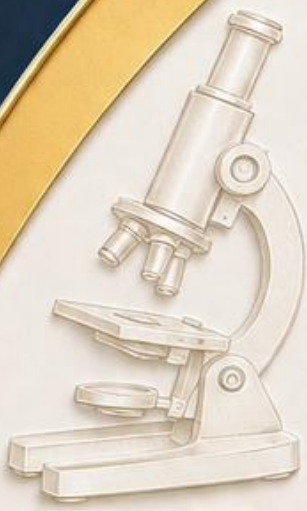

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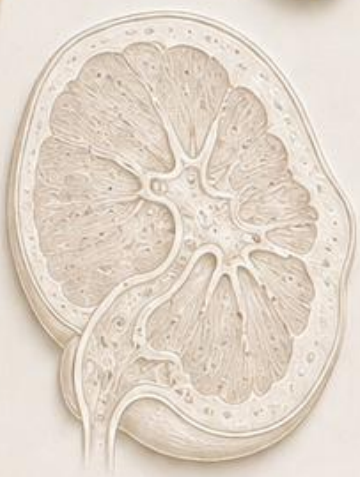
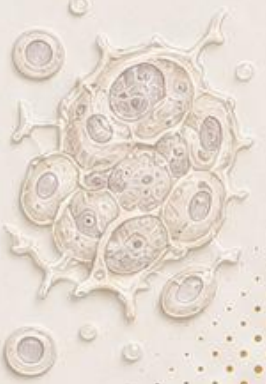


SEMESTER 3

MSK MODULE

— PATHOLOGY —



Lecture 1 & 2 - Pathology of Bone and Skin

Part 1: MCQs (Choose the correct answer):

1. A 24-year-old man sustains a closed fracture of the shaft of the right tibia. A biopsy taken from the fracture site on the fourth day shows a blood clot heavily infiltrated by inflammatory cells, with no cartilage and no osteoid. Which of the following stages of fracture healing does this represent?

A. Hematoma with inflammation
B. Soft callus
C. Hard callus
D. Remodeling
E. Non union

2. A 30-year-old woman fractured her humerus three weeks ago. A biopsy from the fracture site shows cartilage, non calcified osteoid and granulation tissue; osteoclasts are clearing the hematoma and the necrotic debris while osteoblasts are laying down osteoid. Which stage of fracture healing is represented?

A. Hematoma formation
B. Soft callus
C. Hard callus
D. Remodeling
E. Malunion

3. Six weeks after a fracture of the radius, a radiograph shows the fracture bridged by calcified osteoid in the form of woven bone, arranged as external, intermediate and internal components. Which of the following stages does this describe?

A. Hematoma
B. Soft callus
C. Hard callus
D. Remodeling
E. Malunion

4. Nine weeks after a fracture of the femur, lamellation has occurred and the osteoclasts have removed the external and the internal callus. Which of the following remains to re-form the bone cortex?

A. The external callus
B. The internal callus
C. The organized hematoma
D. The granulation tissue
E. The intermediate callus

5. A 62-year-old diabetic woman on long-term corticosteroid therapy sustains a fracture that fails to heal. Which of the following factors that delay bone healing is a LOCAL rather than a systemic factor?

A. Advanced age
B. Diabetes mellitus
C. Corticosteroid therapy
D. Inadequate immobilization of the fracture
E. Haemophilia

6. A 45-year-old man sustained a fracture of the shaft of the tibia one year ago. A radiograph now shows the fracture ends still separated by a wide space with interposed soft tissue and no bony bridging. Which complication of fracture healing has occurred?

A. Malunion
B. Avascular necrosis
C. Osteomyelitis
D. Non union
E. Hard callus formation

7. A 7-year-old boy develops sudden high fever, night sweats and severe throbbing pain with swelling of the lower thigh, two weeks after an attack of tonsillitis. Blood culture is positive. Which of the following organisms is the most likely cause?

