Objectives

- Appreciate the spectrum of non-neoplastic and neoplastic conditions affecting the bones and joints
- Understand the pathogenesis and clinical complications of the more common pathologic conditions
- Be able to describe basic morphologic features of more common conditions and tumours, with clinical and radiologic correlations

Outline

I. Structure and Function of Bone

a. **Function, Structure and Components**
b. **Bone development:** *Endochondral vs intramembranous ossification*
c. **Homeostasis and Remodeling**

II. Developmental Disorders of Bone and Cartilage

a. **Dysostosis vs Dysplasia**
b. **Defects in transcription factors, proteins and metabolic pathways**

III. Metabolic Diseases of Bone

a. **Osteopenia and Osteoporosis**
b. **Osteomalacia and Rickets**
c. **Hyperparathyroidism**
d. **Renal osteodystrophy**
e. **Paget disease (Osteitis Deformans)**

IV. Fractures, Osteonecrosis and Osteomyelitis

a. **Fractures:** *Healing*
b. **Osteonecrosis (avascular necrosis)**
c. **Osteomyelitis:** *Pyogenic, Mycobacterial*

V. Bone Tumours and Tumour-like Lesions

a. **Bone-forming tumours:** *Osteoid osteoma, Osteoblastoma, Osteosarcoma*
b. **Cartilage-forming tumours:** *Osteochondroma, Chondroma, Chondrosarcoma*
c. **Tumours of unknown origin:** *Giant cell tumour, Ewing sarcoma*
d. **Fibrous and fibo-osseous tumours:** *Non-ossifying fibroma, Fibrous dysplasia*
e. **Metastatic tumours**

VI. Structure and Function of Joints

a. **Solid vs Cavitated**

VII. Arthritis

a. **Mechanical injury:** *Osteoarthritis*
b. **Immune reaction:** *Rheumatoid arthritis*
c. **Infections:** *Suppurative, Mycobacterial, Viral, Lyme arthritis*
d. **Crystal-induced:** *Gout, Calcium pyrophosphate crystal deposition disease (pseudogout)*

VIII. Joint Tumours and Tumour-like Conditions

a. **Reactive tumour-like lesions:** *Ganglion cysts, Synovial cysts, Osteochondral loose bodies*
b. **Primary neoplasms:** *Tenosynovial giant cell tumour*

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed.

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. STRUCTURE AND FUNCTION OF BONE

Functions: mechanical support, force transmission, internal organ protection, mineral homeostasis, site of haematopoiesis during postnatal life

Structure: Long bones – dense outer **cortex** and central **medulla** (comprising bony trabeculae interspersed with fatty (white) marrow or haematopoietic (red) marrow). Midshaft = **diaphysis**, longitudinal ends = **epiphysis**

Components:

Extracellular matrix	• **Osteoid** (35%): mainly ***Type I collagen***; also ***glycosaminoglycans***, other proteins e.g. ***osteopontin/osteocalcin*** (produced by osteoblasts and contributes to regulation of bone formation, mineralization and calcium homeostasis). • **Minerals** (65%): mainly ***hydroxyapatite***; repository for 99% of calcium and 85% of phosphorus in the body. Gives bone its hardness.
	Woven bone matrix: produced rapidly (e.g. fracture repair, fetal development) but less structural integrity due to haphazard arrangement of collagen fibers. Always abnormal in adults, but not specific for any particular disease ***Lamellar bone matrix:*** mature; parallel collagen fibers lend more structural integrity
Cells	• **Osteoblasts**: on the surface of osteoid matrix. ***Synthesize, transport and assemble matrix, and regulate mineralization***. Activity tightly regulated by hormonal and local mediators. When quiescent, may either remain on the surface or become embedded within the matrix as osteocytes • **Osteocytes**: interconnected by network of dendritic cytoplasmic processes through canaliculi within the matrix. ***Helps control calcium and phosphate levels in the microenvironment, detect mechanical forces and translate them into biologic activity (i.e. mechanotransduction)*** • **Osteoclasts**: specialized multinucleated macrophages. ***Resorb bone:*** *osteoclasts attach to the matrix via surface integrin proteins, create a resorption pit, and secrete acid and neutral proteases (mostly matrix metalloproteases - MMPs) into the pit to dissolve inorganic and organic bone components*

Development

Endochondral ossification: Most bones that form during embryogenesis

- Mesenchymal precursor cells synthesize a **cartilage mold (anlagen)**
- At 8 weeks, chondroblasts create a **central medullary canal** within the anlagen, while osteoblasts deposit the **cortex** beneath the early periosteum of the diaphysis = **primary center of ossification** (for *radial bone growth*). **Secondary centers of ossification** are formed at the epiphysis
- Plates of cartilage eventually become entrapped between the expanding ossification centers, forming **growth plates** (physes). Chondrocytes here undergo sequential proliferation, hypertrophy and apoptosis; matrix is mineralized and invaded by capillaries which provides nutrients for osteoblast activation and osteoid synthesis. Most calcified cartilage matrix is eventually resorbed, leaving only strut-shaped remnants (primary spongiosa) that serve as scaffolding for bone deposits. This overall process results in *longitudinal bone growth*

Intramembranous ossification: Flat bones e.g. cranium.

- Dense layer of mesenchyme is directly ossified by osteoblasts **without** a cartilage anlagen
- Bones enlarge through **appositional growth** i.e. deposition of new bone on a pre-existing surface

Local and systemic regulatory factors:

Growth hormone (GH)	Secreted by anterior pituitary gland	Maintains chondrocyte proliferation
Thyroid hormone	Thyroid gland	Induces hypertrophy of proliferating chondrocytes
Indian hedgehog (Ihh)	Prehypertrophic chondrocytes	Coordinates chondrocyte and osteoblast proliferation / differentiation
Parathyroid hormone-related protein (PTHrP)	Perichondrial stromal cells, early proliferating chondrocytes	Activates PTH receptor to maintain chondrocyte proliferation
Wnt growth factors	Expressed in the growth plate proliferating zone	Activate b-catenin to promote chondrocyte proliferation and maturation
SOX9	Transcription factor expressed by proliferating chondrocytes	For differentiation of chondrocyte precursors
RUNX2	Transcription factor expressed in early hypertrophic chondrocytes and immature mesenchymal cells	Controls terminal chondrocyte and osteoblast differentiation
Fibroblast growth factors (esp. FGF-3)	Mesenchymal cells	Inhibits proliferation of hypertrophic chondrocytes and promotes differentiation
Bone morphogenic proteins (BMPs)	Expressed at various stages of chondrocyte development	Diverse effects on chondrocyte proliferation and hypertrophy at the growth plate

