Lecture 1

Tumors of unknown origin	
1.Ewing sarcoma	*__Type__—malignant *__Location__—diaphysis in long bone * __target group__— less than 20 years of age *__features__: 1. Radiologic — infiltrating the soft tissue and elevating the periosteum causing __codman triangle__ 2. Molecular : a. fish analysis(most sensitive for Ewing sarcoma using fluorescent hybridization) b. Classic cytogenetic analysis which show the fusion protein produced from translocation(occurs between chromosomes 11(bigger) and 22 3. Histologic: small blue cell tumor(large nucleus , small cytoplasm) & primitive neuro ectodermal tumor *__Genetic mutation__— t(11;'22)(q24;q12) mutation generates transcription factor through fusion of the EWSR1 gene with the FLI1 *__Treatment__—neoadjuvant chemotherapy followed by surgical excision with or without radiation *__Note__ —second most common sarcoma of bone after osteosarcoma& with chemotherapy long term survival now reaches up to 75%
2. Giant cell tumor of bone	*__Type__—rare malignant behavior (95% behaves in the benign forms) *__Location__— epiphses of long bones *__Target group__ — adult (we don't see this tumor children) *__features__: >>locally aggressive neoplasm >>it has a bubble appearance expanding the cortex of the bone without infiltration to the extracortical space >> histologically — it is sheets wall to wall & multi-Nucleated giant cell or osteoclasts like giant cell ^^ *__Treatment__— curetting or resection *__Note__— cells contain high level of RANKL (which stimulates the differentiation of osteoclast in the bone) sometimes they call __osteoclastoma__ because the primary histology is composed of numerous wall to wall osteoclast
3. Aneurysmal bone cyst	*__Type__— benign tumor * __Location__— metaphysis of long bones

	*__Target group__ — affect adults * features: blood-filled cystic spaces and fibrous reaction around it *__Treatment__— curetting , resection *__Note__— some argue that ABC is not a true neoplasm ((probably reactive condition caused by previous trauma or infection)
4. Non ossifying fibroma	*__Type__— benign lesion , maybe reactive not a true neoplasm *__Location__ — metaphysis in long bone * **features:** >> lesion which is not destroying the surrounding structure, is not elevating the periosteum (it is well circumscribed) >> histologically : bland fibroblastic proliferation *__Note__ — other name (fibrous cortical defect & metaphyseal fibrous defect May resolve spontaneously
5. Fibrous dysplasia	*__Type__ — Not a real tumor — developmental abnormality * **mutation**— mutation in GNAS1gene^^ *__features__: is a group of disease or syndrome >> Monostotic (affecting one bone) : Common bone (maxillary and mandibular bone of the face) —> causing cherubism in children >>Polystotic (multiple bone) : 1. Mazabrayd syndrome — can be monostotic or polystotic & soft tissue myxoma 2. McCune-Albright syndrome—* polystotic & multiple brownish pigmentation of the skin & endocrine abnormalities (precocious puberty) *abnormal bone that's somehow similar to paget disease—> differentiate between them histologically which McCune-Albright syndrome has Chinese letters appearance Paget disease the bone appears in a mosaic pattern (pathognomic)
6. Metastatic tumors to bone	* much more common than primary bone tumors *__target group__ : Adults— most are carcinomas (prostate, breast , kidney thyroid, liver , lung * major cause of bone metastatic both female and males) >> most type of carcinoma which cause to the bone is adenocarcinoma (gland forming carcinoma)

Children — neuroblastoma, Wilms tumor (kidney) , rhabdomyosarcoma
>> don't see carcinoma (very rare)
***Location** — usually multiple and axial (vertebral bodies , shoulders , pelvic) — mostly hematogenous spread
* **features**:
Radiographic appearance— lesions appear as a result of secretion of certain mediators and can may be :

1. Purely lytic(bone destroying)— more common
2. Purely blastic(bone forming) — commonly associated with the primary source of prostate metastasis
3. Mixed

