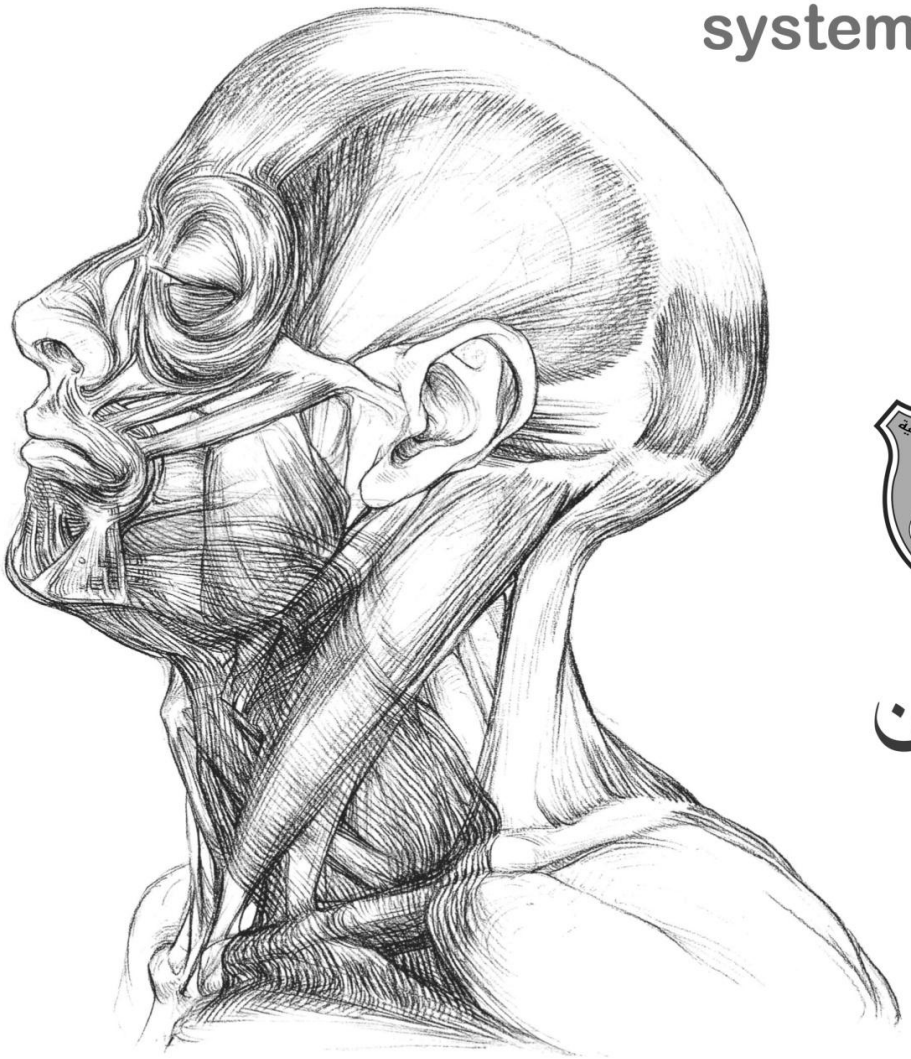
The skin & Muscloskeletal system



PATHOLOGY

SLIDES ☐
SHEET ■
LECTURE # 4

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☒ Diseases in general are categorized in four types:

1-infectious

2-inflammtory

3-neoplastic

4-degenrative (decomposition): tissue start decaying on its own

JOINT DISEASES

Osteoarthritis

-it's a degenerative disease not an inflammatory disease as the name may imply.(arthritis means inflammation)

-it's the most common joint disease, the majority of elderly people who are complaining of joint pain actually have osteoarthritis, it's a major causes of physical disability among them "individuals over the age of 65"

- There are two types of osteoarthritis:

-**Primary**: more common than secondary, its insidious meaning that it's gradual, there is no initiating factor (appears on its own no previous disease), oligoarticular (affects more than one joint of the body)

-**Secondary**: 5% of the cases, happens usually because of physical damage to the joint, appears at younger people, the main causes are: trauma, diabetes, hemochromatosis (excessive deposition of iron), marked obesity, it can affect single or multiple joints (oligoarticular)

Gender influence; knees and hands are more commonly affected in women, whereas hips and back are more commonly affected in men.

