الرجوع للعمل وحده لا يغني عن الرجوع للمصادر الأساسية

PATHOLOGY
TEAM 436

Cell Injury

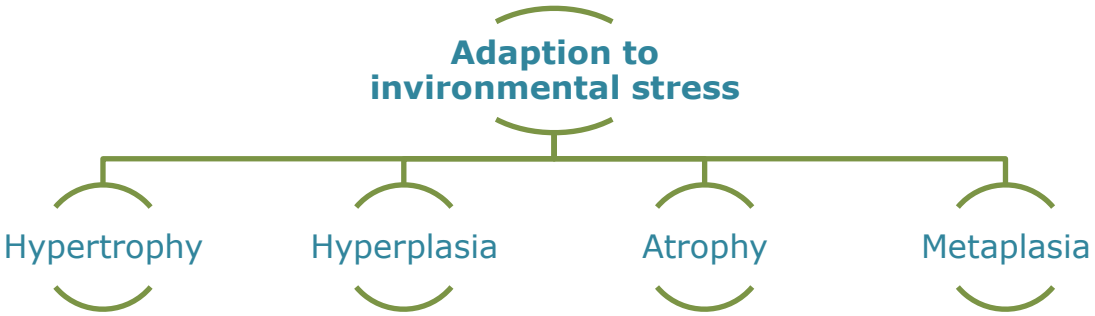
Objectives:

- **A.** Understand the concept of cells and tissue adaptation to environmental stress including the meaning of hypertrophy, hyperplasia, aplasia, atrophy, hypoplasia and metaplasia with their clinical manifestations.
- **B.** Is aware of the concept of hypoxic cell injury and its major causes.
- **C.** Understand the definitions and mechanisms of free radical injury.
- **D.** Knows the definition of apoptosis, tissue necrosis and its various types with clinical examples.
- **E.** Able to differentiate between necrosis and apoptosis.
- **F.** Understand the causes of and pathologic changes occurring in fatty change (steatosis), accumulations of exogenous and endogenous pigments (carbon, silica, iron, melanin, bilirubin and lipofuscin).
- **G.** Understand the causes of and differences between dystrophic and metastatic calcifications.

Definitions: blue
Examples: green
Doctor's note: red
Extra explanation: grey
Diseases names: Highlight

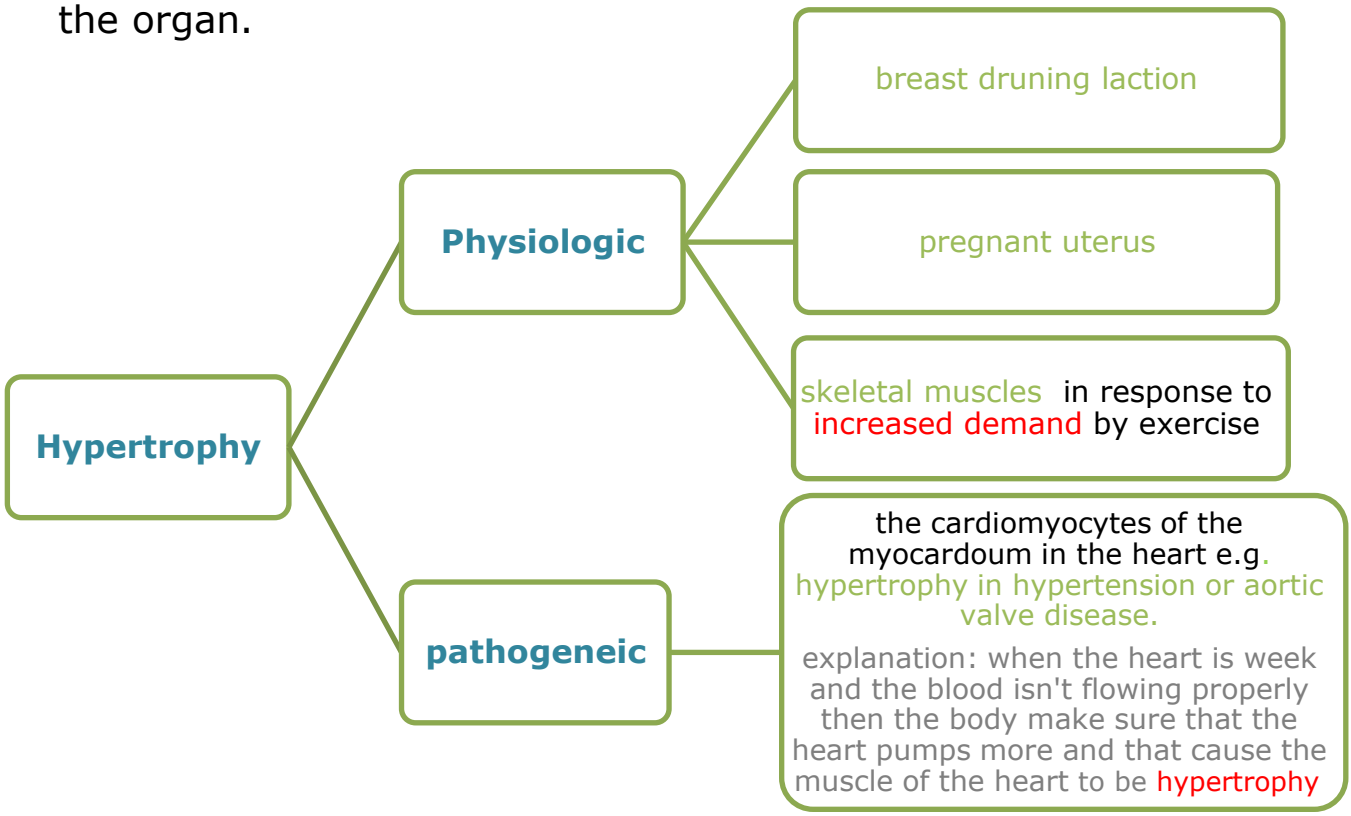
A. Understand the concept of cells and tissue adaptation to environmental stress including the meaning of hypertrophy, hyperplasia, aplasia, atrophy, hypoplasia and metaplasia with their clinical

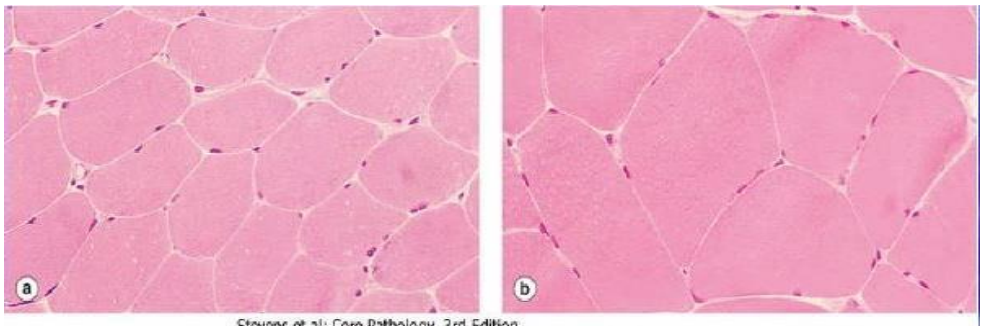
Adaptation: are reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to changes in their environment.



A. Hypertrophy:

is an increase in the size of cells resulting in increase in the size of the organ.



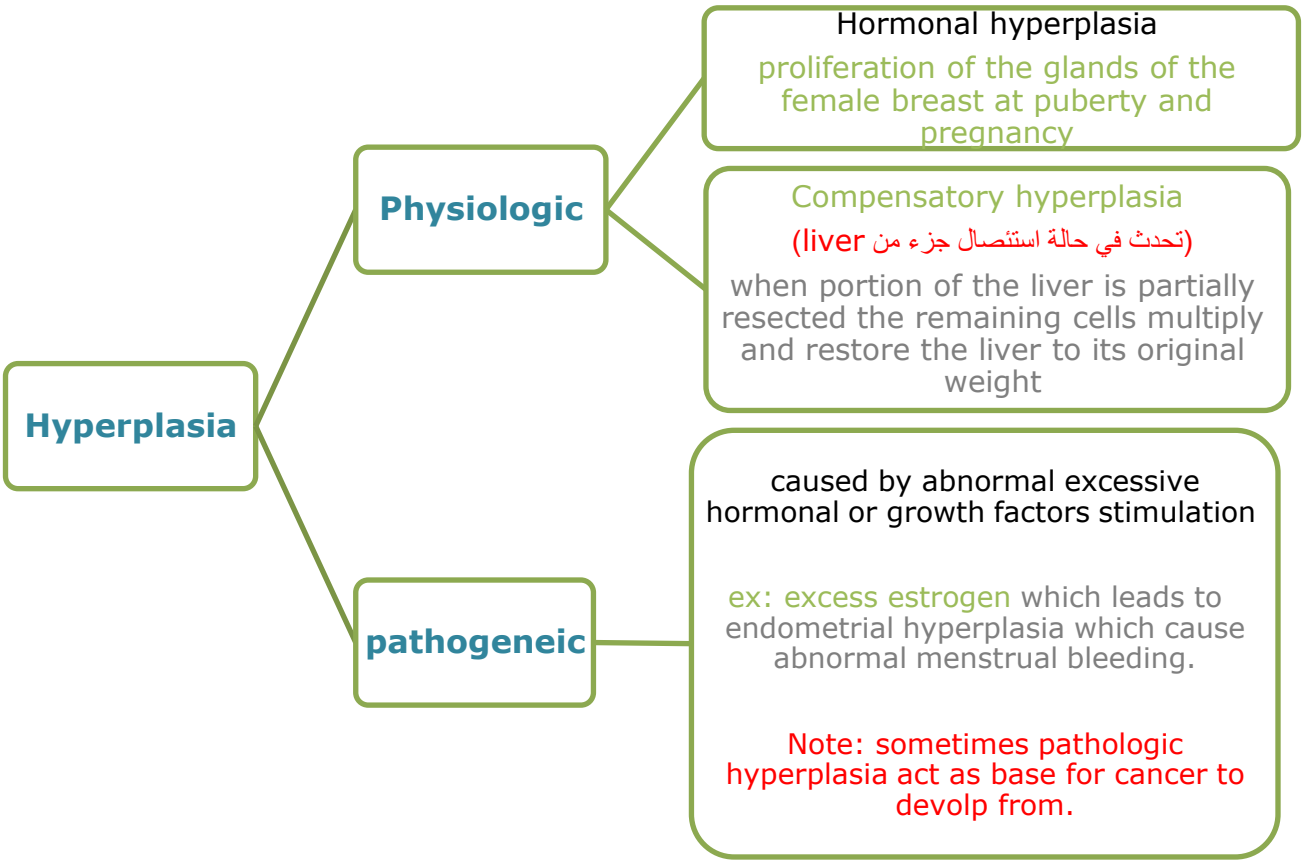


Stevens et al: Core Pathology, 3rd Edition.

Hypertrophy of skeletal muscle in response to exercise. Hypertrophy in the absence of hyperplasia is typically seen in muscle where the stimulus is an increased demand for work. Taken at the same magnification, (a) shows muscle fibers in transverse section from the soleus muscle of a normal 50-year-old man, and (b) shows fibers from the same muscle in a veteran marathon runner. Note the dramatic increase in the size of the fibers in response to the demands of marathon running.

B. Hyperplasia

is an increase in the number of cells. Hyperplasia takes place if the tissue contains cell populations capable of replication

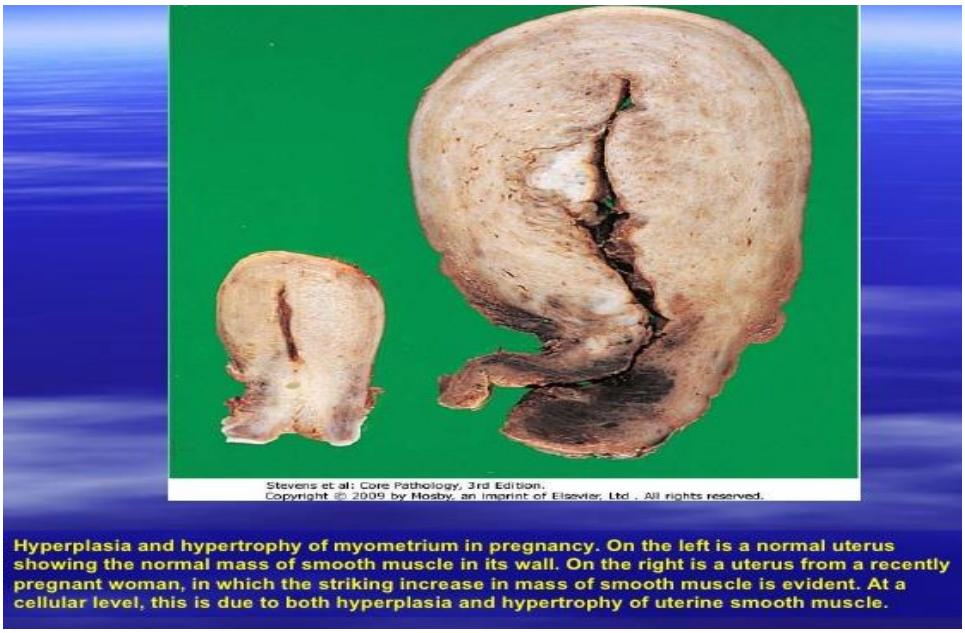


NOTE:

1- hypertrophy and hyperplasia can occur together, e.g.

- Uterus during pregnancy
- Benign prostatic hyperplasia

2- Both hypertrophy and hyperplasia there are increase demands.



Hyperplasia and hypertrophy of myometrium in pregnancy. On the left is a normal uterus showing the normal mass of smooth muscle in its wall. On the right is a uterus from a recently pregnant woman, in which the striking increase in mass of smooth muscle is evident. At a cellular level, this is due to both hyperplasia and hypertrophy of uterine smooth muscle.

C. Atrophy:

- Shrinkage in the size of the cell by the loss of cell substance.
- Reduced demand leads to atrophy.
- When a sufficient number of cells are involved, the entire tissue or organ diminishes in size becoming atrophic.
- Although atrophic cells may have diminished function, they are not dead.
- The mechanisms of atrophy consist of a combination of decreased protein synthesis and increased protein degradation in cells.

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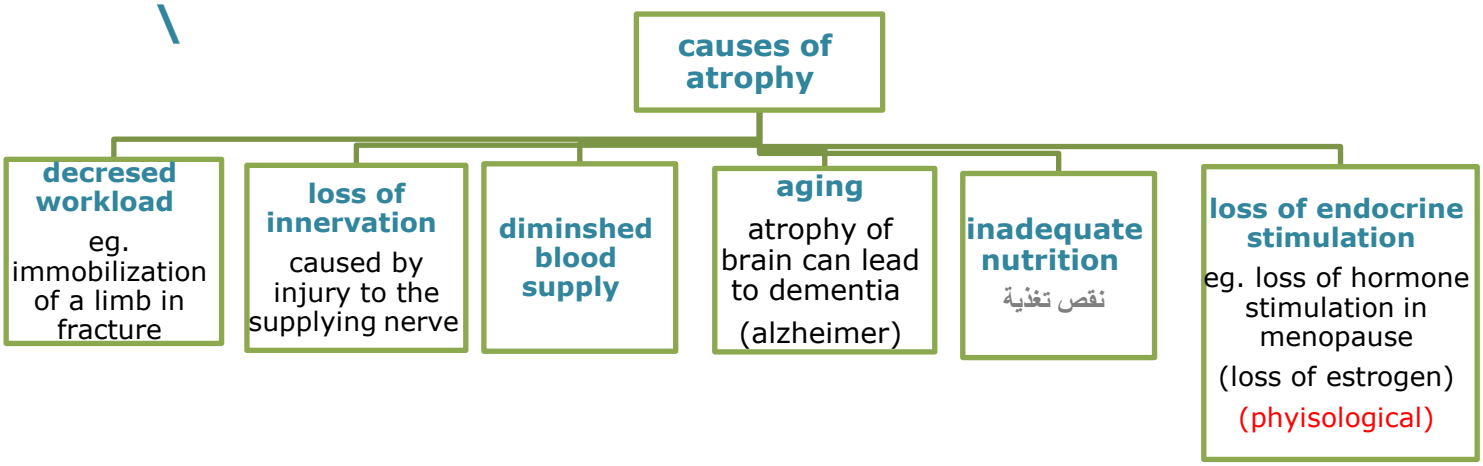


Involution:

It is reduction in the cell number.

Hypoplasia	Aplasia
Refers to an organ that does not reach its full size. **decrease in cell production during embryogenesis, resulting in a relatively small organ (e.g., streak ovary in Turner syndrome)**	Is the failure of cell production. **(e.g., unilateral renal agenesis).**

NOTE:

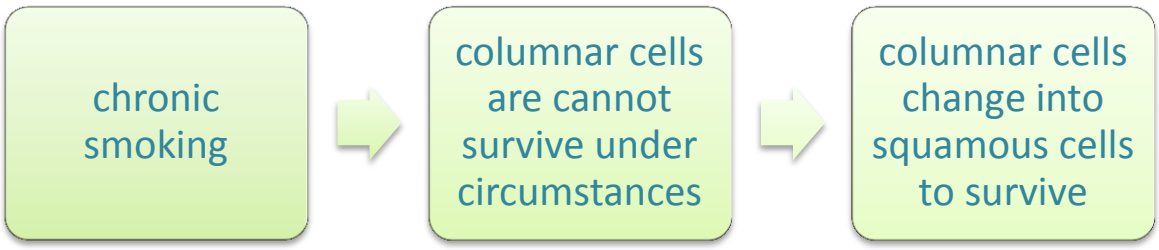
Aplasia and hypoplasia is disorder and NOT adaptive response.

D. Metaplasia:

- Cells adapt by changing from one type of cell to another.
- Cells change because of a sensitivity caused by an agent. The new type of cell is able to tolerate this new difficult environment.
- Usually reversible.