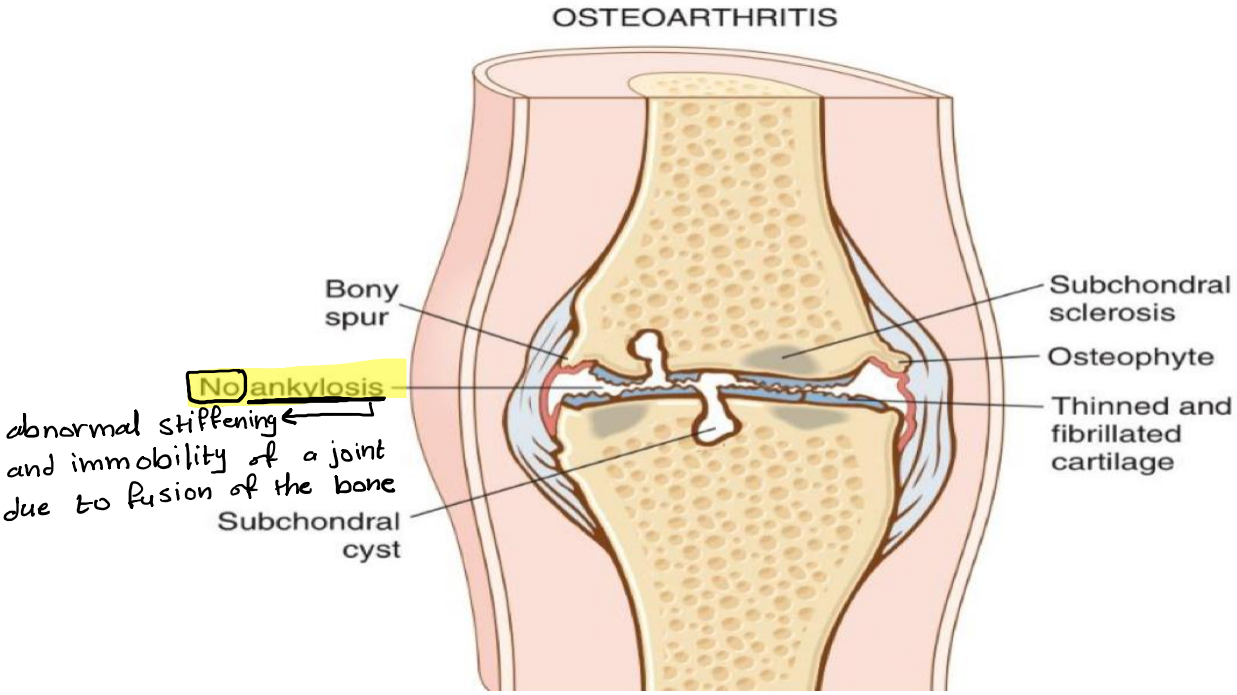
^^ GNAS1gene is responsible for the osteoblast differentiation via cAMP pathway and this will lead to abnormal bone formation

قال صلى الله عليه وسلم : (أنا سيد ولد آدم يوم القيامة وأول من ينشق عنه القبر وأول شافع وأول مُشفّعٍ) رواه مسلم .
اللهم صل وسلم وبارك على سيدنا وحبيبنا وشفيعنا محمد وعلى آله وصحبه أجمعين

Lecture 2 (diseases of the joints)

