CELL INJURY

Lecture 2 & 3 & 4

Team work 434

Colors of text:
Definitions: **Blue**.
Examples: **Green**.
Important: **Red**.
Extra explanation: **Gray**. . It is only there to help you understand. If you feel that it didn't add anything to you just skip it.
Diseases names: Underline.

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Overview of cell responses to stress and noxious stimuli

When cells encounter[1] *physiologic stresses* or *pathologic stimuli*, they must **adapt**[2], achieving a new steady state and preserving viability and function.

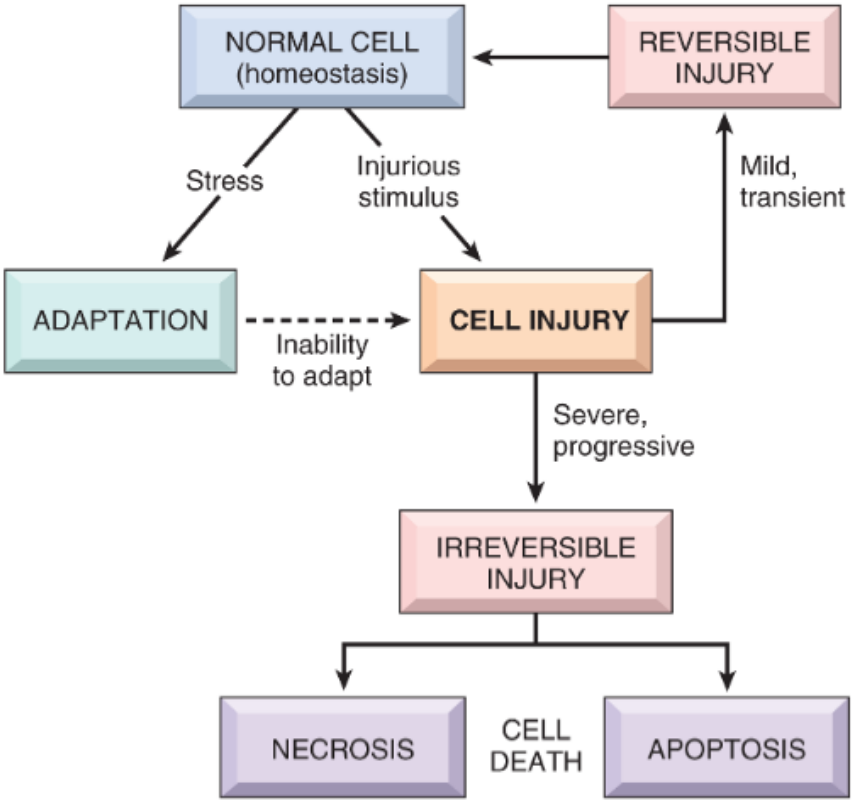
Adaption process could be by:

1. Hypertrophy.
2. Hyperplasia.
3. Atrophy.
4. Metaplasia.

If the adaptive capability is exceeded or if the external stress is harmful, ***cell injury*** develops.
Cell injury could be:

- Reversible.
- Irreversible.

Cell death is a normal and essential[3] process in embryogenesis, the development of organs, and the maintenance of homeostasis; this is physiological cell death. However in some cases cell death is a pathological condition which needs care and treatment.

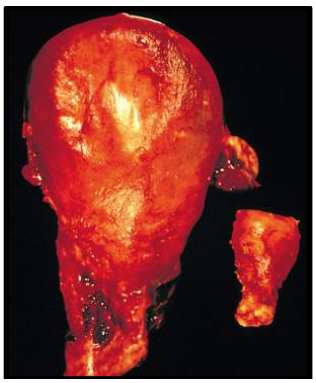


[1] واجهت
[2] التكيّف
[3] أساسي

Hypertrophy[4]: Increased cell and organ **size.** In **pure hypertrophy** there are no new cells, just bigger cells containing increased amount of structural proteins and organelles.
-Hypertrophy can be **physiologic** or **pathologic**.

Examples of physiologic hypertrophy:

1. People who remove one kidney usually experience hypertrophy in the other one, because it compensates the other (removed) one .
2. Sometimes, when a liver tumor is removed, other parts of the liver become hypertrophic to compensates the loss of the other cells.



Gross appearance of a normal uterus (right) and a gravid uterus (left) that was removed for postpartum bleeding[5].

Hyperplasia: Increase in the size of an organ or tissue, caused by an increase in the **number** of cells in response to hormonal stimuli or other growth factors or irritation.

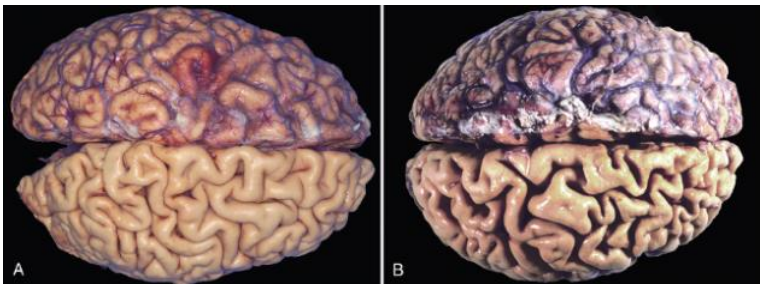
- Hyperplasia occurs in tissues that are able to divide or contain abundant tissue stem cells, so some types of cells are unable to exhibit hyperplasia (nerve, cardiac, skeletal muscle cells).
- hyperplasia can be induced by hormones (endometrial hyperplasia induced by estrogen).

* Usually, hyperplasia occurs together with hypertrophy.

Example: During pregnancy, uterine enlargement is caused by both hypertrophy and hyperplasia of the smooth muscle cells in the uterus.

Atrophy[6] : Shrinkage in the **size** of the cell by the loss of cell substance.
Reason: Decreased nutritious supply or diseases, associated with decreased synthesis of cellular building blocks (proteins) and increased breakdown of cellular organelles.

1. Athletes have **hypertrophy** in their skeletal muscles (large muscles size), If these athletes use anabolic steroids (hormones to build their muscles), male athletes who use these steroids will eventually experience **artrophy** in their testicles; called **testicular atrophy**, and they may have liver cell injury because of the anabolic steroids.



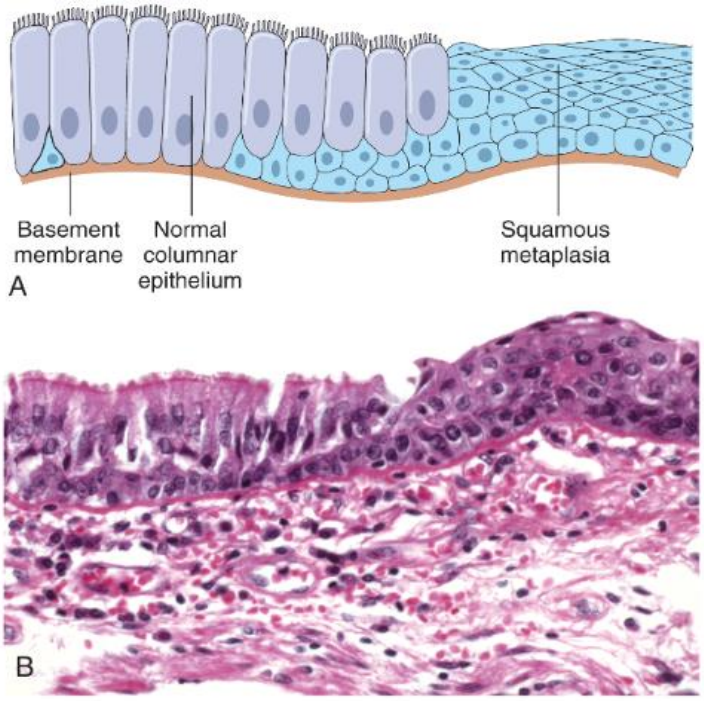
A. Normal brain of a young adult. **B.** Atrophy of the brain in an 82-year-old man with **atherosclerotic**[7] disease.

[4] تضخم
[5] نزيف ما بعد الولادة
[6] ضمور

Metaplasia: Reversible change of one cell type to another, usually in response to irritation.

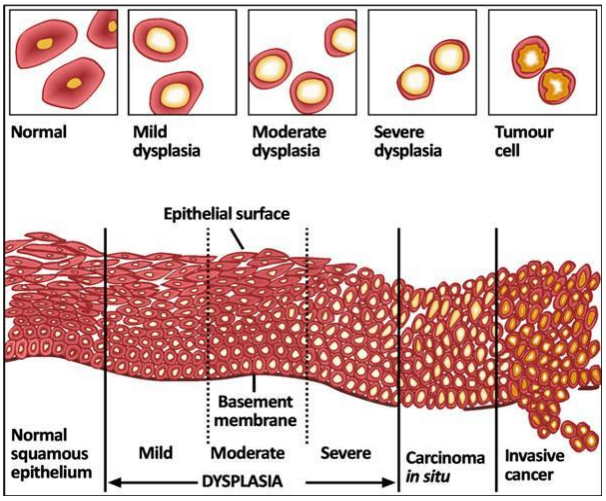
Example:

1. bronchial epithelium undergoes squamous metaplasia in response to the chronic[8] irritation of tobacco smoke.
2. **Barrett's esophagus**: Esophageal squamous epithelium becomes intestinal epithelium (columnar) when it is under constant contact with gastric acid. People who eat spicy foods may experience (heartburn[9]), which leads to Barrett's esophagus.



Metaplasia of normal columnar (*left*) to squamous epithelium (*right*) in a bronchus.

Dysplasia[10]: the enlargement of an organ or tissue by the proliferation of cells of an abnormal type.
* Dysplasia is **not** cancer but may progress to cancer.