Homeostasis and remodeling

- **Remodeling**: continuous tightly regulated process that repairs damage and may change the bone shape in response to mechanical forces; ~10% of the skeleton each year
- Occurs within the bone (or basic) multicellular unit (BMU) i.e. a unit of coupled osteoblast and osteoclast activity on the bone surface
- Sequence of events: (1) osteoclast attachment, (2) bone resorption, (3) osteoblast attachment and proliferation, (4) matrix synthesis
- Regulated by cell-to-cell interactions and cytokines, and several signaling pathways:
    - **RANK/NF-KB signaling**: RANK ligand (RANKL) expressed on osteoblasts and marrow stromal cells interacts with RANK (transmembrane receptor activator for NF-KB, expressed on osteoclast precursors) → activates NF-KB which is essential for generation and survival of osteoclasts
    - **M-CSF** (macrophage colony stimulating factor): produced by osteoblasts and important for generation of osteoclasts
    - **WNT/b-catenin signaling:** Wnt proteins produced by osteoprogenitor cells binds to LRP5 and 6 on osteoblasts → activates beta-catenin signaling and *osteoprotegerin* (OPG) synthesis. OPG is a secreted decoy receptor by osteoblasts that can bind RANKL and prevent its interaction with RANK, thereby preventing bone resorption. WNT/b-catenin signaling is inhibited by *sclerostin* (produced by osteocytes)
- The balance between bone formation and resorption is thus modulated by RANK and WNT signaling, which can be affected by **systemic factors** e.g. hormones (parathyroid hormone, estrogen, testosterone, and glucocorticoids), vitamin D, inflammatory cytokines (e.g. IL-1) and growth factors (e.g. bone morphogenetic factors

- **Paracrine signaling** between osteoblasts and osteoclasts also affects the balance: matrix breakdown by osteoclasts during bone resorption liberates and activates growth factors, cytokines and enzymes e.g. collagenase that may stimulate osteoblasts and initiate bone deposition
- Peak bone mass is achieved in early adulthood after cessation of skeletal growth, and before resorption exceeds formation in the fourth decade onwards (age-related bone loss ~0.7%/yr)

II. DEVELOPMENTAL DISORDERS OF BONE AND CARTILAGE

Often stem from inherited mutations, and thus are apparent during the earliest stages of bone formation (in contrast to acquired disease, that usually appear in adulthood). Complex relationship between specific mutations and phenotypes: different point mutations in a single gene can result in distinct phenotypes, while mutations in disparate genes can have similar phenotypes

- **Dysostosis**: Localised disruption of the migration and condensation of mesenchyme. Usually due to genetic alterations affecting genes encoding transcription factors, cytokines, cytokine receptors e.g.
  - **Aplasia**: complete absence of a bone or entire digit
  - **Supernumerary digit**: extra bones/ digits
  - **Syndactyly, craniosynostosis**: abnormal fusion of bones
- **Dysplasia**: Global disorganization of bone and/or cartilage. Usually due to mutations in genes that control development or remodeling of the entire skeleton. Not a precursor of neoplasia

Defects in transcription factors (abnormalities in mesenchymal condensation and differentiation of osteoblasts and chondrocytes)		
Brachydactyly types D, E	*HOXD13*	Shortening of terminal phalanx of the thumb and big toe, respectively
Defects in hormone and signal transduction proteins (abnormalities in proliferation/maturation of osteoblasts, osteoclasts or chondrocytes)		
Achondroplasia	*FGFR3*	AD. Most common skeletal dysplasia, major cause of dwarfism. *FGFR3* gain of function mutation exaggerates the inhibition of endochondral growth, resulting in shortened proximal extremities (rhizomelic shortening), frontal bossing but a trunk of relatively normal length. Does not affect lifespan, intelligence or reproductive status
Thanatophoric dysplasia	*FGFR3*	Most common lethal form of dwarfism. Different *FGFR3* mutations from achondroplasia, causing a more severe phenotype. Undeveloped chest cavity leads to respiratory insufficiency and death at/after birth
Defects in extracellular structural proteins (abnormalities in collagen types)		
Osteogenesis Imperfecta (OI) **'brittle bone disease'**	*COL1A1* *COL1A2*	AD. Most common inherited disorder of connective tissue caused by deficiency in type I collagen synthesis – mutations in genes encoding type I collagen α1 and α2 chains cause misfolding and defective assembly of collagen chains, with a dominant negative effect. Heterogeneous phenotype (4 major clinical subtypes of varying severity), all characterized by extreme skeletal fragility
Defects in metabolic pathways (enzymes, ion channels and transporters)		
Osteopetrosis		Group of rare genetic diseases characterized by reduced bone resorption due to deficient osteoclast development or function, which leads to diffuse symmetric skeletal sclerosis which are brittle. Different variants based on mode of inheritance and severity of clinical findings. **Pathogenesis**: Most mutations interfere with acidification of the osteoclast resorption pit, which is required for the dissolution of calcium hydroxyapatite within the matrix e.g. carbonic anhydrase

		Morphology and clinical complications: Bulbous misshapen ends of long bones (Erlenmeyer flask deformity) that lack medullary canals. - Small neural foramina compress exiting nerves → cranial nerve defects - Persistent primary spongiosa that fills medullary cavity leaves no room for haematopoietic marrow → cytopenias and compensatory extramedullary haematopoiesis (hepatosplenomegaly)) - Deposited bone often not remodeled, tends to be women rather than lamellar → fractures
Diseases associated with defects in degradation of macromolecules		
Mucopolysaccharidoses	Lysosomal storage diseases caused by enzyme deficiencies (primarily acid hydrolases). Chondrocytes normally degrade extracellular matrix mucopolysaccharides; in these diseases, the mucopolysaccharides accumulate within chondrocytes and induce apoptosis, as well as extracellularly, leading to structural defects in articular cartilage → short stature, malformed bones and chest wall	

III. METABOLIC DISEASES OF BONE

Osteopenia and osteoporosis

Osteopenia: decreased bone mass but normal mineralization of bone
Osteoporosis = osteopenia that is severe enough to significantly increase the risk of fracture