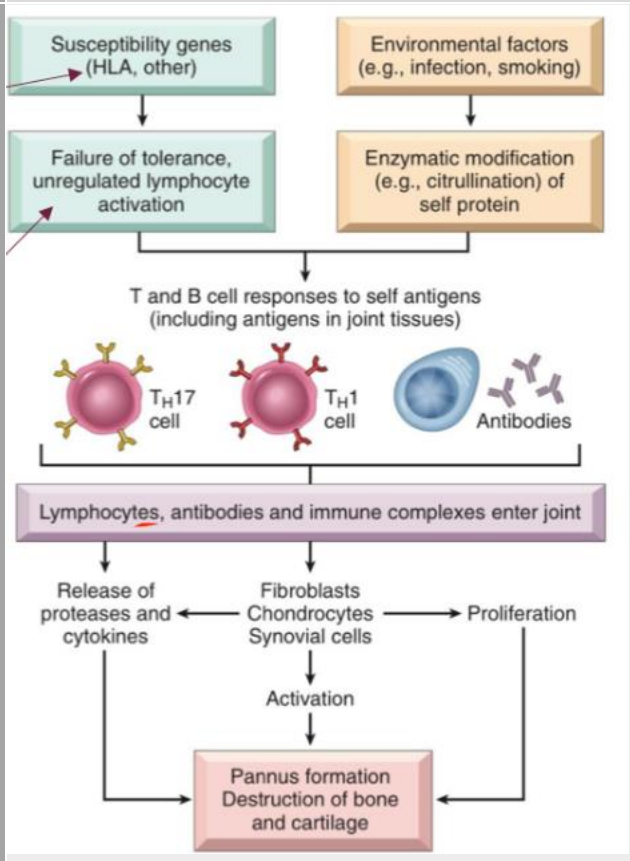
Ostoarthritis	
Definition	* progressive degeneration of **articular cartilage** *Happened mainly because of the imbalance between degeneration and repair of the cartilage (degeneration>> repair and proliferation) —> so we called *Degeneration of cartilage (DJD)* * very common **Insidious disease** (proceeding in a gradual , subtle way , but with harmful effect
Rick factor	1.Age(>50 years) 2.obesity 3.Trauma
Classifications	1.**Primary or idiopathic** : Most common Increasing with the age Affect few major joints (knee , elbow and pelvis) 2.**Secondary** : Less common Occurs due to preexisting diseases — affect the right knee joint but not the left
Pathogenesis	***Normal** : the space between the bones & the edges of the bone and the structure of bone , all of them are normal ones . *** Etiology:** injury to the chondrocyte (genetic and biochemical predisposition with inciting trauma) ***early stage** : >>inflammatory mediators will release (TNF,No,PGE2) >> repair will be inset by stimulation of synovial site (TGF beta) >> multiple mediators will be involved for chondrocyte proliferation (IL-8,BMP) [this process takes weeks, months or years] *insidious* **Advanced (grade III)**: >>the space between the bones is narrowed >> the bone spurs at the lateral side of the joint **Late sever (grade IV**): >>inability of the articular cartilage to proliferate and repair leading— apoptosis & chondrocyte dropout >> subchondral reaction &subchondral sclerosis & subchondral cyst formation >>loos bodies in the space — causing pain and stiffness of joint

	>>bone spurs in the medial side of the joint which lead to sever narrowing of the joint space
Clinically	*joint pain worsens with use *morning stiffness *crepitus *range limitation *radicular pain (pain near to the neurons) *osteophytes impingement on vertebrae , muscle spasm & atrophy
Preventive	No preventive strategies
Treatment	Depends on the stage *pain control * decrease inflammation (NSAIDs) *intra-articular steroids or joint replacement for sever cases Note— if the patient is very obese , losing weight may help relieving symptoms



abnormal stiffening and immobility of a joint due to fusion of the bone

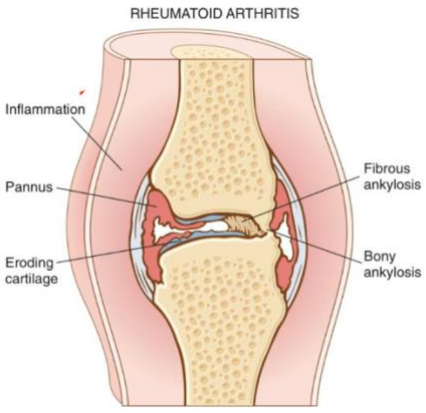
Rheumatoid Arthritis

Definition	*chronic systemic inflammatory disease, autoimmune in nature , attacks joints with nonsuppurative proliferation and inflammatory **synovitis(targets the synovium)** leading to the destruction joints and adhesions **(ankylosis).**
Prevalence	1% in USA , female > male (3f:1m)
Etiology	Both genetic factor (associated with **HLA**) and environmental factor
Pathogenesis	 it's an autoimmune disease, so it's involved , multiple mediators 👇👇