•pathogenesis

Again the name of the disease is misleading, this disease starts in the cartilage *more specifically articular cartilage* not in the bone as the name implies, so we will have degeneration in cartilage, other changes like bone changes and inflammation are minor effects of the disease and appear later on *secondary changes*.

-the normal function of cartilage is shock absorption (spreading the load) and preventing friction, this function is mediated by two types of molecules secreted by chondrocytes, proteoglycans makes the cartilage firm, the second one is collagen type 2 it is important for keeping the cartilage tense, so you can bend cartilage but you cannot break it (flexibility)

-so what happens in osteoarthritis is that these chondrocytes degenerate with aging so they cannot secrete enough collagen and proteoglycans, so the cartilage becomes weak and breaks with movement easily and that's why this disease is more common in old people because it takes years for these changes to take place.
Note:degenerated cartilage contain more water and less proteoglycans.

•Morphology

-Early phase: the patient is asymptomatic, the cartilage starts breaking and decreasing so the chondrocytes start proliferating in order to compensate for the decrease in cartilage, the disease is still unidentified,

-Later phase: with time the chondrocytes will be lost and stops proliferating, cracks start appearing in cartilage (vertical and horizontal cracking of the matrix).

-small particles of cartilage and subchondral bone will fall into the joint forming loose bodies inside the joint called **joint mice**.

-With time, the subchondral bone plate is exposed

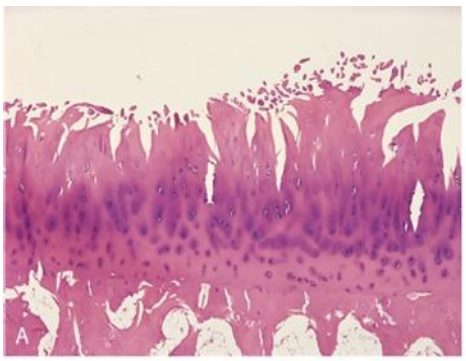
-sometimes when the bone is fractured. friction happens between the exposed bones, Friction smooths and burnishes the exposed bone, giving it the appearance of polished ivory (bone eburnation) bone becomes sclerotic and thickened*because of the deposition of new bone layers*.

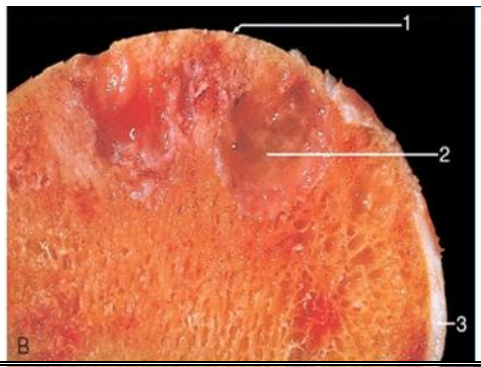
bone eburnation: bone full of osteoid and no bone marrow so it appears very white and thick like ivory.

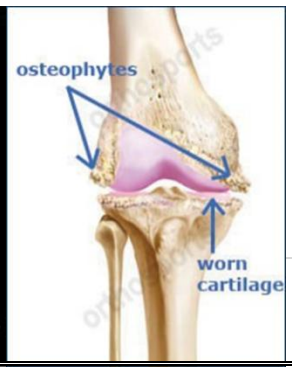
the peripheral part of the bone*margins of the articular surface* because of sclerosis and eburnation will develop protrusions known as osteophytes

osteophytes: mushroom-shaped protrusions at the site of degenerated cartilage, you can fell them as bony masses.

-synovium: is the adhesive lining of the joint from outside normally it is one layer thick, but due to inflammation and damage the synovium will be activated, it starts proliferating and producing very thick synovium (more than one cell layer thick), thickening of synovium is called **pannus**, Synovium moves into subchondral bone and forms cysts(masses).







A B C

A, Histologic demonstration of the characteristic fibrillation of the articular cartilage(degeneration of cartilage).
B, 1- bone eburnation (whiter in color), 2- empty areas and thick synovium(Subchondral cyst), 3-normal cartilage

C, thick protrusions of bone (osteophytes)

•Clinical Features

- Osteoarthritis is always chronic never acute, patients are mostly old(50-60).

-symptoms: deep, aching pain exacerbated by use, morning stiffness(muscles are contracted due to pain), crepitus(noise from constant friction between exposed bones), and limited range of movement

- osteophytes in distal interphalangeal joints(fingers) are called Heberden nodes, characteristic in women.