- May be **localized** to a certain bone/region (e.g. disuse of a limb), or **generalized** (as a manifestation of a metabolic bone disease)
    - **Primary osteoporosis**: Idiopathic, senile, postmenopausal (latter two are most common)
    - **Secondary causes**: Endocrine (e.g. Hyper/hypothyroidism, hyperparathyroidism, pituitary tumours), Gastrointestinal (e.g. malabsorption, vitamin C, D deficiencies), Drugs (e.g. alcohol, corticosteroids, chemotherapy), Miscellaneous (e.g. anaemia, immobilization, multiple myeloma, carcinomatosis)
- **Pathogenesis:** Bone mass is determined by hereditary factors (esp. polymorphisms that influence bone metabolism), physical activity, nutrition, age and hormonal state
    - **Age-related changes (senile osteoporosis)**: reduced proliferative and biosynthetic capacity, and attenuated response to growth factors of osteoblasts. Low-turnover
    - **Reduced physical activity**: increased bone loss because mechanical forces normally stimulate bone remodelling. Load magnitude has greater effect than load repetition. Contributes to senile osteoporosis
    - **Genetic factors**: single gene defects are rare; polymorphisms are more common
    - **Calcium nutritional state**: more impact if it occurs during a period of rapid bone growth. Relative deficiencies of calcium and vitamin D, and elevated PTH may contribute to senile osteoporosis
    - **Hormonal influences**: ~40% of postmenopausal women are affected by postmenopausal osteoporosis, due to estrogen deficiency, which increases bone resorption more than it increases bone formation (via increased secretion of inflammatory cytokines that increase and decrease RANKL and OPG). High-turnover

- **Clinical features**: depending on the bones involved; vertebral fractures (usu. thoracic and lumbar) can cause pain, loss of height and deformities e.g. lumbar lordosis, kyphoscoliosis, while fractures of the femoral neck, pelvis or spine lead to immbolisation and complications e.g. pulmonary embolism, pneumonia. Specialized radiographic imaging techniques (e.g. dual-energy X ray absorptiometry (DEXA)) that measure bone density provide the best estimate of bone loss. **Management**: Prevention /treatment includes exercise, calcium and Vit D intake, drugs e.g. bisphosphonates which reduce osteoclast activity, anti-RANKL antibody denosumab or menopausal hormone therapy (although the latter has other complications e.g. DVT, stroke)
- **Morphology:** Decreased quantity of histologically normal bone, affecting the entire skeleton but more severe in certain bones e.g. those that have increased surface area (e.g. cancellous compartment of vertebral bodies). *(postmenopausal osteoporosis)* perforation and thinning of trabecular plates with loss of interconnections, leading to microfractures and eventually vertebral collapse. *(senile osteoporosis)* cortical thinning by subperiosteal and endosteal resorption, and widening of Haversian systems

Osteomalacia and Rickets

Result from impaired mineralization of bone matrix, usu.due to abnormal Vit D metabolism or deficiency

Rickets = children; causes disturbance of endochondral ossification in the growth plates, leading to overgrowth of epiphyseal cartilage and failure of cartilage cells to mature. Severe deformities e.g. bowing of legs may result

Osteomalacia = adults; undermineralised bone formed during remodeling is prone to fractures

Hyperparathyroidism

- Causes **increased bone resorption**, via the effects of parathyroid hormone (PTH) on calcium homeostasis:
    - Increase synthesis of active Vit D by kidneys, thereby enhancing intestinal calcium absorption, and also inducing RANKL expression on osteoblasts, which then activates osteoclasts, increasing bone resorption and calcium mobilization
    - PTH also increases calcium resorption by renal tubules, and increases urinary phosphate excretion
    - Net elevated serum calcium normally inhibits PTH production; however, in excessive or inappropriate PTH release, **hyperparathyroidism results in unrestrained osteoclast activity**
- **Primary hyperparathyroidism**: Autonomous parathyroid secretion
- **Secondary hyperparathyroidism**: Result of renal disease, which has additional effects besides elevated PTH: loss of renal function and suppressive effects of hyperphosphatemia cause decreased α1-hydroxylase activity, thus decreasing active Vit D synthesis, and thereby limiting intestinal calcium absorption. Can also be complicated by metabolic acidosis, aluminium deposition in bone
- **Morphology**: 3 interrelated skeletal abnormalities (more severe in primary hyperPTH) that can regress or disappear completely when hyperparathyroidism is controlled –

1. **Osteoporosis**: Generalised, but most severe in phalanges, vertebrae and proximal femur. Histology shows **dissecting osteitis**: osteoclasts tunneling into and centrally dissecting along the length of the trabeculae, leaving adjacent marrow spaces to be replaced by fibrovascular tissue
2. **Brown tumour**: Mass lesion that forms from microfractures due to the bone loss, secondary haemorrhage, macrophage recruitment and ingrowth of reparative fibrous tissue ("brown" colour is due to vascularity, haemorrhage and haemosiderin). Cystic change is common
3. **Osteitis fibrosa cystica (von Recklinghausen disease of bone; generalised)**: Hallmark of severe hyperparathyroidism. Combination of increased bone cell activity, peritrabecular fibrosis and cystic brown tumours

Renal osteodystrophy

Collective term for the skeletal changes that occur in chronic renal disease (including dialysis-related): **osteopenia/osteoporosis, osteomalacia, secondary hyperparathyroidism, growth retardation**

- **Pathogenesis**: 3 mechanisms:
  - **Tubular dysfunction**: leads to renal tubular acidosis → systemic acidosis that dissolves hydroxyapatite, resulting in matrix demineralization and osteomalacia
  - **Secondary hyperparathyroidism**: due to reduced phosphate excretion, chronic hyperphosphatemia, and hypocalcemia
  - **Decreased biosynthetic function**: reduced renal vit D hydroxylation to produce active vit D, resulting in hypocalcemia that contributes to secondary hyperparathyroidism. Also disruption of the signaling between secreted proteins BMP-7, FGF-23 and the membrane protein Klotho which are involved in a regulatory hormone feedback loop between kidney and bone that regulates calcium and phosphate homeostasis, thereby contributing to osteopenia and osteomalacia
- **Morphologic types**:
  - **High-turnover osteodystrophy**: increased bone resorption >> increased bone formation
  - **Low-turnover/aplastic disease**: adynamic bone and sometimes osteomalacia
  - **Mixed pattern disease**: areas of high and low turnover