1. Squamous Metaplasia:

- Columnar cells replaced by squamous cells
- Occurs in the cervix and respiratory track
- In the respiratory track:



- **Negatives:** columnar cells loose their protective ability
- ex. Mucus secretion and ciliary movement
- If the agent causing the metaplasia doesn't stop, it could lead to cancer
- Ex. Respiratory(columnar) > squamous cell > cell cancer.
- Ex. Cervix(columnar)> Squamous cell > carcinoma of the cervix.

Doctor's note:
(squamous metaplasia is the ground of the cancer and NOT pre-cancer).

2. Columnar Cell Metaplasia:

- Replacement of squamous lining by columnar cells.
- Seen in chronic gastro-esophageal reflux disease.
- Called Barrett's esophagus.
- Can be precancerous.

3. Osseous metaplasia:

- New bone at sites of tissue injury.
- Cartilaginous metaplasia may also occur.
- Very rare.

4. Myeloid Metaplasia (extramedullary hematopoiesis (production of WBC & RBC)):

- When bone marrow tissue (hematopoietic) develops in abnormal sites.
- Ex. Spleen or liver.

B. Is aware of the concept of hypoxic cell injury and its major causes.

Causes of Cell Injury

- Causes of both reversible and irreversible injury are the same

1) Oxygen Deprivation (Hypoxic cell injury).

- It is *common* cause of cell injury and cell death.

Hypoxic : Low oxygen delivery to tissue

- The most important biochemical abnormality in hypoxic cells that leads to cell injury is reduced intracellular generation of ATP, as a consequence of reduced supply of oxygen

- loss of ATP leads to the failure of many energy dependent cellular systems, including (1) ion pumps (leading to cell swelling, and influx of Ca2+, with its deleterious consequences); (2) depletion of glycogen stores and accumulation of lactic acid, thus lowering the intracellular pH; and (3) reduction in protein synthesis.

Hypoxia can be due to:

a) Ischemia (obstruction of arterial blood flow), E.g. in myocardial infarction and atherosclerosis.

b) Inadequate oxygenation of the blood e.g. lung disease and carbon monoxide (co poisoning.

c) Decreased oxygen-carrying capacity of the blood e.g. anemia.

d) Inadequate tissue perfusion due to cardiorespiratory failure, hypotension, shock etc.

- Ischemia: is decreased blood flow through an organ. Arises with:
1) Decreased arterial perfusion {e.g., atherosclerosis)
2) Decreased venous drainage (e.g., Budd-Chiari syndrome)
3) Shock-generalized hypotension resulting in poor tissue perfusion.

- Ischemia injures tissues faster and usually more severely than hypoxia. The major cellular abnormalities in oxygen-deprived cells are decreased ATP generation, mitochondrial damage, and accumulation of ROS, with its downstream consequences.

- Most of the diseases are caused by changes of the level of the cells. i.e. When the cell become sick you get the disease or the disease will make the cell sick either in its function or will make it die.

- Injury of cells can be caused by many factors, it could be: bacterial, by infection, inflammatory, immunological, due radiation, due toxins, due drugs, due physical agents, due vascular (like if there is problem in the circulation may make blood dose not reach to the organs which mean NO Oxygen reach the cells that caused hypoxemia or (hypoxia) which cause the death of the cells), etc.

- Deficiency in oxygen, hormone and glucose also cause damage for the organelles.

2) Physical Agents

- e.g. mechanical trauma, burns and deep cold, sudden changes in atmospheric pressure, radiation, and electric shock.

3) Chemical Agents and Drugs

- e.g. oxygen in high concentrations, poisons, pollutants, insecticides, industrial and occupational hazards, alcohol and narcotic drugs and therapeutic drugs.

4) Immunologic agents

- e.g. thyroid damage caused by autoantibodies.

5) Genetic Derangements

- eg sickle cell anemia.

6) Infectious Agents

7) Nutritional Imbalances

Reversible and irreversible cell injury

Gross pathology:

it is the changes (in cells or tissues or organs etc.) that can be seen it by naked eye.

Ultra-structural changes:

it is the changes that can't be seen by the naked eye.

Ultra-structural signs of cell injury:

Seen in both reversible and irreversible cell injury

- **Cell swelling (hydropic degeneration):**
  it happens when there is disruption of integrity of cytoplasmic membrane cause that the K+ going outside of the cell and Na with H2O enter to the cell that causing swelling of the cell, it is usually caused by immunological reactions.

- **Mitochondria swelling:**
  there is certain diseases affect mitochondria especially when we have hypoxia or certain poisons, in irreversible changes if the mitochondria swelling this will lead to failure in sodium potassium pump which will cause dysfunction of mitochondria to produce energy which mean that the sodium will not leave the cell which may be cause a lot of diseases like renal failure.

- **Endoplasmic reticulum dilation:**
  it happens when there is disintegration of endoplasmic reticulum that causes losing of its function, which will affect the function of the cell.

- **Lysosomes ingestion (autophagocytosis):**
  it happens when lysosomes engulf other damaged organelles.

As result of all of these changes the cell may die (in irreversible changes) or recovered (in reversible changes).

We determine whether the injury is reversible or irreversible by:

- The type of injury.
- The duration of injury.
- The severity of injury.

Reversible

the cell can recover itself

Earliest changes associated with cell injury is the following :

Swelling of cell cytoplasm with vaculization of cytoplasm

called: hydropic or vacuolar degenration

Mitochndrial swelling

Fatty Change

plasma membrane blebbing

damge to rough endiplasmic reticulum leading to loss of prtein synthesis

Eosiniphilia

due to decresed cytoplasmic RNA

(cytoplasm become more pink)

NOte: within limits the cell can compensate for these derengements and injuries stimulus is removed

(يعني الخلية ترجع لوضعها الطبيعي)

Irreversible

presistent or excessive injury

happens when the cell can not recover itself

this will lead to ultra-structural changes

Severe mitochondrial damge with the appearance large amorphous densities in mitochondria

Extensive damge of cell membrane

increase eosinophilia

Numerous myelin figures

swelling and rupture of lysosomes leakage and enzymatic digestion.

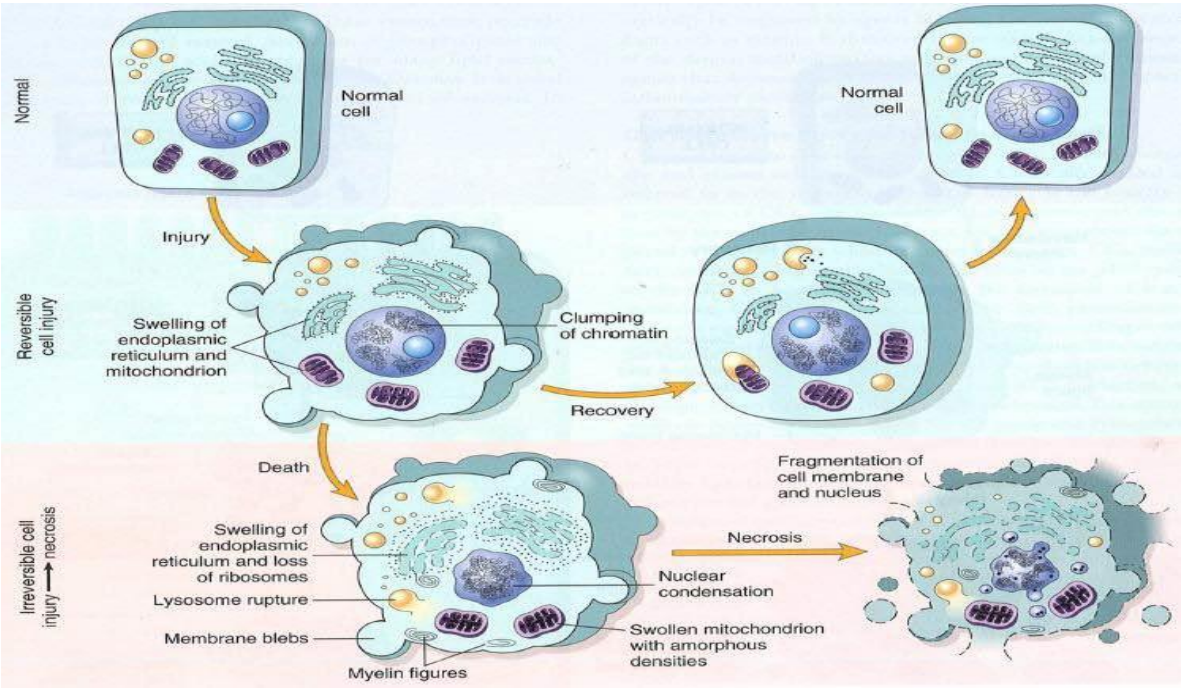
Nuclear damge

A. Pyknosis (shrinkage)
B. Karyolysis (dissolution)
C. Karyohexis (break down)

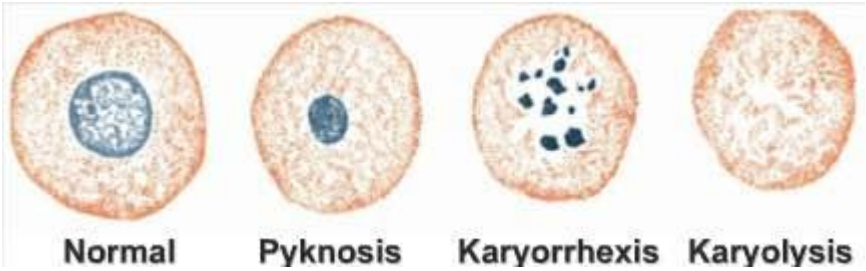
Doctor's Note: Cell stress > cell adapt, but if the stress is severe or harmful it will cause > cell injury>(reversible) Or (irreversible)

Reversible Cell Injury
Irreversible Cell Injury

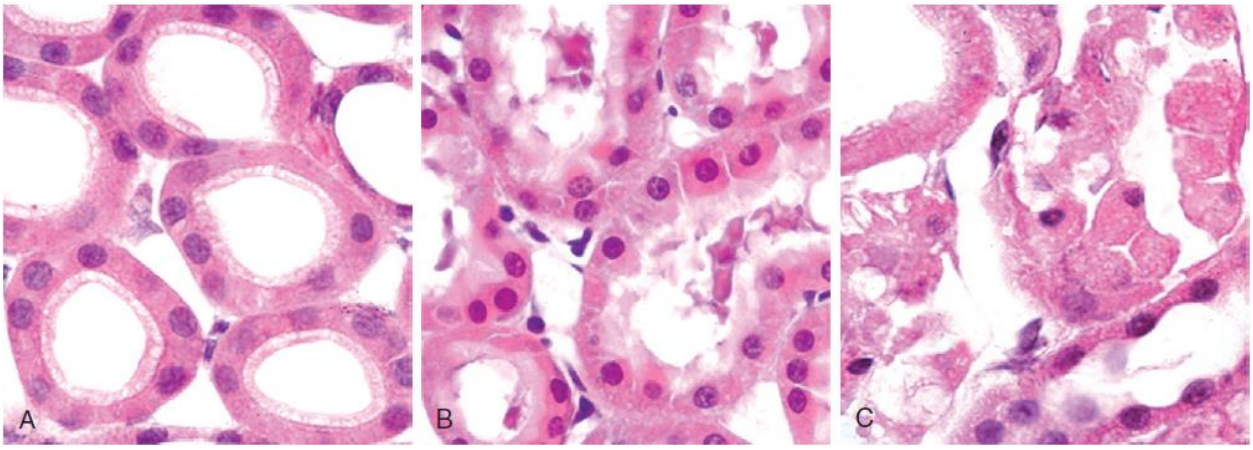
(Cell injury)



(Nuclear damage)



(kidney tubules section)



A. normal tubule:

there is nucleus and cytoplasm, and the kidney functioning well.

B. reversible cellular damage:

there is some sort of injury but it is reversible, we see cellular swelling, disintegration of some cells but the structure is there.

C. irreversible cellular damage:

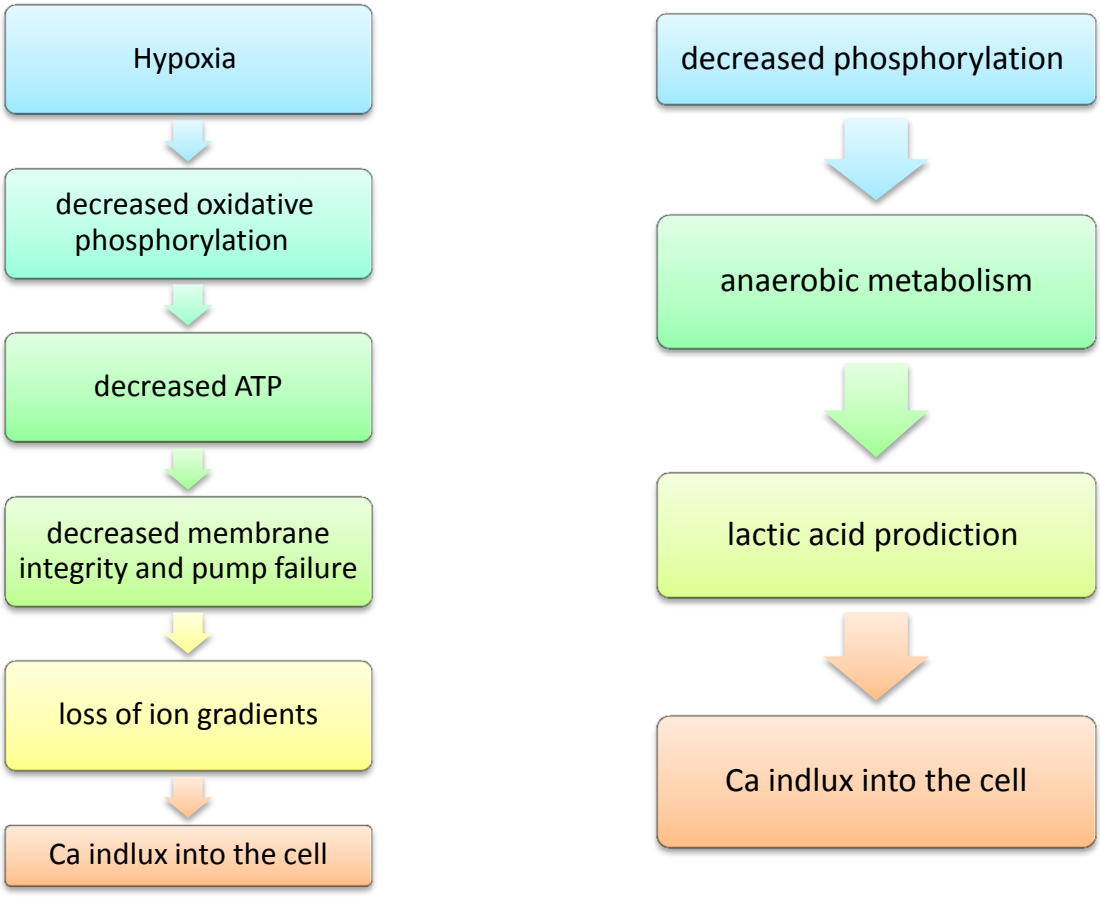
so we have pyknosis, karyolisis and karyorrhexis, we see this always in renal failure.

C. Understand the definitions and mechanisms of free radical injury.

MECHANISM OF CELL INJURY

1- **Mechanism of ischemic cell injury:**

This type of cellular injury is due to increased intracellular calcium, the progression can be detailed as follows:



2- **Accumulation of oxygen-derived free radicals (oxidative stress):**

- Free radicals: are highly reactive and harmful atoms /chemical species that have single unpaired electron in an outer orbit.
- They are referred to as reactive oxygen species (ROS)/free radicals.
  - Free radicals and ROS mean the same thing.
  - Because of certain affects we get formation of free radicals.
  - Membrane damage caused by the free radical or ROS
  - Free radical formed when there is unstable atom (each atom has 2 e0lectrons in its outer orbit and when it loses 1 electron of them it become unstable) and this atom trying to be stable that make it entering in another reactions and these reactions are harmful for the cell which will cause cell death, and it will active enzymes inside the cell which will cause autolysis (like calcium)

- The free radicals are produced in our cells through several ways, called as the free radical generating systems.

- **Ways of generating free radicals:**

- Physiologic generation of free radicals occurs: during oxidative phosphorylation.