- With time, significant joint deformity can occur, but unlike rheumatoid arthritis, fusion does not take place

(0:00-11:29)

◊Gout

-unlike osteoarthritis gout is an acute disease with severe inflammation and sharp sudden attacks.

-Gout is a metabolic disease due to Accumulation of excessive amounts of uric acid (end product of purine metabolism), it binds with sodium and forms monosodium urate crystals.

-There are two types of gout:

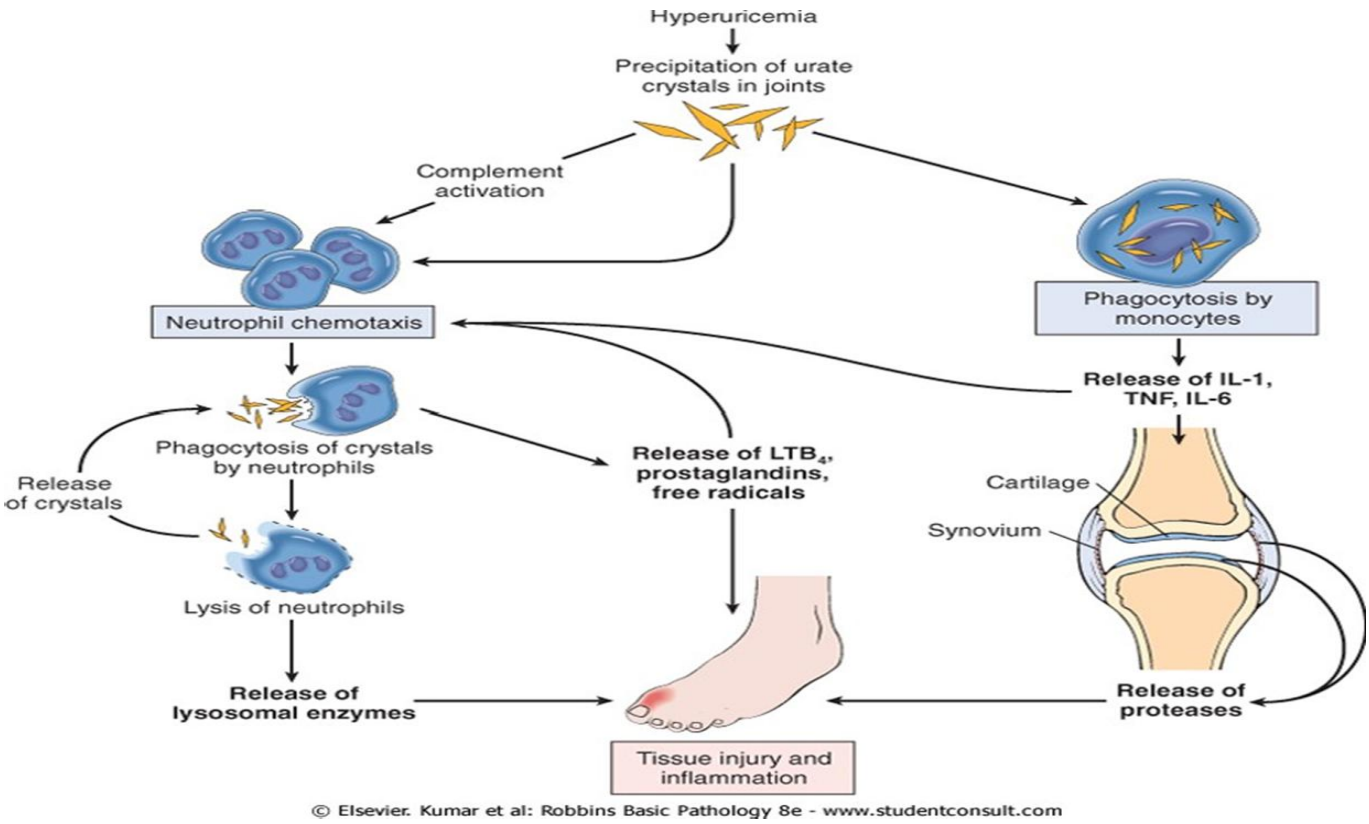
-primary: most common (90% of cases), the primary cause is unknown(idiopathic), most likely the patients have metabolic disorders related to uric acid processing enzymes, resulting in hyperuricemia.