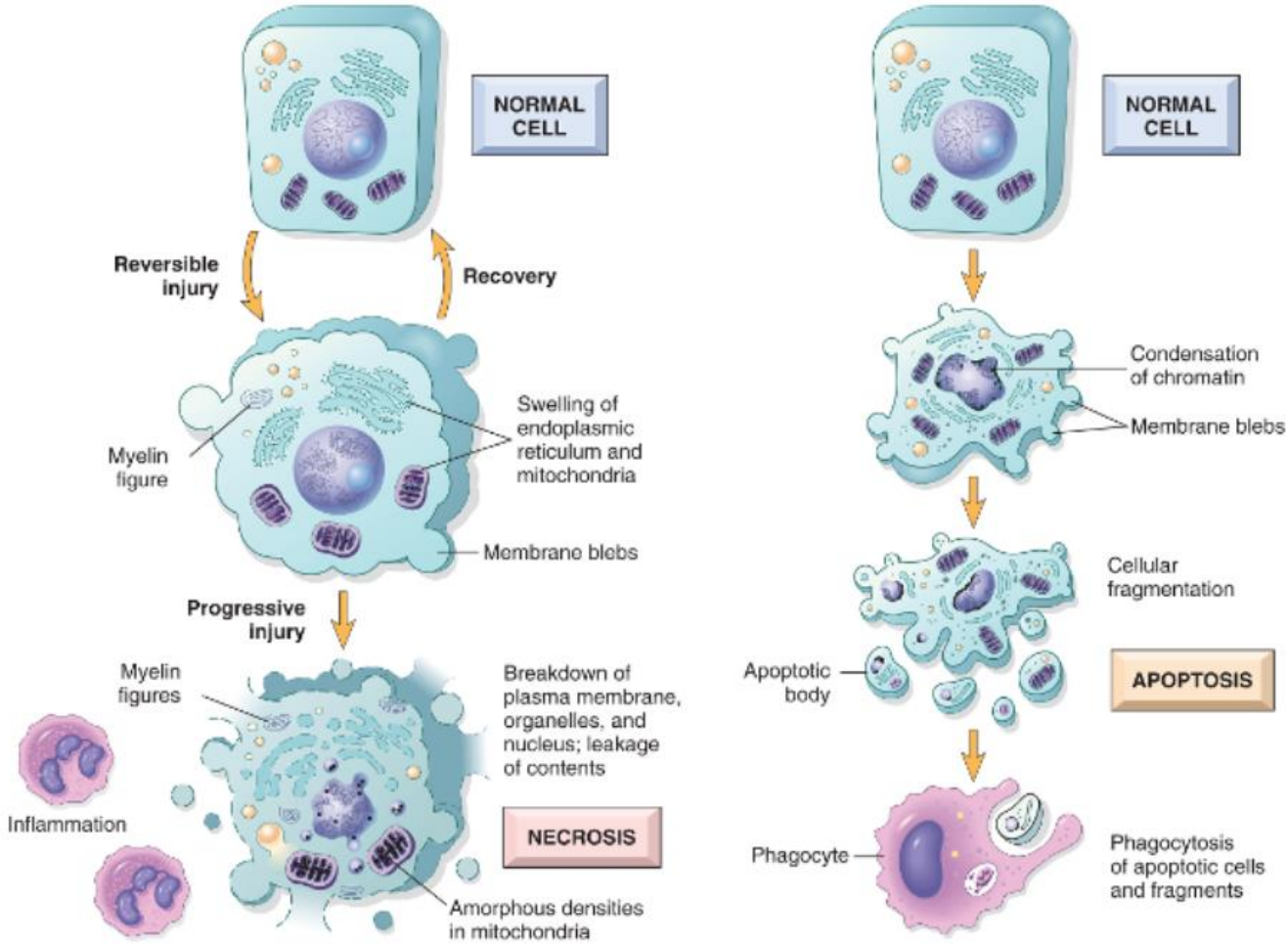
[7] تصلب الشرايين
[8] مزمن
[9] حموضة أو حرقة في المعدة
[10] النمو الشاذ

Overview of cell injury

There are two types of cell death:

1. Necrosis.
2. Apoptosis.

which differ in their mechanisms, morphology, and roles in disease and physiology.



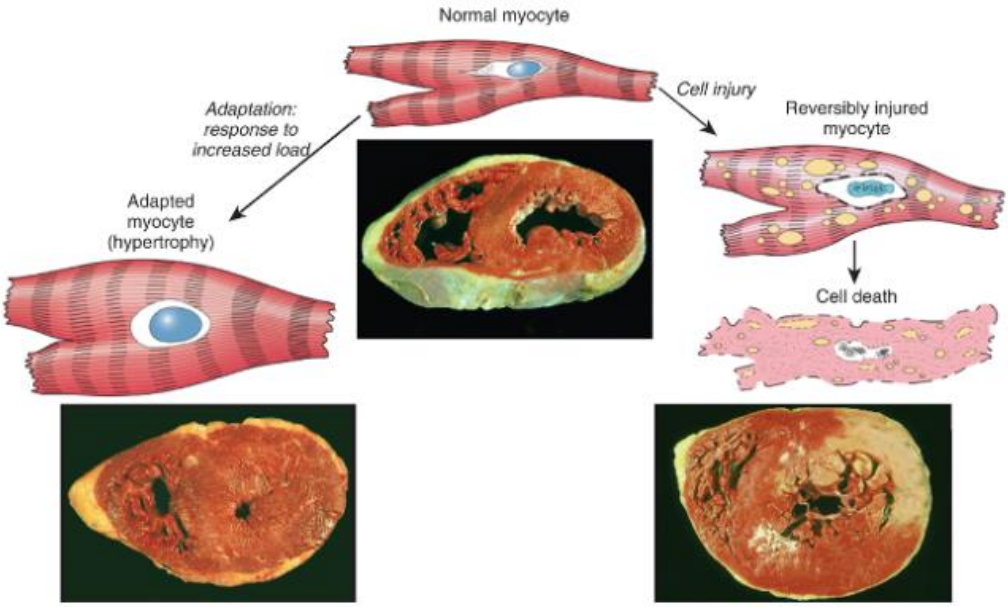
Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak 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 and protein damage

* Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with pathologic cell injury. Moreover, necrosis is always accompanied with inflammation, while apoptosis is NOT usually accompanied by inflammation.

Causes of cell injury

- **Hypoxia:** it's oxygen deficiency. It's a common cause of cell injury and death.

It's most likely caused by **ischemia** (loss of blood supply to the tissue).
Low blood reaching the tissue means that less oxygen is reaching the tissue. This is how ischemia causes hypoxia.
Example: **myocardial infarction[11].**



Myocardium facing persistent[12]and increased work load, as in **hypertension** or with a narrowed (stenotic) valve, adapt by being *hypertroph*ic to generate a higher contractile force.
If the increased demand is not relieved, such as if the myocardium is subjected to reduced blood flow (*ischemia*) from an occluded coronary artery, the cardiac cells may undergo injury. Myocardium may be reversibly injured if the stress is mild or the arterial occlusion is incomplete or sufficiently brief, or it may undergo irreversible injury and cell death (***infarction)*.**

There are other causes for **hypoxia** which include:

a) Inadequate[13] oxygenation of the blood (lung disease and carbon monoxide - CO - poisoning)
b) Lower O2 carries (lower RBC > **anemia**)
c) Inadequate tissue perfusion[14] (cardiorespiratory failure[15], **hypertension**)

[11] ذبحة، سببها عدم وصول الدم للعضلة القلبية
[12] متكرر
[13] غير كاف
[14] عدم كفاية التروية للأنسجة، يعني أن الدم غير قادر على الوصول لكافة الأنسجة في الجسم.
[15] Cardiac arrest: A condition in which the heart stops functioning. It cause is a sudden stop in effective blood circulation.

- **Chemical Agents and Drugs:** (oxygen in high concentrations, poisons, pollutants, insecticides, industrial and occupational hazards, alcohol and narcotic drugs and therapeutic drugs).
- **Infectious Agents:** caused by: (viruses, bacteria, fungi and protozoans).
- **Immunologic Reactions:** autoimmune reactions against one's own tissues.
- **Genetic Factors:** (**Down syndrome**)
- **Nutritional Imbalances:** Obesity increases the risk for type 2 **diabetes mellitus**.

- **Physical Agents: (**Trauma[16], extremes of temperature, radiation, electric shock)

  Radiation: either sun radiation which is ultraviolet light or the radiation used in cancer treatment.

- The basic usage of radiation in cancer treatment is to cause cell injury to the cancer cells resulting in it death and so the patient gets the benefit.
- There's a debate about using radiation in treating a cancer patient because it will damage the normal cells as well, so the patient might benefit more or get injured more.

- **Aging.**

[16] رضة

Morphological Changes of Reversible and Irreversible Cell Injury

Reversible and Irreversible cell injury

Earliest stages of cell injury can be **reversed**, such as:

1. Disturbance[17] in cytoplasmic membrane permeability (gain of Na and loss of K)
2. cytoplasmic membrane blebs[18].
3. **cellular swelling:** result of failure of energy-dependent ion pumps in the plasma membrane, leading to an inability to maintain ionic and fluid homeostasis.
4. swelling [19]of cell organelles (rough ER / mitochondria / lysosomes).
5. loss of ribosomes & microvilli.
6. **fatty change:** appearance of small or large lipid vacuoles in the cytoplasm (e.g. in hepatocytes and myocardial cells)
7. Myelin figures[20].

Reversible cell injury

There's a point where's the injury of the cell becomes **irreversible**[21]. The changes that occurs when the cell injury is irreversible are:

1. Inability to correct **mitochondrial dysfunction** (severe mitochondrial dilatation [22]and damage. Large, shapeless (amorphous) densities [23]are also present) → (lack of oxidative phosphorylation and ATP generation).
2. Profound disturbances [24] in **membrane** function. (lysosomal membranes results in the enzymatic dissolution of the injured cell)
3. Increased **cytoplasmic eosinophilia** (appears red under the microscope.)

Why is there increased eosinophilia?

reason: the DNA is damaged → cannot form RNA → decrease RNA in cytoplasm.

Didn't get it ?

Remember that there are two dyes used when staining a cell; **hematoxylin** and **eosin**. Hematoxylin a base and binds with acidic parts of the cell, especially the nucleus. Eosin is an acid and binds with basic parts of the cell (parts of the cytoplasm). When hematoxylin binds with parts of the cell this part appears in dark blue. On the other hand when eosin binds to parts of the cell they appear pinkish.
Usually, when the cell is active, lots of RNA are being synthesized. (mRNA, tRNA, and rRNA). When the cell is strongly damaged, the DNA is no longer capable of synthesizing RNA, which means that the cell is less capable of building proteins. Less RNA in the cytoplasm means that there is less blue color of

17
18 فقاعات (صعاريز)
19 تورم
20 phospholipid masses from the cytoplasm, which are derived from damaged cellular membranes.
21 غير قابل للعلاج أو التراجع
22 توسع
23 كتل
24 اضطراب عميق

hematoxylin (RNA is an acid and hematoxylin is a base). When the blue color is less, the pinkish color of eosin is clearer; and that is what increased cytoplasmic eosinophilia means.

4. Numerous **myelin figures** are found, more than a normal cell.

What are myelin figures?

