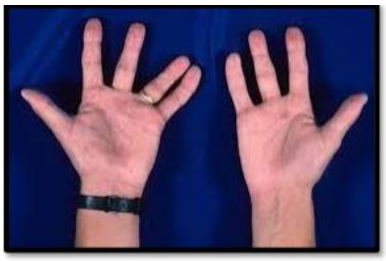
- Abnormal condensation and migration of the mesenchyme, (something wrong happens through growth and development of mesenchyme).
- Caused by genetic abnormalities which aren't simple, involves the homeobox genes (responsible for the development of the musculoskeletal system), and abnormalities in the cytokines and their receptors (the surrounding environment).

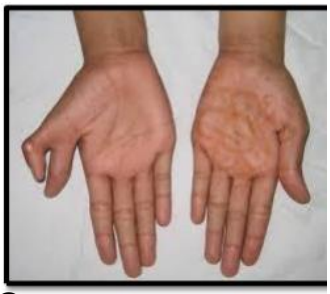
Examples:

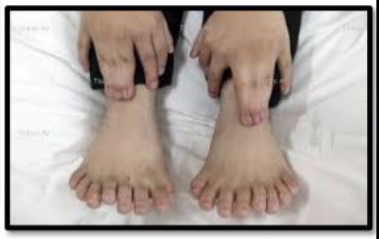
1- **Aplasia:** lack of synthesis of certain group of bone. (4 fingers instead of 5)
2- **Syndactyly & craniosynostosis**:
   - Syndactyly: Fusion of the finger (for some reason the apoptosis that was supposed to happen to the cells between fingers was stopped).
   - Craniosynostosis: an abnormality in the sutures of the skull(cranio:skull)
3- **Supernumerary digit:** an additional finger or toe.

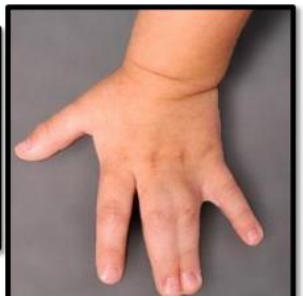


Craniosynostosis


Aplasia


Supernumerary digit


Hands: Syndactyly.
Feet: supernumerary digit


Syndactyly

❖Dysplasia:

Most of the time dysplasia indicates precursor of malignancy but not in the bone.

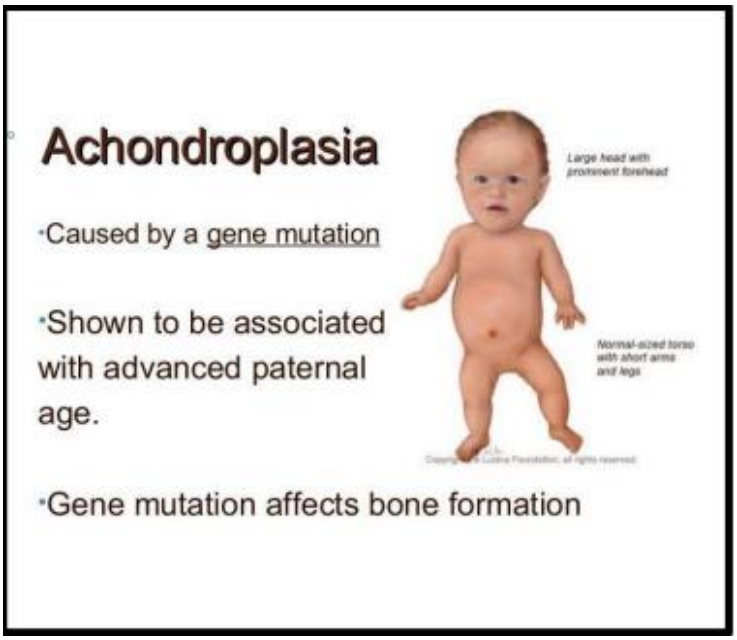
- The basic pathology of this disorder is disorganization of the bone and cartilage.
- Caused by genetic point mutations in the gene that control the development and remodeling of the bone.