-secondary: less common (10% of cases), happens due to complication from previous diseases, ex: leukemia and renal failure, leukemia because during chemotherapy large number of cells that circulate the blood will die and burst, their DNA content will leak out, get metabolized and transformed into uric acid, Renal failure because uric

Clinical Category	Metabolic Defect
Primary Gout (90% of cases)	
Enzyme defects unknown (85% to 90% of primary gout)	Overproduction of uric acid Normal excretion (majority) Increased excretion (minority) Underexcretion of uric acid with normal production
Known enzyme defects-e.g., partial HGPRT deficiency (rare)	Overproduction of uric acid
Secondary Gout (10% of cases)	
Associated with increased nucleic acid turnover-e.g., leukemias Chronic renal disease Inborn errors of metabolism	Overproduction of uric acid with increased urinary excretionReduced excretion of uric acid with normal productionOverproduction of uric acid with increased urinary excretion e.g., complete HGPRT deficiency (Lesch-Nyhan syndrome)

*acid cannot be secreted out of the body

*Note: inborn errors of metabolism and Lesch-Nyhan syndrome(HGPRT deficiency) belongs to the primary gout not secondary.



*Note: doctor said this picture is important.

-so neutrophils and macrophages well try to get rid of uric acid crystals, neutrophils swallow's uric acid crystals and burst because they are sharp, so the components of neutrophils well be released into the tissue like: lysosomal enzymes that damages cells, leukotriene b4 and prostaglandins

the last two are responsible for severe pain and the sudden attacks.

-most common site of gout is the big toe

-macrophage: because of the large size of macrophages they can swallow uric acid crystals, once they have swallowed them they get

activated, releasing tnf, il-1,il6 which in turn activates more neutrophils, also macrophages secrets proteases which degrades the skeleton of the cells causing damage to the cartilage and bone.

-if the gout attacks are repeated continuously they well cause severe damage to the bone and cartliage.

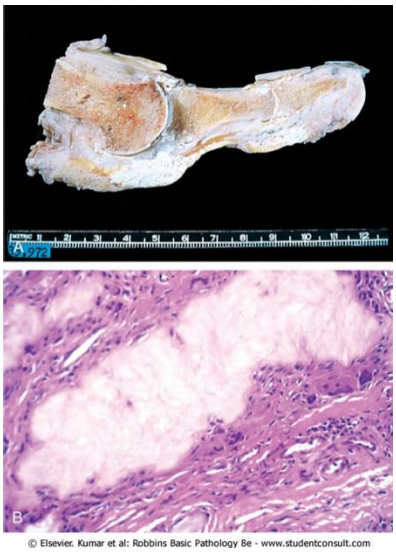
-there are four disease related to gout:

1- **Acute arthritis**:(most common) dense neutrophilic infiltrate permeating the synovium and synovial fluid. Long, slender, needle-shaped monosodium urate crystals are frequently found in the cytoplasm of the neutrophils and in the synovium. Big-toe is a common site.(the same case we have been discussing before).

2- **Chronic tophaceous arthritis**: repetitive acute attacks, not persistent. Synovium forms a pannus that destroys the underlying cartilage, and leads to bone erosions. In severe cases: ankylosis (bone fusion) this well lead to deformity and loss of fuction (characteristic of gout), tophus is the area aggregation of uric acid crystals forming a mass.

3- **Tophi:** large aggregations of urate crystals surrounded by an intense inflammatory reaction of lymphocytes, macrophages, and foreignbody giant cells. Tophi appears in cartilage of joints, ligaments, tendons, and soft tissues, including the ear lobes, nasal cartilages, and skin of the fingertips, face and anywhere in the body.(most common ear and nose).

4- **Gouty nephropathy:** crystals accumulate in the medulla of kidney(medullary tophi), causing renal impairment, closing the ureter so the patient cannot urinate this well cause renal failure. intratubular precipitations, or free uric acid crystals and renal stones causes obstruction, kidney stones that is caused by this type are radiolucent this is a major characteristic because stones from other diseases are radiopaque.



A, Amputated great toe with white tophi involving the joint and soft tissues. B, Photomicrograph of a gouty tophus. An aggregate of dissolved urate crystals is surrounded by reactive fibroblasts, mononuclear inflammatory cells, and giant cells

(11:29-19:20)

◊ Pseudogout

-Also known as : Chondrocalcinosis

-Here we have excess deposition of calcium pyrophosphate crystals unlike gout which is an excess deposition of uric acid crystals, they accumulate in the joints and body causing a similar disease to gout.