A. Mycobacterium tuberculosis
B. Staphylococcus aureus
C. Treponema pallidum
D. Escherichia coli
E. Candida albicans

8. Acute haematogenous osteomyelitis in children characteristically starts in the metaphysis of a long bone. Which of the following best explains this localization?

A. The metaphysis has no periosteal covering
B. The metaphysis is avascular in children
C. The metaphysis lacks a Haversian system
D. The metaphysis is a site of frequent hematoma and slow blood flow
E. The metaphysis contains no osteoclasts

9. A 9-year-old boy with neglected osteomyelitis of the tibia is operated upon. The surgeon removes a piece of dead bone that has been separated from the surrounding living bone by osteoclasts and that was lying within a sinus tract. Which of the following terms describes this piece of bone?

A. Involucrum
B. Cloaca
C. Sequestrum
D. Brodie's abscess
E. Nidus

10. In the same patient, the radiograph also shows a shell of new bone that has been created by the periosteum and deposited around the dead bone. This new bone is known as:

A. Sequestrum
B. Cloaca
C. Hard callus
D. Sclerotic rim
E. Involucrum

11. In acute pyogenic osteomyelitis, subperiosteal abscesses impair the blood supply, causing more necrosis and often draining sinuses through which pus escapes to the surface. These draining sinuses are termed:

A. Sequestra
B. Involucra
C. Cloacae
D. Looser zones
E. Brodie's abscesses

12. A 6-year-old boy with untreated acute haematogenous osteomyelitis of the femur becomes toxic with spiking fever, and develops multiple pyogenic abscesses in the lungs and kidneys. Which complication has developed?

A. Systemic pyaemia
B. Secondary amyloidosis
C. Avascular necrosis
D. Malunion
E. Pathological fracture

13. A 20-year-old man who received an inadequate course of antibiotics for osteomyelitis presents with repeated acute flare ups of pain in the tibia. X-ray shows a circumscribed cavity in the metaphysis filled with pus and surrounded by sclerotic bone. What is the most likely diagnosis?

A. Simple bone cyst
B. Aneurysmal bone cyst
C. Brown tumor of hyperparathyroidism
D. Osteoid osteoma
E. Brodie's abscess in chronic suppurative osteomyelitis

14. A 30-year-old man with pulmonary tuberculosis develops back pain and a progressive angular kyphosis. Imaging shows destruction of two adjacent thoracic vertebral bodies with a paravertebral soft tissue collection that is neither hot nor red. Which of the following statements about this condition is correct?

A. It reaches the bone mainly by direct extension from the lung
B. It typically affects the metaphysis of long bones
C. The soft tissue collection is called a “cold” abscess
D. It never causes paraplegia
E. Secondary amyloidosis does not occur

15. Polydactyly, syndactyly, split hand and aplasia of bones result from localized problems in the migration of mesenchymal cells and the formation of condensations. These congenital bone diseases are classified as:

A. Dysplasias
B. Dysostoses
C. Acquired osteodystrophies
D. Tumor like lesions
E. Metabolic bone diseases

16. A 2-year-old child is referred for suspected child abuse because of repeated fractures. Examination reveals blue sclerae, defective dentition, diminished hearing and a triangular facies, with no bruises or lacerations of the skin. Which of the following is the underlying defect?

A. Autosomal recessive defect in type IV collagen
B. Autosomal dominant defect in type I collagen production
C. Point mutation in FGFR3
D. Reduced osteoclast mediated bone resorption
E. Vitamin D deficiency

17. A 5-year-old boy has very short legs while his trunk and head are normally proportioned, and his intelligence is above average. The underlying mutation causes constitutive activation of a receptor that inhibits chondrocyte proliferation and suppresses expansion of the epiphyseal growth plate. What is the most likely diagnosis?

A. Osteogenesis imperfecta
B. Osteopetrosis
C. Achondroplasia
D. Rickets
E. Fibrous dysplasia

18. A 1-year-old infant has anemia, recurrent infections, hepatosplenomegaly, blindness and repeated fractures. Radiographs show diffusely dense “marble” bones. Which of the following is the basic defect?

