PATHOLOGY

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Welcome to sheet 5 pathology! the last lecture of cell injury by Dr.Manar^-^

Intracellular accumulations :accumulations of certain materials in cells.

- Four mechanisms for deposition of materials inside cells (four types of materials):

- Inadequate removal (accumulation) of a normal substance (fatty change in the liver)
  Fats/Triglycerides are known to be endogenous products that are normally present in many cell types,so when there is inadequate removal of these substances,they accumulate.
  Regarding triglycerides,they are normally transported outside of the cell by binding to proteins (the structure produced may be named lipoprotein ,or apolipoproteins).So,if any defect happens to this transport,like for example having lack of proteins transporting lipids - and we did mention this when explaining cell injury mechanisms,one of them being decreased protein synthesis - ,lipids will accumulate (figure 1👇)

- Accumulation of an abnormal endogenous protein due to folding defect (a1-antitrypsin deficiency)
  A1-antitryosin gene ,which encodes a1-antitrypsin enzyme,can be affected by a mutation that leads to production of abnormally folded a1-antitrypsin proteins,meaning that these proteins become non-functional,unable to be secreted outside the cell,then they accumulate in cells.In peripheral blood or tissue, a notable deficiency of this protein will be seen,because of its abnormal shape that can't be secreted outside the cell so depositing inside them , accumulation of misfolded proteins in endoplasmic reticulum. (Figure2 👇)

- Failure to degrade a metabolite due to inherited enzyme deficiencies (lysosomal storage diseases, glycogen storage diseases)
  What happens here is that we are having deficiency of lysosomal enzymes or glycogen-metabolizing enzymes due to a genetic mutation, leading to

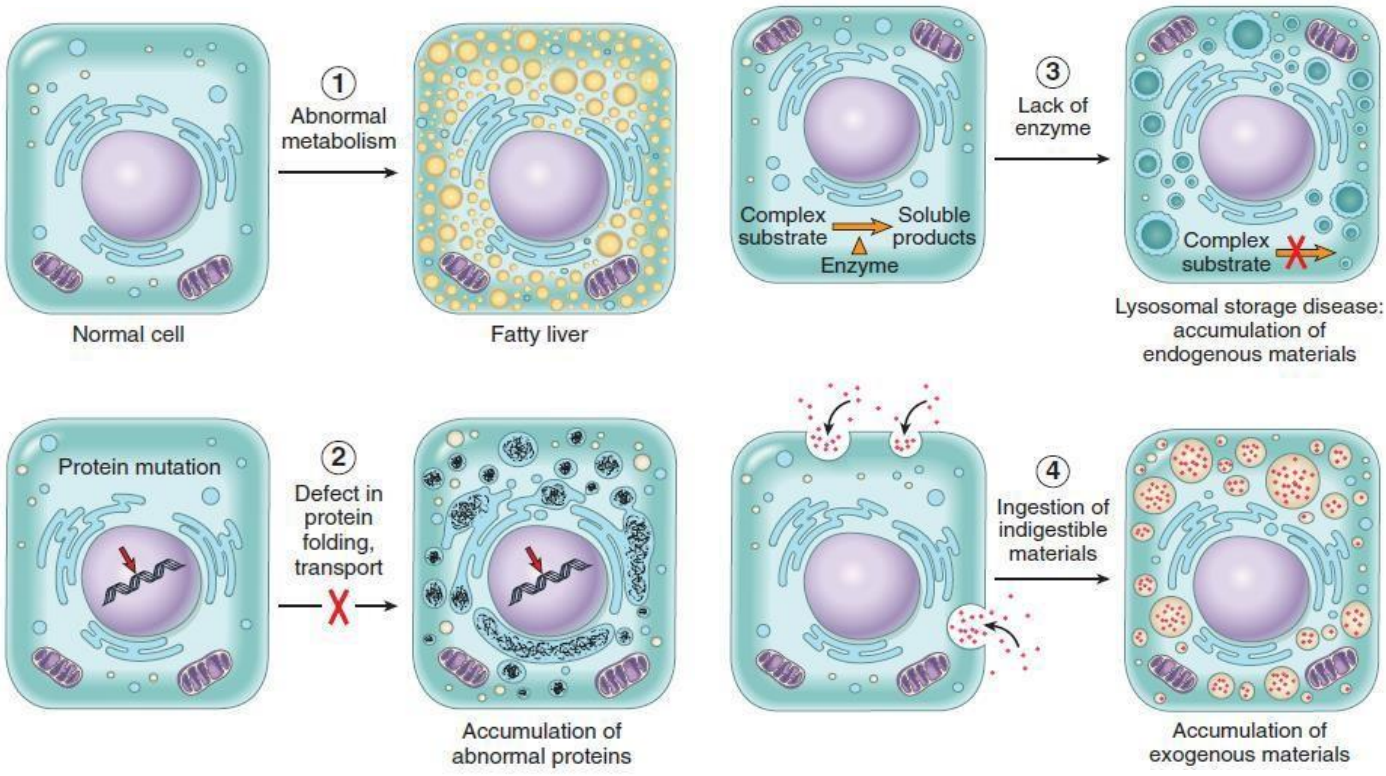
accumulation of for example glycogen or other lysosomal metabolic products that normally get degraded inside the cell. (Figure3👇)

- Deposition and accumulation of an abnormal exogenous substances(Carbon in lungs and Silica).