Paget disease (Osteitis Deformans)

Disorder marked by increased, but disordered and structurally unsound, bone mass. Develops in 3 sequential phases**: initial osteolytic stage**, **a mixed osteoclastic-osteoblastic stage**, and finally, a **burned-out quiescent osteosclerotic stage** (osteoblastic activity >>> osteoclasts)

- **Pathogenesis**: likely both genetic and environmental contributions (e.g. *SQSTM1* gene mutations, chronic infection of osteoclast precursors by RNA viruses)
- **Clinical features**: late adulthood, with geographic variation (Europe, US >> Asia, Africa). Can be monostotic (~15%) or polystotic (~85%), usually involves axial skeleton or proximal femur. Mostly asymptomatic, or pain due to microfractures / bone overgrowth that compresses spinal and cranial nerve roots. Radiographic diagnosis: enlarged bone with thick coarsened cortices and medulla. **Complications**: Increased heavy but weakened bone can cause nerve compression, secondary

osteoarthritis due to distorted weight-bearing bones (e.g. femoral head), chalkstick-type fractures (esp. lower extremities), vertebral compression fractures. Rarely, increased blood flow due to the hypervascularity of Pagetic bone can act as an arteriovenous shunt, leading to high output cardiac failure. <1% can develop sarcoma (usu. osteosarcoma or fibrosarcoma).

- **Histology**: varies over time and across sites
    - Lytic phase: Waves of **osteoclastic activity and numerous resorption pits**, with abnormally large osteoclasts (usually with many more than the normal 10-12 nuclei)
    - Mixed phase: **Osteoclasts persist, and plump osteoblasts** lining bone-forming surfaces, with the adjacent marrow replaced by loose connective tissue containing osteoprogenitor cells and blood vessels. Newly formed bone may be woven or lamellar, but eventually is all remodeled into lamellar bone
    - Sclerotic phase = Hallmark. **Mosaic jigsaw puzzle-like pattern of lamellar bone** due to unusually prominent cement lines joining haphazardly oriented units of lamellar bone. Periosseous fibrovascular tissue recedes and is replaced by normal marrow

IV. FRACTURES, OSTEONECROSIS AND OSTEOMYELITIS

Fractures

Loss of bone integrity. Fracture types and descriptors include: simple vs compound, comminuted, displaced, stress, greenstick. Pathologic fracture refers to bone weakened by an underlying disease process e.g. tumour

- Healing of fractures occurs in overlapping stages, involving regulated expression of multiple genes:
    - Immediately after fracture: **hematoma** forms and surrounds area of injury due to rupture of blood vessels. The clot provides a fibrin mesh that seals the fracture site, and provides a framework for the inflammatory cell influx, fibroblast ingrowth and capillary proliferation that characterize granulation tissue
    - Formation of **soft tissue callus / procallus** (uncalcified tissue): Release of PDGF, TGF-β, FGF and other growth factors by degranulated platelets and inflammatory cells activates osteoprogenitor cells in the periosteum, medullary cavity and surrounding soft tissues to stimulate osteoclastic and osteoblastic activity. Provides some anchorage but not structural rigidity for weight bearing
    - Formation of **bony callus** within 2-3 weeks of injury: the activated osteoprogenitor cells deposit subperiosteal trabeculae of women bone oriented perpendicular to the cortical axis and within the medullary cavity, transforming the procallus into bony callus. Activated soft tissue mesenchymal cells may also differentiate into chondrocytes that produce fibrocartilage and hyaline cartilage, that undergoes endochondral ossification. The fractured bone ends are thus bridged and progressively mineralized, helping to stabilize the fracture site and allow weight bearing
    - **Maturation** of bony callus: portions of excess fibrous tissue, cartilage and woven bone produced in the early stages of callus formation that are not subjected to physical stress are

resorbed, thus reducing the size of the healing bone and recreating lamellar bone. Restoration of the medullary cavity completes the healing process

- **Factors affecting healing:** age (children/young adults usually have near-perfect union), presence of background bone disorders e.g. osteoporosis, inadequate immobilization (callus movement can cause delayed union/non-union; persistent non-union can result in a false joint/pseudoarthrosis when the malformed callus undergoes cystic degeneration), infection of the fracture site, malnutrition, skeletal dysplasia

Osteonecrosis (avascular necrosis)

Infarction of bone and marrow. Relatively common

- **Risk factors:** fractures, corticosteroids, alcohol abuse, bisphosphonate therapy, connective tissue disease, radiation therapy, sickle cell crisis etc.
- **Clinical features**: Symptoms depend on location and extent e.g. subchondral infarcts cause pain that is initially associated with activity but becomes constant due to secondary changes (e.g. collapse of infarct causing deformation and secondary osteoarthritis). Medullary infarcts usually small, asymptomatic
- **Morphology**: Subchondral infarcts = Wedge-shaped segment within the subchondral bone plate; overlying articular cartilage viable due to synovial fluid nutrients. Medullary infarcts = Geographic in shape, involve both trabeculae bone and marrow. **Microscopy**: Dead bone characterized by empty lacunae surrounded by necrotic adipocytes +/- calcium soaps. Osteoclasts resorb necrotic trabeculae, while remaining trabeculae act as scaffolding for deposition of new bone

Osteomyelitis

Inflammation of bone and marrow, almost always secondary to infection. Can be primary solitary focus or complication of any systemic infection

Pyogenic osteomyelitis

- **Causes**: Organisms reach the bone via (1) **haematogenous spread** (usually children), (2) **extension from contiguous site** (e.g. feet infection in diabetics), or (3) **direct implantation** (e.g. in traumatic injury). 80-90% of culture-positive cases due to *Staphylococcus aureus*; ~50% of patients have no specific identifiable organism
- **Clinical features**: Osseous vascular circulation varies with age and affects the location of bone infection: neonates (metaphyseal vessels penetrate the growth plate) → metaphysis, epiphysis or both; older children → metaphysis; adults (growth plate closed, merger of metaphyseal and epiphyseal vessels) → epiphyses and subchondral regions. May present acutely as a systemic illness (esp. haematogenous osteomyelitis), unexplained fever, or localized pain. Biopsy and bone cultures required to identify the pathogen in most cases. **Treatment**: Antibiotics, surgical drainage. **Complications**: 5-25% of acute osteomyelitis may persist as **chronic osteomyelitis** (usually if delayed diagnosis, extensive bone necrosis, inadequate antibiotics/surgical debridement or weakened host defenses), which may be complicated by acute flares, pathologic fracture, secondary amyloidosis, endocarditis, sepsis and rarely, malignant transformation