Examples:

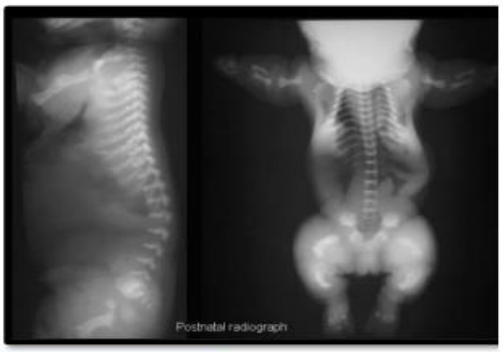
Achondroplasia (dwarfism): (most common)

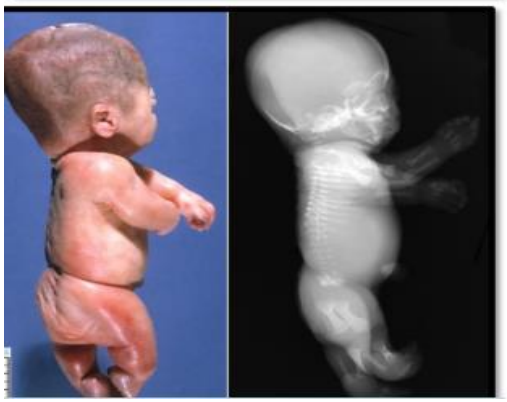
- Caused by a specific mutation in Fibroblast Growth Factor Receptor #3 (FGFR3)
- The most important concept that you must understand that there is no impact on longevity, intelligence, or reproductive status…they live a normal life.

Peter Dinklage: 48-years-old, married with 2 children from USA, New Jersey
"Game of thrones"



Thanatophoric dysplasia:





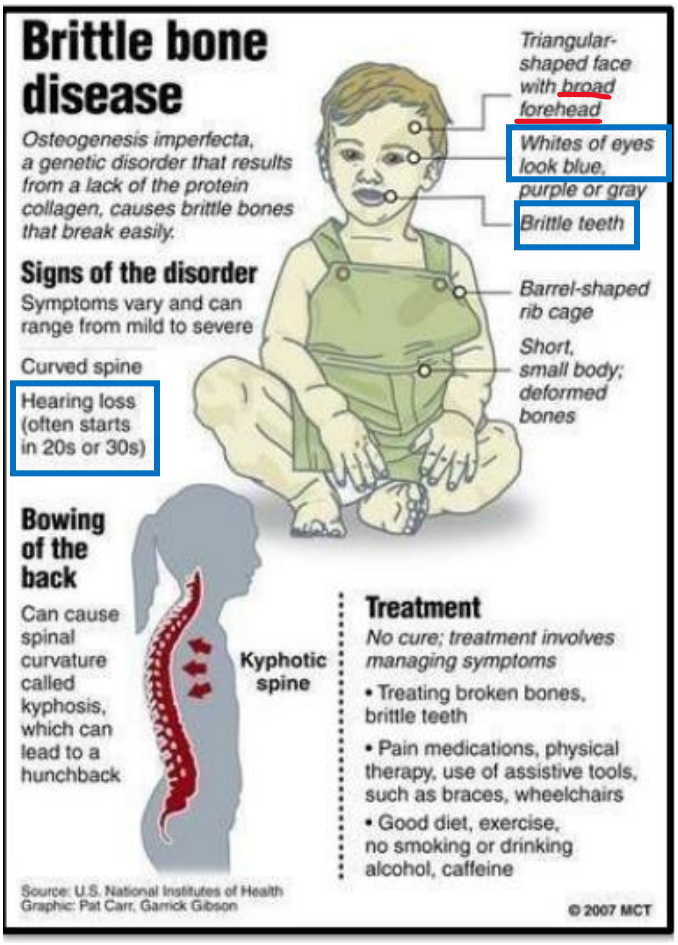
- **Most common lethal form of dwarfism,** less common than achondroplasia.
- This is a severe form of dwarfism affecting another gene in the FGFR3 (it is the same gene of dwarfism but in <u>different location</u>(locus) than the Achondroplasia).
- Begins in the uterus (can be detected by the ultrasound and x-ray) most of the babies die in the uterus or shortly after birth and the **leading cause of death is respiratory insufficiency.** (Small chest leading to resp. insufficiency).