Carbon is an exogenous substance in nature(not a natural mineral that is produced in our bodies),so it get deposited by taking it from outside,there are many ways such as smoking,it causes carbon deposition in lungs,also living in settings with polluted air may lead to carbon deposition in lungs.(figure4 👇)

CLINICAL GLIMPSE:when asking for a lung biobsy then noticing heavy carbon deposition in lungs,the history of the patient will definitely include a strong cause,such as smoking ^-^

Also Silica is an another example of accumulating exogenous materials.



This diagram above summarized all aforementioned mechanisms.

AND NOW,LET'S TALK ABOUT THE SUBSTANCES ABOVE IN MORE DETAIL!!

❖ FATTY CHANGE-STEATOSIS

- The most common affected tissue is LIVER since it is the most organ evolved in fat metabolism ,but also can be seen in HEART,KIDNEY,MUSCLES).

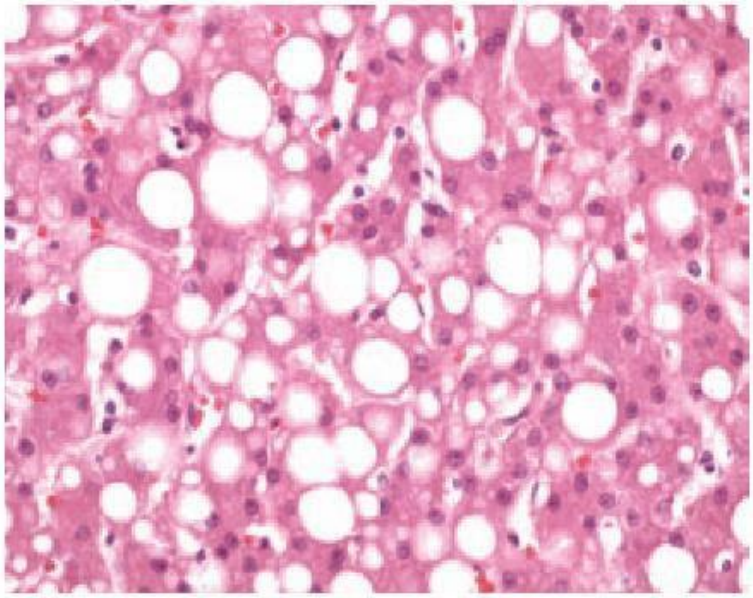
-It is due to the deposition of Triglycerides in the cells, as you see here the fatty position is manifested by white fatty droplets inside the cells which vary in their sizes (some of them are macro and others are micro).

-Alcohol abuse and DM +obesity are the most common causes of fatty liver disease in industrialized countries.

- Causes of fatty liver depend on geographic locations,for example in Western countries alcohol abuse is the most common cause,whereas in our part of the world DM+obesity is the most common cause.

- Histologically,fatty cells in a liver section appear as empty white vacuoles inside the cell,replacing the nucleus to the cell periphery.

- Degree of steatosis may vary between mild steatosis and severe steatosis,depending on the severity of for example alcohol consumption,how obese the patient is,duration of diabetes,…



A histological section of the liver illustrating the presence of fat. (triglycerides)accumulated in cells

OTHER CAUSES THAT SHOULD BE MENTIONED:

1.Toxins – carbon tetrachloride CCL4 (remember when talking about cell injury mechanisms,we mentioned toxi-mediated mechanism,and we gave an example about it,Acetaminophen,being toxic to liver-after exceeding a certain dose threshold-,causing fatty liver change)

2.Protein malnutrition (lipids accumulating in the liver in this context are TRIGLYCERIDES.As we mentioned before, lipids accumulate because of a deficiency in the proteins needed to transport them outside the cell,so logically,patients having protein malnutrition will suffer from lipid accumulation in the liver.

3. DM

4.Obesity

5.Anoxia (differentiate between anoxia and hypoxia,hypoxia is a decrease in oxygen supply,while anoxia means loss of oxygen supply).

❖ CHOLESTEROL AND CHOLESTERYL ESTERS

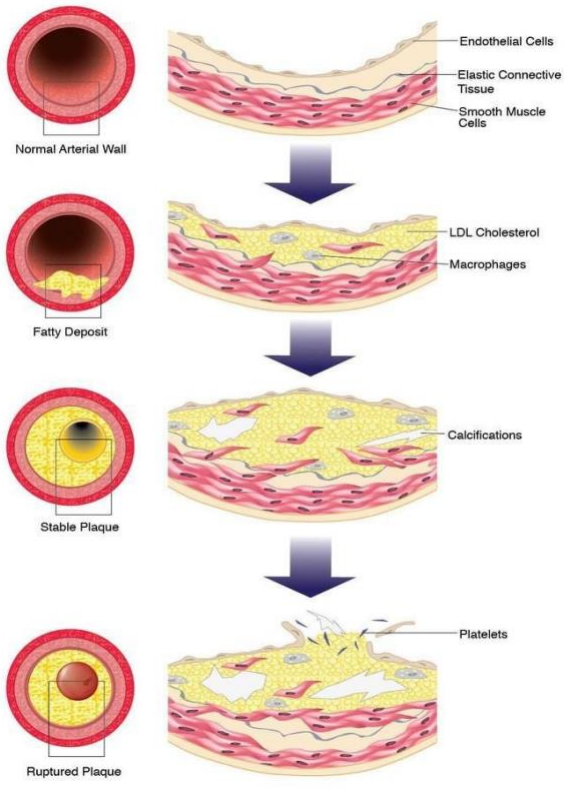
- The most common site for deposition is in the walls of the blood vessels.
  - ➢ Phagocytes and macrophages in the walls of the blood vessels uptake the fat, then they become overloaded with these lipids (triglycerides, cholesterols, and cholesterol esters).
  - ➢ The cause is either increased intake or decreased catabolism of these cholesterol and cholesterol esters.
  - ➢ The best example is Atherosclerosis which can predispose to coronary heart disease or cerebrovascular accidents.