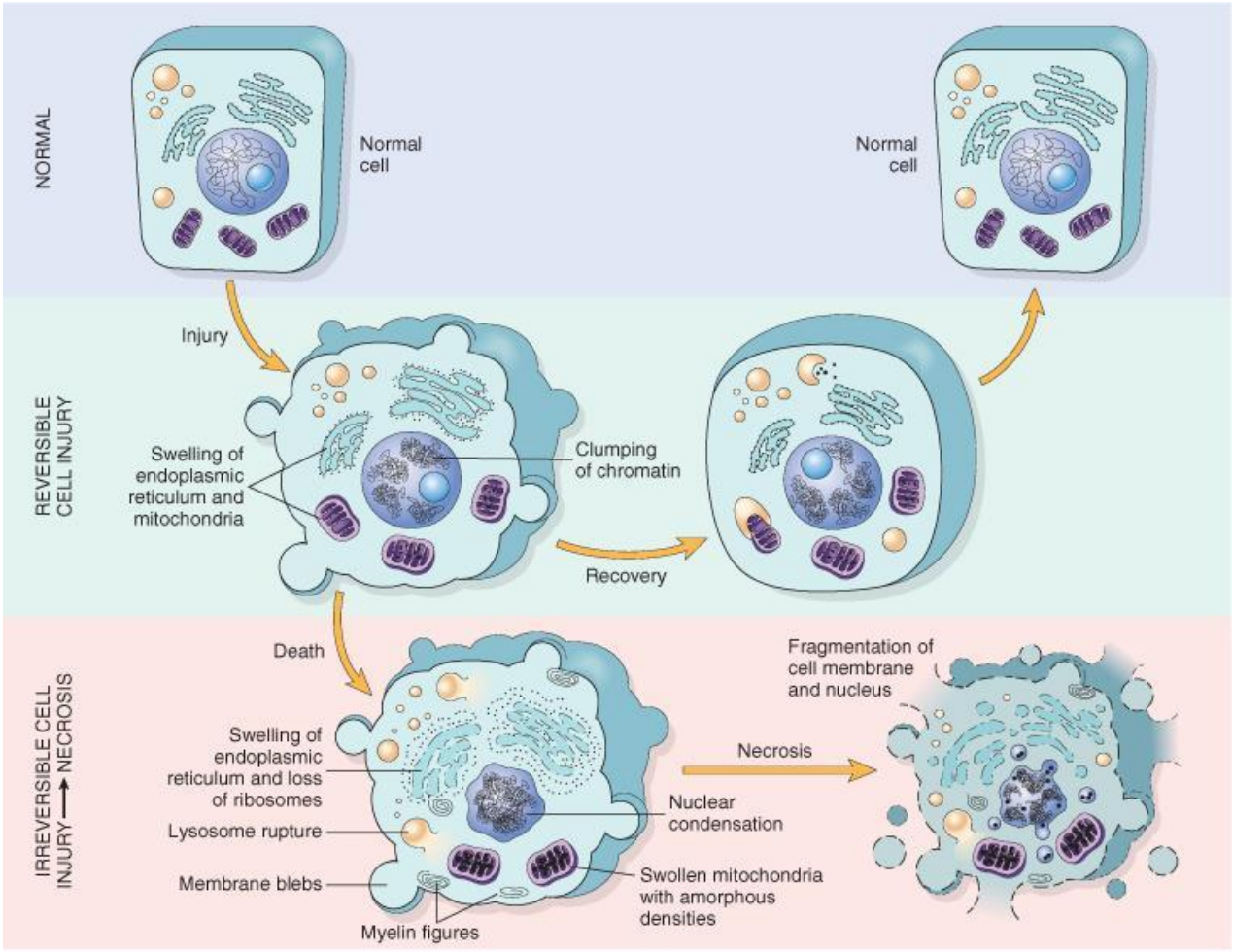
a rolled-up or scroll-like arrangement of a lipid bilayer within a cell, superficially resembling the myelin sheath of nerves.

5. **Swelling** and **rupture** of lysosomes leads to leakage and enzymatic digestion of cellular contents.
6. **Nuclear changes:** nuclear changes assume **ONE** of the three following patterns. These patterns are due to the breakdown of DNA and chromatin.

- **Karyolysis:** in this case the nuclear chromatin is lost, therefore there is a decrease in basophilia.
  Why a decrease in basophilia? the chromatin of the nucleus is lost; therefore hematoxylin stain has less DNA to bind with, hence there is less blue color or basophilia.
- **Pyknosis:** in this case the nucleus shrinks and the DNA condenses into a solid mass. There is an increase in the nucleus' basophilia.
  Why an increase in the basophilia? because the DNA comes together and the stain makes it look very dark blue.
- **Karyorrhexis:** (this happens after pyknosis) The pyknotic nucleus undergoes fragmentation.

Irreversible cell injury

* Necrosis is irreversible.
* If the damage is not removed from the reversible stage, then the cell will ultimately die.



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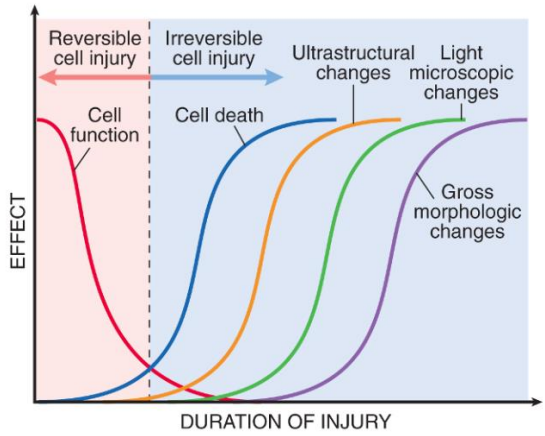
Cellular function may be lost long before cell death occurs, and the morphologic changes of cell injury (or death) lag far behind both.



For example: Myocardial cells become:

- **after 1 to 2 minutes of ischemia:** noncontractile.
- **after 20 to 30 minutes of ischemia:** they become necrotic.
- **after 2 to 3 hours of ischemia:** myocytes may not appear necrotic by electron microscopy.
- **after 6 to 12 hours of ischemia:** myocytes appear necrotic under light microscopy.

Mechanisms of Cell Injury

Fun Fact: the cells of a healthy human burn 50 to 75 kg of ATP a day!!

What happens when we have cell injury that may result in cell death?

1) **ATP depletion:**

is caused by :

1- reduced supply of oxygen and nutrients.
2- mitochondrial damage
3-some toxins e.g: cyanide

results in :

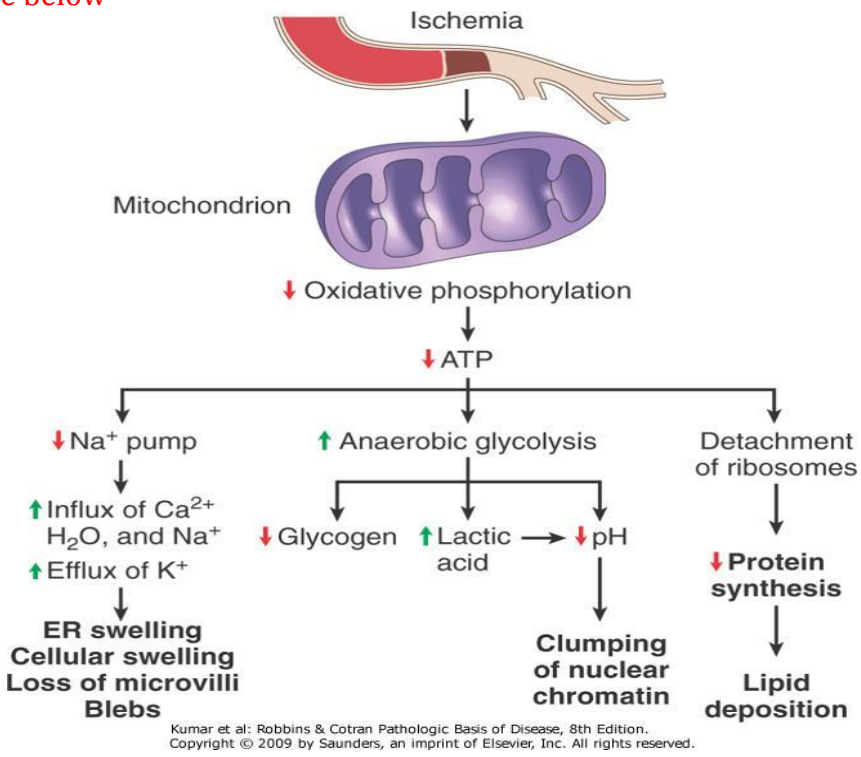
1- reduction of plasma membrane pumps activity → imbalance of substances disturbing the solutes concentration causes the cell to swell and ER to dilate.
2- detachment of RER proteins > less protein synthesis.
3- increase **in anaerobic glycolysis** using stored glycogen

causes: decrease in glycogen.

- lactic acid accumulation[25] > decrease intracellular pH.

What is the problem with decreased pH? the enzymes' work rate decreases.

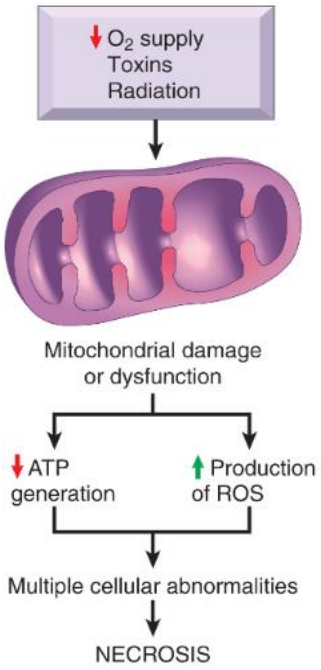
*see picture below

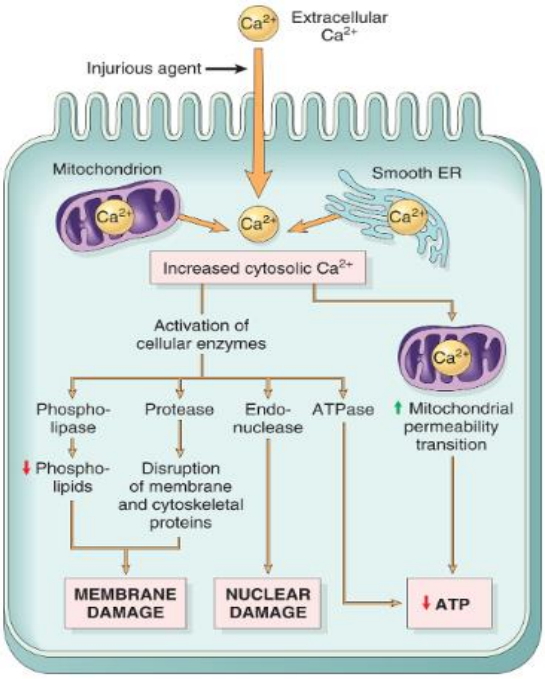


2) **mitochondrial damage:** in case of (low O2 supply/toxins/ radiation) the mitochondria fails to produce ATP, and instead it produces oxygen derived free radicals. These are harmful to the cell and can lead to necrosis.

[25] تراكم

3) influx of calcium activation of enzymes: when calcium enters the cell, because of the damage in the plasma membrane pumps, it participates in chemical reactions that will activate a number of enzymes that trigger apoptosis.





4) Accumulation of Reactive Oxygen Species: (ROS) (Free radicals).
atoms that have lost 1 or more electrons from their outer orbit are usually harmful. Free radicals in the cell are usually from Oxygen. The free radicals are considered unstable, therefore its hyper reactive (searches for a way to become stable), therefore it must enter biochemical reactions in order to bind to another atom to form a new compound and become stable. This causes cell injuries**. Why**? Because the reaction it enters might be dangerous and toxic to the cell.