A. Increased osteoclastic resorption with accelerated remodeling
B. Defective mineralization of osteoid
C. Defective type I collagen synthesis
D. Reduced osteoclast mediated bone resorption with defective bone remodeling
E. Compensatory hypersecretion of parathyroid hormone

19. In the infant described above, the anemia and the hepatosplenomegaly are best explained by which of the following mechanisms?

A. Chronic blood loss from the repeated fractures
B. Bone expansion leading to bone marrow narrowing with extra medullary hematopoiesis
C. Secondary amyloidosis of the bone marrow
D. Vitamin D deficiency
E. Compression of the optic and auditory nerves by the extra bone

20. Which of the following bone diseases is classified as an ACQUIRED osteodystrophy?

A. Achondroplasia
B. Osteogenesis imperfecta
C. Osteopetrosis
D. Renal osteodystrophy
E. Syndactyly

21. A 68-year-old woman has lost height over the past years and complains of back pain. Examination shows a “dowager's hump” with lumbar lordosis and kyphoscoliosis, and a DEXA scan confirms low bone density. What is the most likely diagnosis?

A. Osteomalacia
B. Osteoporosis
C. Paget disease of bone
D. Osteopetrosis
E. Primary hyperparathyroidism

22. Which of the following biochemical patterns is expected in the patient described above?

A. Low serum calcium, low phosphorus and high PTH
B. High serum calcium with low PTH
C. Normal serum calcium, phosphorus and PTH
D. Low serum calcium with high alkaline phosphatase
E. High serum phosphorus with low serum calcium

23. A 66-year-old postmenopausal woman with osteoporosis is started on a bisphosphonate. Which of the following best describes the mechanism of action of this drug?

A. It binds to bone and inhibits osteoclasts
B. It stimulates osteoblastic bone formation
C. It increases parathyroid hormone secretion
D. It increases renal excretion of calcium
E. It replaces the deficient type I collagen

24. A 70-year-old man of European descent has an enlarging skull with headache, a bowed tibia, arthritis and warmth over the affected bones. Which of the following best describes the basic disturbance in this disease?

A. Defective mineralization of bone matrix
B. Reduced osteoclast activity with dense bone
C. A localized defect in the migration of mesenchymal cells
D. Impaired production of type I collagen
E. Increased bone destruction with an accelerated rate of bone remodeling

25. In Paget disease of bone, which of the following phases is characterized by intense osteoclastic resorption?

A. Lytic phase
B. Mixed phase
C. Sclerotic phase
D. Remodeling phase
E. Mineralization phase

26. A bone biopsy from a patient with Paget disease shows profound bone resorption with numerous large osteoclasts containing multiple nuclei per cell, together with woven bone and irregular broad trabeculae. Which additional microscopic feature is most characteristic of this disease?

A. Lace like osteoid deposited by atypical osteoblasts
B. Caseating granulomas
C. Non calcified osteoid seams
D. Disorganized cement lines in a mosaic pattern
E. Peritrabecular fibrosis with hemorrhage

27. A 72-year-old man with long standing Paget disease of the femur develops new intense pain and swelling of the thigh. Which of the following complications should be suspected first?

A. Osteomyelitis
B. High output heart failure
C. Cranial nerve impingement
D. Secondary amyloidosis
E. Paget's sarcoma

28. A 2-year-old child who is rarely exposed to sunlight has bowing of the legs (genu varum), a rachitic rosary, a prominent frontal bone, craniotabes and delayed closure of the fontanelles. What is the most likely diagnosis?

A. Osteomalacia
B. Achondroplasia
C. Osteogenesis imperfecta
D. Rickets
E. Osteopetrosis

29. A 45-year-old woman with chronic malabsorption has diffuse bone and joint pain with proximal muscle weakness. X-ray of the pelvis shows osteopenia with Looser zones (pseudofractures) of the pubic rami. Which set of laboratory findings is expected?