Looking at the histological section of the blood vessel,we can see these lipids,accumulating sometimes in MACROPHAGES,they intake these lipids in the wall of the blood vessel.

NORMAL BLOOD VESSEL IS PRESENT

Here it starts depositing this yellow material (Cholesterol,CE,and even triglycerides)

They keep accumulating ,narrowing the lumen



❖ PROTEINS

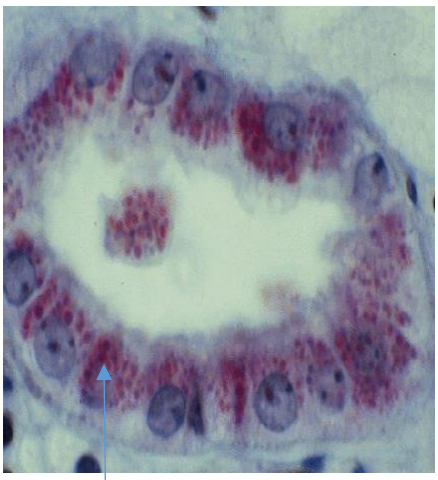
- much less common than lipid accumulations.
- Proteins can be either produced inside the cell or derived from outside the cell.

Examples:

1.Proximal renal tubules in nephrotic syndrome
2.Russell bodies in plasma cells.
3.Alcoholic hyaline in liver of alcoholic patient.
4.Neurofibrillary tangles in neurons, protein accumulations in the neurons of the brain (Alzheimer disease)

1.nephrotic syndrome (increasing in albumin conc.)

An example is what happens in the cells of kidney, particularly proximal renal tubules, in nephrotic syndrome.
What happens is that patients suffer from a high rate of eliminating protein (albumin) in the urine. Normally, glomeruli prevent the escape of proteins from the blood to urine.But here in this disease, the permeability of glomeruli for proteins is abnormally high, so we start to lose these proteins in the urine.As a response, the renal tubules will try to conserve as much amount of proteins as they can, so they reabsorb them from the urine in order to bring them back to blood.

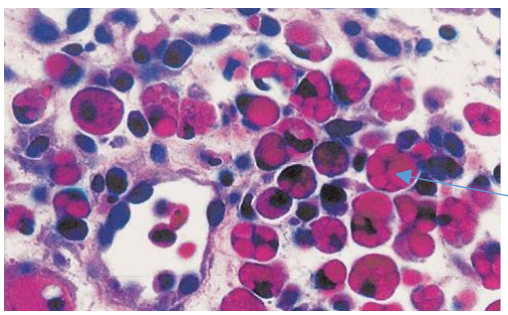


Epithelial cells of renal tubules

NOTICE HERE the pinkish appearance of accumulating proteins inside proximal renal tubular cells.**

2. Russell bodies in plasma cells

We already know that plasma cells are a main source of antibodies, which are proteins. So when an inflammation or tumor occurs, plasma cells produce so much antibodies that will accumulate in their cytoplasm, these are called Russell bodies

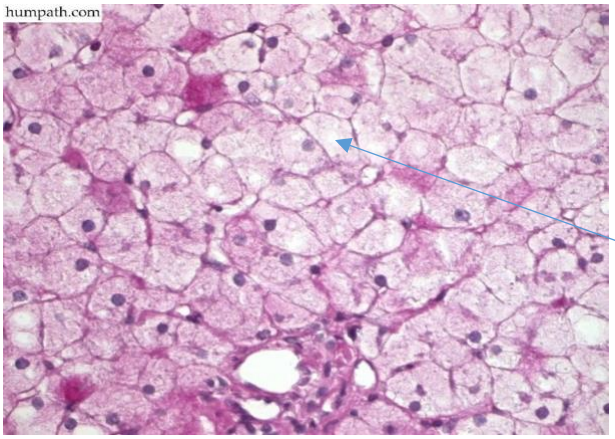


Notice here the heavy pinkish appearance of the cytoplasm-this is how Russell bodies The dark blue-black bodies are nuclei

*Russell bodies:excessive protein(antibody) deposition in the cytoplasm of plasma cells

❖ GLYCOGEN

- Abnormality in glucose or glycogen metabolism(glycogen storage disease, deficiency of glycogen-metabolizing enzymes,leads to glycogen deposition)
- DM(glycogen deposition in renal tubules, vessel cells of pancreas ,heart, liver)
- Also, glycogen storage diseases *(inherited abnormality)* may manifest in the bone marrow, where bone marrow biopsies show macrophages full of deposited glycogen.