Osteogenesis Imperfecta *important disease

(Imperfect bone formation)

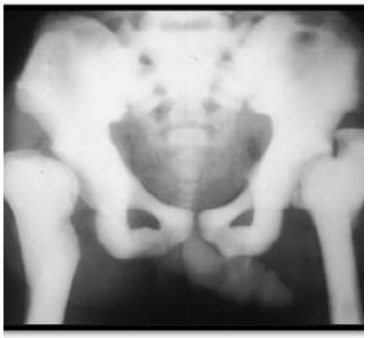
- **Most common inherited disorders of connective tissue**.
- Group of disorders: it's not a single disease, group of disorders classified according to the severity of disease (type 1, type 2 …) & its clinical features.
- AD: Autosomal Dominant.
- Deficiency of **type I collagen** synthesis.
- Too little bone; fragility.
- Patient has blue sclera; hearing loss (the bones of the middle ear are impaired); teeth abnormalities.
- **Type 2** is the most severe, patients die early (lethal), and **Type I** (relatively normal life).
- It's also called "**Brittle bone disease**": the quantity and quality of the bone are not normal; it will be weaker (easy to break).

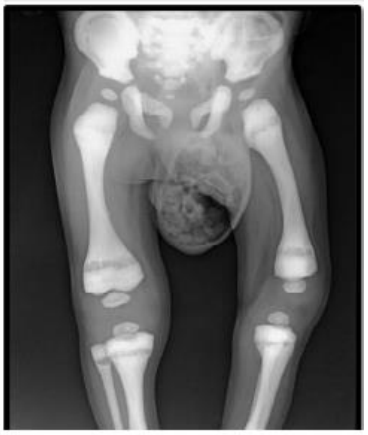
Features of Osteogenesis Imperfecta:



Osteopetrosis:

- Marble bone disease "**stone bone**"
- Exactly the opposite of osteoporosis.
- Group of disorders; rare.
- **Impaired osteoclast function:** reduced bone resorption leading to diffuse sclerosis (hardening of the bone).
- Dx: X-ray.
- Fractures and leukopenia (penia: deficient) in severe forms (immunodeficient people will be exposed to more opportunistic bacterial infection).





Summary

Congenital Disorders of Bone and Cartilage

Abnormalities in a single bone or a localized group of bones are called **dysostoses** and arise from defects in the migration and condensation of mesenchyme. They manifest as absent, supernumerary, or abnormally fused bones. Global disorganizations of bone and/or cartilage are called **dysplasias.** Developmental abnormalities can be categorized by the associated genetic defect.

- FGFR3 mutations are responsible for achondroplasia and thanatophoric dysplasia, both of which manifest as dwarfism.
- Mutations in the genes for type I collagen underlie most types of osteogenesis imperfecta (brittle bone disease), characterized by defective bone formation and skeletal fragility.
- Mutations in *CA2* and *TCIRG1* result in osteopetrosis (in which bones are hard but brittle) and renal tubular acidosis.

Metabolic Disorders:

Osteo: bone

Penia: loss

Osteopenia: decreased bone mass (1-2.5SD below the mean), but not severe enough to reach the exact definition of osteoporosis.

Osteoporosis: severe osteopenia; > than 2.5 SD below the mean with increased risk for fractures.

- ✓ To measure the bone density: use bone density measurements on Dexa scan machine, then you get numbers, and you already have the normal measurement and chart of the bone (for a specific age and sex), if your measurements are less than normal, but the deficiency is less than 2.5SD then it's osteopenia, more than 2.5SD then it's osteoporosis.
- ✓ The bone density examination is done before starting the aggressive treatment of osteoporosis.

- ✓ When the bone density decreases, the risk of fractures will increase, so the major complication (not the only) of osteoporosis is increased risk of fractions especially the central bones, vertebral column.