A. Low vitamin D, low blood calcium, high PTH, low phosphate and high alkaline phosphatase
B. Normal vitamin D, normal calcium, normal PTH and normal alkaline phosphatase
C. High vitamin D, high calcium and low PTH
D. Low vitamin D, high calcium, low PTH and high phosphate
E. Normal calcium with low alkaline phosphatase

30. A 52-year-old woman with a parathyroid adenoma complains of bone pain. Radiographs of the hands show subperiosteal bone resorption of the phalanges with cysts, and a biopsy shows peritrabecular fibrosis with hemorrhage and osteoclasts tunnelling centrally along the length of the trabeculae. Which term best describes this bone lesion?

A. Osteitis deformans
B. Brodie's abscess
C. Osteitis fibrosa cystica (von Recklinghausen's disease of bone)
D. Fibrous dysplasia
E. Aneurysmal bone cyst

Part 2: Essay / Short-Answer Questions:

1. A 24-year-old man sustained a closed fracture of the shaft of the left tibia after a road traffic accident. The fracture was properly reduced and immobilized and healing proceeded normally.

A. Enumerate the four stages of healing of a bone fracture, mentioning the time of each.

B. Describe the soft callus, mentioning the role of the osteoclasts and the osteoblasts in this stage.

C. Describe what happens during the stage of remodeling.

2. A 62-year-old diabetic woman on long term corticosteroid therapy sustained an open fracture of the tibia contaminated with debris. Six months later the fracture had not united.

A. Enumerate the local factors that affect bone healing.

B. Enumerate the systemic factors that affect bone healing.

C. Mention the causes of delayed union and non union.

3. Enumerate the complications of healing of a bone fracture, defining malunion and non union.

4. A 7-year-old boy developed sudden high grade fever, night sweats and malaise, with severe throbbing pain, redness and swelling over the upper part of the left leg two weeks after an attack of otitis media. Movement of the knee was restricted.

A. Give your provisional diagnosis and define it. Mention the most common causative organism, the usual source of infection, the mode of transmission and the usual age of the patient.

B. Mention the part of the long bone that is usually affected and explain why.

C. Describe the pathogenesis of this condition.

D. Define sequestrum, involucrum and cloaca.

5. Regarding acute haematogenous osteomyelitis:

A. Mention the sites usually affected in children.

B. Mention the clinical picture.

C. Mention the methods used for diagnosis.

D. Enumerate the complications.

6. A 20-year-old man who had received an inadequate course of antibiotics for acute osteomyelitis presents with repeated acute flare ups of pain in the tibia. X-ray shows a circumscribed cavity in the metaphysis filled with pus and surrounded by sclerotic bone.

A. Give your provisional diagnosis and name the lesion shown in the X-ray.

B. Mention the causes of this condition.

C. Describe the pathology of the lesion.

D. Enumerate the complications.

7. A 30-year-old man with pulmonary tuberculosis developed back pain, a progressive angular deformity of the spine and weakness of both lower limbs. A fluctuant swelling later appeared in the groin, which was neither hot nor red.

A. Name the disease affecting the spine and mention the mode of spread of the organism to the bone.

B. Mention the bones that are mainly affected.

C. Explain the deformity of the spine and the nature of the swelling in the groin.

D. Enumerate the complications.

8. Define bone dystrophy and classify it, giving two examples of each group. Mention the difference between a dysostosis and a dysplasia, and enumerate the developmental bone diseases that behave as tumor like lesions.

9. A 2-year-old child was referred by a social worker for suspected child abuse because of repeated fractures of the ribs and of the upper and lower limbs. Examination revealed blue sclerae, defective dentition, diminished hearing and scoliosis, with no contusions or lacerations of the skin.

A. Give your provisional diagnosis, and mention its mode of inheritance and its pathogenesis.

B. Enumerate the manifestations of this disease.

10. Tabulate the differences between achondroplasia and osteopetrosis as regards the basic defect, the effect on the bone and the main clinical manifestations. Mention the treatment that was first used successfully in osteopetrosis.