	Pseudogout	Gout
Type of crystals	Calcium pyrophosphate	Uric acid
Age group	Older than 50	Younger age
Common site	Knee	Big toe
Pathogensis	Completely idiopathic (associated with trauma)	Related to several causes like metabolic enzyme defects
Treatment	Difficult(unlike gout) Only supportive treatment(pain killers)	Uric acid synthesis blockers

*Note: this table is important

-Some points doctor didn't mention but they are in the slides:

• Recruitment and activation of inflammatory cells

• Joint involvement can last from several days to weeks (subacute)

• may be monoarticular or polyarticular; the knees, followed by the wrists, elbows, shoulders, and ankles, are most commonly affected

• Ultimately, approximately 50% of patients experience significant joint damage

•Therapy is supportive; no known treatment prevents or retards crystal formation

◊ Infectious diseases of joints

- Infectious arthritis:

-most common root of infection is through blood *__Hematogenous*__ (most common), or contiguous from osteomyelitis as we said before, the contiguous spread is more common in infants than adults and it well cause destruction of the joint .

-symptoms are sharp sudden and quick onset of severe pain in joints accompanied with fever and leukocytosis (systemic signs of inflammation)

-most common bacteria is S. aureus.*older children(>2) and adults*

-special cases:

1- Haemophilus influenza most common cause of Infectious arthritis in children (<2 years).

2- gonococcus is prevalent during late adolescence and young adulthood sexually transmitted bacteria also cause genital tract infection .

3- Individuals with sickle cell disease are prone to infection with Salmonella at any age.

◊ Lyme disease

-not common in our region

- Borrelia burgdorferi, this Bactria is similar to syphilis bacteria both of them are spirochete, transmitted by deer ticks, common in the United States.

-if it reaches the systemic phase it can cause damage to any part in the body

-just like syphilis phases primary, secondary, tertiary, Lyme disease has three stages one, two and three:

1-first stage: only cutaneous, they multiply at the site of the tick bite and cause an expanding area of redness(rash) (erythema chronicum migrans) Circle with tick mark in the middle(target or bull's-eye), this skin rash moves from one site to another that's they call it migrans. Sometime it is accompanied with fever and lymphadenopathy but usually disappears in a few weeks' time.

2-seconed stage: visceral and joint involvement, joints start to get inflamed ***migratory arthritis*** (large joints), one joint gets inflamed the and then the next joint and so on.

Different explanation from the slides: second stage also known as the **early disseminated stage**, spirochetes spread hematogenously and cause secondary annular skin lesions, lymphadenopathy, muscle pain, cardiac arrhythmias, and meningitis, often with cranial nerve involvement

3-third stage(the late disseminated stage), start after several years*2-3years* after the bite, if not treated it well cause **chronic arthritis** and **joints deformity**.

-Under the microscope * Histologically *:,prolifration of synovium with special characteristics (a chronic papillary synovitis(long toungs of synovial cells) with synovial hyperplasia), fibrin deposition, chronic inflammation with mononuclear cell infiltration (leukocytes and macrophages), pannus formation

-Diagnosis: clinical, and we can in some cases see bacterial cells with silver stains.

Note: in only 25% of cases do silver stains reveal organisms.

◊ Rheumatoid arthritis

- (doctor said not very common but it is a common disease)

-autoimmune disease, with persistent inflammation.

-systemic disease, chronic and affecting many tissues

- Affects 1% of population, stars at 2nd-4th decade of life, Femal:Male 5:1 , women are more susceptible for autoimmune diseases in general.

- characteristics: systemic, persistent non-infectious disease, autoimmune inflammation, attacking the joints to produce a nonsuppurative proliferative synovitis that frequently progresses to destroy articular cartilage and the underlying bone resulting in disabling arthritis. It can cause fibrosis in organs like lungs,skin and the heart.

-Extra-articular inflammation can occur: skin, heart, blood vessels, muscles, and lungs

•Pathogensis

- Genetic predisposition: you have increased chance of getting the disease if you inherited certain mutated genes.