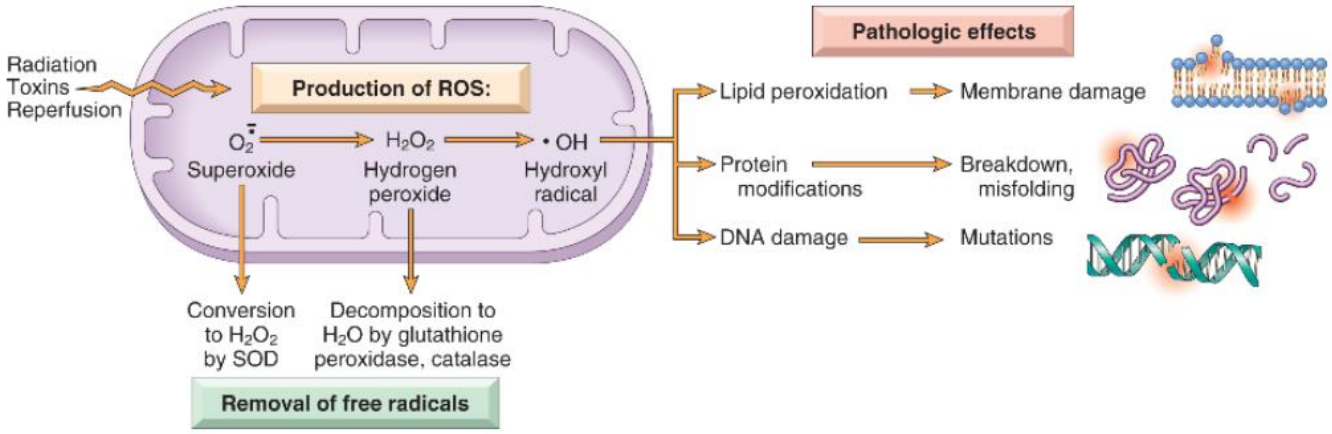
The common free radicals are:

1-superoxide anion radical (**O_2-**).
2-hydrogen peroxide (**H_2O_2**).
3- hydroxyl group (**OH**).
4- Nitrogen oxide (**NO**)

They attack (**nucleic acids / proteins / lipids**). When reacting with other molecules, they initiate a reaction to transform the other molecules into free radicals.

Free radicals increase under these circumstances :
1-radiation
2-leucocyte response to inflammation
3- toxins
4- oxygen therapy and reperfusion injury

Removal is done by:
1- **Antioxidants:** vitamins E, A and C (ACE)
2- **Enzymes:**
a) $O_2 \rightarrow H_2O_2$ by: **superoxide dismutase** (SOD).
b) $H_2O_2 \rightarrow H_2O$ by:
1. **Glutathione peroxidase** (found in cytoplasm).
2. **Caspase** (found in peroxisomes).



5) increased permeability of the cellular membrane: typically culminate in necrosis.

Several **biochemical mechanisms** contribute[26] to membrane damage:

1. decreased phospholipid synthesis because the ATP is less available.
2. increased phospholipid breakdown : when the Ca levels are high, it activates the phospholipase enzyme that breaks down the membrane.
    - the products of the broken lipids also affect the membrane.
3. oxygen free radicals.
4. **cytoskeletal abnormalities:** when the **Ca** levels are high it activates the protease enzyme that damages the cytoskeleton.

The affected membranes are :

1. **Mitochondrial membrane:** → decrease of ATP formation → many deletions → necrosis.
2. **Plasma membrane:** → imbalance to the permeability → influx of fluids + ions / loss of cellular contents. the also can lose metabolic products thus further reducing the energy stores.
3. **lysosomal membranes:** → leakage of enzymes → digestion of cellular components → cell death by necrosis.

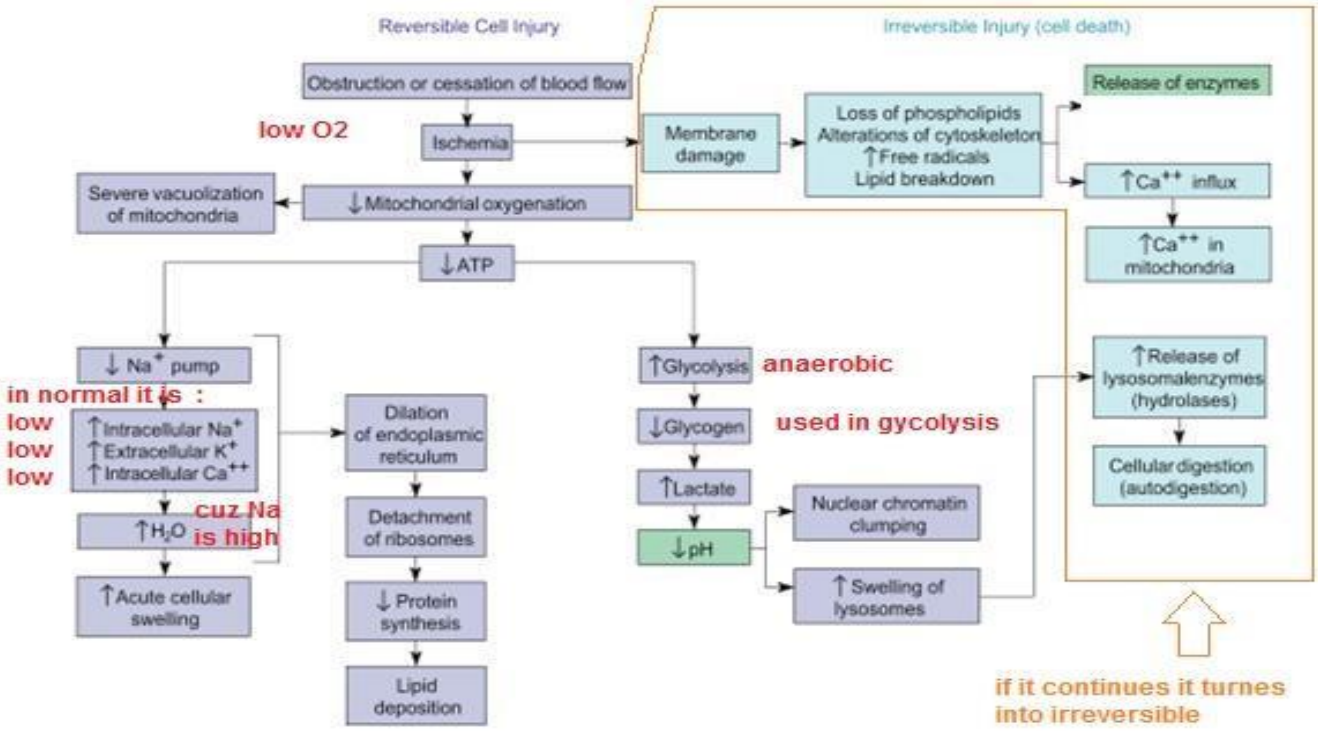
6) accumulation of damaged DNA and misfolded protein (abnormal protein): this triggers apoptosis to prevent mutations[27].

[26] تساهم
[27] الطفرات

SUMMARY

Mechanisms of Cell Injury

- *ATP depletion:* failure of energy-dependent functions → reversible injury → necrosis
- *Mitochondrial damage:* ATP depletion → failure of energy-dependent cellular functions → ultimately, necrosis; under some conditions, leakage of mitochondrial proteins that cause apoptosis
- *Influx of calcium:* activation of enzymes that damage cellular components and may also trigger apoptosis
- *Accumulation of reactive oxygen species:* covalent modification of cellular proteins, lipids, nucleic acids
- *Increased permeability of cellular membranes:* may affect plasma membrane, lysosomal membranes, mitochondrial membranes; typically culminates in necrosis
- *Accumulation of damaged DNA and misfolded proteins:* triggers apoptosis



Types of necrosis

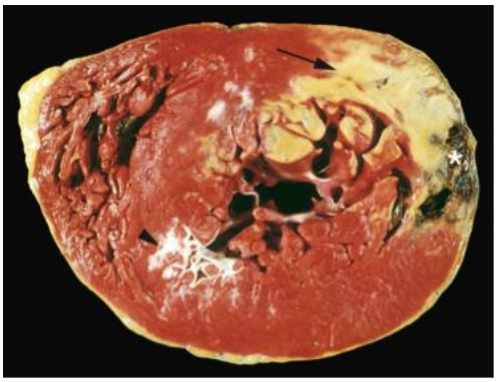
NECROSIS: Necrosis is changes that follow cell death in living tissues, due to enzymatic digestion and denaturation of intracellular proteins in the injured cell.

There are **5 types** of necrosis:

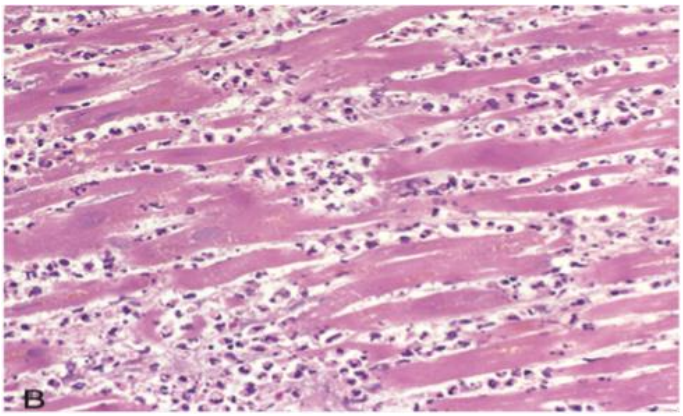
1. coagulative necrosis.
2. liquefactive necrosis.
3. caseous necrosis.
4. fat necrosis.
5. fibrinoid necrosis.

First: coagulative necrosis

Clinical case:
A man died of myocardial infarction: (also known as heart attack)
Necrosis of heart muscles resulting from ischemia. The major cause of this disease is atherosclerosis (accumulation of cholesterol on the blood vessels)
Symptoms: retrosternal chest pain.