Liver section, look at the hepatocytes. Normally, the cytoplasm appear pinkish in color, but in this case of excessive glycogen deposition we notice that it becomes faint or slightly white.

❖ PIGMENTS

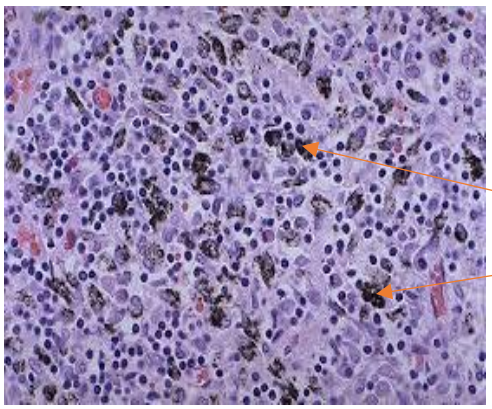
(ANY COLORED MATERIAL DEPOSITED INSIDE CELLS)

Exogenous

Most common exogenous, CARBON (coal dust-mining- ,air pollution, smoking) – All people exposured will have carbon deposited in their lungs.

Deposition can occur in the lung tissue itself, or in the alveoli.

If deposited in alveoli,it will be uptaken and engulfed by alveolar macrophages → lymphatic channels → tracheobronchial LN. and it may reach mediastinal LN.



Notice that the black discolorations here represent carbon deposition, which is called ANTHRACOSIS

Carbon is an undegradable substance, thus appears as black deposits.

Endogenous

1.Lipofuscin

Brown pigment

Tissues affected: **heart, liver and brain**.

Its deposition indicates **aging**, **atrophy**, or previous **cell injury** mostly mediated by free radicals.

It is a lipid and protein-derived (composition): mostly due to the membrane damage or organelles damage in the cell.

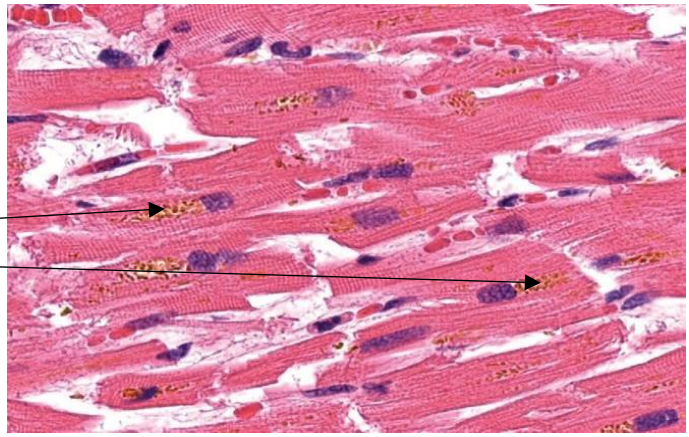
When the tissue is severely atrophied, and it turns brown, due to lipofuscin atrophy, it appears as 'BROWN ATROPHY'

Also named 'wear-and-tear pigment'.

((لما يتعرّض النسيج لأيّ من عوامل الحتّ والتعرية بترسّب))

NOTICE THE BROWN COLOR!

LIPOFUSCIN DEPOSITION



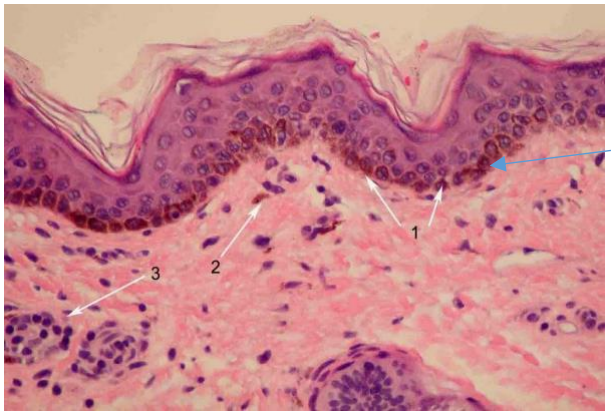
2.Melanin

Source: melanocytes from the skin.

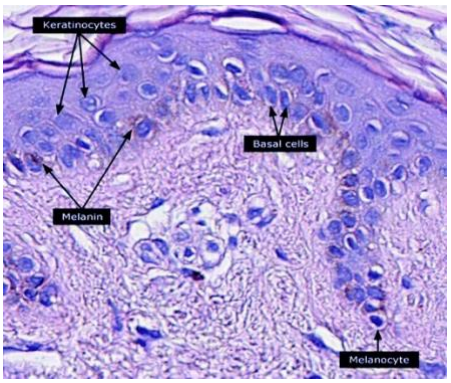
It offers up protection against UV light

In cases of increased exposure to UV light, especially fair-skinned people, they develop excessive production of melanin, which can also be transported to adjacent keratinocytes and dermal macrophages.

Examples on skin mainfestions: FRECKELS, which are brown dots (discolorations) due to UV light exposure in fair-skinned people.