11. An 82-year-old woman broke her right hip while attempting to go to the bathroom in the middle of the night. She had a history of wrist fracture 20 years ago when she slipped and fell on a wet floor. She is a strict vegan who rarely goes out in the sun, has lost height and has a "dowager's hump".

A. Give your provisional diagnosis and define the condition.

B. Mention the most common sites of fracture, and explain why this disease is called a "silent disease".

C. Enumerate the risk factors.

D. Mention the investigations with their expected results, and the lines of treatment.

12. A 70-year-old man of European descent complains of severe bone pain in the pelvis, femur and tibia, an enlarging skull with headache, and bowing of the tibia. There is erythema and warmth over the affected bones.

A. Give your provisional diagnosis and define the condition.

B. Mention the phases of this disease.

C. Describe the microscopic picture.

D. Enumerate the clinical features and the complications.

Part 1: MCQ Answer Key

1 **A** – Hematoma with inflammation Slide 3 (hematoma on day 1, inflammation day 3 – one week; cartilage and osteoid appear later)
2 **B** – Soft callus Slide 3 (up to w3: cartilage + non calcified osteoid + granulation tissue; osteoclasts clear the debris, osteoblasts lay osteoid)
3 **C** – Hard callus Slide 3 (up to w6: calcified osteoid (woven bone), with external, intermediate and internal components)
4 **E** – The intermediate callus Slide 3 (up to w9: lamellation with removal of the external and internal callus; the intermediate callus forms the cortex)
5 **D** – Inadequate immobilization of the fracture Slide 5 (immobilization is a local factor; age, diabetes, steroids and haemophilia are systemic)
6 **D** – Non union Slide 6 (due to a wide space between the fracture ends or soft tissue interposition; malunion = wrong alignment)
7 **B** – Staphylococcus aureus Slide 8 (commonest organism; source = septic focus (tonsillitis, otitis media, sinusitis); hematogenous spread, mainly in children)
8 **D** – The metaphysis is a site of frequent hematoma and slow blood flow Slide 9 (this is why acute osteomyelitis starts in the metaphysis of a long bone)
9 **C** – Sequestrum Slide 9 (dead bone separated from living bone by osteoclasts; may pass through the sinus tract)
10 **E** – Involucrum Slide 9 (new bone created by the periosteum and deposited around the sequestrum)
11 **C** – Cloacae Slide 9 (the draining sinuses formed as subperiosteal abscesses impair the blood supply and cause more necrosis)
12 **A** – Systemic pyaemia Slide 12 (with septicaemia and toxaemia, chronic suppurative osteomyelitis, chronic suppurative arthritis and direct spread)
13 **E** – Brodie's abscess in chronic suppurative osteomyelitis Slide 14 (follows delayed treatment, inadequate antibiotics, incomplete debridement or weak immunity (15-30%); a pus filled cavity in a sclerotic metaphysis with acute flare ups)
14 **C** – The soft tissue collection is called a “cold” abscess Slides 15 & 16 (TB reaches bone by hematogenous spread and affects the thoracic and lumbar vertebrae (Pott disease); a cold abscess lacks heat and redness)
15 **B** – Dysostoses Slides 18-20 (localized problems in mesenchymal cell migration and condensation; dysplasias are mutations affecting bone or cartilage formation)
16 **B** – Autosomal dominant defect in type I collagen production Slide 23 (osteogenesis imperfecta (brittle bone disease), with decreased bone mass)
17 **C** – Achondroplasia Slides 26 & 27 (FGFR3 point mutation → constitutive activation → inhibits chondrocyte proliferation → stunted endochondral growth; the cranial vault is spared)
18 **D** – Reduced osteoclast mediated bone resorption with defective bone remodeling Slide 28 (osteopetrosis (marble bone disease), AR or AD; bones dense yet more brittle than normal)
19 **B** – Bone expansion leading to bone marrow narrowing with extra medullary hematopoiesis Slide 29 (explains the anemia, recurrent infections and hepatosplenomegaly of osteopetrosis)
20 **D** – Renal osteodystrophy Slide 21 (the acquired group = osteoporosis, Paget disease, rickets and osteomalacia, hyperparathyroidism and renal osteodystrophy)
21 **B** – Osteoporosis Slides 30, 32 & 33 (low bone density and fragility; loss of height, back pain and vertebral collapse (dowager's hump); DEXA is diagnostic)
22 **C** – Normal serum calcium, phosphorus and PTH Slide 33 (the bone that remains is of normal composition)
23 **A** – It binds to bone and inhibits osteoclasts Slide 33 (with exercise, calcium and vitamin D intake, and estrogen replacement in postmenopausal women)
24 **E** – Increased bone destruction with an accelerated rate of bone remodeling Slides 34 & 35 (Paget disease of older adults, more prevalent in people of European descent; osteoblasts increase to compensate)
25 **A** – Lytic phase Slide 36 (then the mixed and the sclerotic phases; all three may co-exist in the same bone)
26 **D** – Disorganized cement lines in a mosaic pattern Slide 37 (with large multinucleated osteoclasts and irregular broad woven trabeculae)
27 **E** – Paget's sarcoma Slides 38 & 39 (osteosarcoma or fibrosarcoma; other complications are fractures, cranial nerve impingement and high output heart failure)
28 **D** – Rickets Slides 40 & 44 (vitamin D deficiency before epiphyseal fusion; craniotabes and delayed closure of the fontanelles are rickets specific)
29 **A** – Low vitamin D, low blood calcium, high PTH, low phosphate and high alkaline phosphatase Slides 43 & 45 (osteomalacia, with Looser zones (pseudofractures) of the pubic rami)
30 **C** – Osteitis fibrosa cystica (von Recklinghausen's disease of bone) Slides 47 & 48 (increased bone cell activity = osteitis, peritrabecular fibrosis = fibrosa, cystic brown tumors = cystica)