PRIMARY OSTEOPOROSIS	SECONDARY OSTEOPOROSIS
Much more common Senile (aging) & postmenopausal	Much less common Hyperthyroidism, malnutrition, steroids

Primary osteoporosis(generalized):

- Much more common
- A general disease that is associated with: senile(aging), postmenopausal.

Secondary osteoporosis:

- Much less common.
- less serious.
- easily treatable associated with:
  - Hyperthyroidism (cause systemic osteoporosis)
  - Malnutrition (low intake of calcium from dairy products)
  - Steroids (for auto immune disease) …. they activate osteoclast.

*If the cause was fixed, osteoporosis can be stopped.

*Very Important

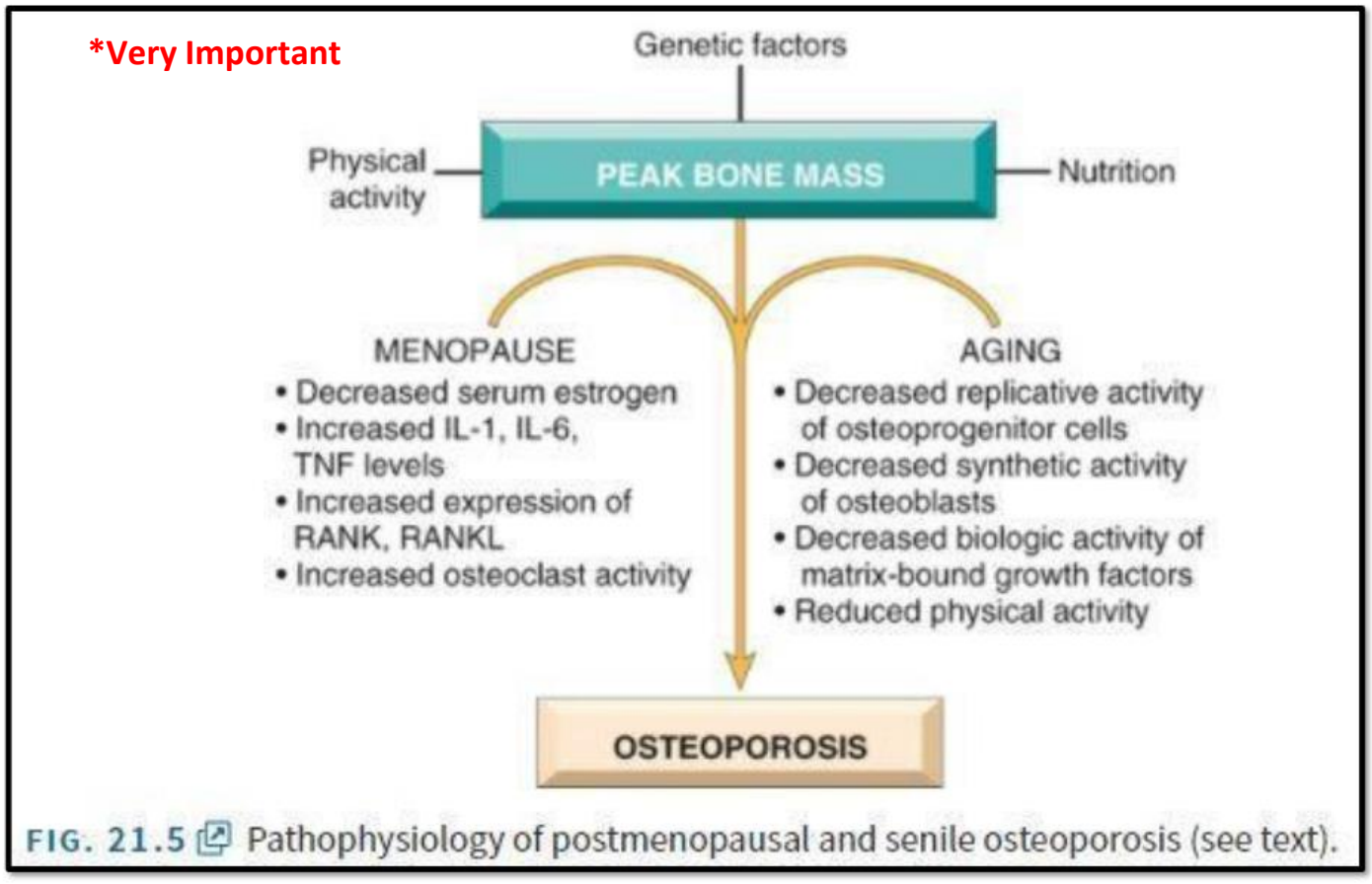


FIG. 21.5 Pathophysiology of postmenopausal and senile osteoporosis (see text).

Osteoporosis is a multi-factorial disease; the factors could be:

1-Genetic factors: some people are susceptible to osteoporosis depending on their genes.

2-Nutrition: low intake of dairy products contains calcium, also low vitamin D levels and sun exposure.