1. Cytochrome c oxidase (complex IV) transfers electrons to oxygen.

2. Partial reduction of O2 yields superoxide. hydrogen peroxide, and hydroxyl radicals ("OH).

- Pathologic generation of free radicals arises with:

1. Ionizing radiation-·water hydrolyzed to hydroxyl free radical

2. Inflammation-NADPH oxidase generates superoxide ions during oxygen dependent killing by neutrophils.

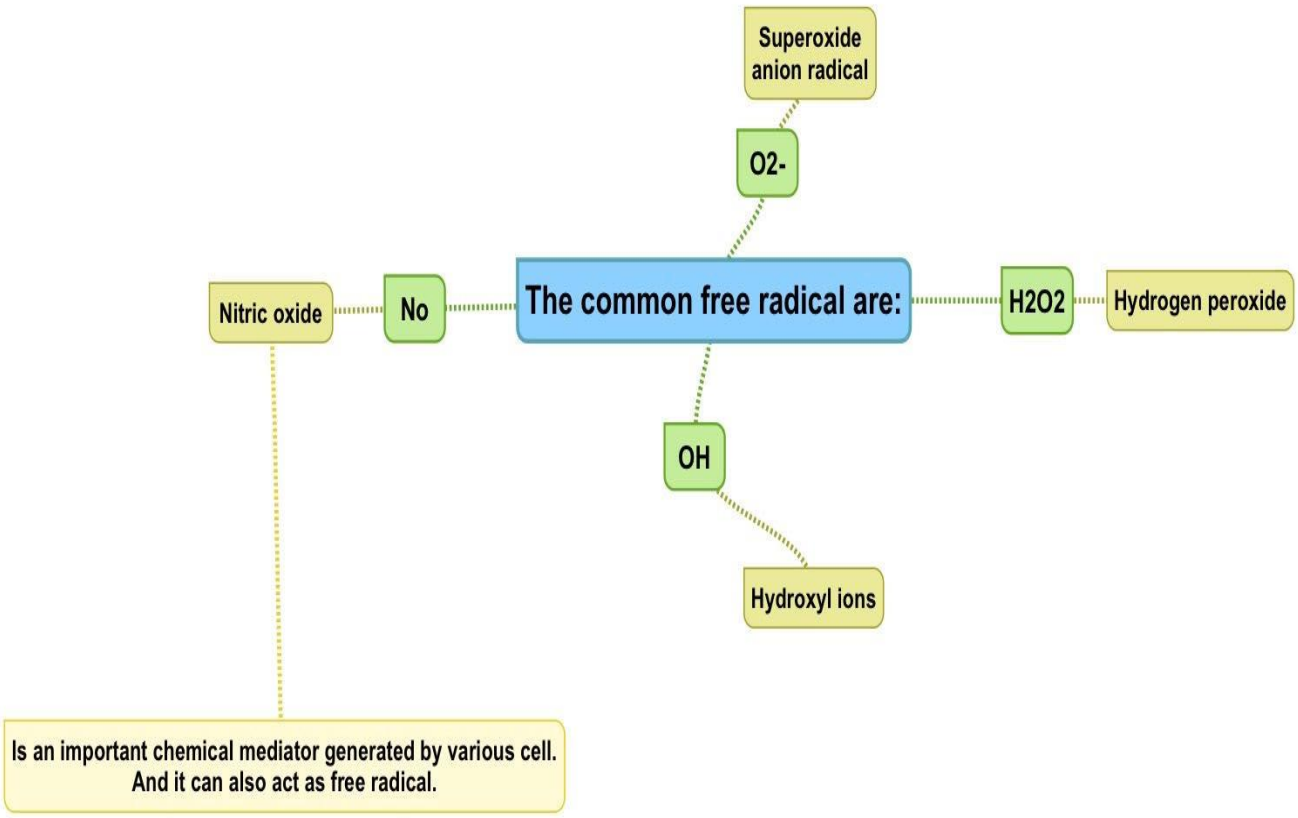
3. Metals (e.g., copper and iron)- Fe2+ generales hydroxyl free radicals (Fenton reaction).

4. Drugs and chemicals-P450 system of liver metabolizes drugs (e.g. acetaminophen).

- generating free radicals:

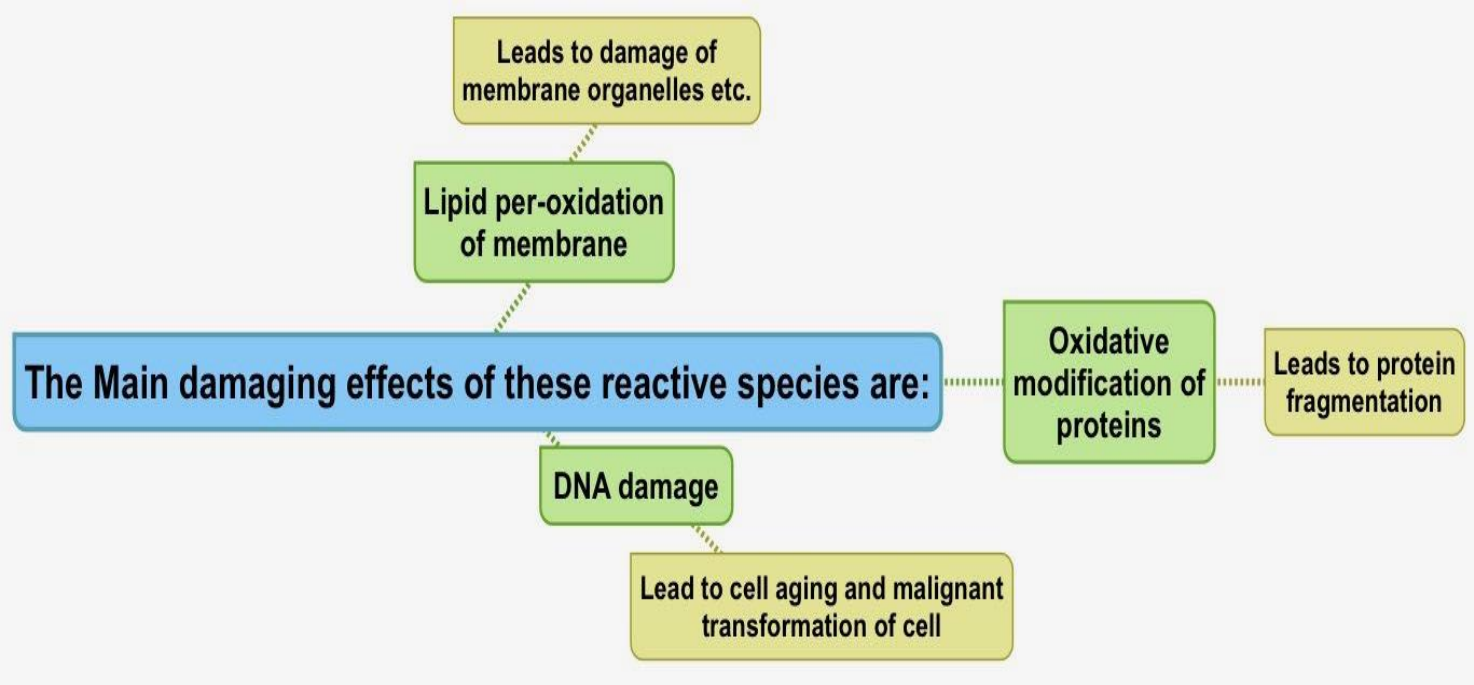
1. Cross-linking and other changes in proteins. Free radicals promote sulfhydryl-mediated protein cross-linking, resulting in enhanced degradation or loss of enzymatic activity. Free radical reactions may also directly cause polypeptide fragmentation.
2. DNA damage. Free radical reactions with thymine in nuclear and mitochondrial DNA produce single-strand breaks. Such DNA damage has been implicated in cell death, aging, and malignant transformation of cells.

*Extra Information



The free radicals are produced via **(Causes of Free radicals (ROS))**:							
Normal metabolism/ respiration: small amounts of harmful reactive oxygen is produced as a bi-product of mitochondrial respiration during normal respiration (reduction-oxidation reactions that occur during normal metabolic processes).	**Ionizing radiation injury.** e.g. - ultraviolet light - x-rays result in production of free radicals.	**Chemical toxicity:** enzymatic metabolism of exogenous chemicals or drugs.	**Oxygen therapy**	**Immune response or inflammation (neutrophilo xidative burst)** ***Inflammation:** affects the cell membrane which will lead to formation of free radicals.	**Transitio n metals can trigger productio n. such as:** - iron. - copper.	**reperfusion injury:** giving a lot of fluids to the patient it may lead to cell injury.	**Ischemia:** localize poor blood supply, and it leads to hypoxemia, which will cause free radical

- Free radicals <u>cause damage</u> to **lipids**, **proteins**, and **nucleic acids**



- **How does our body fight the free radicals?**
  free radical scavenging system: Certain substances in the cells remove/ inactivate the free radicals in order to minimize injury caused by them.

Antioxidants:	• vitamins E, A and C (ascorbic acid).
Enzymes:	• which break down hydrogen peroxide and superoxide anion • e.g. Catalase, Superoxide dismutases, Glutathione peroxidase and mannitol.

***NOTE: Any imbalance between free radical-generating and radical-scavenging systems results in oxidative stress causing cell injury.

D. Knows the definition of apoptosis, tissue necrosis and its various types with clinical examples.

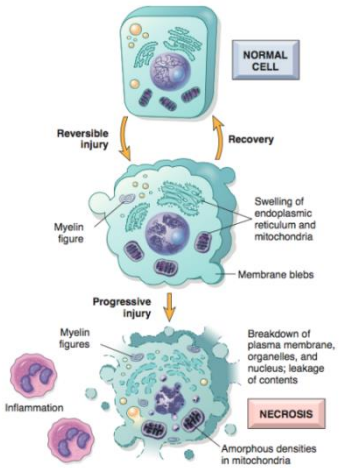
Necrosis:

- A type of cell death, in which there is enzymatic digestion in lethally injured cells that causes loss of membrane integrity and denaturation of intracellular protein and leakage of cellular contents.
- The leaked cellular contents often elicit (يثير) a local host reaction, called inflammation, that attempts to eliminate the dead cells and start the repair process.
- The enzymes responsible for digestion of the cell may be derived from the lysosomes of the dying cells themselves (Autolysis) and from the lysosomes of neighboring leukocytes (heterolysis) that are recruited as part of the inflammatory reaction to the dead cells.

(يعني الإنزايمز اللي بتحلل الخلية الميتة جاية إما من اللايسوسومز للخلية نفسها او من اللايسوسومز حقات خلايا الدم البيضاء)

- It occurs in irreversible injury. It is usually associated with inflammation in the surrounding tissue.

It involves the death of a group of cells in one area.



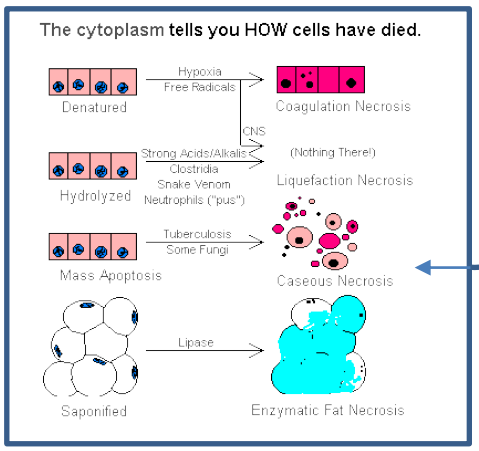
Necrosis can **result in**:

1)**Cessation** (loss of function of the involved tissue/organ).
2)**Release of** certain cellular **enzymes** that can be detected in blood. The level of these enzymes can be used as markers to diagnose the injury and also can help determine the time and the extent of injury eg. Cardiac enzymes in myocardial infarction (heart attack).
(بيفرز انزيمات في الدم وبواسطتها نقدر نشخص المرض) (يعني لما العضو يحدث لهnecrosis)
3)An **inflammatory response**

Types of necrosis: -

1) **coagulative necrosis**
2) **liquefactive necrosis**
3) **caseous necrosis**
4) **fat necrosis**
5) **fibrinoid necrosis**

If the patient has necrosis his/her WBC count will be higher than normal



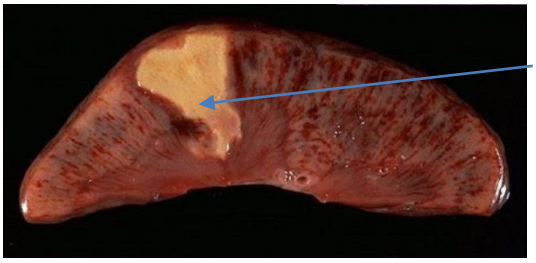
Helpful

1. Coagulative necrosis:

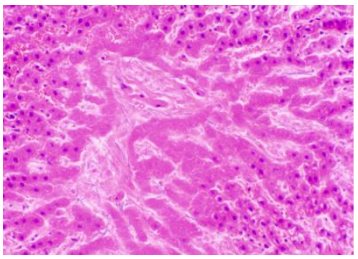
It is characteristically seen when blood flow to an organ is affected leading to ischemic/hypoxic death of cells in that organ. It is the most common type and it is seen in all organs except the brain. It causes infarction of the affected organ. It can be seen in **heart** (called as myocardial infraction), **kidney** (called as renal cortical necrosis/ infarct), **spleen, liver** (infarct) etc.
It causes the underlying tissue architecture to be preserved for at least several days

Morphology:

Gross: The affected organ looks pale and firm/solid shape because no enzymatic lysis occurs as the enzymes. like all other proteins, have been "coagulated ". It looks like cooked meat or boiled egg. '

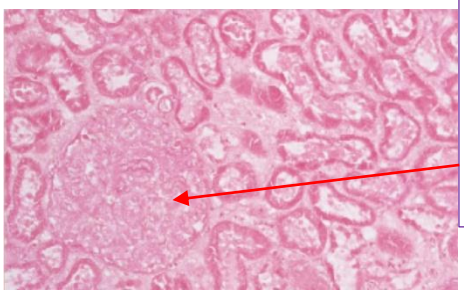


Damage to the blood source caused ischemia (kidney)

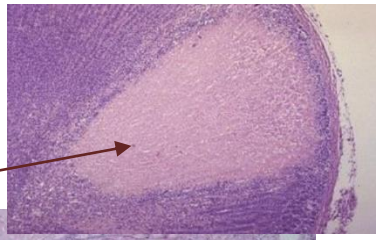


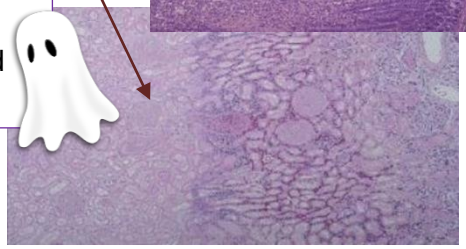
Liver coagulative necrosis
(لاحظو ان مكان النكروسس تختفي الأنوية)

Microscopy: In tissue or organ showing coagulative necrosis, there is preservation of the general tissue architecture and initially the basic ghost outline of the affected/coagulated cell remains preserved for a few days but the nucleus is lost. The cell cytoplasm is eosinophilic. Ultimately, the necrotic cells are removed by phagocytosis by the macrophages.

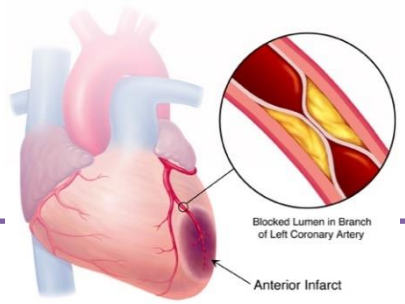


Kidney: coagulative necrosis Micro: Cell outlines are preserved (cells look ghostly), nucleus disappear , and everything looks **red**





Clinical Example



Example of Coagulative necrosis:

Abdullah Fahad is a 65-year-old man, comes to the hospital and he has very severe chest pain and this pain spreading to his neck, shoulder and his left arm. (The most common symptom of myocardial infarction "heart attack").

So, he has atherosclerosis which affect his aorta and other blood vessels, and he has coagulative necrosis in the myocardial. In the Gross pathology the overall structure of the body it will be approximately maintained except some yellowish color in the damaged area.
But, if we look at section by microscope we will notice that the cells are dead, and when cell dies it will have disruption in the cytoplasmic membrane, and we see some Pyknosis, Karyolysis and Karyorrhexis, and there are enzymes which are coming out of the cell, and there is some died cells.
We will use all of these to diagnose the disease by analyzing the blood and see the rate of some enzymes and proteins like**: troponin** I (which are released from the dead cells to the circulation), and see if it is in high levels or not, if it is high that means he has myocardial infarction (heart attack).

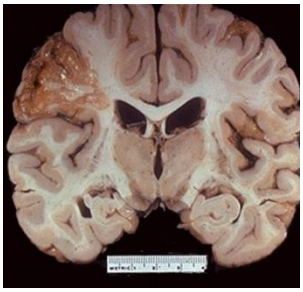
2. Liquefactive necrosis:

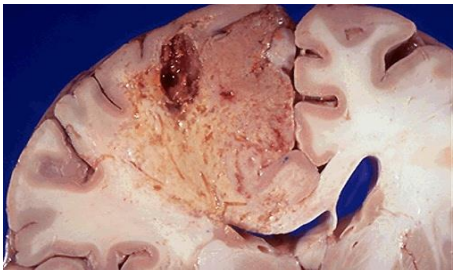
It is a type of necrosis which results in transformation of the tissue into a liquid viscous mass. **seen in** focal bacterial or fungal infections, because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digest ("liquefy") the tissue
characteristically seen in: -
a) hypoxic cell death in the central nervous system/brain
b) suppurative (pus or abscess producing) infections especially bacterial infection.

The affected tissue is softened/liquefied by the action of **hydrolytic enzymes** which are either-
a) released from the lysosomes in the brain cells
b) or released from the neutrophils in the pus/abscess.

Morphology:
Gross:

Brain: The affected area is soft with liquefied creamy yellow center

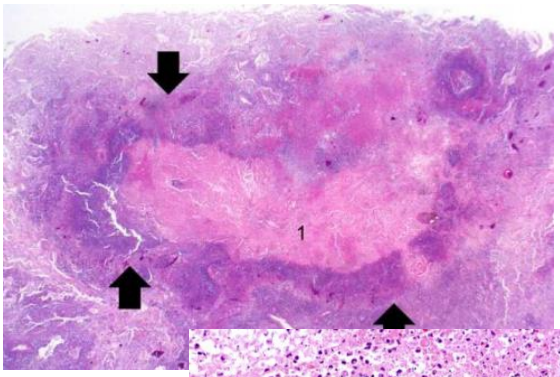


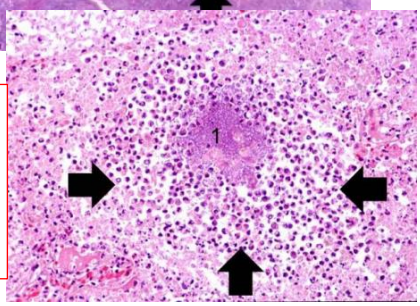


Microscopic:

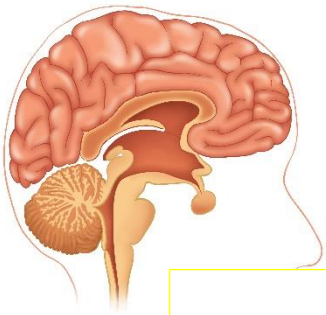
center containing necrotic cells, and neutrophils and is called pus/abscess.
* Ultimately, most necrotic cells are phagocytosed.

Note: للخلية ghost outline هنا مافيه





The center labeled one is necrosis and surrounding is neutrophils).