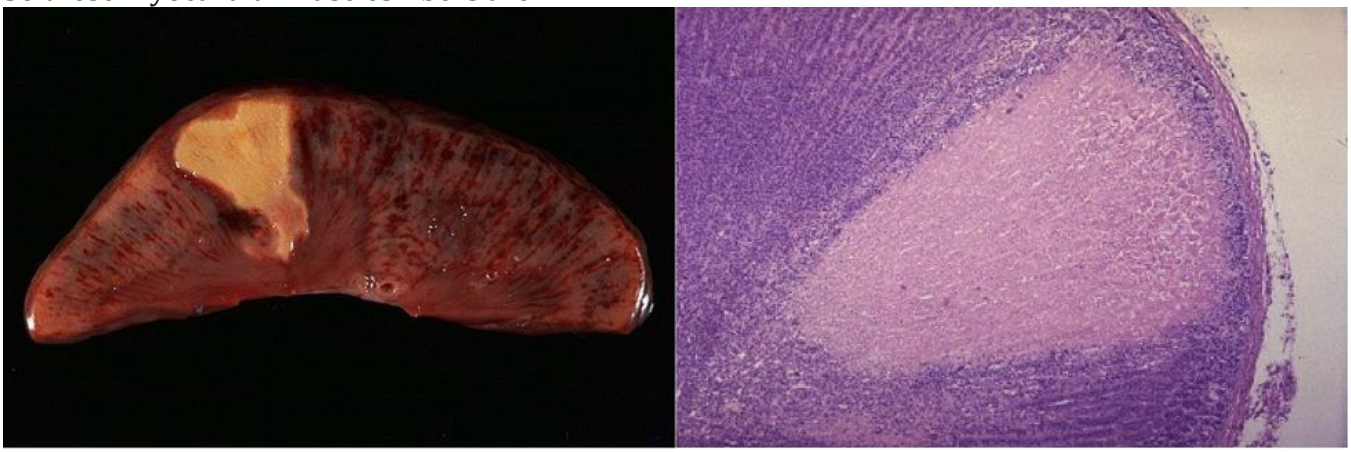


Myocardial infarct of the left ventricle is acquired by partly pale yellowish and partly hemorrhagic area, this area is most likely necrosis. This called (**Coagulative necrosis).**



If we look under the microscope we find that the general architecture of the cardiac muscles is preserved (muscle cell) but if we look closely those cells don't have a nuclei! they are disintegrated and karyorrhexis (fragmentations of the nuclei)
And some of the cells don't have nuclei at all **WHY?** Because there's lysis of nuclei (**karyolysis**).

So these myocardial muscles fibers are DEAD.

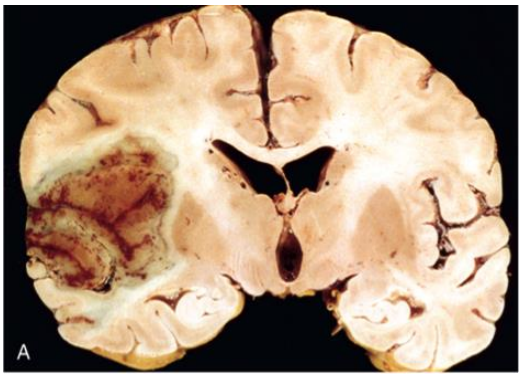


This is a section of the kidney that has undergone an infraction + coagulative necrosis
* architecture is preserved.

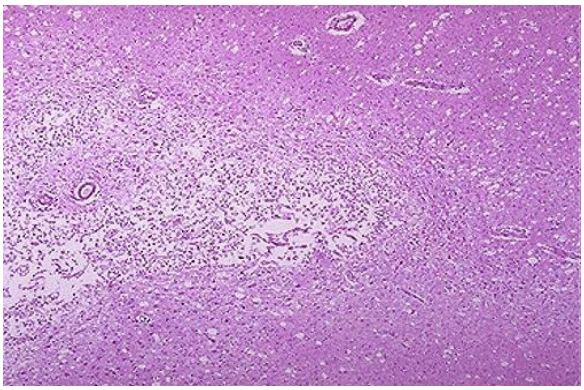
coagulative necrosis usually occurs in the **heart**, **kidney**, **liver** and **spleen** and it's characterized by all the features of irreversible cell injury but with **preservation of the architecture.**

Second type: Liquefactive necrosis

Which usually occurs in organs that are rich in fluids such as th**e Brain**. It occurs in **abscess**[28] (cavity filled with pus[29]) and this type of necrosis leads to a complete **loss of architecture.**



An area in this brain tissues showing yellowish discoloration with hemorrhagic region



This is how the area will look under the microscope, there's a complete loss of the architecture, all we can see is a big cavity surrounded by inflammatory cells (macrophages).

[28] الخراج
[29] صديد

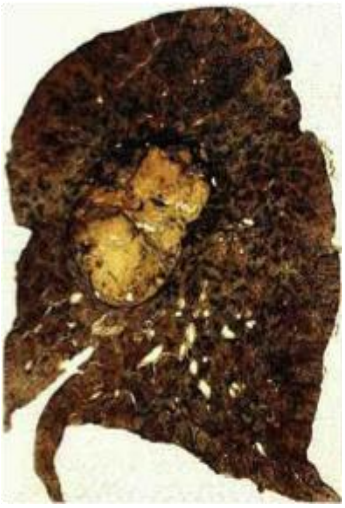
Symptoms when liquefactive necrosis takes part on the brain include:

1) Can't move his right or left arm and leg.
2) Can't speak.
3) Can't swallow.
4) Can't breath.

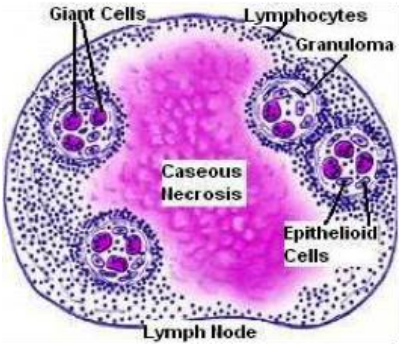
- This depends on the affected area of the brain.

Third type: Caseous necrosis

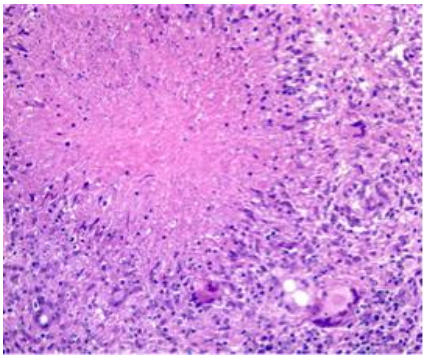
- **Caseous** means "cheese-like," referring to the friable yellow-white appearance of the area of necrosis.



This is how the lung looks grossly: **pale area** and then you find a large **necrotic area** with cavitation containing yellow-white (**cheesy**) debris.



If you look under the microscope at one of his lymph node you can see the granulomas (chronic inflammatory cells). There's no nuclei there's no structure of the cell **the architecture is lost.**



We can see that there's a **chronic inflammatory** cells and **giant** cells (cells with a lot of nuclei) forming granulomas.

Fourth type: Fibrinoid necrosis

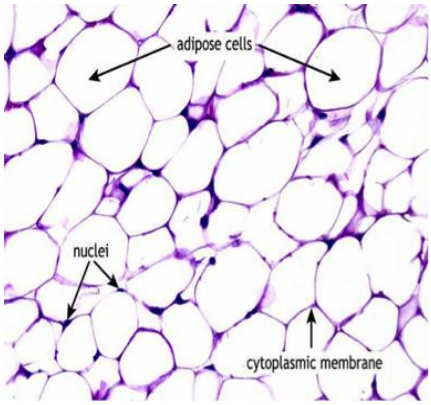
Is a type of necrosis, which occurs in **blood vessels** usually as result of immune mediated diseases.

Immunology: is a branch of clinical pathology in which studies the antigen-antibody reactions. It is the source of many immune mediated diseases such as **eczema**.

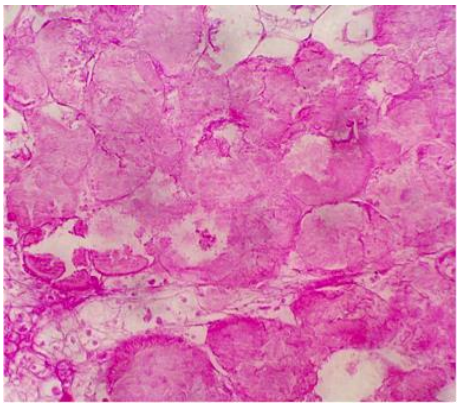
* An autoimmune disorder occurs when the body's immune system attacks and destroys healthy body tissue.

Fifth type: Fat necrosis

Occurs in any **organ contains fats.**

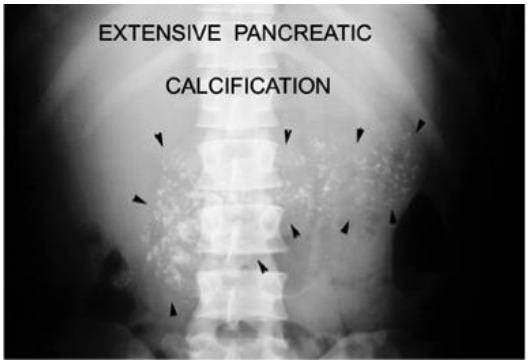


Normal Adipose Tissue



Fat necrosis

once these enzymes act on the adipocyte the cells die. This action called **saponification of fat**.
Once you have fat necrosis it attract calcium salt to it and the calcium accumulate[30] in the fat.
When you look under the microscope we find dead adipocyte (because there's no nuclei + the cytoplasmic membrane in many areas ruptured) so the patient will have calcifications.



When you have a patient with a chronic abdominal pain and you do a chest X-ray you can find the calcification (because the calcium is very dense).

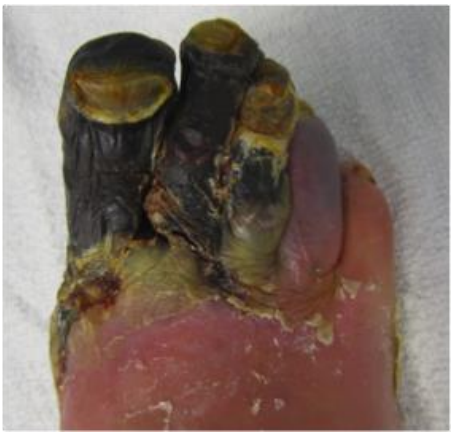
Inflammation of pancreas → necrosis of the pancreatic cells → cell injury → release of lipase and amylase to the blood (this is why you do blood test) and to the abdominal →when it goes to the abdominal it will attract calcium salt→ when you do X-ray you can see the calcium this is will help you in the diagnosis.

Fat necrosis can also be seen in breast fat due to traumatic injury to the fatty tissue.

[30] يتراكم

Final type: Gangrenous necrosis:

1. **Dry gangrene:** Very common in patients who have diabetes mellitus, diabetes increases the incidence of atherosclerosis.



An incident of atherosclerosis à obstruction of the blood vessels à ischemia à hypoxemia à low o_2 coming to the tissues à cell injury, which is irreversibleà the patient comes to you with black fingers (for example) and loss of sensation àthe area infected has to be amputated.

2. **Wet gangrene:** Rare and it occurs in certain circumstances (like war) when an open wound comes in contact with soil.

Caused by gram-positive Clostridia species and this is anaerobe (does not require oxygen for growth) so it needs to produce gas forming bubbles and a very bad smell.
This could be life threatening.

How do I use the information that I got about necrosis to make the diagnosis?