3-Physical activity: it can prevent osteoporosis to a big extent, more physical activity will slow down the process of osteoporosis.

4-Aging: by age there is decrease in replicative activity of osteoprogenitor cells, also the synthetic activity of the osteoblast decrease.

5-Menopause: because the serum estrogen will decrease, increased IL-1/IL-6/TNF levels as well as increased expression of RANK/RANKL leading to increased osteoclast activity. (Treatment: hormone replacement therapy, give estrogen after menopause, but there is better drugs).

Normal:

There are less spaces, and more bone trabeculae.

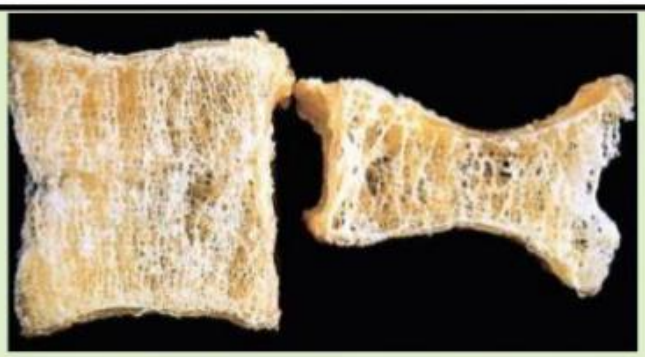


FIG. 21.6 Osteoporotic vertebral body *(right)* shortened by compression fractur..

Compression fracture happened to this bone.

A lot of matrix and the bone trabeculae is very thin.

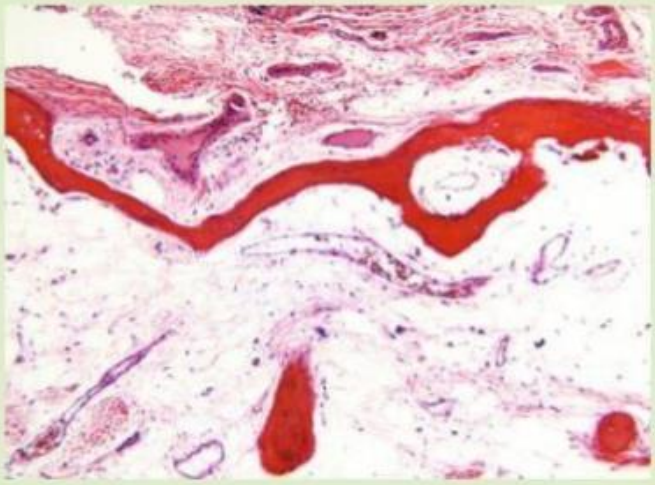
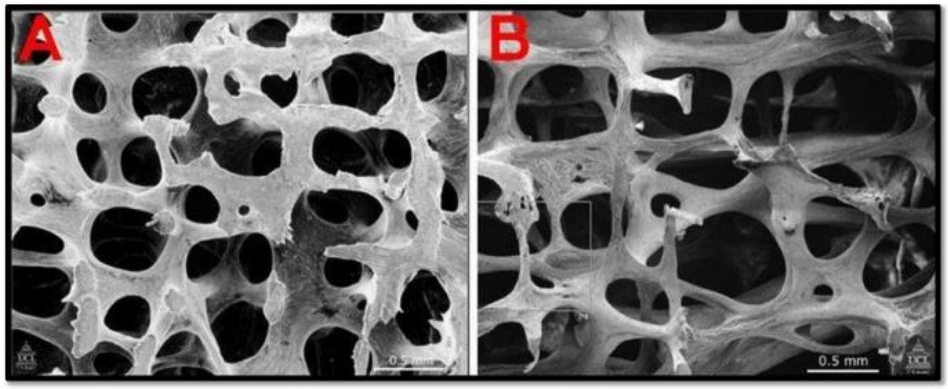
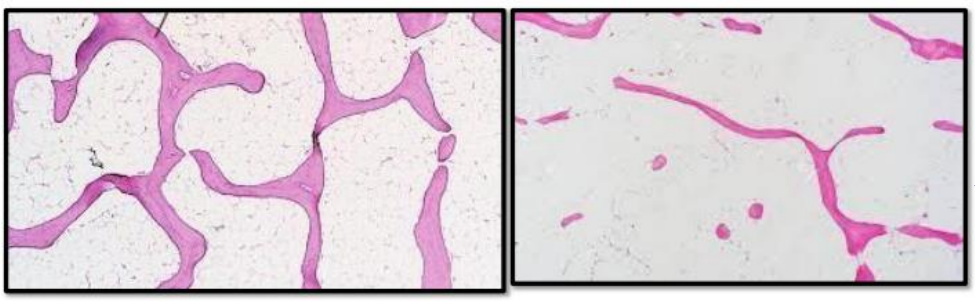