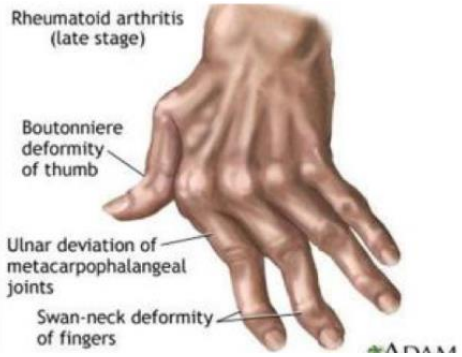
IFN-γ from TH1	Activates macrophages & synovial cells
IL-17 from TH 17	Recruits neutrophils and monocytes
RANKL from T cells	Stimulates osteoclasts & bone resorption
TNF (major player) & IL-1 from macrophages	Stimulates residents synoviocytes to secrete proteases that destroy hyaline cartilage

Clinically	*Begins slowly and **insidiously** *involve multiple **symmetrical** joint : hand , feet , wrists , ankles and (metacarpophalangeal[**MCP**]& proximal interphalangeal[**IP**] are commonly affected) * warm, swollen and painful ***stiffeness** when inactive and in the **morning** * waxing and **waning chronic** * autoimmune synovitis with **pannus formation** leading to 1. distraction of the cartilage with narrowing 2. **ankylosis** of the joint space * **Rheumatoid nodules** * **Rheumatoid granulomas** * **Ulnar deviation :** affect the bananas formation of the small joint of the hand (both hand are affected) which MCP joint toward the ulnar side
Diagnosis	1.Rheumatoid factor : a blood test to look autoantibodies (IgG&IgM) against the FC portion of their own IgG (80%positive) 2. Anti- citrullinated protein antibodies (70% positive
Treatment	*steroids *anti-TNF *methotrexate(immunosuppfessor drug)

Osteoarthritis is much common than Rheumatoid arthritis



☑ Boutonniere deformity of the thumb→ thumb is tended and the patient unable to hyperextend the IP joints.
☑ Ulnar deviation→ deviate of the MCP joint toward the ulnar side.
☑ Swan-neck deformity of fingers→ Hyperflexion in the distal IP Joint.



Juvenile Idiopathic Arthritis

*__Definition__: A heterogeneous group of diseases characterized by the presence of arthritis of unknown. (another form of RA)
* **Target group** : affect children less than 16 years
* **pathogenesis**: similar to adults RA
* **in contrast to adult RA, JIA is characterized by** :
  - oligoarthritic is more common
  - systemic disease is more common
  - Large joints are affected more than small joints
  - Rheumatoid nodules and Rheum factor are usually absent
  - anti-nuclear antibody seropositivity is common which is a simple screening test for autoimmune diseases

*__Note__ : the symptoms should be last for least 6 weeks before making up the diagnosis & only 10% will have a serious functional disability

Seronegative Arthritis

*__Definition__: family of joint disorders in which the patient doesn't have the same antibodies that a person who is "seropositive",but has Arthropathies
>> normal — seropositive >> abnormal— seronegative Arthropathies
*__pathogenesis__ : Autoimmune T cell response to unidentified antigen that cross -react with self musculoskeletal antigens
* **heterogeneous group of diseases share the following features** :
  - Absence of rheumatoid factor
  - **Ligament's pathology** rather than synovium
  - Sacroiliac joint are mainly affected
  - They are strongly associated with **HLA-B27**
  - Bony ankylosis (fusion)

***Examples :**

1. Ankylosing spondylitis	*The most common prototype *destructive arthritis, bony damage , and ankylosis of axial sacroiliac joint *90% of patients have HLA-B27 & adolescents boy *anti Il-17 has shown some efficacy as a treatment
2.Reiter syndrome	*Triad of arthritis, urethritis/cervicitis conjunctivitis * Autoimmune but initiated by a bacterial infection
3.Enteropathic Arthritis	*Secondary to bowel infection (salmonella, shigella) *HLA B27 positive
4.psoriatic Arthritis	5% of patients starts in DIP joint , similar to RA