- **Morphology**: Depends on timing and location
  Acute phase: proliferation of bacteria, neutrophils recruited, bone and marrow necrosis (**sequestrum**) within 48 hours. Bacteria and the associated inflammatory response then spread longitudinally and via the Haversian system to reach the periosteum. In children, periosteum is loosely attached to the cortex; subperiosteal abscesses may thus form, with associated periosteal lifting further impairing blood supply and contributing to bone necrosis. Periosteal rupture can also lead to soft tissue abscesses, which can channel to the skin as draining sinuses
  Chronic phase: chronic inflammatory cells recruited during the first week release cytokines that stimulate bone resorption, fibrous tissue ingrowth and peripheral deposition of reactive bone that forms a living shell (**involucrum**) around the devitalized infected bone

Mycobacterial osteomyelitis

- More destructive and resistant to control than pyogenic osteomyelitis. Increased risk in those with pulmonary or extrapulmonary tuberculosis (mycobacteria are usually blood borne and originate from a focus of active visceral disease during the initial stages of primary infection, but can also occur via direct extension e.g. pulmonary focus into adjacent rib). Usually solitary in immunocompetent patients, but can disseminate in the immunocompromised
- **Complications:** Spine involvement (Pott disease) with infection breaking through the intervertebral discs to involve and destroy multiple vertebrae and surrounding soft tissue, causing compression fractures and resulting scoliosis, kyphosis, neurologic deficits. Joint involvement (tuberculous arthritis), sinus tract formation, psoas abscess, amyloidosis
- **Histology**: Typical findings of necrotizing granulomatous inflammation

V. BONE TUMOURS AND TUMOUR-LIKE LESIONS

Primary bone tumours rare compared to **metastatic** / haematopoietic tumours. Specific tumour types have predilection for certain **anatomic sites** and **age groups**. Common clinical presentations include incidental findings (usually benign tumours), pain, slow-growing mass or pathologic fracture. Radiologic findings (Xray, MRI/CT scan, radionuclide bone scan, PET) are important to correlate with histologic findings (especially biopsy samples) for tumour diagnosis. Bone tumours often have a predilection for specific sublocations within a bone, e.g. osteosarcoma favours the metaphysis while giant cell tumours are often epiphyseal in location. **General prognostic factors** include: tumour size, histoathologic grading, location of tumour and margin clearance, site of metastatic disease, response to chemotherapy (for osteosarcoma and Ewing sarcoma) and specific molecular changes

Bone tumours are classified according to their normal tissue counterparts / matrix produced, or clinicopathologic features. Most common primary bone tumours are **osteosarcoma**, **chondrosarcoma** and **Ewing sarcoma**

Bone-forming tumours (30%): *produce unmineralized osteoid or mineralized woven bone*			
Histologic type	**Site**	**Age**	**Description**
Benign			

Osteoid osteoma	Metaphysis of long bones	10-20 yo	Similar histologic features but differing size, sites and symptoms: **Osteoid osteoma**: < 2cm. Present with severe nocturnal pain, relieved by aspirin/NSAIDs (probably caused by PGE2 by proliferating osteoblasts) **Osteoblastoma**: > 2cm. Pain unresponsive to aspirin **Radiology**: Round radiolucency with central mineralization +/- rim of reactive cortical bone **Histology**: Well-circumscribed mass of woven bone rimmed by cytologically benign osteoblasts
Osteoblastoma	Vertebral column (esp. posterior spine)		
Malignant			
Osteosarcoma *(20% of bone cancers)*	Metaphysis of long bones (esp distal femur/ proximal tibia)	Bimodal (75% <20 yo)	Most common primary malignant tumour of bone **Pathogenesis**: Increased proliferation in the growth plate of rapidly growing bones may predispose to oncogenic mutations (e.g. *RB, TP53, CDKN2A, MDM2/CDK4* mutations/amplifications). In older adults, usually associated with predisposing conditions e.g. Paget disease, prior radiation **Clinical features**: Pain +/- pathologic fracture. Treatment: chemotherapy and surgery. Metastasis is via haematogenous spread, usually lungs, bones, brain etc. **Radiology**: Destructive mixed lytic and blastic mass with infiltrative margins. May break through cortex and lift the periosteum, inducing periosteal bone formation (Codman triangle) → aggressive feature **Histology**: Bulky gritty gray-white tumours with frequent haemorrhage, cystic change and cortical destruction with soft tissue invasion. Pleomorphic tumour cells producing unmineralized osteoid or mineralized bone (usually lace-like); may also produce variable amounts of cartilage
Cartilage-forming tumours (40%): *produce hyaline/myxoid cartilage. Benign >>>> malignant*			
Benign			
Osteochondroma (aka exostosis)	Metaphysis of long bones (endochondral origin)	10-30 yo M>>F	Most common benign bone tumour. Bony excrescence with cartilage cap. **Pathogenesis**: 85% solitary and sporadic. 15% as part of multiple hereditary exostosis syndrome (AD, germline loss of function mutation in *EXT1* or *2* gene) **Clinical features**: Usually incidental +/-pain. Stop growing at the time of growth plate closure. Malignant transformation is rare, usually in multiple hereditary exostosis **Histology**: disorganized growth plate-like hyaline cartilage cap undergoing endochondral ossification, with underlying newly made bone in continuity with the bone from which it arises
Chondroma	Small bones of hands/feet (endochondral origin)	30-50 yo	**Enchondroma**: within the medullary cavity; most common intraosseous cartilage tumour **Juxtacortical chondroma**: on the bone surface **Pathogenesis:** Heterozygous *IDH1* and *2* gene mutations. Ollier disease and Maffuci syndrome are nonhereditary disorders characterized by multiple enchondromas **Clinical features**: Incidental +/- pain, fracture. Rare malignant transformation