Part 2: Essay Answer Key

1. **Healing of a bone fracture — Slides 3 & 4** — A. (1) Hematoma (day 1) then inflammation (day 3 – one week); (2) Soft callus (up to w3); (3) Hard callus (up to w6); (4) Remodeling (up to w9). B. Soft callus = cartilage + non calcified osteoid + granulation tissue; osteoclasts clear the hematoma and necrotic debris while osteoblasts lay the osteoid (hard callus = calcified osteoid / woven bone: external, intermediate, internal). C. Remodeling = lamellation with removal of the external and internal callus by osteoclasts; the remaining intermediate callus forms the bone cortex.

2. **Factors affecting bone healing — Slides 5 & 6** — A. Local: immobilization; improper reduction with an abnormal position; infection, debris and dead tissue in the wound; joint involvement; damage to nerves or blood vessels; bone pathology (tumors, osteoporosis). B. Systemic: age; nutrition – vitamin and mineral deficiency; immune status; systemic diseases (chronic disease, diabetes); drugs – steroids; genetic disorders (haemophilia). C. Delayed and non union are due to the same factors that affect bone healing.

3. **Complications of healing of a bone fracture — Slide 6** — Malunion (union in a wrong alignment); non union (wide space between the fracture ends or soft tissue interposition); delayed union; infection – osteomyelitis; avascular necrosis. Delayed and non union may be due to the same factors that affect bone healing.

4. **Acute haematogenous osteomyelitis — Slides 7-11** — A. Inflammation of bone (osteo) and marrow (myelo) and the surrounding soft tissue; Staphylococcus aureus; source = a septic focus (tonsillitis, otitis media, sinusitis); hematogenous spread; mainly a disease of children. B. The metaphysis of a long bone — frequent hematoma and slow blood flow. C. Bacteria proliferate → inflammation and necrosis → spread along the Haversian system or the medullary cavity to the periosteum → subperiosteal abscesses impair the blood supply → more necrosis and draining sinuses. D. Sequestrum = dead bone separated by osteoclasts (may pass through the sinus tract); involucrum = new periosteal bone deposited around it; cloaca = the draining sinus.