FIG. 21.7 In advanced osteoporosis, both the trabecular bone of the medulla *(b.*

Normal bone : Osteoporosis





Less bone and more matrix, and there are fractures.

This is the histology that belongs to severe osteoporosis.

Osteoporosis clinically:

- ✓ Vertebral fractures. (Osteoporosis can occur anywhere but it has a higher incidence in vertebral column, pelvic and femur).
- ✓ Femur and pelvic fractures: immobility, PE (Pulmonary embolism), pneumonia (hospital acquired) (40-50K death/yr in USA)
- ✓ Diagnosis: special imaging technique, bone mineral density (BMD scan (Bone Minerals Density): dual- energy X-ray absorptiometry (DXA or DEXA scan; the most common) or bone densitometry.

Prevention and treatment: (prevention is better and easier than treatment)

- ✓ Exercise.
- ✓ Calcium & vitamin D.
- ✓ Bisphosphonates: reduce osteoclast activity; induces its apoptosis
- ✓ Denosumab: anti-RANKL; blocking osteoclast activation.
- ✓ Hormones (estrogen): we give the patient estrogen after being sure that she's not risking DVT (Deep Vein Thrombosis) and stroke.

Multiple Choice Questions

1) A 2-year-old boy is treated for recurrent fractures of his long bones. Physical examination reveals blue sclerae, loose joints, abnormal teeth, and poor hearing. Molecular diagnostic studies will most likely demonstrate a mutation in the gene encoding which of the following proteins?

a) Collagen
b) Dystrophin
c) Lysyl hydroxylase
d) Fibrillin
e) Fibroblast growth factor receptor

2) A 30-year-old man with dwarfism is admitted to the hospital for hip replacement due to severe osteoarthritis. He has short arms and legs and a relatively large head. His parents do not show signs of this congenital disease. This patient most likely has a spontaneous mutation in the gene encoding which of the following proteins?

a) Collagen type I
b) Collagen type II
c) Fibroblast growth factor receptor
d) Growth hormone receptor
e) Insulin-like growth factor

3) A 24-year-old man on chronic corticosteroid therapy for severe asthma presents with a 6-month history of increasing hip pain. This patient most likely exhibits symptoms of which of the following metabolic bone diseases?

a) Gaucher disease
b) Osteomalacia
c) Osteopetrosis
d) Osteoporosis
e) Paget disease

Answers: 1) A 2) C 3) D

BEST OF LUCK