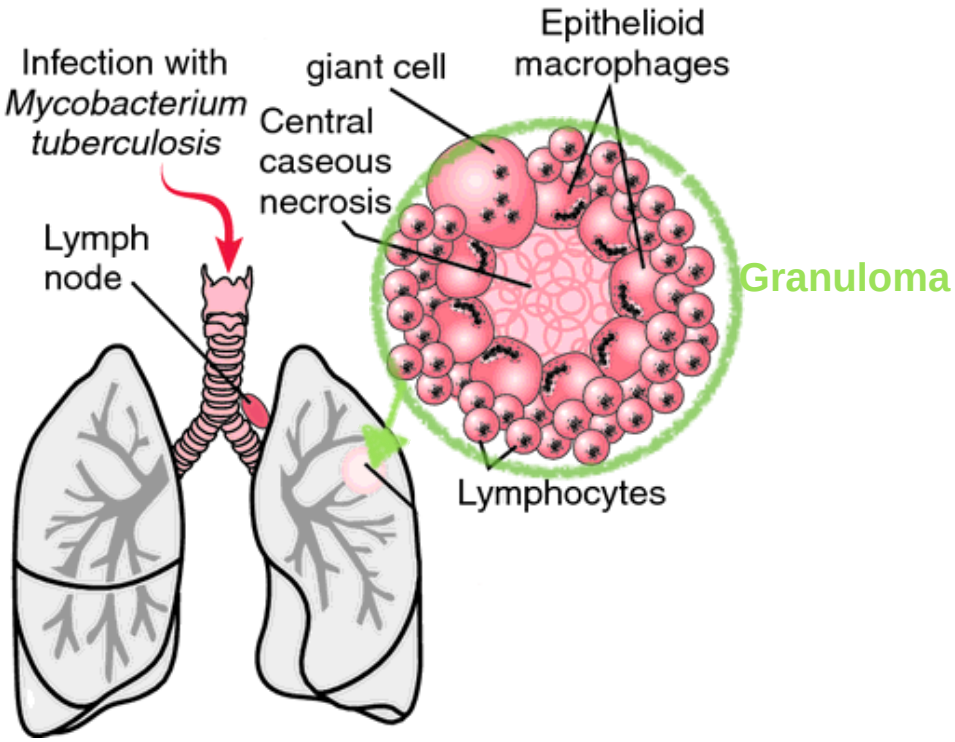
Symptoms of a patient with liquefactive necrosis in a section of his/her brain:

1- Patient can't move his arm or leg
2- Patient can't see in his right eye
3- Can't talk
4- Stopped being able to swallow
5- Coma

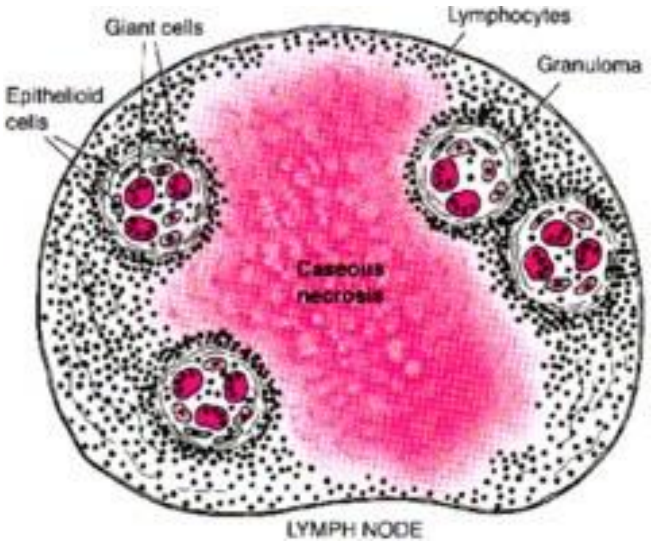
3-Caseous[1] necrosis:

-TB is endemic (مستوطن) in Saudi Arabia.
-TB affects many organs: spleen, liver, testis, fallopian tube.

- is a type of coagulative necrosis classically seen in tuberculosis (infection by mycobacterium tuberculi).
- Grossly: it is white, soft, curdy, cheesy-looking "caseous" material.
- On microscopic examination, the necrotic area appears as amorphous pink granular debris surrounded by a collar of epitheloid cells (they are modified macrophages), lymphocytes and giant cells (cells with multiple nuclei). This is known as granuloma.
- Here the tissue architecture is completely obliterated[2].

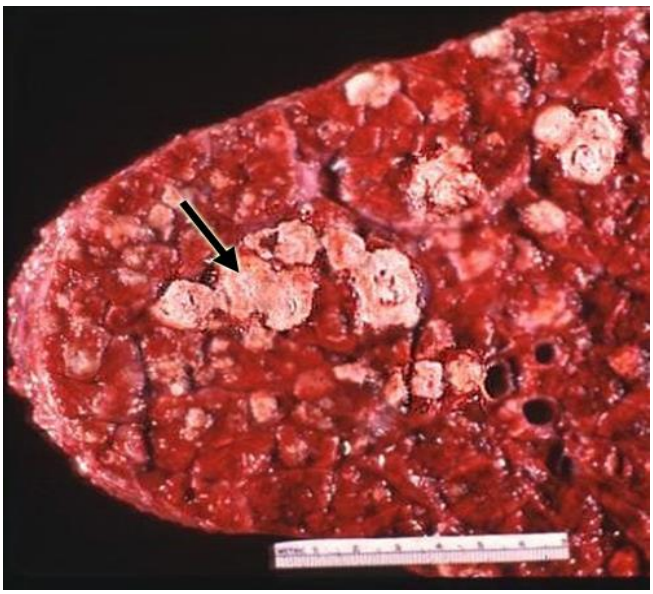


1- cheese-like (due to the friable yellow-white appearance of the area of necrosis)
2- مطموسه



this is showing a process of tuberculosis granuloma formation by the T-cells in the lymph node.

The bacteria can survive for decades inside the granuloma in a latent state. Due to some environmental or genetic factors, the bacteria will reactivate and provoke the death of the infected macrophages. A necrotic zone (called caseum due to its milky appearance) will develop in the center of the granuloma. Ultimately the structure will disintegrate allowing exit of the bacteria, which will spread in other parts of the lungs and more lesions will be formed. Infection will also be transmitted to other individuals due to release of the infected droplets by coughing.

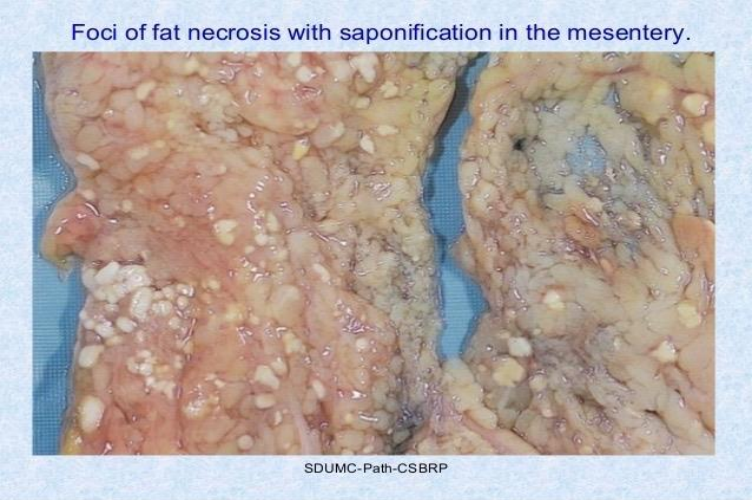


4- Fat Necrosis:

What is fat necrosis?
'Necrosis' means 'cell destruction' or 'cell death and decay'.
The blood-supply to a fat lobule becomes disrupted, and when the fat cells don't get enough oxygenated blood, they die. Once a cell dies, chemical-molecules are released that start the process of trying to get rid of the dead cells. That process includes some enzymes that break-up fat into smaller molecules that can be adsorbed by the bloodstream. The calcium deposits found in fat necrosis are essentially the result of the action of these enzymes.

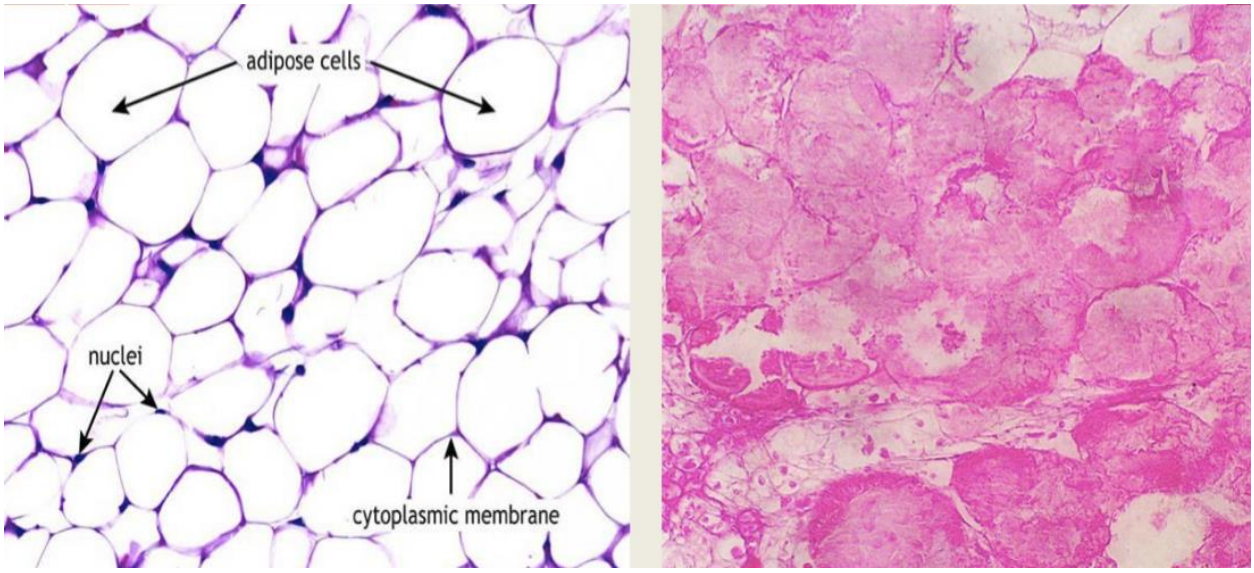
- It is necrosis of fat cells (adipose cells) Dose not have fat on it but it is surrounded by an abdomen fat.
- the cell membrane are thickened and eosinophilic with no nuclei (or barely seen nuclei)
- fat necrosis will cause karyolysis[3] lump
- Typically, it is seen in acute pancreatitis (inflammation of pancreas)in which the injured pancreatic cells release the lipase enzyme (digestive enzyme) into the fat in the abdominal cavity and cause enzymatic digestion of fat cells.
- The released lipase breaks down the fat cells into glycerol and free fatty acids. The produced fatty acids combine with calcium circulating in the blood to produce calcium soaps which looks like chalky white spots in the necrotic fat. This process is called as fat saponification.

3- Karyolysis: is the complete dissolution of the chromatin of a dying cell due to the enzymatic degradation by endonuclease. It is usually associated with karyorrhexis and occurs mainly as a result of necrosis, while in apoptosis after karyorrhexis the nucleus usually dissolves into apoptotic bodies.



Foci of fat necrosis with saponification in the mesentery. The areas of white chalky deposits represent calcium soap formation at sites of lipid breakdown (necrosis).

- The outlines of necrotic/dead fat cells can be seen. Inflammation is minimal.



Normal adipose tissue

Fat necrosis

NOTE: On histologic examination, the foci of fat necrosis contain shadowy outlines of necrotic fat cells with basophilic calcium deposits, surrounded by an inflammatory reaction.

- Fat necrosis can also be seen in breast fat , abdomen and other fatty areas due to traumatic injury.

- Fat Necrosis requires no treatment. the situation will just resolve on its own.

5- Fibrinoid necrosis

Where does it

Is necrosis in the **blood vessels** (arteries, arterioles and capillaries)

How does it happen ?

There is deposition of fibrin material in the arterial walls, which appears smudgy and acidophilic/eosinophilic

Why does it happen ? (

-It is seen in **immune mediated diseases** (autoimmune diseases) and also seen in malignant hypertension.

Its cause antigens – antibodies complexes (auto immune) diseases (anti DNA-anti RNA) the body loses the capability of differentiating between what is self and what is not self

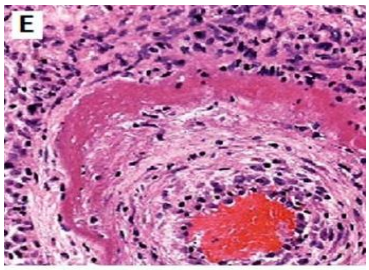
(note : Antibodies come from inside while antigens come from outside)

-Food or لسعة حشرة result in immune complexes

-Immune complexes are very high molecular weight and therefore they got interrupt from area with a lot of circulation (blood vessels)

- Fibrin(مادة موجودة في الدم) comes out of the cell .

morphological changes →



Fibrinoid necrosis in an artery. The wall of the artery is bright pink with dark neutrophils

Gangrenous necrosis

dry

it is a form of **coagulative necrosis** that develops in **ischemic tissue (where the blood supply is inadequate)**. Dry gangrene is usually seen in a limb that has lost its blood supply and undergone coagulative necrosis.

Dry gangrene is **non-infected** ischemic necrosis of tissue. It is **without superadded infection**

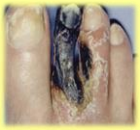
It is seen as a complication of peripheral artery disease e.g. **atherosclerosis and diabetes mellitus.**

The affected part is dry, shrunken and dark reddish-black

NOTE: Diabetes mellitus is a risk-factor for dry gangrene, and also a risk factor for wet gangrene (patients with poorly controlled blood-sugars, as elevated serum glucose (the level of glucose in the blood) creates a favorable environment for bacterial infection)

Doctor's notes about dr gangrene :

*It happens if there is a blockage in the blood supply .
*It depends on which part of the vessel blockage in and where is the blockage (Ex: if the vessel which supply the finger is blocked then just the finger will be affected).
*it usually affects the limbs (arms – legs) ,when it blocks the blood vessel ,it causes coagulative necrosis and that is called a dry gangrene .
*Gangrenous necrosis (dry gangrene is very common)
Pathogenesis :
Uncontrolled diabetes or increased atherosclerosis
leads to
Obstruction of blood vessels and that leads to ischemia (cell injury)
Dry gangrene



wet

it is dry gangrene with **superadded bacterial (putrefactive) infection**. **The coagulative necrosis is modified by the action of the bacteria into liquefactive necrosis**, and it is called wet gangrene. So, initially there is coagulative necrosis and then there is superadded infection leading to liquefactive necrosis. Wet gangrene usually develops rapidly due to blockage of venous (mainly) and/or arterial blood flow.

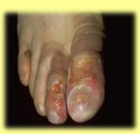
The bacteria is usually saprogenic (i.e. it lives in the gut or the soil and it can thrive in low oxygen states) e.g. **gram-positive Clostridia or Bacillus fusiformis**. It has a poor prognosis compared to dry gangrene because the **infection can spread to the rest of the body (septicemia) and be life threatening (death)**

so the limb has to be amputated. The limb becomes foul smelling and black and starts decomposing

* wet gangrene is a dry gangrene infection, so the patient has dry gangrene already and on top of that he has infection and that is very very dangerous because the patient has super added infection this infection will go to the blood stream and it will spread over the whole body and the patient will die because of the severe infection or (septicemia) ,so in order to prevent that you have to amputate the area .
*dry gangrene is very common Ex: a patient who suffers from diabetes or bad atherosclerosis may suffer from dry gangrene as a complication (ischemia which leads to coagulative) wet gangrene may happen to patient who do not go to a doctor right away.
* it can happen when there is an injury or a cut and the blood supply is blocked such as, when a person fills down on the ground (note : on the ground or in the soil bacteria called (Clostridia "gram + bacteria") the bacteria inters to the injury and causes infection , in this case we have to cut the part that is infected so that it doesn't inters the blood stream.

*wet gangrene is rare NOT as dry gangrene.

*The Cause is infection by putrefactive bacteria and this bacteria can be found in soil- wound.
* They are anaerobic bacteria



Apoptosis

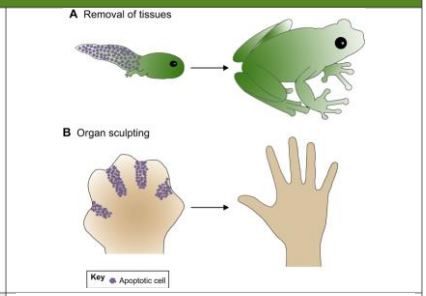
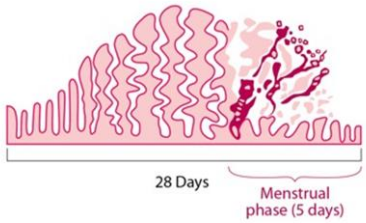
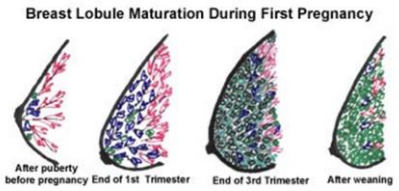
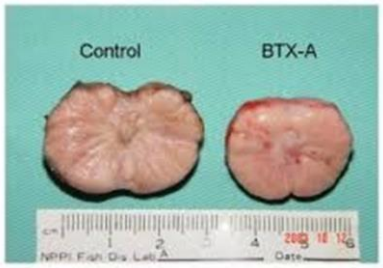
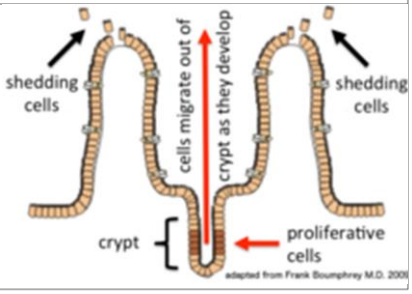
● Apoptosis means “falling off”. It is a type of cell suicide.