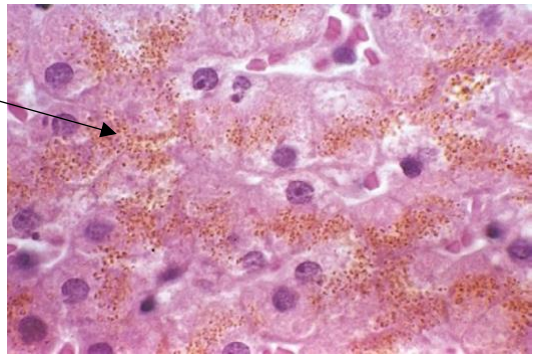


Note in this section of the skin, the brown-colored cells are NOT only melanocytes, it is also keratinocytes which take the pigment, but they don't produce melanin–MELANOCYTES DO -,they only take it, also macrophages in the dermis take the pigment



Additional pic for melanin pigment.

3.Hemosiderin



→ Hb-derived iron pigment (produced from hemoglobin degradation)

****Iron** in cells usually binds to **apoferritin** (protein), to give **ferritin micelles.**

Deposition of Iron can be physiologic or pathologic

1.Physiologic in organs or tissues that have frequent RBCs turnover activity such as:bone marrow,the factory of RBCs synthesis,also RBCs die in BM before even being transported to blood,thus we'll find iron deposition in BM when examining biopsies,which is a normal finding.Also,we see Iron deposition is tissues or organs that destroy RBCs like spleen and liver,as a result its normal to find a lot of deposited Iron in spleen and –to a less extent- in the liver.

2. Pathological

a. in localized depositions such as bruises (from hemorrhage),here the affected region will express different discolorations(e.g:bluish and yellowish discolorations) which indicates Iron deposition. After a

while,macrophages will arrive ,engulf Iron,in order to return to the blood ,where it can be used again in RBC production.

b. In hemosiderosis:

systemic pathologic deposition of hemosiderin can result from hemochromatosis, hemolytic anemias and repeated blood transfusion.

*****Pathologic deposition can be generalized, systemic, everywhere(skin, heart ,liver, muscles).**

There are different causes of hemosederosis:

1.HEMOLYTIC ANEMIA

-Sickle Cell Anemia,Thalassemia

*Any condition that increases RBCs destruction is hemolytic anemia,and it can cause general deposition of Iron.

*Hemolytic anemia patients were found to have a deeply brownish skin.

2.HEMOCHROMATOSIS

Autosomal dominant condition that causes high Iron deposition in different organs in the body, for example deposition is the heart may lead to heart failure, deposition in the pancreas may lead to Diabetes and so on

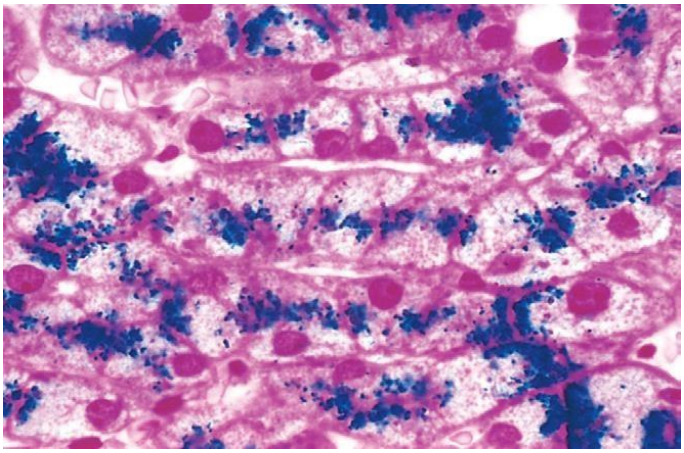
3.REPEATED BLOOD TRANSFUSIONS

e.g:thalassemia,leukemia,cytopenia

-Patients with thalassemia receive blood transfusions approximately every 3 months, so you can imagine how much Iron will get deposited in their bodies, so they have an extra procedure called IRON CHELATION, in order to take out excess Iron, to eventually protecting them from organ damage due to excessive Iron deposition

Q:: How can we make sure that the brown pigment in the liver is an iron pigment, not lipofuscin pigment or melanin pigment for example?

We use Prussian blue stain, Prussian blue stain gives these granules the blue color if it contains iron, but if it is lipofuscin or melanin it will not take the stain.



PATHOLOGICAL CALCIFICATION

- Abnormal deposition of calcium salts,together with smaller amounts of Iron,Magnesium,Phosphorus,and other minerals –note that calcium isn't usually deposited alone-

TWO TYPES OF CALCIFICATION:

☑ Dystrophic calcification

- Deposition occurs in dead/injured(necrotic) tissues
- Normal Ca^{+2} metabolism(peripheral blood calcium levels are normal,not elevated)
- Exacerbated by hypercalcemia(but it's not necessary that the patient will present with hypercalcemia).