-disease begins due to Abnormal activation of CD4+ helper T cells responding to local antigens, it identifies normal antigens from the macrophages in joints as foreign ones so it get activated releasing cytokines(TNF),that activates **macrophages**, **B-lymphocytes** and **endothelium**, Activated B transforms into plasma cells and both of them produce IgM antibodies (called rheumatoid factor) that bind normal IgG, forming immune complexes, that well be deposited in the synovium of joint and attract inflammatory cells that damages the synovium , this well cause the synovium to proliferate,(igM antibody is not a normal antibody), the second cells to be activated by t-cells are endothelium, they start to proliferate and forming new vessels in the joint, the third one is macrophage, the macrophages becomes more active secreting more cytokines(TNF) , that well activate fibroblasts, they well proliferate in the synovium increasing their size which causes fibroses, and start releasing proteases that damages cartilage and bone, the last cell to be activated is osteoclast by RANK ligand secreted from the T-cells that results in bone resorption.

-most important thing to know about Rheumatoid arthritis is the proliferation of the synovial cells; the synovium thickens, instead of one layer of cells it becomes multiple layers.

-below the synovial cells, we can see a lot of lymphocytes (that are getting recruited) and small blood vessels.

•Radiology

1) Narrowing in the joint space; due to the thickened synovium.

2) Osteopenia; due to the high activity of osteoclast.

3) Joint edema causes swelling, mostly prominent in the

Interphalangeal joints.

4) Bone erosion.

5) Joint fusion (ankylosis) could happen; due to fibrosis during repair.

6) loss of articular cartilage

~~note please see slide 19 for the morphology of the disease.~~

Muscle diseases

◊ Duchene & Becker Muscular Dystrophy:

-Dystrophy means abnormal formation of the muscle.

-**X-linked inheritance**, so the affected gene came from the mother

-affecting 1 boy from 3500, so its fairly **common**

- At early life, the patient will be normal, and then **at the age of 5**, the disease will become more evident.

-The patients will suffer from **muscle weakness**

-The muscle will be replaced by fat, and once the disease reachs the muscle of the chest the patient will die.

•Pathogenesis

-The disease will result from a mutation in dystophin gene, which encode for dystrophin protein

-The dystrophin protein is responsible for the stabilization of muscles , it connects the sarcomere with the cell membrane; so when its absent, we will get damage with each contraction

-In **Duchene**, we will have **complete absent** of the protein, while in **Becker**, the protein will bepresent, but with **abnormal structure (weak structure)**.

-the symptoms of **Becker** are **milder** that in **Duchene** because of the reason mentioned above.
-The dystrophin function not only present in skeletal muscles, it can be present in other somatic cells, such as nerve cells, but the main pathology of them happens in the skeletal and cardiac muscles.
-The carriers (infected females) are clinically **a**symptomatic, but often have elevated serum creatine kinase (normally found in the muscle cells) and they show mild histological abnormalities on muscle biopsy. And they are at risk of developing **dilated cardiomyopathy**
- 2/3 of the cases are **maternal inheritance**, but one third of cases result from **acquired mutation** (during embryogenesis).
- We can diagnosis the disease **microscopically or clinically**:
* Under the microscope, we will see thin, elongated and slightly bluish muscle fibers with prominent nuclei.
*Also, we can take a biopsy from the muscle, then by western blotting we compare our sample with the control sample(from normal humane), then will see that in the Duchene , the gene will be absent, but in the Becker the gene will be found but smaller in size than normal.

•Clinical

-normal at birth
-Delayed waking, then they will develop muscle weakness, and this will be more obvious during getting up after they fall.
- Muscles will be replaced by fat, so the muscles will appear larger but soft.
-At the age of 10, they will use wheelchair.
-The heart might be affected, they could develop heart failure.
-The last stage, once the disease reaches the muscles of the chest, and they die; due to respiratory failure.
-Some patient can develop cognitive impairment (remember that dystrophin is present in the brain).

◊ Myotonic Dystrophy

-**mytonia** means abnormal movement
-Inheritance as AD (atosomal dominant), here we don't have mutations but we dealing with nucleotide repeats (CGT). Normally we can have some repeats especially in introns, but in this disease we have above normal repeats.
-These repeats will affect the mRNA, and the synthesis of dystrophelia-myotonia protein, and this will affect the contraction of the skeletal muscles.
-These Tri-nucleotides repeats will be increased from generation to another, so the disease will be worse in the next generations, and we call this **anticipation** (to expect that the next generation will have worse symptoms of the same disease).
- So the muscles will have abnormal function, they will develop excess involuntary contraction
-Manifest in late childhood with gate*walking* abnormality, and Muscle atrophy.