5. **Sites, clinical picture, diagnosis and complications of acute osteomyelitis — Slides 12 & 13** — A. In children, at areas of rapid growth or increased risk of trauma — distal and proximal femur, proximal tibia, humerus, distal radius. B. Sudden high fever, night sweats, malaise, weight loss, chills and intense throbbing pain; local edema, tenderness, erythema and restricted movement. C. Signs and symptoms; X-ray = a destructive lytic focus surrounded by edema and a sclerotic rim; blood cultures +ve in 70%; biopsy. D. Septicaemia and toxaemia; systemic pyaemia; chronic suppurative osteomyelitis; chronic suppurative arthritis; direct spread to nearby tissues.

6. **Chronic suppurative osteomyelitis — Slide 14** — A. Chronic suppurative osteomyelitis; the lesion is a Brodie's abscess. B. Develops in 15-30% due to delayed treatment, inadequate antibiotics, incomplete surgical debridement of necrotic bone and weak immunity. C. Starts as a chronic suppurative inflammation forming a Brodie's abscess in the metaphysis of long bones of children and young adults — a circumscribed cavity filled with pus surrounded by sclerotic bone; clinically acute flare ups. D. Pathological fracture and secondary amyloidosis.

7. **Tuberculous osteomyelitis — Pott disease — Slides 15 & 16** — A. TB of the spine; hematogenous spread into the bones (rarely direct extension or lymphatic spread). B. Mainly the thoracic and lumbar vertebrae. C. Extensive necrosis and bone destruction with a compressed fracture and vertebral collapse → kyphosis; the groin swelling is a “cold” abscess — liquefied caseous material tracking down the sheath of psoas major (psoas abscess), lacking the heat and redness of a pyogenic abscess. D. Kyphosis; cold abscess; spinal cord compression → paraplegia or quadriplegia; secondary amyloidosis.

8. **Bone dystrophy — Slides 18-22** — A disturbance of bone growth, structure or development; congenital or acquired. Congenital: dysostosis = a developmental anomaly from localized problems in mesenchymal cell migration and condensation (aplasia, extra bones, abnormal fusion — polydactyly, syndactyly, split hand); dysplasia = abnormal formation from mutations interfering with bone or cartilage formation, growth or matrix (osteogenesis imperfecta, achondroplasia, osteopetrosis). Acquired (environmental): osteoporosis, Paget disease, rickets and osteomalacia, hyperparathyroidism, renal osteodystrophy. Tumor like lesions: fibrous dysplasia, simple bone cyst, aneurysmal bone cyst, brown tumor of hyperparathyroidism.

9. **Osteogenesis imperfecta — Slides 23-25** — A. Brittle bone disease; autosomal dominant defect in type I collagen production with decreased bone mass. B. One or more of: blue sclerae, triangular facies, macrocephaly, hearing loss, defective dentition, barrel chest, scoliosis, limb deformities, fractures, joint laxity, growth retardation, constipation and sweating.

10. **Achondroplasia versus osteopetrosis — Slides 26-29** — Achondroplasia: a point mutation in FGFR3 → constitutive activation → inhibits chondrocyte proliferation → suppresses expansion of the epiphyseal growth plate → severely stunted long bone growth; endochondral ossification is affected while intramembranous (cranial vault) is spared — very short limbs with a normally proportioned trunk and head. Osteopetrosis: AR or AD; reduced osteoclast mediated resorption → defective remodeling; bones dense (“stone” / marble bone) yet more brittle — deformity and fractures, anemia, recurrent infections and hepatosplenomegaly (marrow narrowing with extra medullary hematopoiesis), blindness and facial palsies, bone ache, cranial nerve palsies, hearing impairment. It was the first genetic disease treated with bone marrow transplantation.