			Radiology: solitary circumscribed lucency with central irregular calcifications, sclerotic rim and intact cortex **Histology**: well-circumscribed nodule of hyaline cartilage with cytologically benign chondrocytes +/- peripheral endochondral ossification
		Malignant	
Chondrosarcoma	Pelvis, shoulder	40-60 yo M>F	2nd most common malignant matrix-producing bone tumour (after osteosarcoma) Histologic subclassification into **conventional**, **de-differentiated, clear cell** and **mesenchymal** variants, with some differing clinicopathologic characteristics **Pathogenesis**: genetically heterogeneous with some recurrent driver mutations (e.g. IDH1 or 2, epigenetic silencing of *CDKN2A*). 15% of conventional chondrosarcomas arise from endochondromas /osteochondromas **Clinical features**: painful, progressively enlarging masses. Histologic grade of conventional chondrosarcoma correlates directly with biologic behaviour – most are grade 1, which only rarely metastasize and have 80-90% 5 year survival rates vs grade 3 tumours, with 70% metastasis and 43% 5 year survival rate. Treatment: wide surgical excision (mesenchymal and dedifferentiated tumours are more aggressive, need adj chemotherapy) **Radiology**: flocculent densities (calcified matrix), reactive cortical thickening if slow-growing, cortical destruction with soft tissue mass if aggressive **Histology**: **Conventional** chondrosarcoma - large bulky nodular tumours of gelatinous/myxoid cartilage . Neoplastic cartilage infiltrates the marrow space and surrounds per-existing bony trabeculae. Graded from 1-3 based on cellularity, cytologic atypia and mitotic activity. **Dedifferentiated** – low grade chondrosarcoma with high grade component that does not produce cartilage
Tumours of unknown origin (20%)			
		Benign	
Giant cell tumour	Epiphysis of long bones; may extend into metaphysis	20-40 yo	Can be locally aggressive **Pathogenesis**: Most cells within the tumour are non-neoplastic osteoclasts and their precursors. The neoplastic cells are primitive osteoblast precursors with acquired gene mutation encoding histone 3.3 and express high levels of RANKL (which promotes proliferation of osteoclast precursors and their differentiation into mature osteoclasts → localized highly destructive bone resorption) **Clinical features**: GCT often arise near joints → present with arthritis-like symptoms or pathologic fractures. Treatment: Curettage, but ~50% recur locally. Rarely lung metastases but these can regress spontaneously and are seldom fatal **Histology**: large red-brown bulging soft tissue mass with thin shell of reactive bone; frequent cystic degeneration. Characterised by numerous multinucleated osteoclast-type giant cells (with >100 nuclei) and uniform oval mononuclear tumour cells. Not matrix-producing

Malignant			
Ewing sarcoma	Diaphysis of long bones	10-20 yo	2nd most common bone sarcoma in children (after osteosarcoma). Aggressive. **Pathogenesis:** >90% have *EWSR1* gene translocation (usually t(22;11) *EWSR1-FLI1* fusion gene). ?cell of origin, possibly mesenchymal stem cell/primitive neuroectodermal cells **Clinical features**: painful enlarging mass +/- systemic findings that mimic infection. Treatment: chemotherapy + surgery **Radiology**: destructive lytic tumour with permeative 'moth-eaten' margins extending into surrounding soft tissue, and reactive layers of periosteal bone deposition ~ 'onion-skin' **Histology**: soft tan-white tumour arising in medullary cavity with frequent haemorrhage and necrosis. Sheets of small round cells with scant clear cytoplasm (abundant glycogen) +/- Homer-Wright rosettes (indicative of neuroectodermal differentiation)
Fibrous and fibro-osseous tumours			
Benign			
Non-ossifying fibroma	Metaphysis of distal femur and proximal tibia	2-20 yo	Usually asymptomatic benign self-limiting tumour, detected incidentally on radiography. Can be multifocal (esp. in patients with *NF1* and *KRAS*). Treatment not necessary usually; curettage for pathologic fracture **Radiology**: small sharply demarcated radiolucent mass surrounded by thin rim of sclerosis (findings are usually specific enough for diagnosis without biopsy) **Histology**: storiform arrangement of bland fibroblasts, with scattered osteoclast-type giant cells, foamy macrophages and haemosiderin.
Fibrous dysplasia	Femur, tibia, ribs, craniofacial bones	5-20 yo	Benign medullary fibro-osseous neoplasm that arises during skeletal development (reflecting a localized development arrest). **Monostotic** (involve single bone) or **polyostotic** (multiple bones); can be associated with **Mazabraud syndrome** or **McCune-Albright syndrome** **Pathogenesis**: Somatic gain-of-function mutations in *GNAS1* **Clinical features**: Aysmptomatic, pain, discrepancies in limb length, deformities, pathologic fracture. Monostotic forms usually stop enlarging at the time of growth plate closure. Polystotic forms may continue to cause problems into adulthood. Recurrence is common even after curettage. **Radiology**: non-aggressive lesion with ground-glass matrix (characteristic = Shepherd's crook deformity of the proximal femur, whereby the lesion causes bowing and cortical thinning) **Histology**: curvilinear trabeculae of woven bone ("chinese characters") surrounded by moderately cellular fibroblastic proliferation without prominent osteoblastic rimming. ~20% of cases have nodules of hyaline cartilage resembling disorganized growth plates
Metastatic tumours			
Pathways of spread include (1) direct extension, (2) lymphatic or haematogenous spread, (3) intraspinal seeding. Most involve the axial skeleton (marrow has rich capillary network). Often multifocal, but can be			

solitary. For adults, common primary sites = prostate, breast, kidney, lung; children = neuroblastoma, Wilms tumour, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma

VI. STRUCTURE AND FUNCTION OF JOINTS

Joints: allow movement while providing mechanical stability

Solid (nonsynovial; synarthroses)	Provide structural integrity, lack a joint space, allow only minimal movement • **Fibrous**: e.g. cranial sutures • **Cartilaginous**: e.g. pubic symphysis
Cavitated (synovial)	Have a **joint space** that allows wide range of motion, between bones formed via endochondral ossification and strengthened by a dense fibrous capsule reinforced by muscles and ligaments. Joint space is lined by **synovial membrane** (which is anchored to the underlying capsule; does not cover the articular surface) which lacks a basement membrane, allowing efficient exchange of nutrients, waste and gases between blood and synovial fluid. Synovial membrane is lined by Type A synoviocytes (~macrophages) and Type B synoviocytes (~fibroblasts, synthesize hyaluronic acid and proteins). **Synovial fluid** within the joint space is a hyaluronic acid-rich plasma filtrate; acts as a viscous lubricant and provides nutrition for the articular hyaline cartilage. **Hyaline cartilage**: serves as elastic shock absorber and wear-resistant surface (70% water, 10% type II collagen, 8% proteoglycans and chondrocytes). Chondrocytes synthesize matrix but also secrete degradative enzymes like matrix metalloproteases (MMPs) in inactive forms, as well as enzyme inhibitors