☑ Metastatic calcification (OPPOSITE TO DYSTROPHIC)

- Deposition in normal tissues
- Almost always abnormal Ca^{+2} metabolism(hypercalcemia)

DYSTROPHIC CALCIFICATION

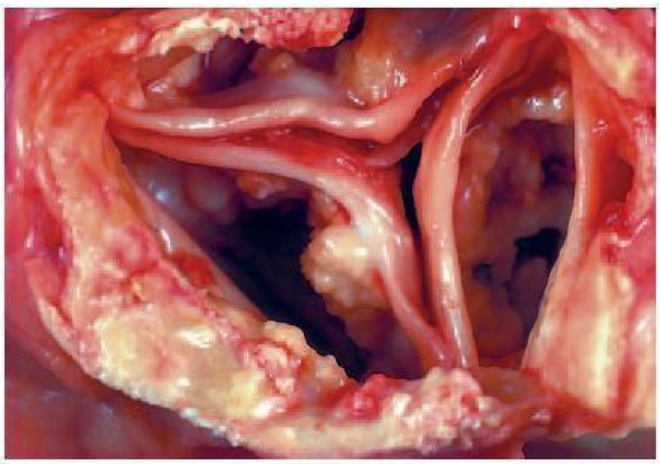
Necrosis of any type in any tissue:coagulative,caseous(TB),fat necrosis(acute pancreatitis).Atherosclerosis,aging,damaged heart valves,aortic stenosis

-Atherosclerosis has recently been considered an inflammatory reaction,because of macrophages being at the site engulfing lipids in the walls of blood vessels,so atherosclerotic vessels can deposit calcium,thus vessels become more rigid.

-Aging of cells can also lead to calcium accumulation,like aged heart valves that underwent degeneration as a consequence for aging,they show calcium deposition.

-Aortic stenosis,either due to aging or other earlier conditions,can lead to calcium accumulation in aortic heart valves,making them more stiff.

-Complications depend on the degree of calcium accumulation,that is,small or trace amounts of deposited calcium in necrotic doesn't indicate clinical significance,because the problem here is the necrosis itself,and calcium deposition won't be worse.But sometimes aged heart valves may have excessive amounts of calcium deposited.



As shown here,this heart valve is severely filled with deposited calcium that has a white-chalky appearance,and this may lead to HF,so the valve should be changed,because of organ dysfunction.

☑ calcium depositions may be an incidental finding indicating past insignificant cell injury

☑ Long-term calcium accumulation may eventually cause organ dysfunction.

METASTATIC CALCIFICATON (The same tissue doesn't have any problems, except for elevated calcium levels in the blood):

- **CAUSES OF HYPERCALCEMIA:**
  - Hyperparathyroidism(elevated Parathyroid hormone in the blood,and we know it is the main responsible hormone for calcium balance,so disordered levels of it would induce hypercalcemia)
    **Hyperparathyroidism can be primary(problem in the parathyroid itself) or secondary(problem in the hypothalamus) or it could be a tumor (lung cancer as an example) that produces PTH-like proteins in the blood,exerting the same effect of PTH,hypercalcemia.

  - Bone destruction: any destruction to the bone causes calcium release to the blood,causing hypercalcemia.It can be caused by different conditions like metastasis(breast cancer,prostatic cancer,… can metastatize to bones thus elaborating calcium from them to the blood leading to hypercalcemia.Another cause is Multiple Myeloma(MM),which is a tumor in plasma cells –which are present in the bone,in BM_,thus hypercalcemia happens. Also Leukemia,which occurs in the bone marrow,can eventually lead to bone destruction.Pagets disease,which is a benign disease,is a cause of bone destruction,presents with excessive bone turnover and remodeling(breakup and synthesis at the same time).Immobilization can also lead to hypercalcemia.
  - Vit D intoxication:Vit D increases calcium absorption from kidneys,GIT,… to the blood.So people taking vit D without prescription will continuously build up high levels of it in their blood,causing intoxication,thus hypercalcemia.
  - Sarcoidosis:autoimmune systemic disease accompanied with hypercalcemia
  - Renal failure:presents with low phosphate levels in the blood (hypophosphatemia),this will trigger sec. hyperparathyroidism in order to absorb more phosphorus (and PTH elevation at the same time leads to more calcium absorbance(hypercalcemia)).

- **Calcium deposition can occur in various organs in the body such as kidney,lung and blood vessels**

- **Metastatic calcification is a MISNOMER(MISNAMED),because metastasis in conventional medicine means spread of cancer(malignancy) to distant sites in the body ,but here metastasis is NOT malignant,although it can accompany malignancies,but calcification isn't generally malignant,so it was named as metastatic because it can spread everywhere.**

CELLULAR AGING

- Age is one of the strongest independent risk factors for many chronic diseases like Ischemic heart disease,DM,Alzheimer disease,cancer,atherosclerosis.
- Aging affects the body as a whole and affects cells,their life span will keep decling progressively as well as their functional capacity.
- Aging doesn't necessary mean an older age,for example,we –as young people- have continuous turnover and resynthesis of our skin cells,that they age at a certain point,also GIT cells undergo aging normally.
- SEVERAL MECHANISMS:
  - Accumulation of mutations in DNA
  - Decreased cellular replication(replicative senescence).They get arrested in the cell cycle, thus they can't replicate anymore
  - Defective protein homeostasis (synthesis) .Protein imbalance occurs.
  - Replicative senescence:progressive shortening of telomeres which ultimately results in cell cycle arrest.

