

Lecture

2

CONGENITAL DISORDERS

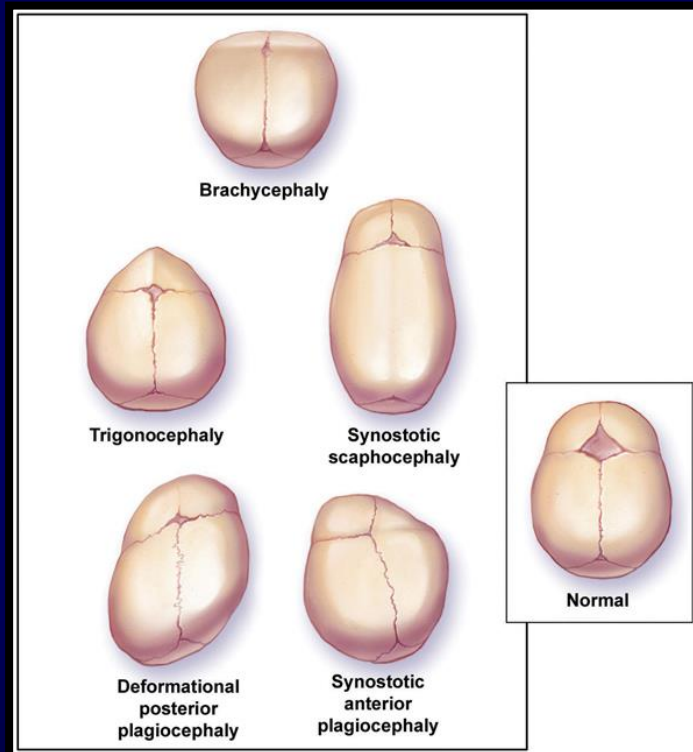
DYSOSTOSIS

- Abnormal condensation & migration of mesenchyme
- Genetic abnormalities of homeobox genes, cytokines and its receptors
 - Aplasia
 - Supernumerary digit
 - Syndactyly & craniosynostosis

DYSPLASIA

- Disorganized bone & cartilage
- Gene mutations that control development and remodeling
- Dysplasia here: not premalignant

DYSOSTOSIS




DYSPLASIAS

- **Achondroplasia (dwarfism): most common**
- **Mutations in FGFR3**
- **No impact on longevity, intelligence or reproductive status**

◦ **Achondroplasia**

- Caused by a gene mutation
- Shown to be associated with advanced paternal age.
- Gene mutation affects bone formation



Large head with prominent forehead

Normal-sized torso with short arms and legs

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



THANATOPHORIC DYSPLASIA

- Most common lethal form of dwarfism
- **FGFR3** mutations (different from Achondroplasia)
- Die at birth or shortly after (small chest leading to resp. insufficiency)



OSTEOGENESIS IMPERFECTA

• Most common inherited disorders of connective tissue

- Group of disorders; AD; deficiency of type I collagen synthesis
- Too little bone; fragility
- Blue sclera; hearing loss; teeth abnormalities
- Type 2 (lethal) and type I (relatively normal life)

Brittle bone disease

Osteogenesis imperfecta, a genetic disorder that results from a lack of the protein collagen, causes brittle bones that break easily.

Signs of the disorder

Symptoms vary and can range from mild to severe

Curved spine

Hearing loss (often starts in 20s or 30s)

Bowing of the back

Can cause spinal curvature called kyphosis, which can lead to a hunchback



Triangular-shaped face with broad forehead
Whites of eyes look blue, purple or gray
Brittle teeth

Barrel-shaped rib cage
Short, small body; deformed bones

Treatment

No cure; treatment involves managing symptoms

- Treating broken bones, brittle teeth
- Pain medications, physical therapy, use of assistive tools, such as braces, wheelchairs
- Good diet, exercise, no smoking or drinking alcohol, caffeine

OSTEOPETROSIS

- **Marble bone disease**
“stone bone” (group of disorders); rare
- **Impaired osteoclast function: reduced bone resorption leading to diffuse sclerosis**
- **Dx: X-ray**
- **Fractures and leukopenia in severe forms**





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

- **Osteopenia:** decreased bone mass (1-2.5 SD below the mean).
- **Osteoporosis:** severe osteopenia; > than 2.5 SD below the mean with increase risk for fractures
- **Generalized (much more common) or localized**