Damage in the organ	Enzymes elevated
Cardiac muscle (myocardium)	Troponin I & Troponin T
Liver (Hepatocytes)	Alanine transaminase (ALT), Aspartate transaminase (AST)
Striated (skeletal) muscles	Creatine Kinase (CK-MM4)
Pancreas	Lipase, Amylase

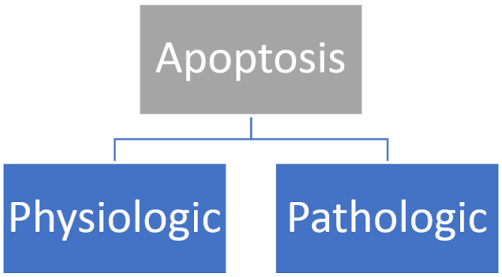
Apoptosis

Apoptosis: is **programmed** cell death.

- Based on activation of specific " death pathway genes"
- The control of apoptosis is important in the process of carcinogenesis[31]

(e.g.: bcl2 oncogenes[32] which switch off apoptosis and allows the neoplastic cells to live indefinitely) bcl2: is an anti apoptotic oncogene located on chromosome 18.

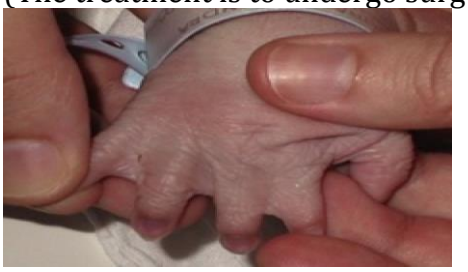
- When a cell undergoes apoptosis for whatever reason, the nucleus and other cell organelles degenerate and form apoptotic bodies. After that, phagocytes swallow these bodies.
- Usually, there is just a single cell undergoing apoptosis; NOT a group of cells or a whole tissue. In addition, no inflammatory reaction is found during apoptosis.



1- Examples of physiologic apoptosis:

a- Programmed death: (death of embryonic cells in the limb buds, (fingers of your hand) leading to the formation of finger and toes if apoptosis doesn't happen then he has a congenital malformation[33] and some of his fingers are stuck together)

(The treatment is to undergo surgery to remove the excessive skin).



b- Predetermined death: (death of cells on the surface of the intestinal mucosa).

c- Hormone- induced cell death: (death of endometrial cells at the end of the menstrual cycle).

- Columnar epithelium is always renewing.
- Cells die (undergo apoptosis) for new cells to come in place.
- When women stop breastfeeding, or take drugs to stop the secretion of milk, apoptosis of the mammary glands will be triggered; therefore no more milk will be produced.
- Endometrial cells undergo apoptosis in females' menstrual cycle.

[31] التسرطن
[32] الجينات المسرطنة
[33] تشوه خلقي

2- Examples of pathologic apoptosis :

a- **Hepatitis virus:** induced liver cells apoptosis (Acidophilic bodies).

b- **Immune injury:** related skin keratinocytes (Civatte bodies) seen in certain skin diseases.

c- **Corticosteroid:** induced atrophy[34] of the neonatal thymus. (Thymus of infants)

- **The Difference between necrosis and apoptosis:**

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling, Bigger)	Reduced (shrink, smaller)
Nucleus	nuclear changes: **karyolysis**, **pyknosis**, **karyorrhexis**	Fragmentation (break down) into nucleosome sized fragments.
Plasma membrane	Disrupted (braked)	Intact (held together), with altered structure, especially the orientation [35](إتجاه) of lipids.
Cellular contents	Digested by enzymes and may leak out of the cell	Intact [36] and may be released in apoptotic bodies.
Adjacent inflammation	Inflammation is usually present	No inflammation
Physiologic or pathologic role	ALWAYS pathologic.	Physiologic most of the time. It may be pathologic in some times especially if there is DNA damage.

[34] ضمور
[35] إتجاه
[36] متماسكه

Intracellular accumulations

Cellular accumulations[37]**:** abnormal substances in the cell they may or may not cause diseases.

There are four kinds of intracellular accumulations:

1- **Glycogen** accumulates in the liver, muscles or kidneys in patients with inborn errors of glycogen metabolism or diabetes mellitus[38].

2- **Fat** accumulates in the liver in patients with **chronic alcoholism**, and who are extremely obese. Also called **steatosis**.

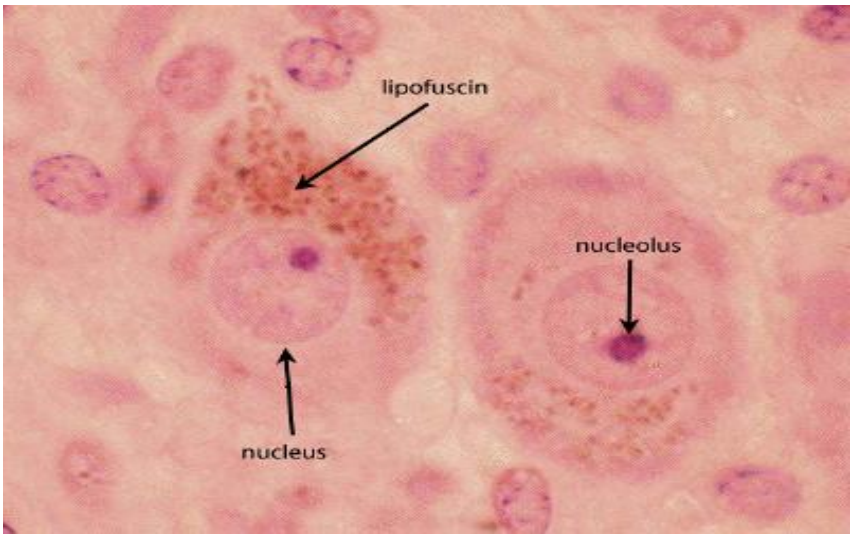
3- **Protein** accumulates in the proximal renal tubules in patients with **proteinuria**[39].

4- **Pigments** are the accumulation of **bilirubin** and **bile** pigments.

Types of pigments:

a. **Lipofuscin** (the aging pigment) (the tear and wear pigment): It looks brown yellowish found in The lysosomes of older people. It is mostly found in the liver & the heart. It is a sign of aging & it is **NOT** pathologic.

If it isn't pathologic why should we know it? To not mix it with other pigments and make wrong diagnosis.

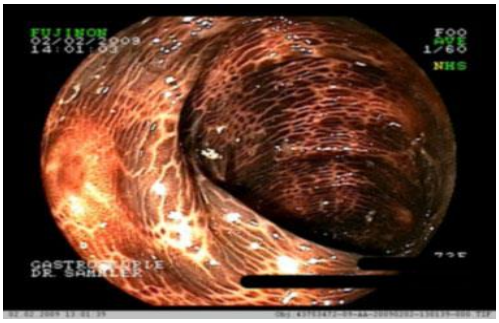


b. **Melanin** is the brown pigment found in the melanocytes and melanomas that gives the dark color to the skin.

Melanosis coli it isn't pathological. It is found in people who have chronic constipation (امساك مزمن), especially if laxatives [40]or purgatives were used. The cells of the colon become black and (melanine like) chemicals are accumulated in the cells of the colon.

- **Don't mix between melanin pigment and Melanosis coli. They are not the same thing.**
  In melanosis coli a pigment which looks very much like melanin is found in the intestines.

[37] تراكم
[38] السكري
[39] بروتينية
[40] مسهلات



c. **Hemosiderin (iron)** the iron-rich brown pigment derived from hemolyzed red blood cells. **Hemochromatosis** is a genetic disorder or ion absorption characterized by the deposition of hemosiderin in the **spleen**, **liver** and **bone marrow.**

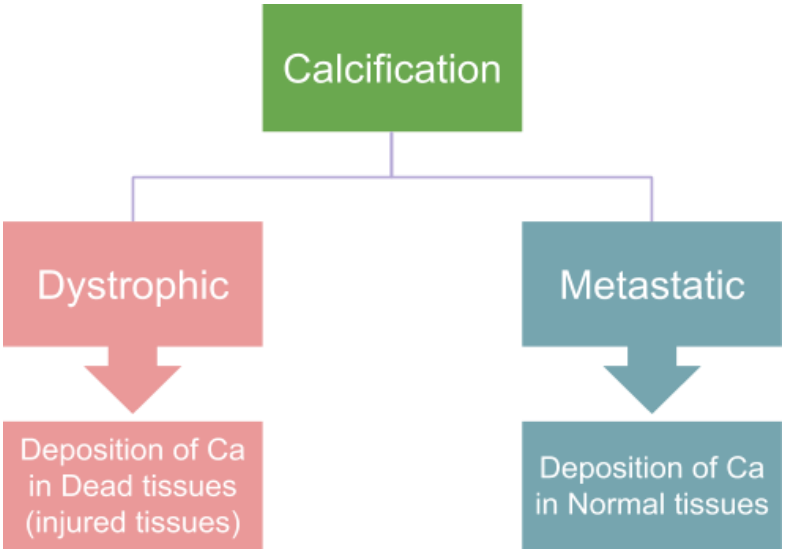
Patients with **cirrhosis**, **diabetes** and **skin discoloration** (**bronzed diabetes**).

There is a fifth kind of pigments caused by **Tattoos (Indian ink)**: Indian ink may be used by tattoo parlors to make a tattoo. This ink is antigen and forms an allergic reaction. It is a foreign chemical. Macrophages engulf the ink but can't digest it. Macrophages stay in the dermis of the skin (2nd layer of the skin). When taking a biopsy, we find macrophages containing blue granules of pigments.

Abnormal Pathologic Calcification

Hypercalcemia: An increase of **Calcium** in the blood.

Calcification: Deposition of **Ca** in the cells and extracellular matrix.

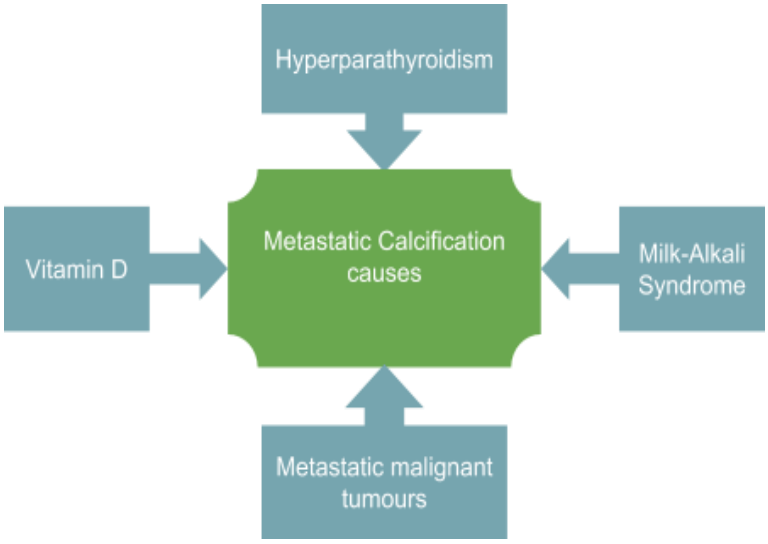


Dystrophic calcification: accumulation of calcium in diseased cells caused by extracellular circulation or interstitial fluid. This process is not associated with Hypercalcemia.