Notes about the diagram:

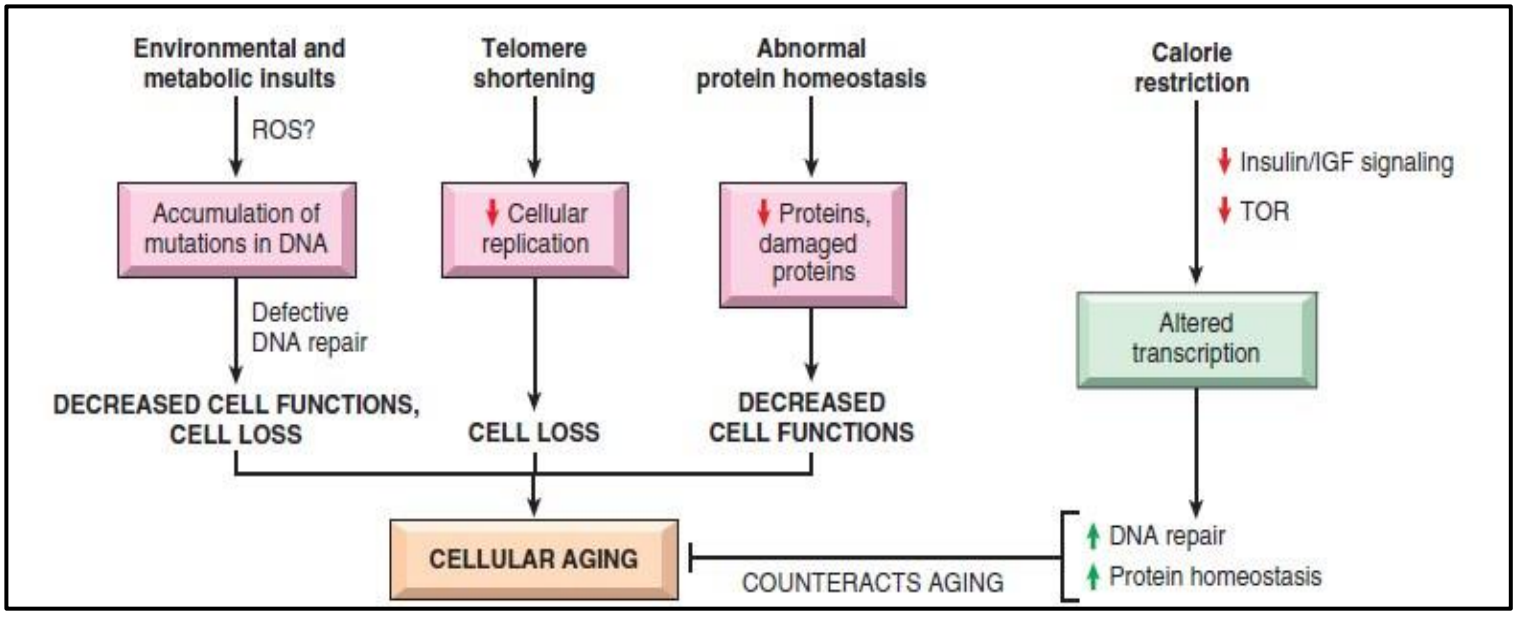
- ☑ We always accumulate mutations in our DNA,because of frequent contact with radiation,UV light,certain carcinogens in our food and environment.
- ☑ In the second mechanism,why cellular replication is reduced? Because of some defect in TELOMERES,which will be explained in the next few lines.

TELOMERES

- Short repeated sequences of DNA at both ends of chromosomes(they are non-coding regions;don't code for genes)
- Ensure complete replication of chromosome ends and protecting them(protecting the coding part of DNA)
- Progressively shortened upon replication(aging)
  For example in the first cell cycle,we lose the last nucleotides,then we lose two and so on,until we reach a state where chromosome ends are exposed and this means that danger is their,that if DNA kept replicating,it will lose part of its material,the coding part.
- Signals cell cycle arrest