11. **Osteoporosis — Slides 30-33** — A. A metabolic skeletal disease with low bone density, increased bone fragility and susceptibility to fracture; PTH and corticosteroids depress the osteoblast side while vitamin D, calcitonin and the estrogen/androgen receptors act on the osteoclast side. B. Vertebrae, wrist and hips; a “silent disease” because bone mass is lost over many years with no signs or symptoms. C. Female > male, increasing age, inadequate calcium and vitamin D, estrogen deficiency or menopause, family history, lack of physical activity, smoking and alcohol, corticosteroids and antiseizure drugs, low weight and BMI, Caucasian and Asian. D. Loss of height, back pain, vertebral collapse (dowager's hump), lumbar lordosis and kyphoscoliosis; DEXA is diagnostic and serum calcium, phosphorus and PTH are normal (the remaining bone is of normal composition); treatment = exercise, calcium and vitamin D, bisphosphonates (bind bone and inhibit osteoclasts) and estrogen replacement.

12. **Paget disease of bone — osteitis deformans — Slides 34-39** — A. A metabolic disease of increased bone destruction and remodeling causing skeletal deformities; older adults, common (2-9%), rising with age, more prevalent in people of European descent; increased osteoclastic activity with accelerated remodeling and compensatory osteoblastic activity; skull, lumbar vertebrae, pelvis, femur and tibia. B. Lytic (osteoclastic), mixed (osteoclastic and osteoblastic) and sclerotic (osteosclerotic) phases, which may all co-exist in the same bone. C. Numerous large osteoclasts with multiple nuclei per cell, and woven bone with irregular broad trabeculae showing disorganized cement lines in a mosaic pattern. D. 75% asymptomatic; severe bone pain (pelvis, femur, tibia), bowed tibia, arthritis, erythema and warmth, enlarged skull with leontiasis and headache. Complications: fractures, Paget's sarcoma (new intense pain and swelling — osteosarcoma or fibrosarcoma), cranial nerve impingement (optic, auditory) and high output heart failure.

13. **Rickets and osteomalacia — Slides 40-46** — Rickets: in children, prior to epiphyseal fusion — vitamin D deficiency causes growth retardation with expansion of the growth plate. Osteomalacia: in adults — the hypocalcemia and hypophosphatemia impair mineralization of bone matrix proteins. Vitamin D must be sufficient (food, sunlight) and activated: liver 25-hydroxylase → 25-(OH)-D, kidney 1-α-hydroxylase → 1,25-(OH)-D (calcitriol), which raises renal reabsorption of calcium and intestinal absorption of calcium and phosphate. A. Common: diffuse bone and joint pain, proximal muscle weakness, bone fragility, increased fracture risk, muscle spasms and numbness; rickets specific: craniotabes and delayed closure of the fontanelles (also prominent frontal bone, rachitic rosary, protruding abdomen, genu varum). B. Low vitamin D and calcium → high PTH → low phosphate, with high alkaline phosphatase; X-ray = osteopenia with Looser zones (pseudofractures) of the pubic rami, and in rickets metaphyseal cupping, flaring and fraying with bowing of the legs. C. Vitamin D supplementation and treating the underlying cause; prevention by vitamin D in pregnancy and for neonates and infants.

14. **Hyperparathyroidism — Slides 47 & 48** — A. Primary = hyperplasia or adenoma; secondary = prolonged hypocalcemia with compensatory hypersecretion of PTH. B. Increased PTH → activates the osteoblast → RANK-L → stimulates osteoclast activity → bone resorption. C. Osteitis fibrosa cystica (von Recklinghausen's disease of bone) = the severe changes, now rare as the disease is detected early; subperiosteal resorption produces thinned cortices, hemorrhage and cysts, and osteoclasts tunnel into and dissect centrally along the trabeculae — increased bone cell activity = “osteitis”, peritrabecular fibrosis = “fibrosa”, cystic brown tumors = “cystica”. D. Brown tumor = a large osteolytic lesion resembling a bone tumor, brown due to hemorrhage.