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

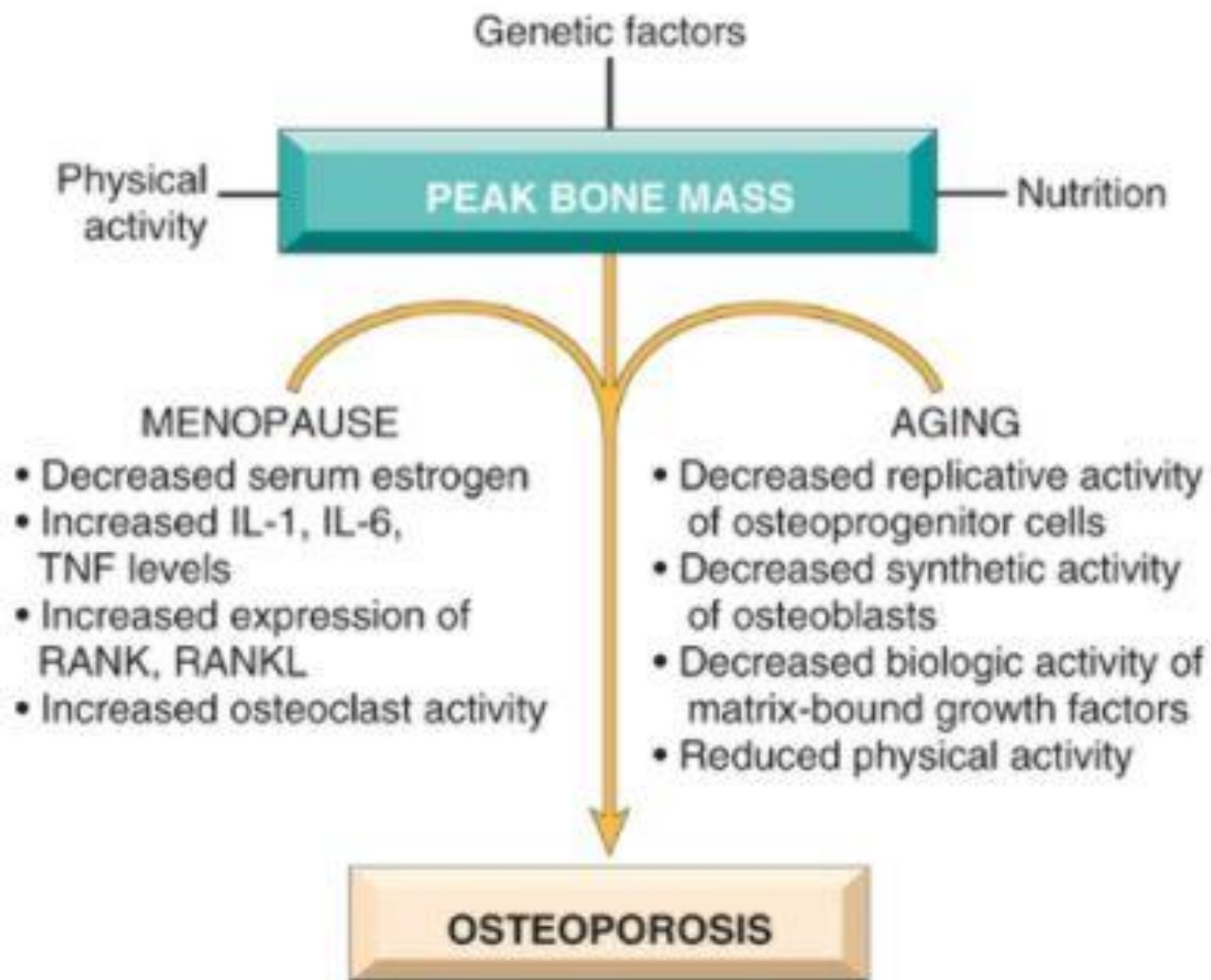


FIG. 21.5 Pathophysiology of postmenopausal and senile osteoporosis (see text).