Skin diseases

☒ We will discuss the most common tumors related to the skin

◊Squamous cell carcinoma

-The most common tumor affecting the skin
-Usually affect elderly people
-More common in men

-Predisposition factors:
1) Exposures to the sun light (the most important), due to the damage caused by the UV light, the skin will develop cancer

2) Chemicals, so the tumor has a high incidence in smokers*mouth*.
3) Chronic ulcers, some patients (such as diabetic patients) have poor healing, so they develop repeat ulceration, that doesn't heal well, and with regeneration it might develop tumor.
4) Burn, same as ulcer, but the tumor appears in late stages
5) Ionizing radiation, it causes damage in any tissue
6) Immune suppression (especially with AIDS) can develop squamous cell carcinoma.

-may be preceded by carcinoma in-situ lesions (it is always there, and can attack at any time)

•Pathogenesis

-TP53 mutation that can appear in any cancer, mainly it is caused by UV light
-UV light (UVB in particular) a transient
Immunosuppressive effect on skin, higher chance for cancer cells to grow.

•morphology

-The cells appear pleomorphic.
-The tumor cells appear in nests (cells adhesive to each other).
-**Carcinoma in-situ**: the cells appear above the level of basement membrane (they still in the epidermis), but if they reach down the basement membrane, we will call it: **invasive squamous cell carcinoma**.
-The invasive **squamous cell carcinoma** could be well differentiated (the cell appears like the normal,less pleomorphism).Also, it could be poorly differentiated consisting of anaplastic cells with necrosis.
-Under the microscope we can see something called **acantholysis;** which is characterized by empty spaces in the tumor
*** acantho** means **squamous**

Basal Cell Carcinoma

-This is the best human cancer.
- local,Slow-growing cancer that rarely metastasizes
- It tends to occur at sites of chronic sun exposure and in lightly pigmented individuals.
-In most cases, it is sporadic, but sometimes it can be familial (Gorlin syndrome).

• PATHOGENESIS

- Mutations in **TP53** are also common in both familial and sporadic tumors**.**
- associated with dysregulation of the **Hedgehog pathway(**It controls cell division of adult stem cells in the skin, and has been implicated in development of some cancers**)**

• Clinical Features

-Clinically, it is good, and usually **cured by local excision**.
-less than 40% of population will have **recurrence** of the cancer within 5 years, because.
- Advanced lesions **may ulcerate**, and extensive local invasion of bone or facial sinuses may occur if the lesions are neglected for many years.

• Morphology

-Grossly: papule, with dilated blood vessels
-Micro: The cell looks like the stratum basale (stratum basale characterized by large nucleus. The function of it : compensate upper layers), So the tumor cells will appear dark; because most of cell is nuclei in contrast to **squamous cell carcinoma** that have moderate nuclei. Again, they appear as nests with bluish color

-At the periphery, the cells aligned behind each other in a way called **peripheral palisades,** and under that structure there is an empty space called **retraction artifact** (retraction of tumor cells , during slide preparation).

Melanocytic tumors

-Either benign or malignant
-Benign lesions are called **nevi (pleural of nevus)**; the **nevi** have a mutation in **BRAF gene**, but the vast majority **never** transform to malignant.
-**Dysplastic nevi:** It is a nevi, but with abnormal cells. Usually, it appears by it-self.
-**Melanoma:** It is a malignant tumor**,** it has the ability to invasive and Metastasis. It is one of the worse human cancers. Is a highly aggressive malignancy; tumors only a few millimeters in thickness can give rise to deadly metastases.
-The prognosis of **Melanoma** is determined by the **thickness** of the tumor (Depth of melanoma is **the most important** factor to determine the prognosis of the patients)
Grossly: Melanoma appears as dark regions, with irregular contours and pigmentation.
Under the microscope: we can see nests of cells, but the epidermis is normal in contrast to squamous cell carcinoma. Also, we can see other feature of tumor cells such as: hyper chromatin, mitosis….etc.

تمسك بأحلامك وإن كانت بعيدة المنال, وقل دائماً يا رب

فليس عند الله شيءٌ مُحال

A day without sunshine is like, you know, night. *–steve martin*