* Dystrophic calcification may happen with normal calcium in the blood.

Metastatic calcification: it is secondary to Hypercalcemia (associated with elevated calcium levels in the blood). It can causes calcification in such inappropriate locations as pulmonary alveolar septa, renal tubules and blood vessels.

Dystrophic Calcification	Metastatic Calcification
Occurs in necrotic tissue	Occurs in normal tissue
Doesn't cause Hypercalcemia	Causes Hypercalcemia



Hypercalcemic disorders that causes Metastatic Calcification:

1) **<u>Hyperparathyroidism</u>**: parathyroid hormone is secreted by parathyroid glands.
   It increases the absorption of calcium from the intestines.
   In hyperparathyroidism, the hormone levels are elevated; which leads to higher levels of calcium in the blood.

   What are the causes of hyperparathyroidism?
   - A disease in the gland (parathyroid hormone): due to a tumor in the gland, or hyperplasia.
   - Secondary parathyroidism: a chronic renal failure makes the body loose lots of calcium with urine, the parathyroid gland is excited to produce more parathyroid hormone.

2) **Metastatic malignant tumor:** A part of a primary tumor has moved (metastasised) to another organ (extension of a tumor). If this organ is the bone, the bone is lysed (broken down) and the blood calcium levels are elevated.
3) **Vitamin D intoxication (hypervitaminosis D) :** vitamin D helps the body to absorb calcium, however, if it is consumed in large quantities it could lead to this condition & the blood calcium levels rise.
4) **Milk Alkali Syndrome**

Note: Mild (little) hypercalcemia can normally occur in older people. But if seen in youngsters, we must know the cause.

* Pancreatitis[41] does NOT necessarily cause hypercalcemia. Pancreatitis may be present with normal calcium levels in the blood.

How does pancreatitis cause dystrophic calcification?

1) After Pancreatitis (pancreatic necrosis),
   pancreatic enzymes (amylase & Lipase) are released in the bloodstream toward the abdomen.
2) Because they are lipolytic enzymes, fat will get digested (fat saponification/fat necrosis)
3) This mechanism will attract Ca to the necrosed area
   which will cause masses of Ca to be deposited in the damaged area
   This is why the Ca in the blood remains normal. (Dystrophic Calcification).
4) Under the X ray, areas of calcium deposits will be found in the abdominal area.

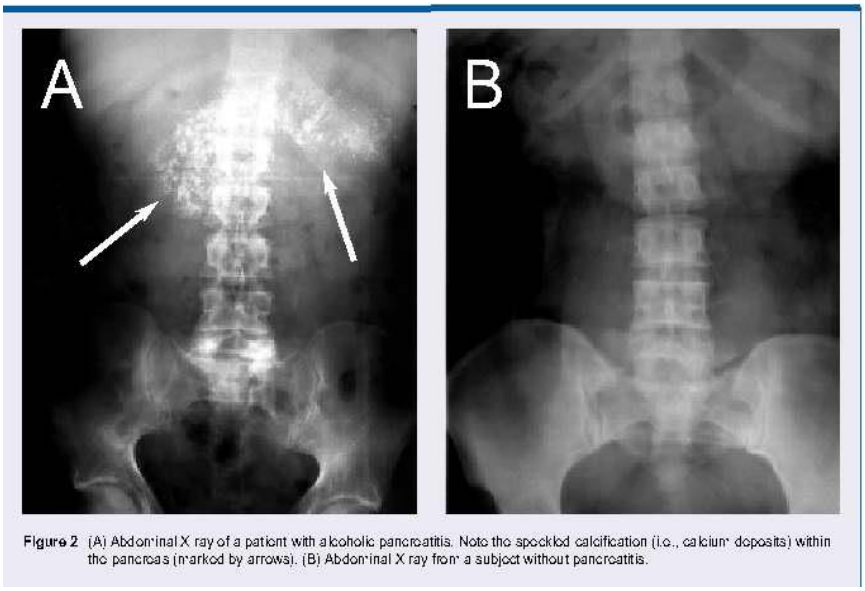


Figure 2 (A) Abdominal X ray of a patient with alcoholic pancreatitis. Note the speckled calcification (i.e., calcium deposits) within the pancreas (marked by arrows). (B) Abdominal X ray from a subject without pancreatitis.

[41] التهاب البنكرياس

Amyloid deposition

[Amyloidosis: what you need to know]

- **What is the amyloid ?**
- It is a *proteinaceous* substance formed from a variety of *polypeptides* and it is an extracellular fibrillar material .
-
- **Where does the amyloid deposition happen ?**
- Between the cells of various tissues .

- **What does the amyloid deposition cause ?**
- It leads to group of clinical conditions collectively known as *amyloidosis* .

Histologic appearance of amyloid

1. BY light microscopy : amyloid appears like *hyaline*[42] *(homogenous* eosinophilic material *)* .
2. Although biochemically *heterogeneous* , all forms of amyloid have the following common features :
   - **A.** Beta pleated sheet structure on x-ray crystallography and infrared spectroscopy .
   - **B.** Beaded fibrillar appearance when stained with congo red dye and examined under polarized microscopic light .

Important clinic forms of amyloidosis

There are two types of amyloidosis : primary and secondary amyloidosis .
The primary amyloidosis is a typical feature of multiple *myeloma* .

	Primary amyloidosis	Secondary amyloidosis
Characterized by deposits of	*AL* amyloid	*AA* amyloid
Source of amyloid	AL amyloid derived from the *immunoglobulin light chain*	AA amyloid derived from *serum amyloid- associated protein*
Site of amyloid deposits	AL amyloid deposits are found in the *kidneys , blood vessels and heart*	AA amyloid deposits are found in the *kidneys , liver and spleen*

NOTE: serum amyloid-associated protein is produced by the liver in chronic inflammatory or autoimmune diseases like :

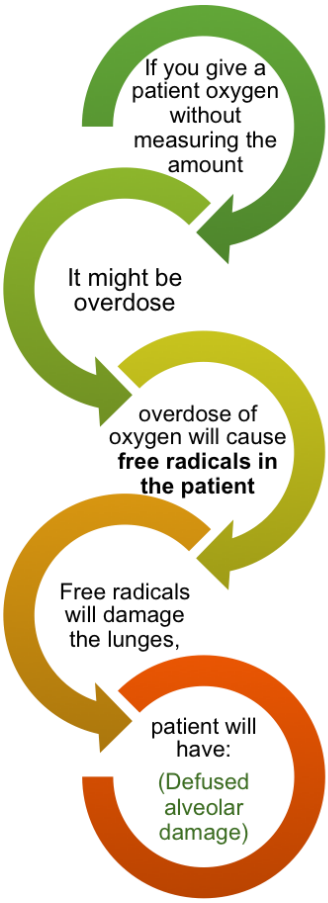
1. Chronic osteomyelitis (التهاب العظم ونقي العظم المزمن)
2. Tuberculosis (السل)
3. Rheumatoid arthritis (التهاب المفاصل الروماتويدي)

The diagnosis of amyloidosis can made ONLY by biopsy.

[42] زجاجي

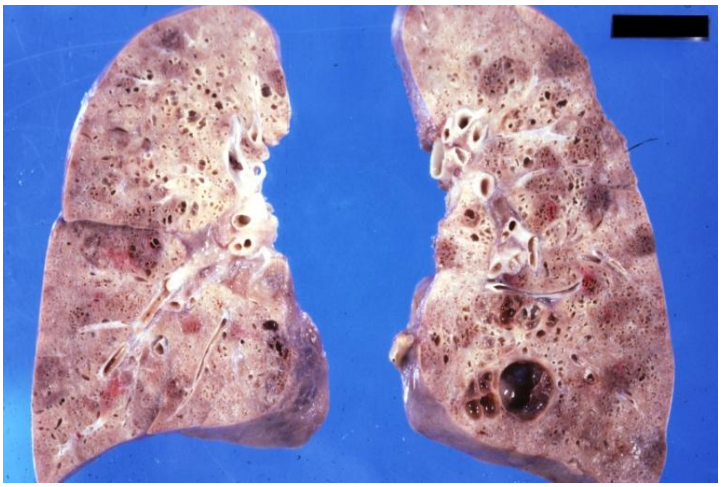
Clinical Cases

Diffuse alveolar damage

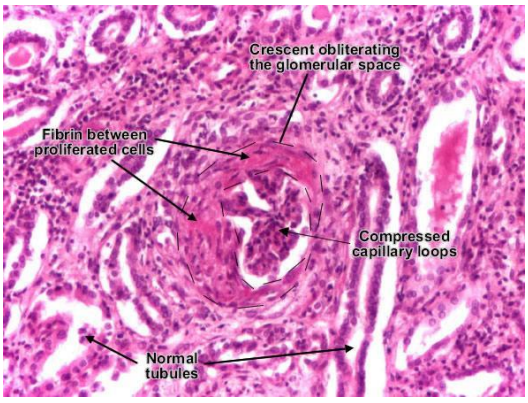


For example: patients that are in the intensive care unit (ICU) and are given oxygen for long periods of time might experience some injuries.

Also when a part of the body is trapped in a crash or something like that, it is very risky to re oxygenate that part of the body; and doctors may cut that part (usually limbs - hand or feet). The injury which might develop in attempt to save that limb is called reperfusion injury.



Glomerulonephritis[43]



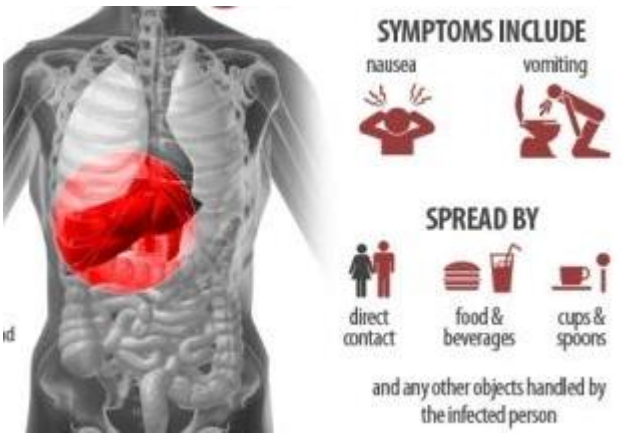
This's a blood vessel taking from the **kidney**, this person has got an **autoimmune disease** so this patient has and immune complex inside his blood (a large molecule consisting of antigens + antibodies bound together) this molecule goes into the circulation, but because it has got a very large molecular weight, it gets entrapped[44] in the

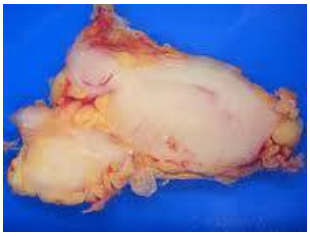
[43] التهاب كبيبات الكلى
[44] يُحبس

walls of the blood vessels, then it creates an inflammatory reaction and this reaction will lead to cell injury and the injury will lead to **Fibrinoid necrosis**.