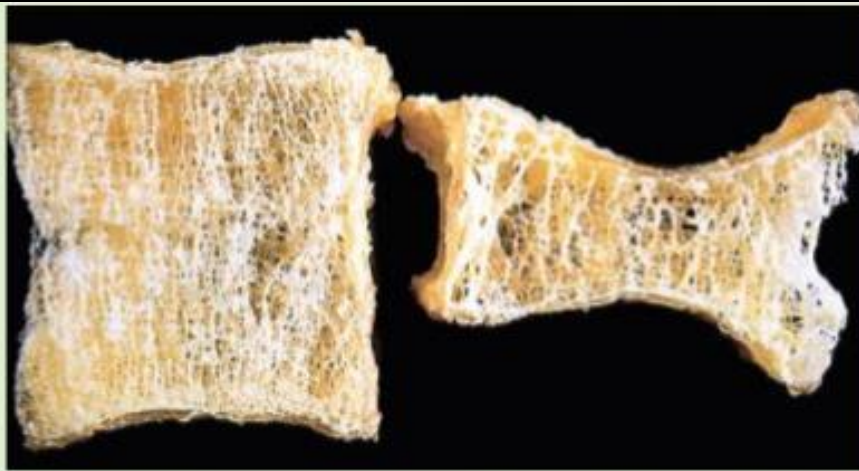



FIG. 21.6  Osteoporotic vertebral body (*right*) shortened by compression fracture.