VII. ARTHRITIS

Arthritis = inflammation of joints. Can be caused by **mechanical injury** (osteoarthritis), **immune reaction** (rheumatoid arthritis, juvenile idiopathic arthritis, seronegative spondyloarthropathies e.g. anklyosing spondylitis), **infections** and **crystal deposition** (gout and pseudogout)

Osteoarthritis (OA) *(aka degenerative joint disease)*

- Most common joint disease. Characterised by **cartilage degeneration** that results in structural and functional failure of synovial joints (rather than because of inflammation)
    - **Idiopathic (primary) OA**: More common. No apparent initiating cause, related to aging. Often oligoarticular, rarely generalized. Knees and hands more commonly in women, hips in men.
    - **Secondary OA**: 5%. Younger individuals with predisposing conditions e.g. joint deformity, previous joint injury, underlying systemic disease e.g Haemochromatosis, marked obesity

- **Pathogenesis:** Due to degeneration of the articular cartilage and disordered repair, resulting from **biomechanical stress** and accelerated by **genetic factors** that may predispose to chondrocyte injury, causing extracellular matrix alteration. Continued degradation exceeds repair by chondrocytes (who proliferate and synthesize proteoglycans, but also secrete MMPs and other cytokines e.g. prostaglandins, NO, TNF). Synovial cells add to the chronic low-level inflammation by secreting TGF-β, contributing to disease progression.
- **Clinical features:** Usually asymptomatic until >50yo for primary OA; may be symptomatic at younger age if secondary OA. Characteristically deep achy pain worse with use, morning stiffness, crepitus and limited range of movement. Severity of radiologic features does not correlate with symptoms. **Complications**: nerve root compression and neurologic deficits (due to impingement on spinal foramina by osteophytes at cervical/lumbar region in spondylosis); joint deformities (but without fusion unlike RA). **Treatment**: Symptomatic e.g. NSAIDs, steroids, activity modification, arthroplasty
- **Morphology:** Granular and soft articular surface due to fibrillation (microscopic fissures and clefts) of the articular cartilage; full-thickness portions of necrotic cartilage can slough off and form loose bodies in the joint. The now exposed subchondral bone becomes **eburnated** due to friction with the opposing articular surface, with **subchondral sclerosis**, **subchondral cyst** formation (as synovial fluid is forced through small fractures) and formation of **osteophytes** (bony outgrowths) at the margins of the articular surface. Synovium shows reactive changes

Rheumatoid arthritis (RA)

- **Chronic autoimmune disorder** that causes a **non-suppurative proliferative and inflammatory synovitis**, but can also have extra-articular lesions (e.g. skin, blood vessels, lungs)
- **Pathogenesis:**
    - **CD4+ T-helper cells** initiate the autoimmune response, by releasing inflammatory mediators that stimulate other inflammatory cells and lead to tissue injury e.g. IFNγ from Th1 cells activates macrophages and synovial cells, IL-17 from Th17 cells recruits neutrophils and monocytes. RANKL is expressed on the activated T cells and stimulates bone resorption, while **TNF** and IL-1 from macrophages stimulate resident synovial cells to secrete proteases that destroy hyaline cartilage
    - Plasma cells (in lymphoid organs and synovium) secrete **autoantibodies** including **anti-citrullinated peptide antibodies** (citrullinated peptides are found in several proteins found in joints), which are diagnostic markers found in 70% of RA patients and possibly drive disease persistence. **Rheumatoid factor** (IgM and IgA autoantibodies that bind IgG Fc regions) may also be dpositied in joints as immune complexes, but are not specific
    - **Genetic predisposition** (HLA-DR4) and **environmental factors** (e.g. infection, smoking that may promote citrullination of self-proteins) also contribute to disease development
- **Clinical features:** F:M = 3:1. Usually begins with systemic symptoms (fatigue, generalized musculoskeletal pain) before joint involvement after weeks-months (usually symmetrical, small joints of hands and feet). Chronic waxing and waning course of joint swelling, pain, and decreasing range of motion (morning stiffness does not subside with activity). **Complications**: joint deformities due to inflammation of tendons and ligaments, articular cartilage destruction and joint fusion

(ankylosis), extra-articular involvement, amyloidosis. Increased risk of opportunistic infections when on immunosuppressants. **Treatment**: Immunosuppressants (e.g. steroids, methotrexate and TNF antagonists) aimed at pain relief, improvement of inflammation and slowing/arresting joint destruction

- **Morphology: Pannus** formation comprising oedematous, thickened and hyperplastic synovium with bulbous villi, dense inflammation (frequent lymphoid follicles with fibrinopurulent exudate on the synovium and joint surfaces), granulation tissue (increased vascularity) and fibroblasts, accompanied by osteoclastic activity in the subchondral bone allowing the inflamed synovium to penetrate the bone and cause **periarticular erosions** and subchondral cysts. As the cartilage is destroyed, the pannus bridges apposing bones to form a **fibrous ankylosis** that can ossify (bony ankylosis). Extra-articular manifestations include **rheumatoid nodules** (firm non-tender nodules resembling necrotizing granulomas with central zone of fibrinoid necrosis; often in subcutaneous tissue) and **leukocytoclastic vasculitis** (acute necrotizing vasculitis of small and large arteries; may involve the lung and skin)

Infectious arthritis

Joints can be seeded by micro-organisms through haematogenous spread, direct inoculation or contiguous spread from adjacent osteomyelitis or soft tissue abscess. Infections can cause rapid joint destruction leading to permanent deformities because cartilage has limited regenerative capacity – medical emergency!