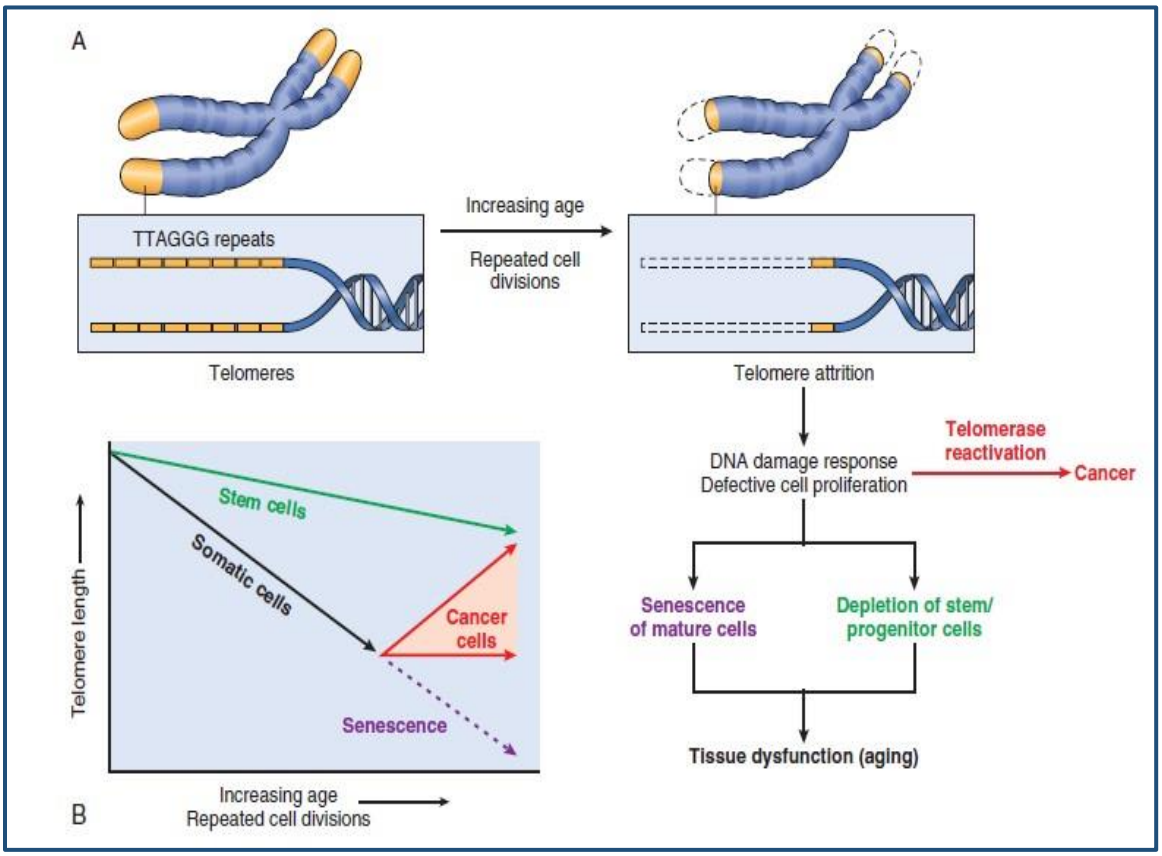
سبحان الله

- As a gift of God,we have the enzyme telomerase,which maintains telomere length(BUT THERE IS SOME PROBLEM HERE,CHECK THE NEXT POINT!)
- Telomerase in expressed variably in different cells.In germ cells(cells of reproductive system of men and women) ,it's very highly expressed,because we want them to keep replicating for a long time.Additionally, in stem cells(progenitor cells for mature organs' cells),we have high expression of telomerase,but to a less extent compared with germ cells(lower levels).However,in the case of most somatic cells,which are terminally differentiated cells(for example:skin cells,GIT epithelial cells) ,they have only a limited capacity to divide for few number of divisions,and the telomerase in notably absent,thus telomeres will keep shortening,then the cell get arrested in cell cycle.
  *Note:this is how cells age,because they develop loss of telomerase enzyme,thus shortening of telomeres.Finally entering cell cycle arrest.



- **FURTHER SPEAKING,cancer cells have their telomerase reactivated,so they will continue to divide forever {THAT'S WHY WE CALL THEM IMMORTAL CELLS}**

NOW LET'S TALK ABOUT THE 3rd MECHANISM OF CELLULAR AGING: DEFECTIVE PROTEIN HOMEOSTASIS



- **Increased turnover**
- **Decreased synthesis**
- **Defective activity of chaperons and proteasomes(leading to misfolded protein production)**
- **Overall decrease in intracellular proteins**
- **Accumulation of misfolded proteins → aging → apoptosis**

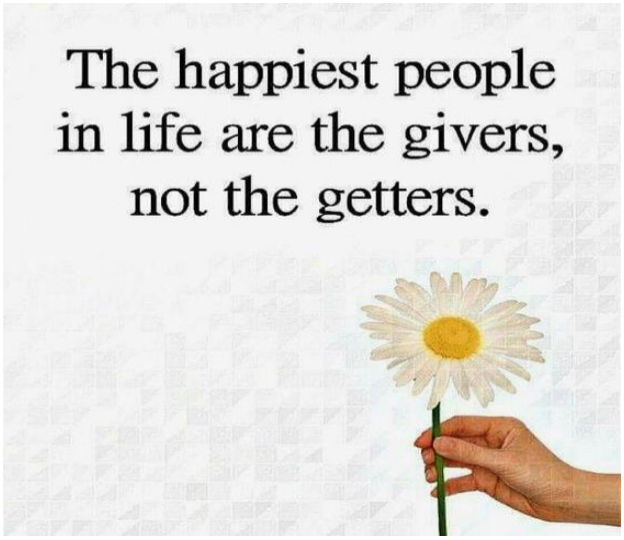
ANTI AGING-SLOWING OF AGING (ELIXIR OF YOUTH)

calorie restriction
improve immunity
reduce IGF

Physical activity
Stress
accelerates aging

Precise mechanisms
underlying these effects
remain to be defined

Persistent
inflammation,
chronic
metabolic
diseases,
accelerate
aging



وختامًا،بنهنّيك إنك وصلت هون وأخيرًا،إن شاء الله تكون استفدت وسهّلنا عليك،ولا تنس أن تذكرنا بدعوة في ظهر الغيب ❤

NOTE:

بتقدروا ترجعوا لشيت 019 و هي ممتازة , لكن بهاد الشيت ركزنا اكثر على كلام الدكتورة.