- *Apoptosis* is programmed cell death.
- *Is results from activation of ‘death pathway genes’.*
- It is a pathway of cell death in which cells destined to die activate their own enzymes to degrade their own nuclear DNA and proteins.

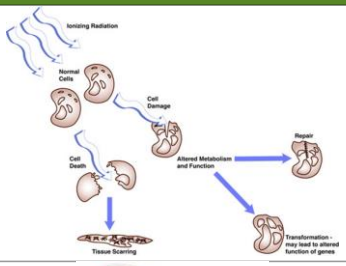
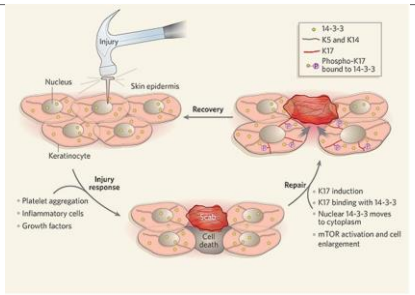
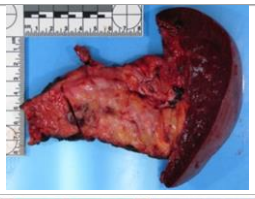
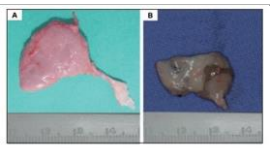
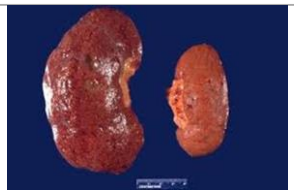
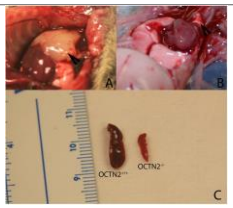
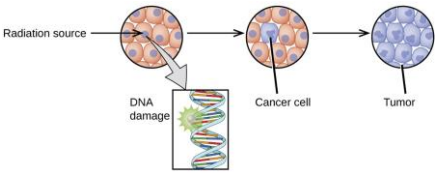
It can be

- Physiological/ adapative.
- Pathologic.
-
- NOTE: Apoptosis and necrosis can sometimes coexist.

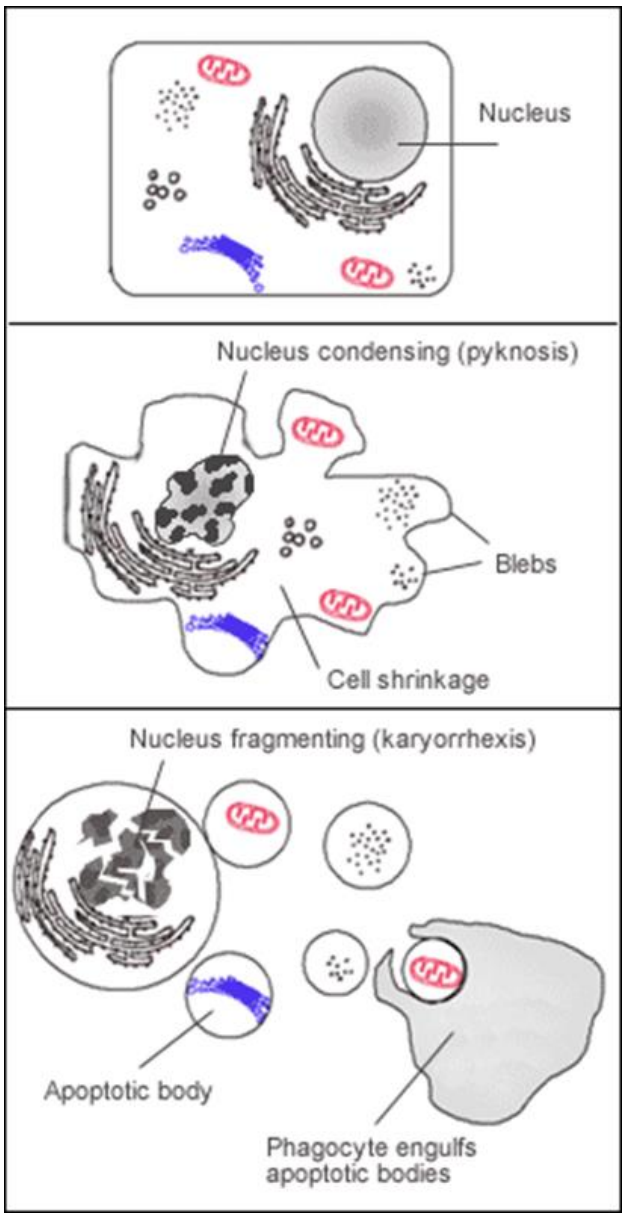
Physiological conditions

condition	Example	Picture
The programmed cells of destruction	Embryogenesis	
Hormone-dependent	1) Endometrial cell breakdown during the menstrual cycle	
	2) The regression of lactating breast during weaning	
	3) Prostatic atrophy after castration (adaptive atrophy)	
Apoptosis of proliferating cells	Intestinal epithelial lining is always being replaced	

Pathological conditions

condition	Example	Picture
Cell death by injury	radiations	
Certain diseases	1) viral hepatitis, where the infected hepatocytes undergo apoptosis (acidophilic bodies)	
	2) Injury of skin cells (keratinocytes) leads to apoptosis of keratinocytes (Civatte bodies).	
Pathologic atrophy in organs	1) pancreas	
	2) Parotid gland	 Figure 2. Characterization of the parotid gland after experimental radiotherapy in BR-1 Minipigs: (A) non-irradiated gland and (B) irradiated gland.
	3) Kidney	
Corticosteroids induced by atrophy	Neonatal thymus	
Cell death	Tumors (usually accompanied by necrosis)	

Mechanism of Apoptosis



- **The death pathway genes are activated.**
- **Cell shrinkage.**
- **Chromatin condensation in the nucleus:** This is the most characteristic feature of apoptosis. The nucleus may break up into fragments.
- **Formation of cytoplasmic blebs and apoptotic bodies:** The apoptotic cell first shows surface blebbing, then fragments into membrane-bound apoptotic bodies. The apoptotic bodies contain cytoplasmic content with or without nuclear material.
- **The cell's plasma membrane remains intact**. The plasma membrane of the apoptotic cell sends signal to macrophages, inviting the macrophages to phagocytose it.
- **Phagocytosis of apoptotic bodies by the macrophages.** Because, during the entire process, the apoptotic body is bound by plasma membrane, there is no release of the cytoplasmic content into the surrounding tissue and therefore there is no inflammation.

Doctor's NOTE:

In apoptosis the membrane is always intact, but in necrosis is <u>NOT</u> intact and that cause cytoplasmic content to comes out and that cause inflammation .

Important enzymes of apoptosis

1.Cysteine proteases named *caspases*

2.Ca2+- and mg2+-dependent endonucleases

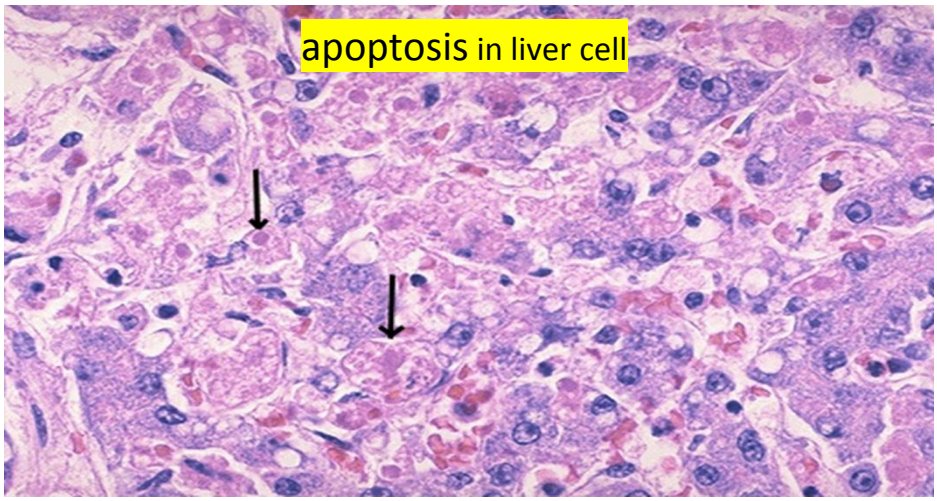
Regulation of apoptosis

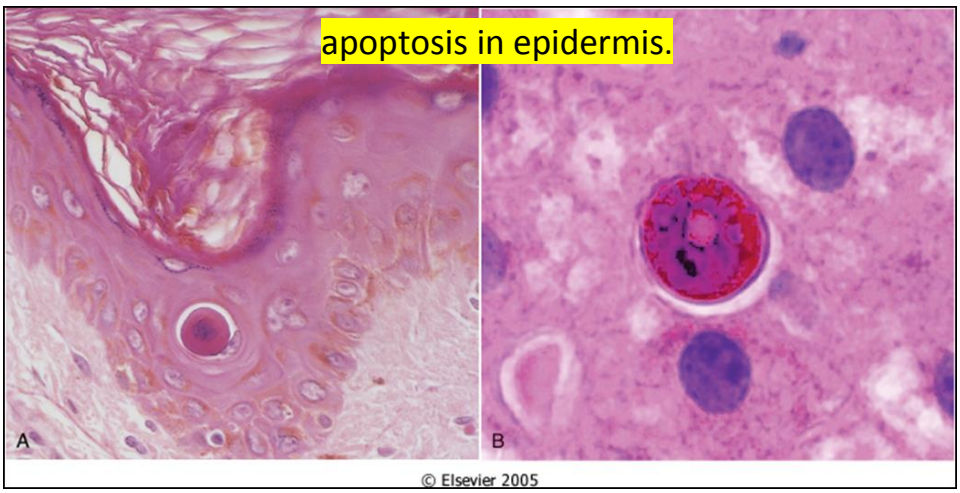
It is mediated by a number of genes and their products e.g:

- *bcl-2* gene inhibits apoptosis
- *bax* genes facilitates apoptosis

Morphology of Apoptosis:

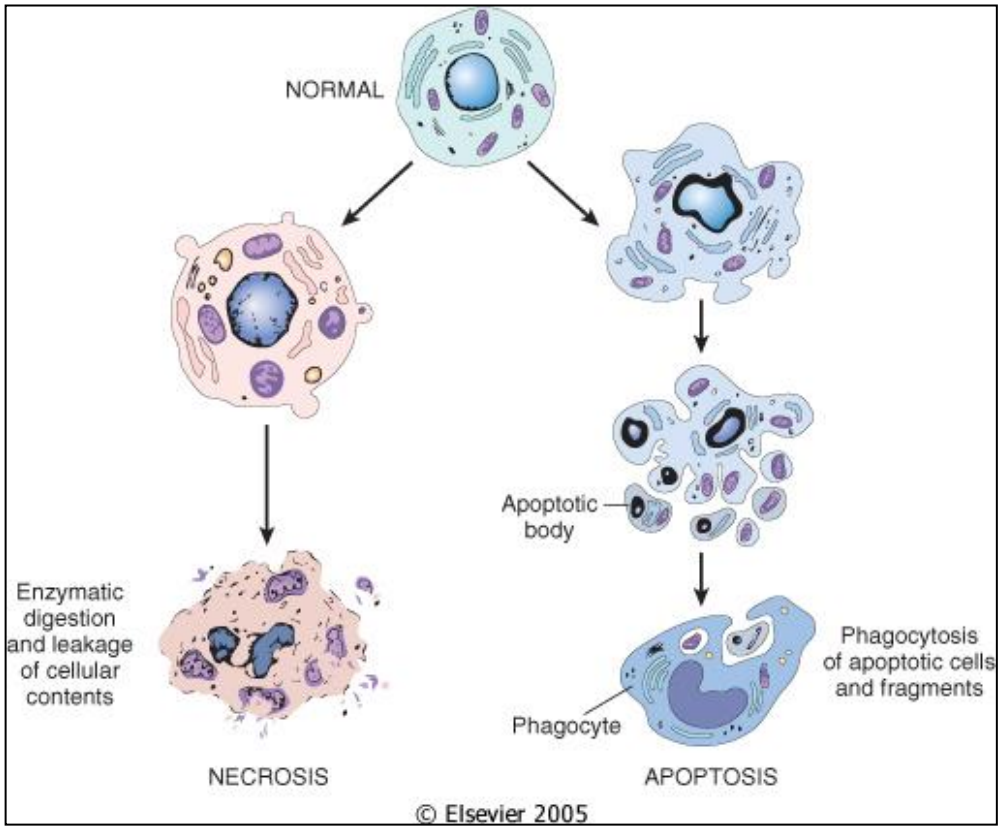
On histology apoptosis involves single cells or small clusters of cells. The apoptotic cell appears as a round or oval mass of intensely eosinophilic cytoplasm with dense nucleus. There is no inflammation.





E. Able to differentiate between necrosis and apoptosis.

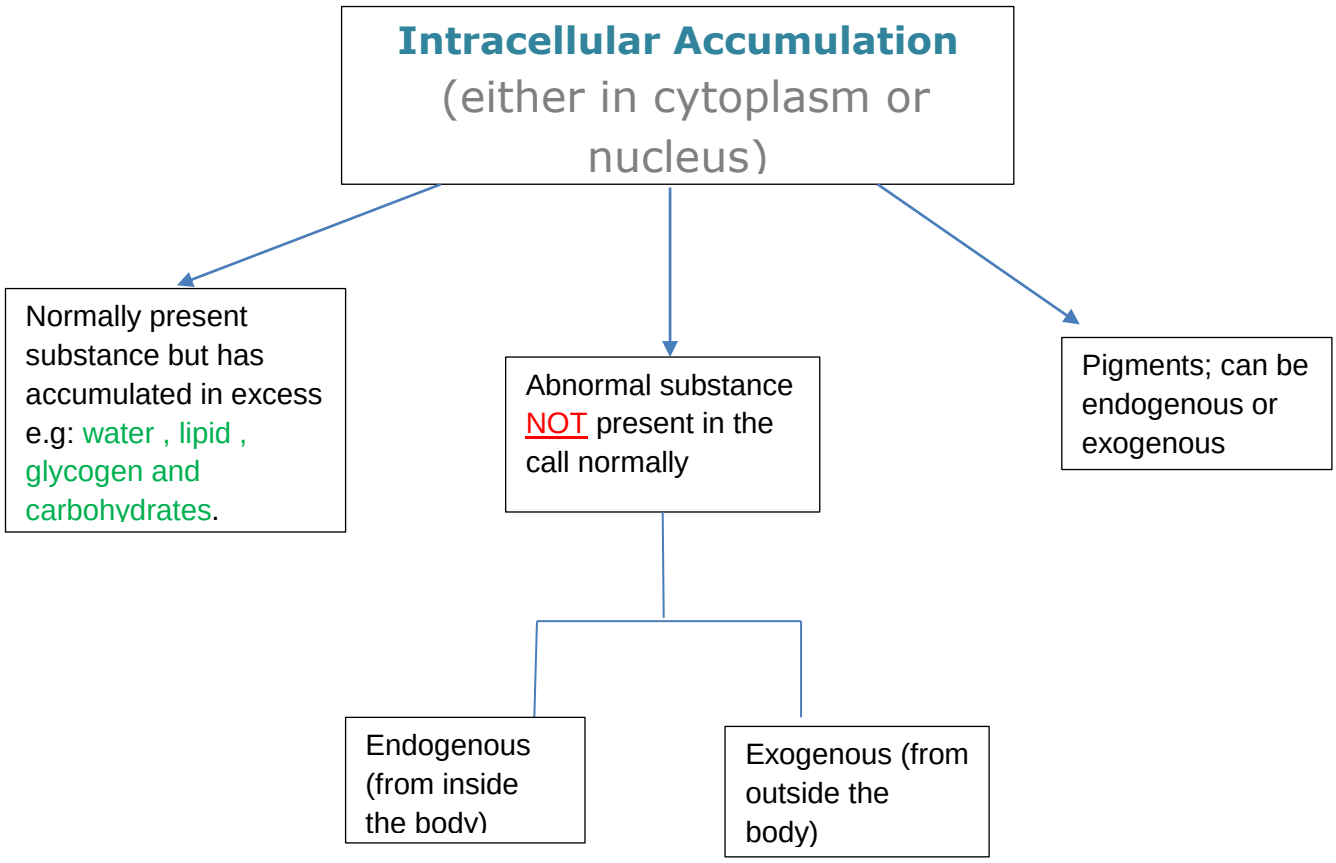
Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage



F. Understand the causes of and pathologic changes occurring in fatty change (steatosis), accumulations of exogenous and endogenous pigments (carbon, silica, iron, melanin, bilirubin and lipofuscin).

Intracellular Accumulation:

Some substances can accumulate inside the cell in large amounts and cause problems in the cell and the organ.