- **Suppurative arthritis:** usually from haematogenous spread, although contiguous spread from epiphyseal osteomyelitis more common in neonates. Infective bacterial organism depends on age (<2yo – *Haemophilus influenza*; older children and adults – *Staphylococcus aureus*; late adolescence/young adult – *Neisseria gonorrhoea*) and predisposing conditions (sickle cell disease – *Salmonella*). Presents with sudden acute painful swollen joint with systemic findings (fever, leucocytosis). Treatment: effective antibiotic therapy
- **Mycobacterial arthritis:** usually as complication of adjacent osteomyelitis or haematogenous spread from pulmonary infection. Chronic progressive monoarticular infection caused by *M.tuberculosis,* often insidious and affecting weight-bearing joints e.g. hips, knees; may result in fibrous ankylosis
- **Viral arthritis:** can be due to direct infection by the virus (e.g. rubella) or a virus-induced autoimmune reaction (e.g. reactive arthritis)
- **Lyme arthritis:** spirochete infection with *Borrelia burgdorferi*, transmitted by deer ticks. Initial infection of skin, with subsequent dissemination to other sites esp. joints. Migratory arthritis that primarily involves large joints esp. knees, shoulders. Treatment: Antibiotic therapy

Crystal-induced arthritis

Endogenous (monosodium urate, calcium pyrophosphate dihydrate) and **exogenous** (talc, prosthetic joint materials polyethylene and methyl methacrylate) crystals produce disease by triggering a cytokine-mediated cascade that destroys cartilage. Joint fluid analysis is important for diagnosis

Gout

- **Transient attacks** of acute arthritis initiated by crystallization of **monosodium urate** within and around joints, and characterized by **hyperuricaemia**
- **Pathogenesis:** Hyperuricaemia can result from **overproduction, reduced excretion or both**
    - Normal uric acid synthesis: uric acid is the end product of purine catabolism; overproduction of urate is therefore usually due to abnormalities in purine production. Purine nucleotides are synthesized de novo (from nonpurine precursors) or salvaged (from free purine bases from dietary intake and catabolism of purine nucleotides)
    - Normal uric acid excretion: uric acid is filtered by the glomerulus and resorbed by the proximal tubule; a small fraction is then secreted by the distal nephron and excreted
    - **Primary gout** (90%): usually due to reduced excretion; less commonly due to uric acid overproduction. Majority due to unknown enzyme defects; minority due to known enzyme defects (e.g. partial HGPRT deficiency)
    - **Secondary gout** (10%): known underlying disease causing decreased uric acid secretion (e.g. in chronic renal disease), or increased production (increased nucleic acid turnover due to rapid cell lysis during chemotherapy in leukemia)

  Precipitation of monosodium urate crystals into the joints triggers inflammation, via **phagocytosis by macrophages and neutrophils** (which release IL-1 and other cytokines, further recruiting macrophages and neutrophils) as well as **activation of complement pathway**. The ingested crystals can also cause rupture of phagolysosomes, causing further release of proteases and inflammatory mediators, resulting in an acute flare.

  Hyperuricaemia itself is necessary but not sufficient to develop gout; **additional determining factors** include: patient's age and duration of hyperuricaemia (usually after 20-30 years), male sex, genetic predisposition, heavy alcohol intake, obesity and drugs that reduce urate excretion (e.g. thiazides)
- **Clinical features**: First attack usually a monoarticular acute arthritis with sudden excruciating joint pain; rarely constitutional symptoms. Acute attack remits when the episode of crystallization rebates and crystals are solubilized. Without therapy, attacks can recur at shorter intervals and become polyarticular; repeated attacks of acute arthritis (~10 years) lead to formation of tophi (aggregates of urate crystals and inflammatory tissue), severe cartilage damage and comprised joint function. **Treatment**: lifestyle modifications (weight loss, diet to reduce purine intake), uricosuric drugs, xanthine oxidase inhibitors, urate oxidases, NSAIDs, colchicine
- **Morphology**: Four distinctive patterns:
    - **Acute arthritis**: dense neutrophilic infiltrate in synovium and synovial fluid. Needle-shaped negatively birefringent urate crystals
    - **Chronic tophaceous arthritis**: repetitive precipitation of urate crystals during acute attacks encrust the articular surface and forms visible deposits in the synovium, which becomes hyperplastic, inflamed and fibrotic (pannus), destroys cartilage, causes juxta-articular bone erosions and may cause fibrous/bony ankylosis
    - **Extra-articular tophi**: pathognomonic hallmark of gout; in soft tissue, kidneys, articular sites. Large aggregates of urate crystals surrounded by foreign body giant cell inflammatory reaction

- **Gouty nephropathy**: renal complications caused by urate crystals or tophi in the kidney e.g. uric acid nephrolithiasis, pyelonephritis

Calcium pyrophosphate crystal deposition disease (CPPD) aka pseudogout

- Deposition of **calcium pyrophosphate dihydrate crystals** within the joint
- **Pathogenesis**: basis for crystal formation unknown, but studies suggest that degradation of articular cartilage proteoglycans (which normally inhibit mineralization) allows crystallization around chondrocytes. Crystal deposition activates inflammation in macrophages (as in gout)
- **Clinical features**: usually >50yo (more common with increasing age). Can be **sporadic (idiopathic)**, **hereditary** or **secondary** (e.g. previous joint damage, hyperparathyroidism). Often asymptomatic but can produce acute, subacute or chronic arthritis (mimicking OA or RA). Knees mostly commonly affected. Radiographic findings show calcification of hyaline or fibrocartilage (chondrocalcinosis) but does not necessarily correlate. **Treatment**: Supportive
- **Morphology**: enlarging chalky white friable crystal deposits in articular cartilage, menisci and intervertebral discs, which may rupture and seed the joint. Rhomboid weakly positively birefringent crystals. Inflammation usually mild if present

VIII. JOINT TUMOURS AND TUMOUR-LIKE CONDITIONS

Reactive tumour-like lesions: common; usually result from trauma or degenerative processes

- **Ganglion cysts:** small cyst arising from cystic or myxoid degeneration of connective tissue near a joint capsule or tendon sheath. No communication with joint space
- **Synovial cysts:** formed from herniation of synovium through a joint capsule, or massive enlargement of a bursa (e.g. Baker cyst in the popliteal space in RA)
- **Osteochondral loose bodies:** fragments of cartilage in degenerative joint disease (see 'OA')

Primary neoplasms: rare, recapitulate cells and tissue types native to joints and related structures

- **Tenosynovial giant cell tumour:** usually benign intra- or extra-articular lesion arising from the synovium of joints, bursa and tendon sheaths, and showing synovial differentiation. **Localised-type**: painless mass usually in the hand/fingers. **Diffuse-type**: pain/swelling or limitation of motion, usually in the knee. Local recurrence more common (vs localized-type)