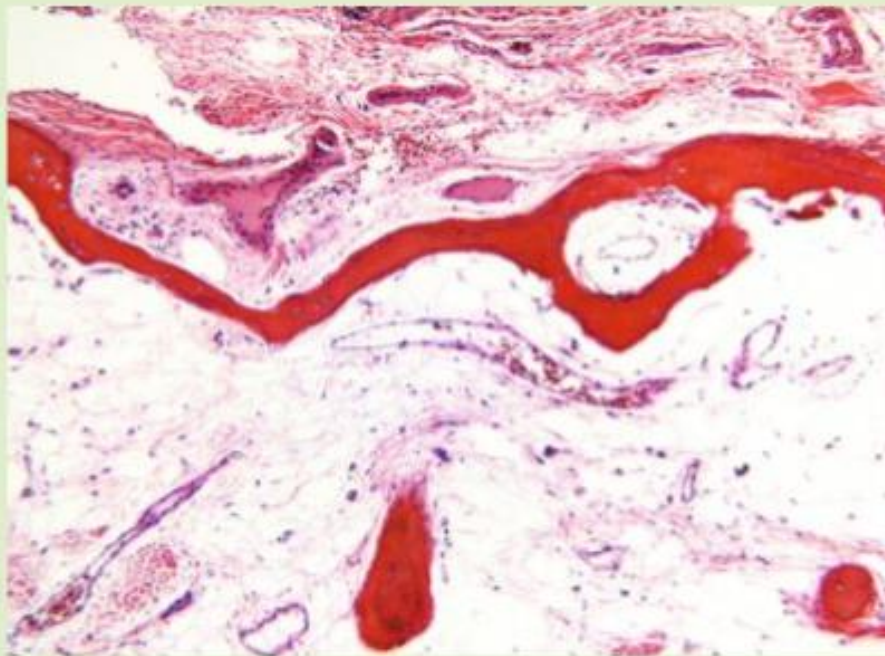

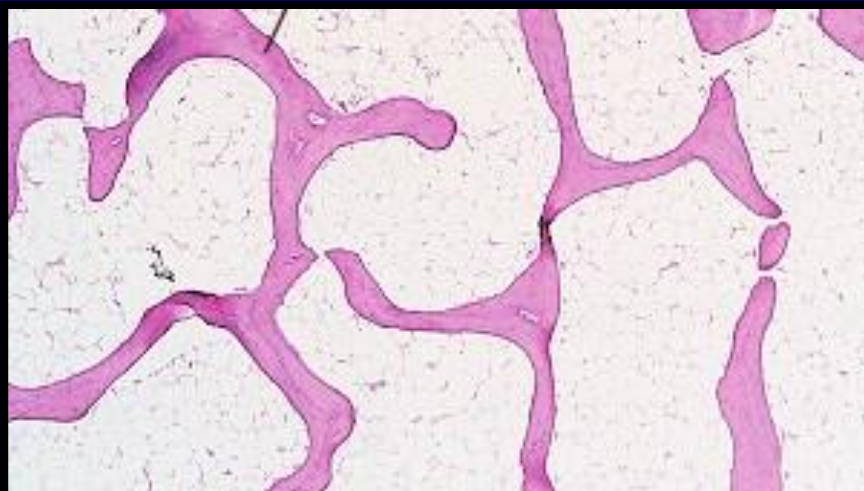
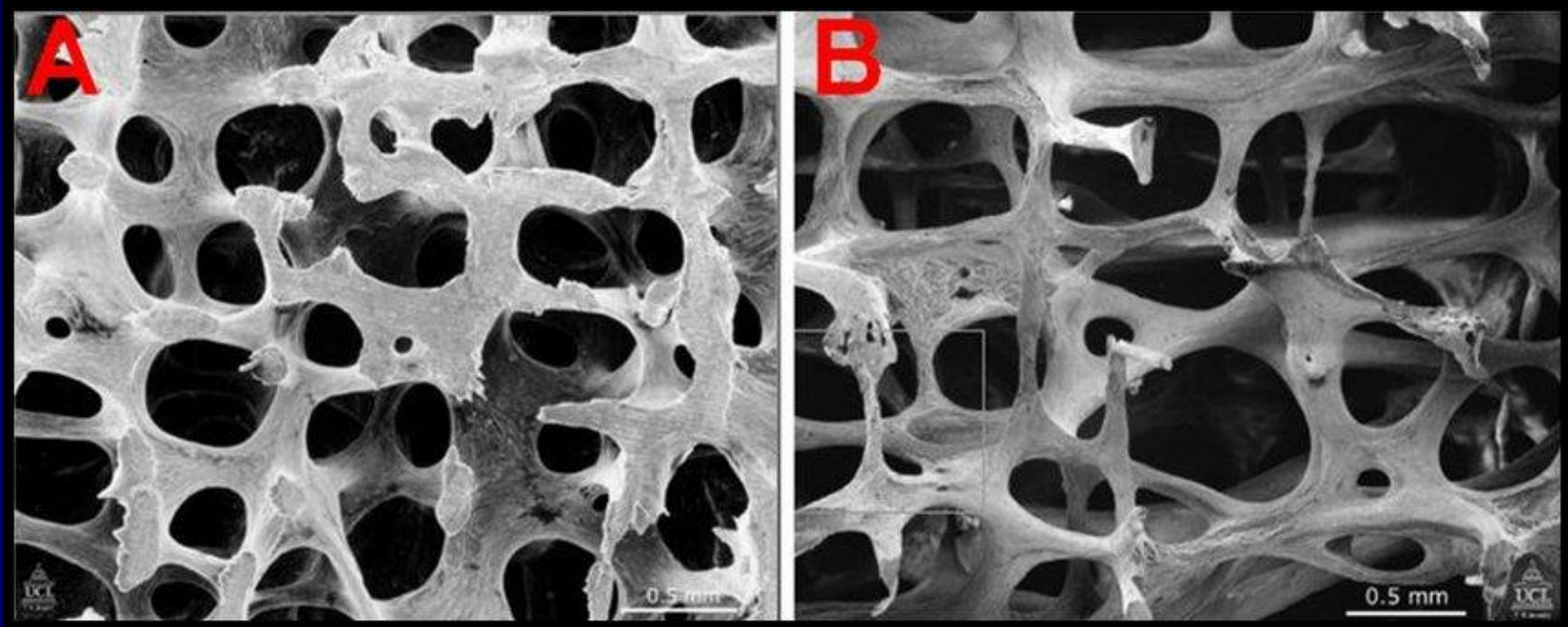


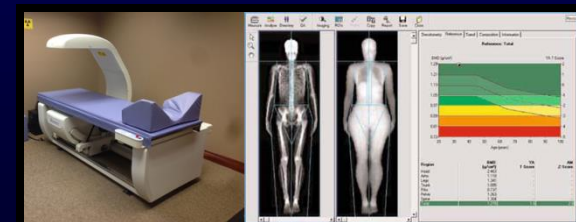
FIG. 21.7  In advanced osteoporosis, both the trabecular bone of the medulla (*b.*

Normal bone : Osteoporosis



OSTEOPOROSIS CLINICALLY

- **Vertebral fractures**
- **Femur and pelvic fractures: immobility, PEs, pneumonia (40-50K death/yr in USA)**
- **Diagnosis: special imaging technique, bone mineral density (BMD scan): dual-energy X-ray absorptiometry (DXA or DEXA scan) or bone densitometry**



PREVENTION AND TREATMENT

- **Exercise**
- **Calcium & vitamin D**
- **Bisphosphonates: reduce osteoclast activity and induce its apoptosis**
- **Denosumab: anti-RANKL; blocking osteoclast activation**
- **Hormones (estrogen): risking DVT and stroke**