Lipids Accumulation

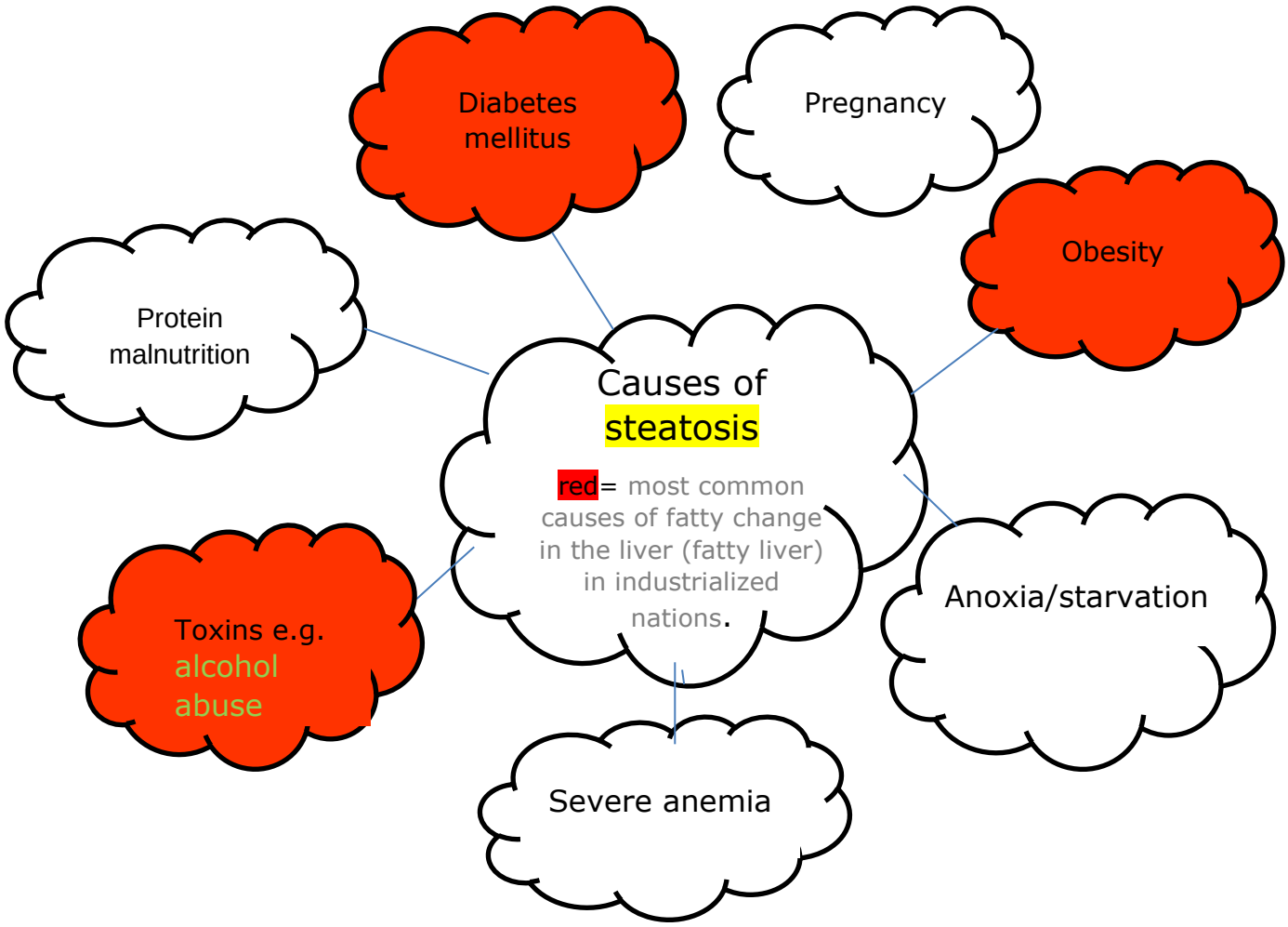
All major classes of lipids can accumulate in cell:

1-Triglycerides e.g (steatosis=fatty change): it accumulates in the cytoplasm of the cell

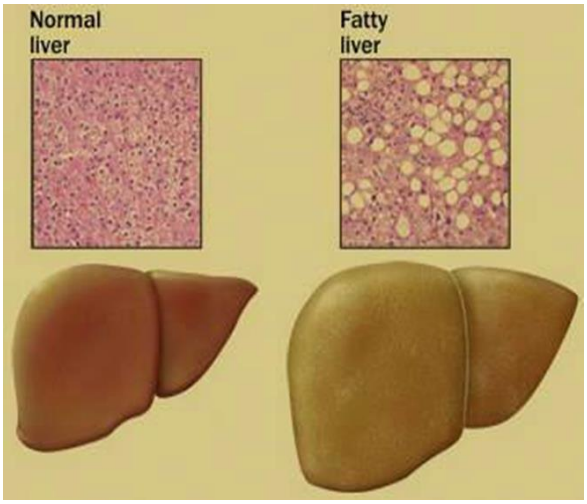
Fatty change : abnormal accumulation of triglycerides within parenchymal cells. It is mainly seen in liver since this is the major organ involved in fat metabolism, but it is also seen in heart, muscle, and kidney.

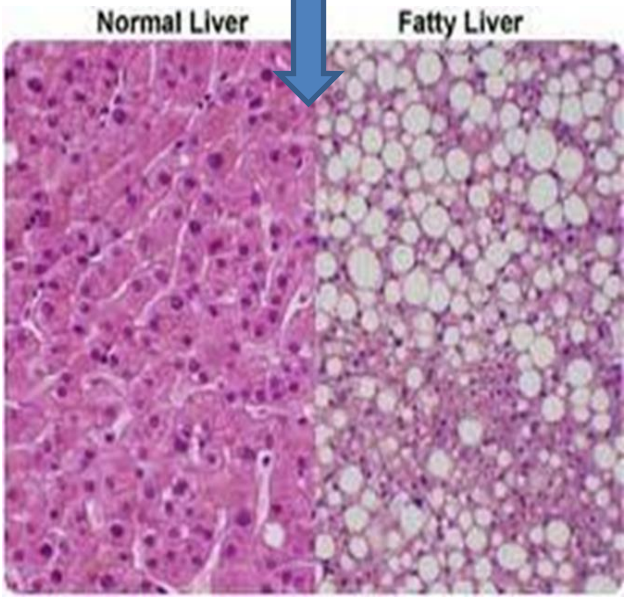
Excess accumulation of triglycerides within the hepatocytes occurs when there is an imbalance between the uptake, utilizationاستهلاك, & secretion of fat by the affected cell.

Morphology of steatosis (Fatty change):



Gross	Light microscopy
▪ Mild cases(الحالات البسيطة):Liver looks normal. ▪ Severe cases: Liver is enlarged, yellow ,and greasy.	▪ Clear vacuoles in the cytoplasm displacing the nucleus to the periphery of the cell. ▪ Occasionally, cells rupture , and fat globules merge, producing fatty cysts. ▪ Stain :the lipid stains **orange-red** with **(Sudan IV)** or **(Oil Red-O)** stains. ▪ Fat does NOT stain with eosin. يعني صبغة eosin ما تستخدم في هذي الحاله لان الفات (ماتبين وتكون كانها vacuoles)

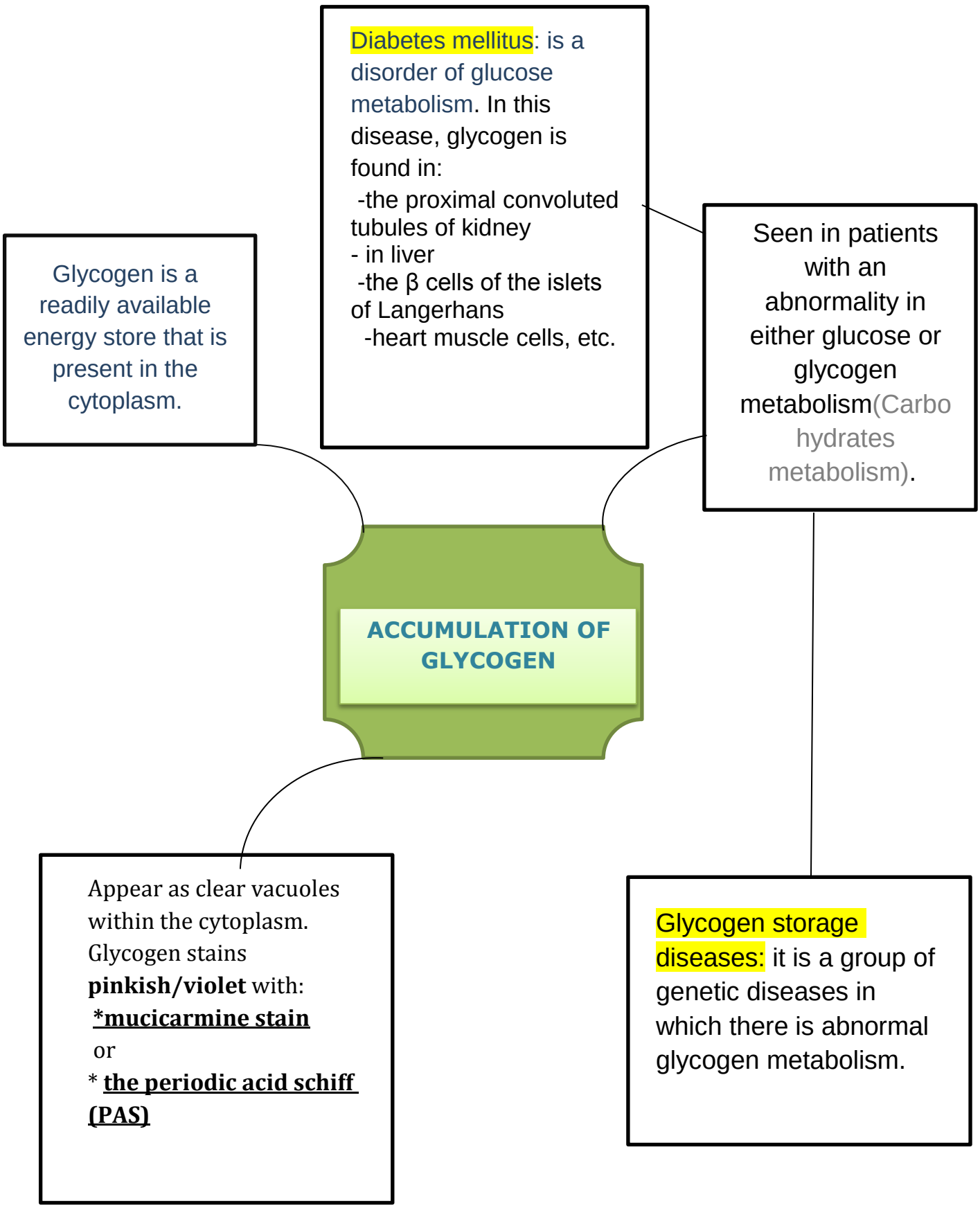




2- Cholesterol/cholesterol esters :

(accumulation of cholesterol in the form of intracellular vacuoles can be seen in atherosclerosis in which there is accumulation of cholesterol in the smooth muscle cells and macrophages in the wall of arteries).

3- phospholipids.


Diabetes mellitus: is a disorder of glucose metabolism. In this disease, glycogen is found in:
-the proximal convoluted tubules of kidney
- in liver
-the β cells of the islets of Langerhans
-heart muscle cells, etc.
Glycogen is a readily available energy store that is present in the cytoplasm.
Seen in patients with an abnormality in either glucose or glycogen metabolism(Carbo hydrates metabolism).
ACCUMULATION OF GLYCOGEN
Appear as clear vacuoles within the cytoplasm. Glycogen stains pinkish/violet with:
*mucicarmine stain
or
* the periodic acid schiff (PAS)
Glycogen storage diseases: it is a group of genetic diseases in which there is abnormal glycogen metabolism.

Pigments

Pigments:
colored substances.

Types of pigments:
1-Endogenouse pigments: synthesized within the body.(melanin).
2-Exogenouse pigments: synthesized outside the body.(carbon)

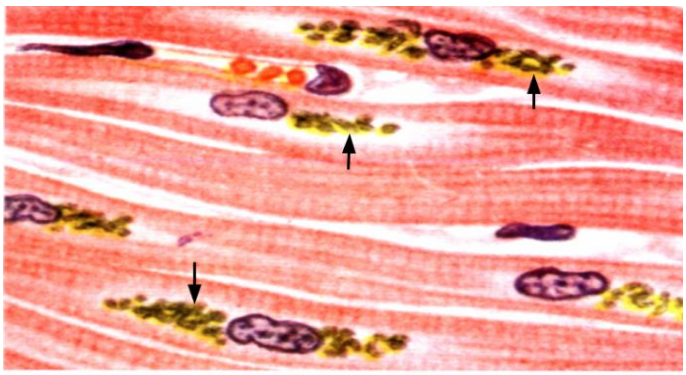
Endogenous
Types of endogenous pigments:

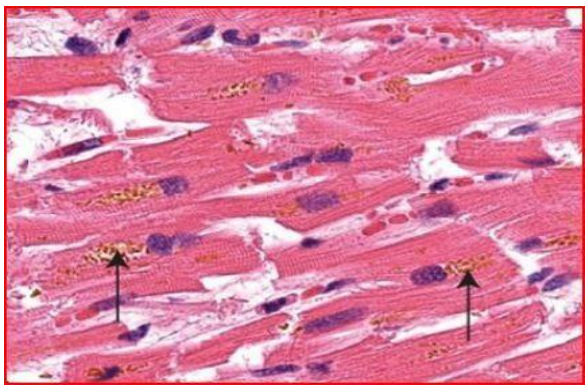
1. Lipofuscin
2. Melanin
3. Bilirubin
4. Hemosiderin

A) Lipofuscin:

is also known as wear-and-tear or **aging pigment.** Lipofuscin is endogenous and causes no damage to cells.

1.
2. It indicates history of free radical injury and lipid peroxidation.
3. It is yellow-brown, granular intra-cytoplasmic pigment
4. It is prominent in the liver and heart of aging patients, in atrophic tissue, patients with severe malnutrition and cancer cachexia.


lipofuscin in cardiac cells

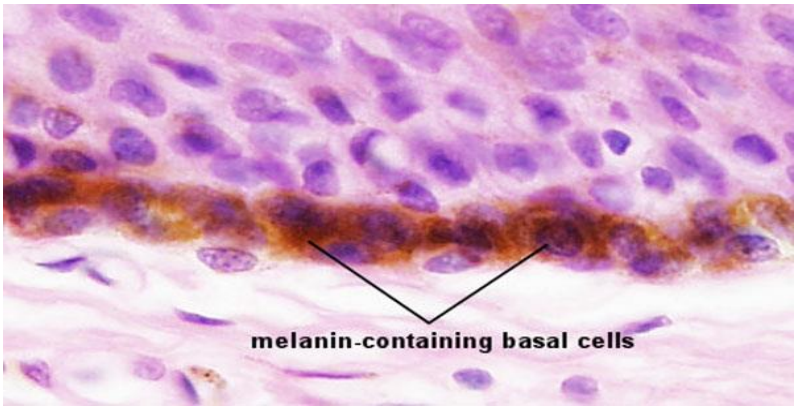


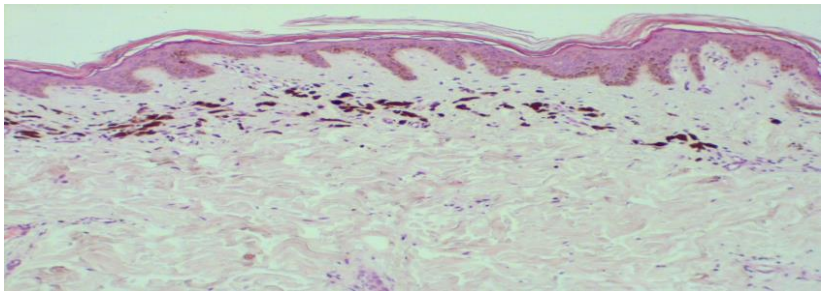
Doctor's note: if we see lipofuscin in a child it means that the child suffers from malnutrition.

B) Melanin:

an endogenous, **non-hemoglobin**, **brown-black pigment** normally present in the cytoplasm of melanocytes in the skin's epidermis. It is responsible for the color of our skin.

1. It is derived from **tyrosine** and stored in melanosomes of the melanocytes.
2. The function of melanin is to prevent the harmful effects of UV light.
3. It accumulates in large amounts in benign and malignant melanocytic tumors.
4. In inflammatory conditions of the skin it spreads from epidermis into the underlying dermis. This is called as **post inflammatory hyperpigmentation of the skin.**
5. Masson-Fontana stain is used to identify melanin.

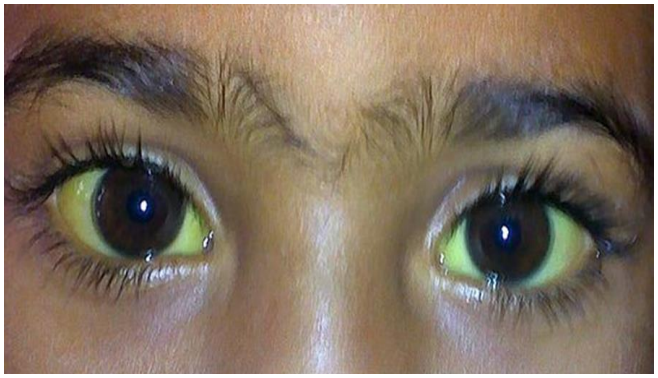


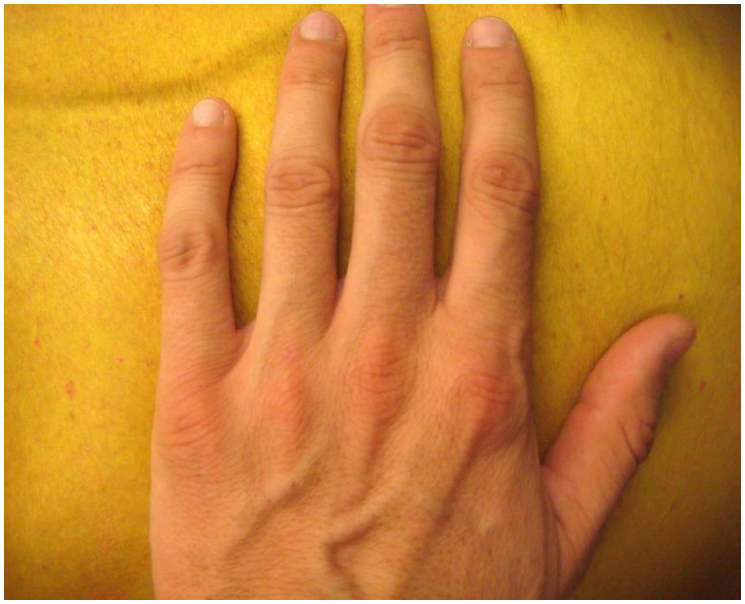


C) Bilirubin:

is a **yellowish pigment** found in **bile**, a fluid made by the liver.

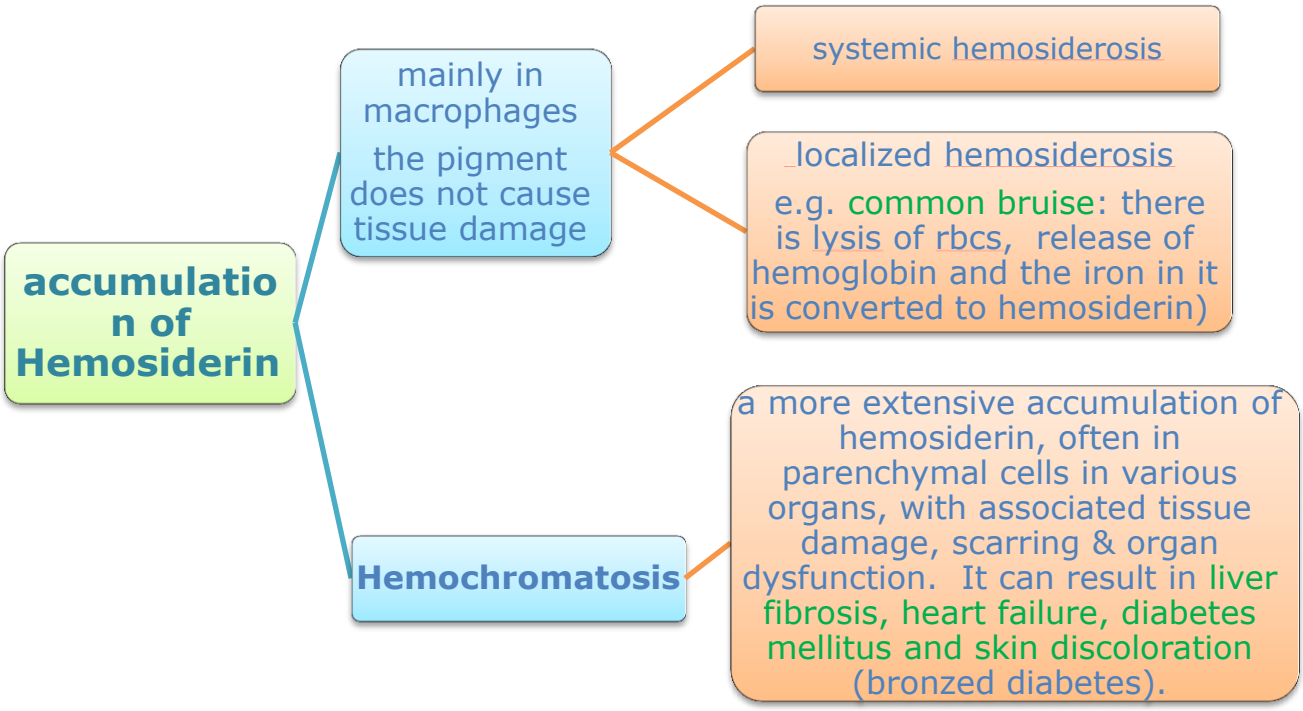
1. Bilirubin is a breakdown product of heme catabolism. Most of the bilirubin is derived from the break down of hemoglobin.
2. High levels of serum bilirubin leads to a condition called as jaundice.
3. **Jaundice** (also known as **icterus)** is a yellowish pigmentation of the skin, the conjunctiva, the sclerae (whites of the eyes), and other mucous membranes and it is caused by high blood bilirubin levels. Urine is also dark in color. It can also cause itching. Jaundice is often seen in liver disease such as **hepatitis** or **liver cancer** or obstruction of the biliary tract by gallstones or tumors.



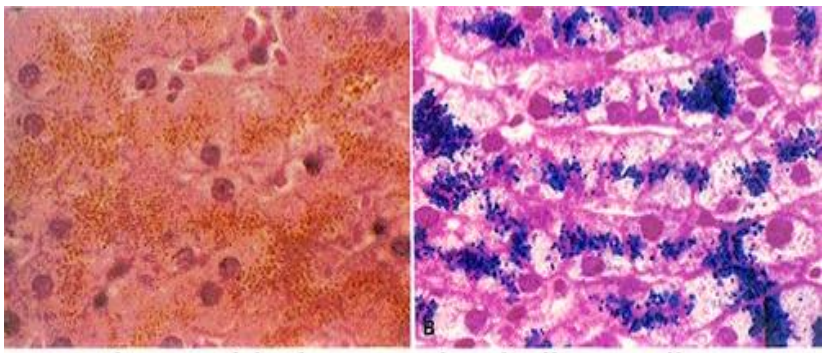


Hemosiderin :

is a hemoglobin-derived **golden brown** iron containing pigment and it is a product of hemolysis of red blood cells. Hemosiderin exists normally in small amounts in tissue macrophages of the bone marrow, liver, & spleen.

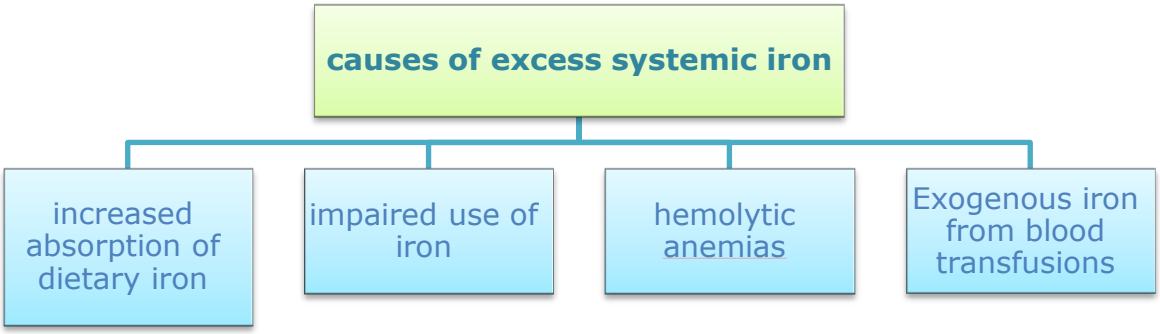


Doctor's Note: if it hemosiderin starts getting depositing in the Langerhans cells of the pancreas > it will effects the production insulin > which will cause diabetes.



hemosiderin granules in liver cells

Left: HE stain, Right: Prussian blue stain



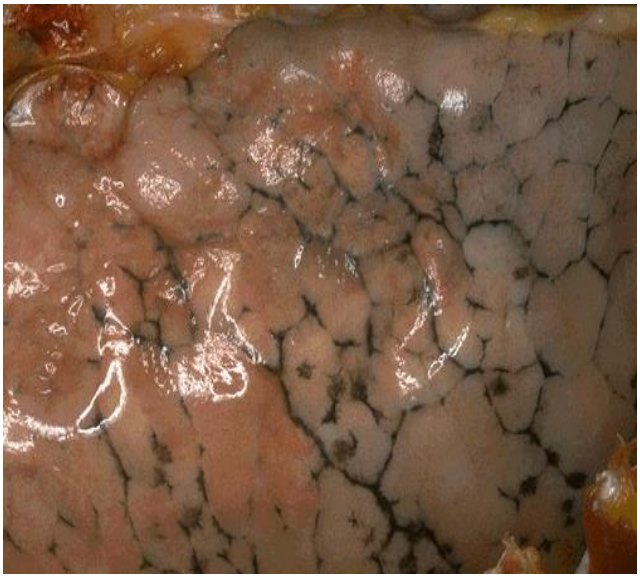
Morphology: Iron pigment is golden and granular in cytoplasm of macrophages or in cells of the liver, pancreas, heart etc. It appears blue-black with Pearl Prussian blue stain.

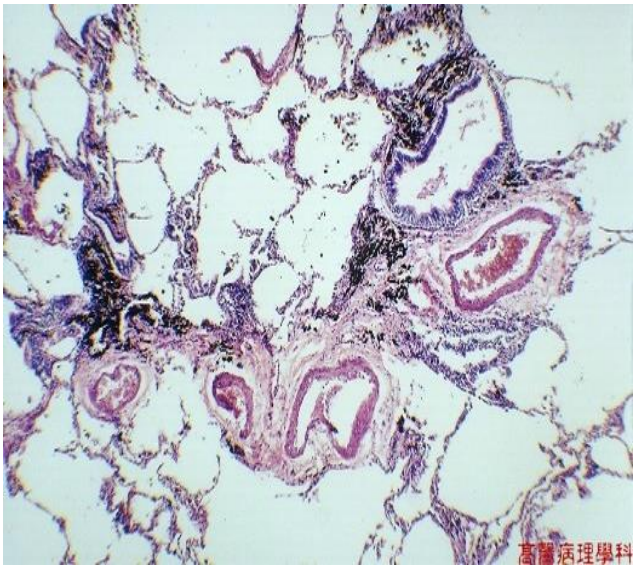
pigments	Lipofuscin	Melanin	Bilirubin	Hemosiderin
The name of the stain	-	Masson-Fontana stain		Prussian blue stain
color	Yellow-brown	Brown-black	yellowish pigment	Blue- black

Exogenous Pigments

1-anthracosis:
most common exogenous pigments and it's a carbon pigment or coal dust.
Smoking or carbon particles are inhaled and enter the lungs, the macrophages try to clean them up but it takes a long time. So when we take the Lungs we will see that it will have black spots these are the carbon pigments.

(Anthracosis of the lung)





2-caol worker's pneumoconiosis: it's a lung disease. Too much carbon dust.
The different between 1 and 2 is that 1 have kind of normal carbon(smoking or air pollution) but 2 it is too much carbon and they will be down under 500m(caul miners).
يعني انه الاول الكميه للكربون تكون اقل من النوع الثاني غير انه النوع الثاني بيكونون تحت الارض فطبيعي الاكسجين بيكون اقل.

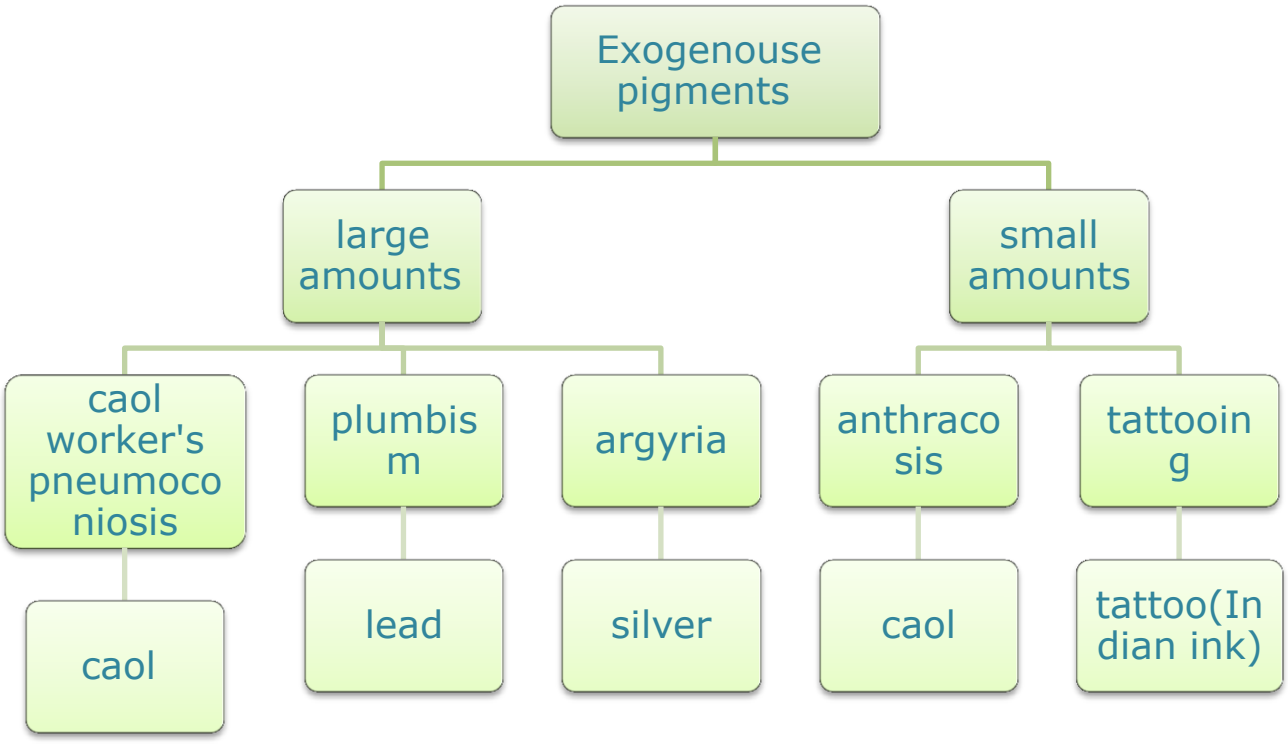
3-Plumbism: excess of leads.

4-Argyria: excess of silver.

Both 3 and 4 will have gray discoloration of the skin.

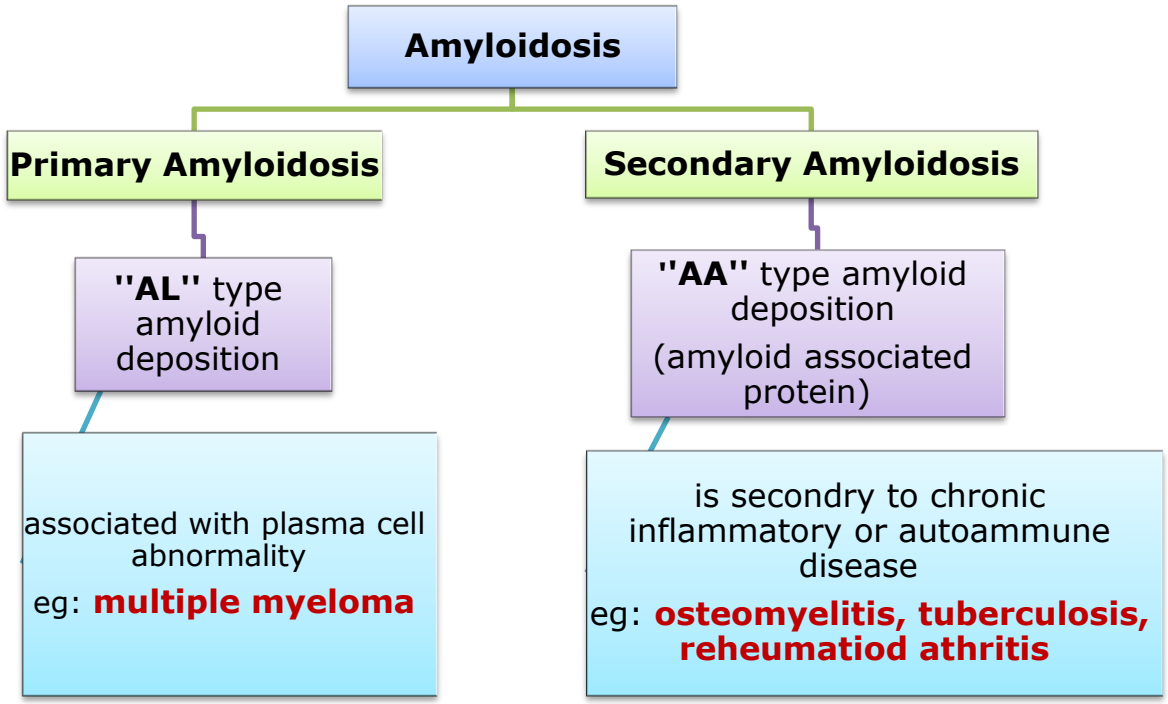
5-tattooing: allergic reaction caused by the tattoo (Indian ink). Macrophages engulf the ink but can't digest it. We will find macrophages in the dermis (2nd layer of the skin) and it will have blue granules of pigments.

Summary



Amyloid Deposition (Additional information)

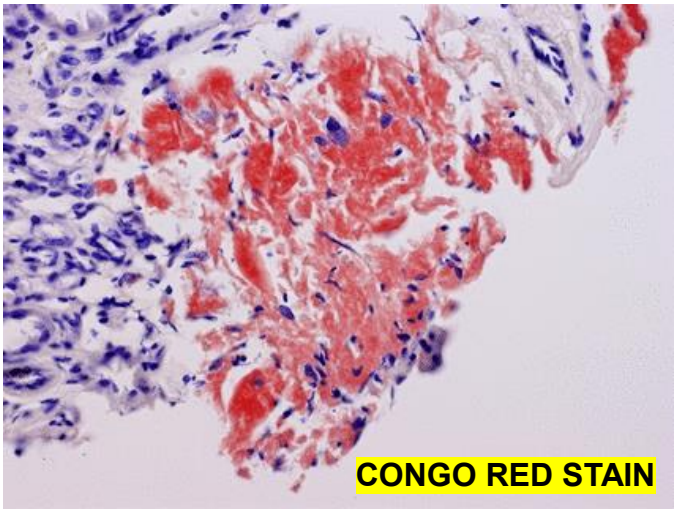
- Is an extracellular deposition of fibrillary amyloid protein in various organs (e.g. kidney, liver, blood vessels, heart etc).
- Associated with a number of inherited and inflammatory disorder.
- Amyloidosis : is a disorder of protein mis-folding
- Amyloid is composed of non-branching fibrils of β- pleated sheet.

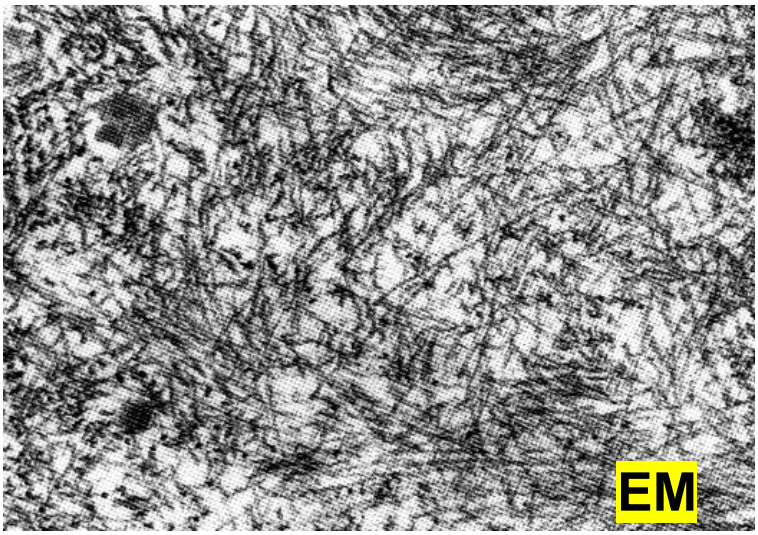


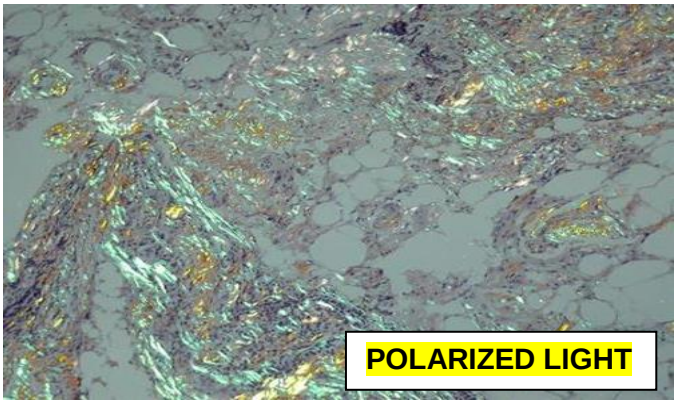
Morphology of amyloid:

—

Light microscopy	Electron microscopy
— it is pink eosinophilic material. — With Congo red stain: it appears bright orange. And when the congo red stained tissue is exposed to polarized light it produces an apple-green birefringence.	— amyloid deposits are composed of non-branching fibrils, 7.5 to 10 nanomicron in diameter. —







Diagnosis: can be made with **biopsy** of organs like the kidney, rectum, gingiva and skin**.**

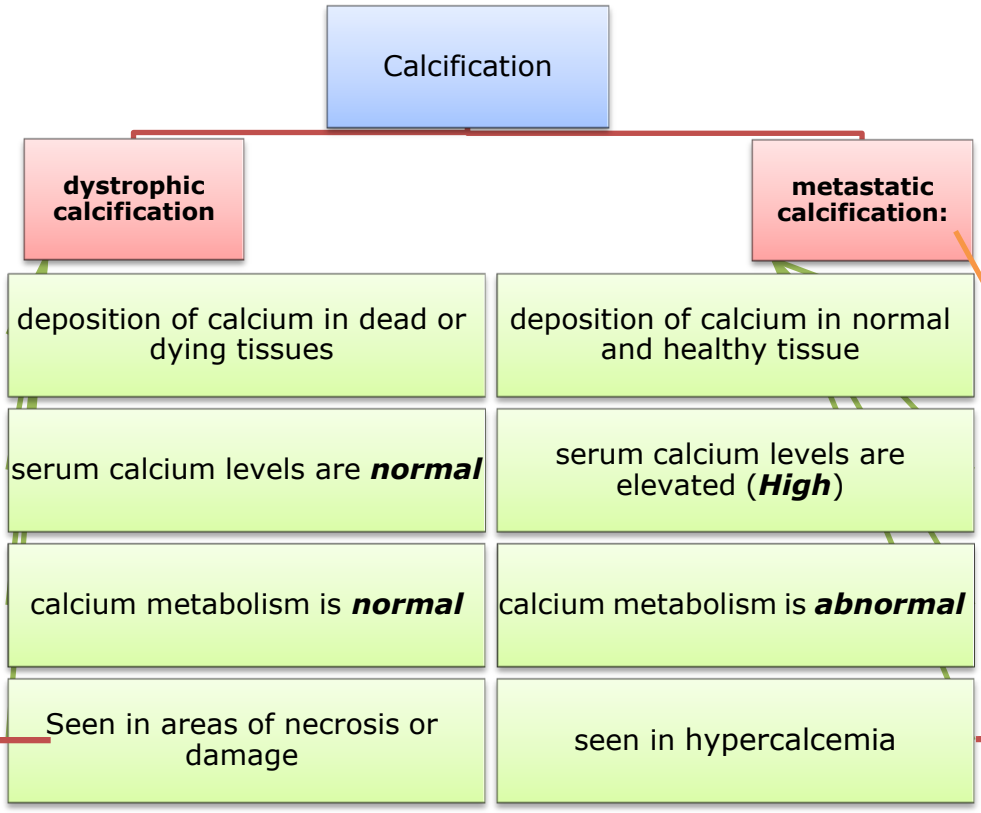
Amyloidosis

G. Understand the causes of and differences between dystrophic and metastatic calcifications.

Abnormal Pathologic Calcification

-it is a common process in a wide variety of disease states; it implies the abnormal deposition of calcium salts.

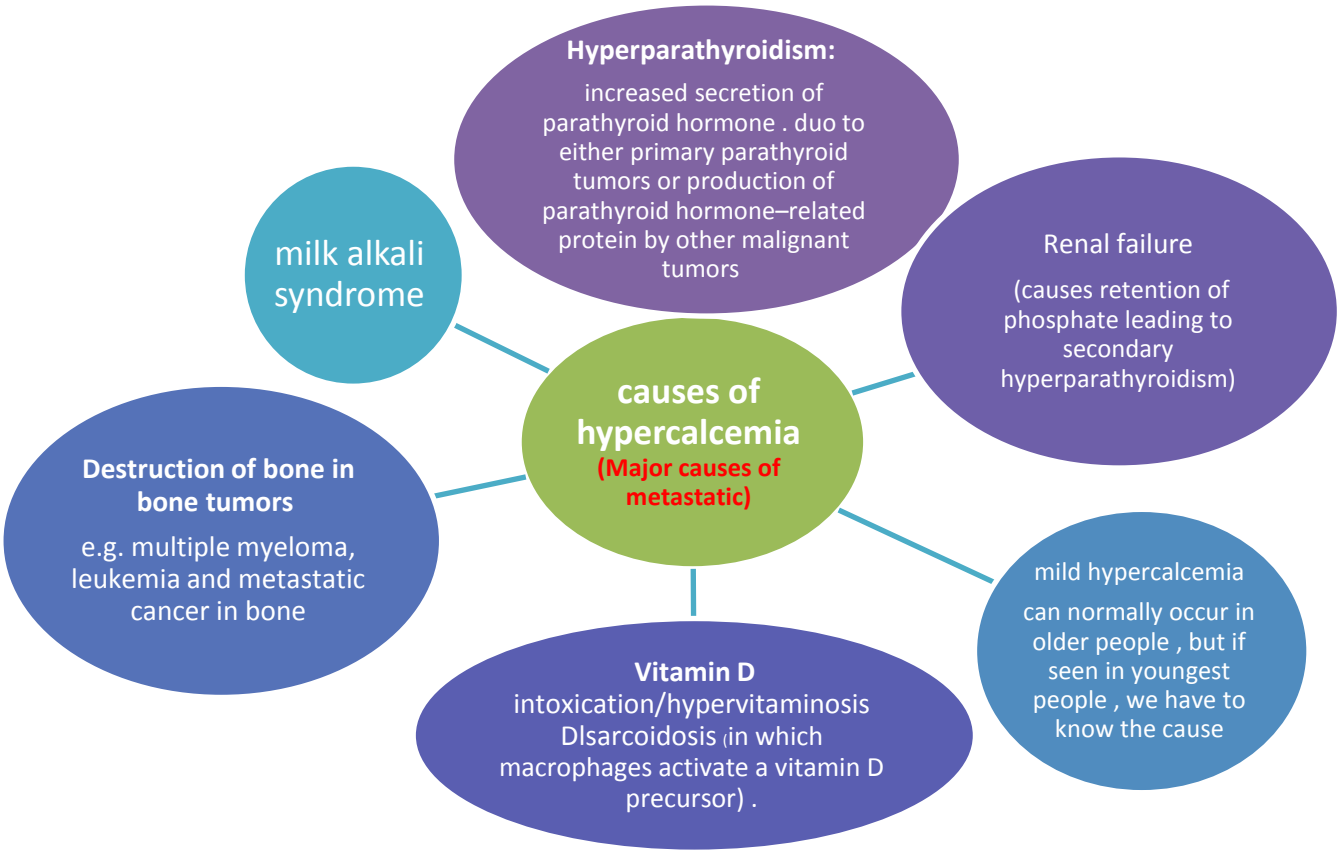
Calcification أي تكلس
وهو تراكم الكالسيوم في أنسجة الجسم



dystrophic
يكون مستوى الكالسيوم في الدم طبيعي لأنه بعضه راح لأنسجة ميتة فمحد يدري عنه
metastatic
مستوى الكالسيوم في الدم مرتفع لأنه كله في الأماكن اللي من المفترض يكون فيها

e.g.:
1- Blood vessels: in the atheromas of advanced atherosclerosis
2- Heart: in aging or damaged/scarred heart valves.
3-A tuberculous lymph node can be converted to stone by the calcium.
4-In fat necrosis.
5- Psammoma body (see later)
6- Areas of trauma

e.g. : mainly in kidneys, lung and stomach.

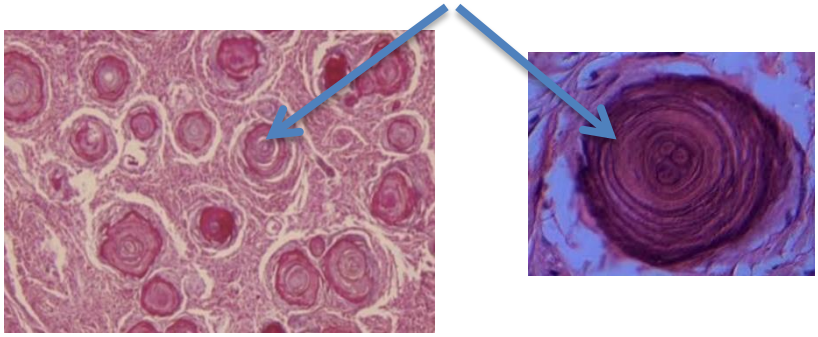


Morphology of pathologic calcification

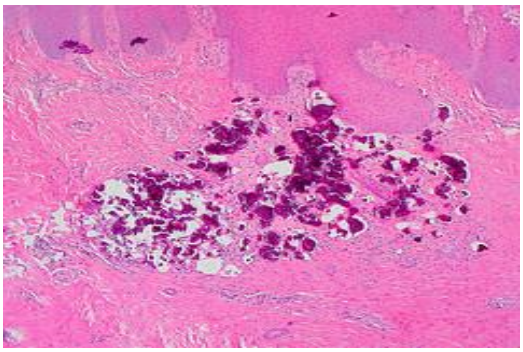
(dystrophic or metastatic, both look the same)

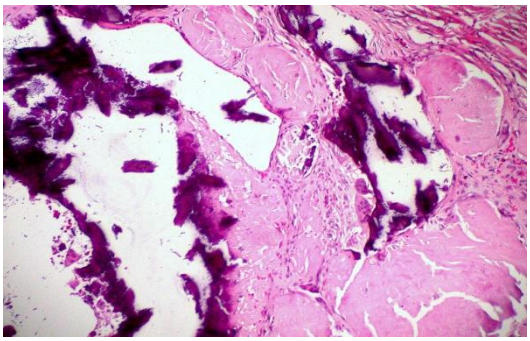
- Ca deposition occurs anywhere in the body e.g. in wall of blood vessels, kidneys, lungs, stomach, skin etc.
- Whatever the site of deposition, the calcium salts appear macroscopically as fine, white granules or clumps, often felt as gritty deposits.
- Histologically, calcium salts are basophilic, amorphous granular. They can be intracellular, extracellular, or both.
- **Psammoma body** is a special type of dystrophic calcification made up of concentric lamellated calcified structures, They are seen in papillary (حليمي=من حلمة) cancers in the body (e.g. thyroid, ovary, kidney) and in the meningioma of the brain.

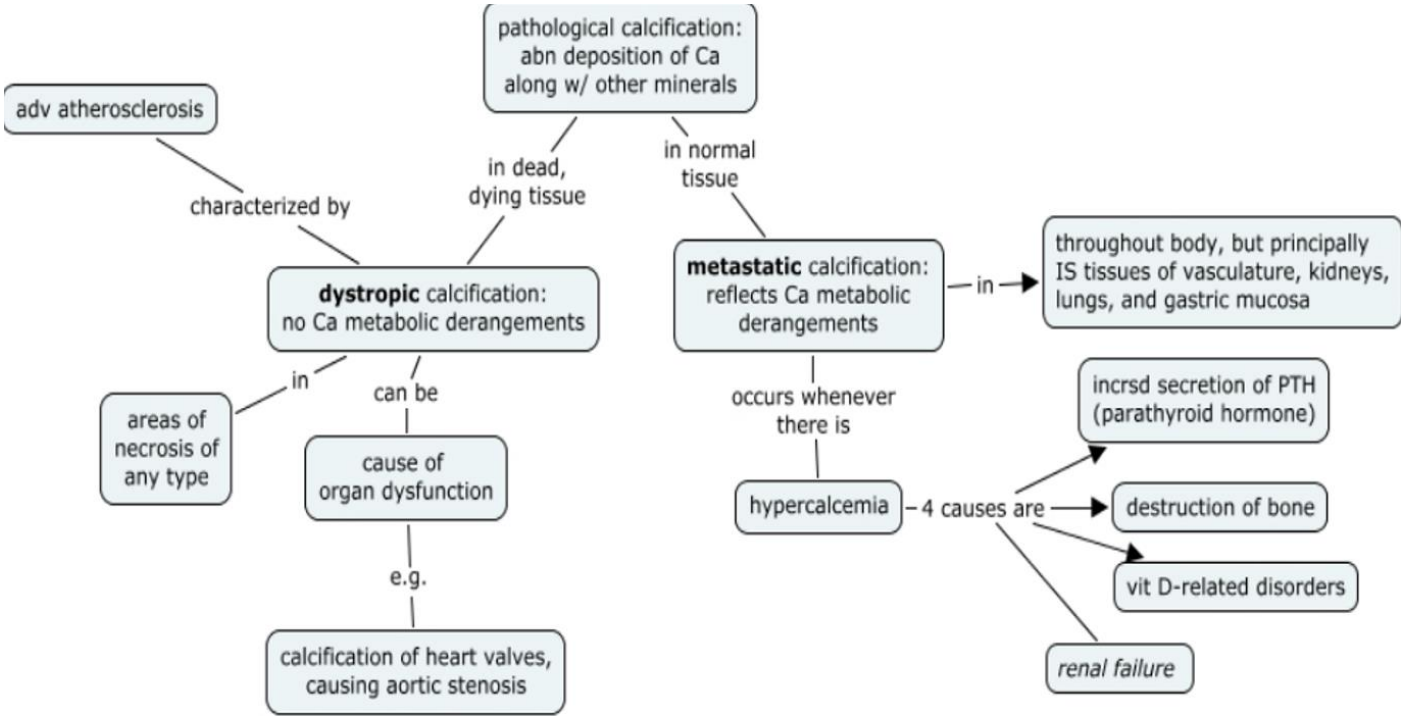
Psammoma body



Pathologic Calcification







Feature	Dystrophic calcification	Metastatic calcification
Definition	Deposition of calcium salts in dead & degenerated tissue.	Deposition of calcium salts in normal tissue.
Calcium metabolism	Normal	Deranged
Serum calcium levels	Normal	Hypercalcemia
Causes	Necrosis, Infarcts, thrombi, haematomas, dead parasites, old scars, atheromas, monckebrg`s sclerosis, calcinosis cutis	Hyperparathyroidism,prolonged immobilsation,hypervitaminosis D,milk alkali syndrome,hypercalcemia of infancy
Pathogenesis	Initiation and propogation	High pH at certain sited e.g lungs, stomach,blood vessels,cornea.

MCQS

1. Is an increase in the number of cells.

   a- Metaplasia.
   b- Hypertrophy.
   c- Atrophy.
   d- Hyperplasia.
   e- Dysplasia.

2. Nuclear fragmentation is known as:

   a- Karyolysis.
   b- Hypoxia.
   c- Karyorrhexis.
   d- Ischemia.
   e- Pyknosis.

3. Which of the following is not a type of ROS:

   a- Oxygen peroxide (Superoxide).
   b- Ethanol.
   c- Hydrogen peroxide.
   d- Hydroxyl ions.
   e- Nitric oxide.

4. Apoptosis can be:

   a- Physiologic.
   b- Pathologic.
   c- Both a, b.
   d- Necrosis.
   e- None of the above.

5. What type of necrosis does TB cause:

   a- Liquefactive necrosis.
   b- Fibrinoid necorsis.
   c- Coagulative necrosis.
   d- Fat necrosis.
   e- Caseous necrosis

6. All accompany apoptosis except:

   a- Inflammation.
   b- Reduced cell size.
   c- Nucleosome-size fragments.
   d- Pathologic change after DNA damage.
   e- Altered plasma membrane structure.

7. Which of the following isn't a cause of metastatic calcification:

   a- Increased secretion of parathyroid hormone.
   b- Atherosclerosis.
   c- Vitamin D related disorders.
   d- Mild hypercalcemia.
   e- Milk alkali syndrome.

Best Wishes and Good Luck

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Faris Aljaafar
Mohammed Hakami
Mohammed Almania
Moayed Ahmed
Moataz Altokhais
Sultan Almalki
Turki Alobathani
Waleed Almajlad
Waleed Al-askah

Girls:

Nehal Beyari
Najd AlTheeb
Muneerah Alzayed
Atikah Kadi
Ghada AlHadlaq
Atheer AlRsheed
Amal AlShaibi
Haneen Alsubki
Doaa Walid
Rania Alessa
Raneem Alghamdi
Reema Alshayie
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Fatimah AlTassan
Lama AlTamimi
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Aldanah Almutib
Ghadah AlMuhana
Deena AlNowiser