Hepatitis

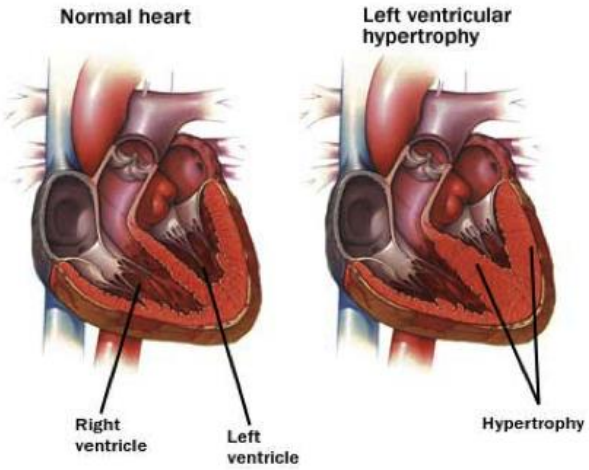
a male has **hepatitis B&C** (التهاب كبد) common in Saudi Arabia
Cause: pathological apoptosis in hepatocytes (liver cells)induced by a virus.





BCL2 gene which is on the chromosome number 18 acts as an anti-apoptotic gene.
In some diseases, there is a malfunction in this gene and tumors form **Follicular Lymphoma**.
Patients always have a lot of BCL2 because it's anti-apoptosis so the cells in the lymph nodes will proliferate[45] above each other's and apoptosis won't happen, resulting **cancer**.

Left Ventricular hypertrophy



A man has hypertension for 20 years, after his death we took a perpendicular section of his heart and found that his left ventricle is very thick (3-4 times). Left ventricular myocardial hypertrophy causes this enlargement of the left ventricular wall.

What is the reason of this left ventricular myocardial hypertrophy?
The hypertension is characterized by the increased of the pressure exercised by the blood on the vessels' walls. The vessel walls would be solid because this disease is usually accompanied with atherosclerosis[46]. This makes the heart work more to pump the blood because there is some resistance from the atherosclerotic blood vessels. When taking an X Ray, we find the heart enlarged and the left ventricle thickened. The next stage (if no medication is taken), the heart can't hypertrophy anymore and there will be heart failure, and can lead to death.

[45] تتكاثر
[46] تصلب الشرايين

How to reduce the hypertension?

1. Reduce weight.
2. Change his lifestyle by being more active.
3. Taking medications (drugs) and these drugs must be taken for a life time.

Benign Prostatic Hyperplasia (BPH)

A normal man goes to the toilet to urinate three to four times a day. This patient goes about 20 times a day. He wakes up at night to urinate. He can't empty his bladder. The prostate of our patient is full of nodules, there is a **benign prostatic hypertrophy** & it is usually associated with hyperplasia[47], which is called **nodular prostatic hyperplasia.** The urethra becomes smaller and the patient has difficulties in micturition (urination). It is very common in men after the age of 50. In this case, the **prolonged effect of testosterone** causes this problem in different levels and different intensities. In very intense cases, the patient can't urinate and we put a catheter (tube) inside his urethra to his urinary bladder and urine passes. The prostate contains glandular epithelium which is surrounded by smooth muscles, drugs may be used to relax the muscles at early stages where there isn't a big problem. At severe stages nothing works and a surgery (TURP) must be done to remove some of the area that is blocking the urethra. (something I forgot to write: a symptom of this problem is that the patient has dribbling when urinating (ينقط البول) this is because his bladder isn't empty yet.

Benign Prostatic Hyperplasia

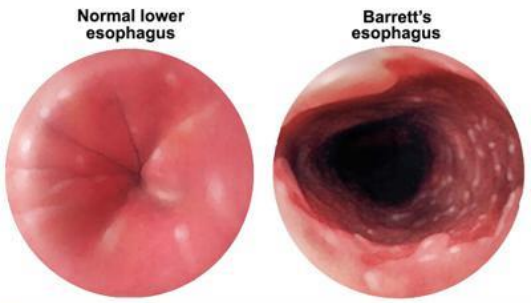
Metaplasia

First Example: A section is taken from the **uterine cervix**[48] of a female. The endocervix is lined by a **glandular epithelium** (in may be columnar or cuboidal) it became **squamous**.

Why? there is an irritation by the chronic inflammation leading to the squamous metaplasia. It is not a disease, it is mostly an adaptive phenomenon. If there are no pre cancerous tumors or dysplasia there isn't a great problem.

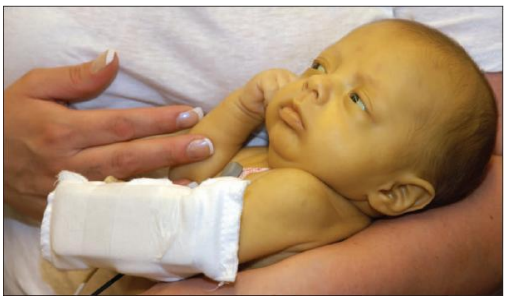
Second Example: squamous metaplasia of the **bronchial mucosa**. This may become dysplasia especially if the irritating factor (such as smoking) is still present. Later this may become a cancerous tumor.

Third Example: **Barrett's esophagus.** (squamous epithelium → glandular epithelium)
in the lower esophagus. Some people may have hyperacidity in the stomach. GERD (Gastroesophageal reflux disease) may happen when eating spicy food and sleeping immediately after it. The juices in the stomach go to the lower esophagus and create a chronic irritation. The esophagus is normally lined by **squamous epithelium**. The squamous epithelium undergoes metaplasia and is changed to glandular epithelium in lower esophagus.



[47] تضخم
[48] عنق الرحم

Jaundice



(Accumulation of bilirubin and bile pigments in the skin and mucosa)

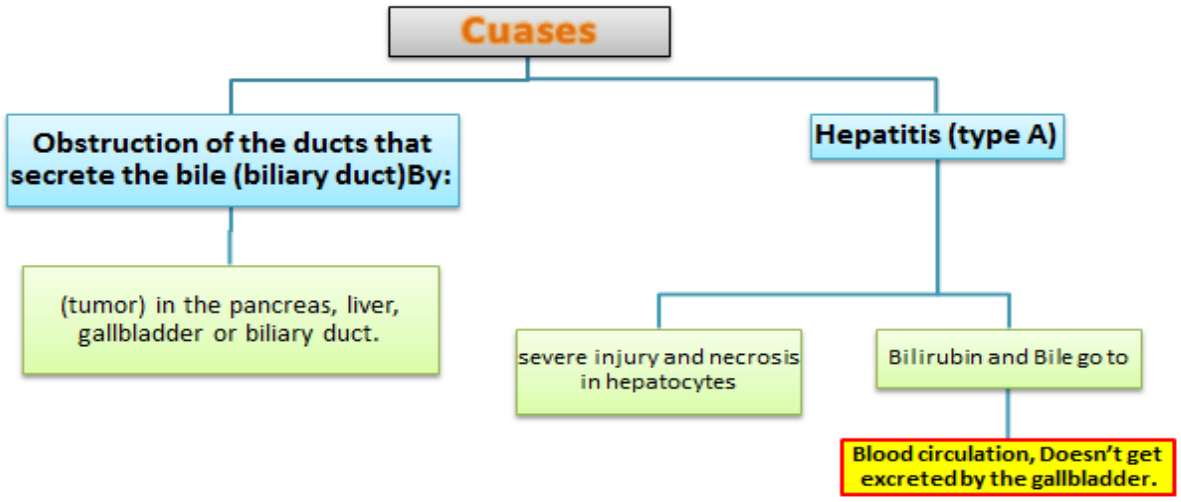
Symptoms:

1. Dark urine (with blood).
2. green yellowish color in the skin.
3. yellowish green in the sclera[49].

What is happening?

something is preventing the bile and bilirubin from going to the large intestines and small intestines and instead it is going to the blood and deposition in the skin.

Diagnose: Jaundice (اليرقان)and in infants is called kernicterus.(غ(اليرقان النووي



So which one is the cause??

A. Enzymes that indicate hepatocytes injury (secreted by the liver): AST & ALT (aspartate and alanine transaminase). If these were high, and the patient is young the case is most probably hepatitis.

B. If the patient is old, has anemia, and has rapid weight loss, the case is most probably an obstructive tumor. We can see it by X-Ray.

[49] The white outer layer of the eyeball.

Hemochromatosis

What is hemochromatosis?

When the patient has:

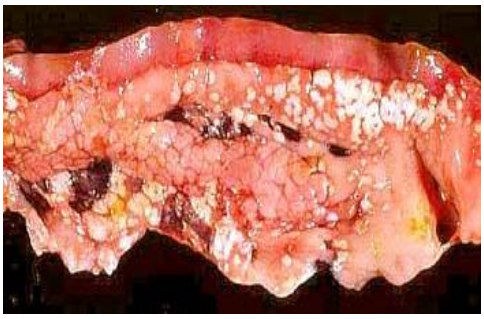
- Skin pigments (face+hands)
- Enlarged liver
- Liver cirrhosis[50]
- Accumulation of iron in the liver
- Iron level in serum is very high

In order to identify iron in the cells ➡ we use pearl stain ➡ iron is colored blue

Diagnosis: Hemochromatosis[51](This disease is rare in KSA).

Causes: mutated gene responsible of the metabolism of iron.
It causes pigmentation, liver cirrhosis, and diabetes.
But, people can have iron overload but for different reasons
When a patient has an inherited disease called sickle cell anemia[52] , which is common in KSA, the patient needs several blood transfusion. This leads to increased amounts of iron in the blood.
In normal cases the excessive iron is stored in the liver, but the patient won't have hemochromatosis.

Pancreatitis



Patient came to the ER suffering from **abdominal pain**, one of the causes of abdominal pain is **pancreatitis** (inflammation in the pancreas) could be acute or chronic.
There are 2 enzymes, which are secreted by the pancreas **lipase** and **amylase** and those are **lipolytic** enzymes (their function is to help in digestion of lipids)

Inflammation → irreversible cell injury → distraction of the cells of the pancreas → the enzymes (amylase + lipase) are released to the blood vessels and to the abdomen (the abdominal cavity always contain fats (**adipocyte:** is the name of the cells that form fat tissues)→ the enzymes (lipolytic enzymes) lyse and digest the fat → saponification of fats (تصبن) → Calcium deposits on this fat (X-Ray shows this) → **fat necrosis.**

- The enzymes in the blood helps us in diagnosis.

How can the doctor make sure that this patient has a pancreatitis?
You should take a blood sample and look for the amount of lipase and amylase if it's raised and he has abdominal pain then he has acute or chronic pancreatitis.

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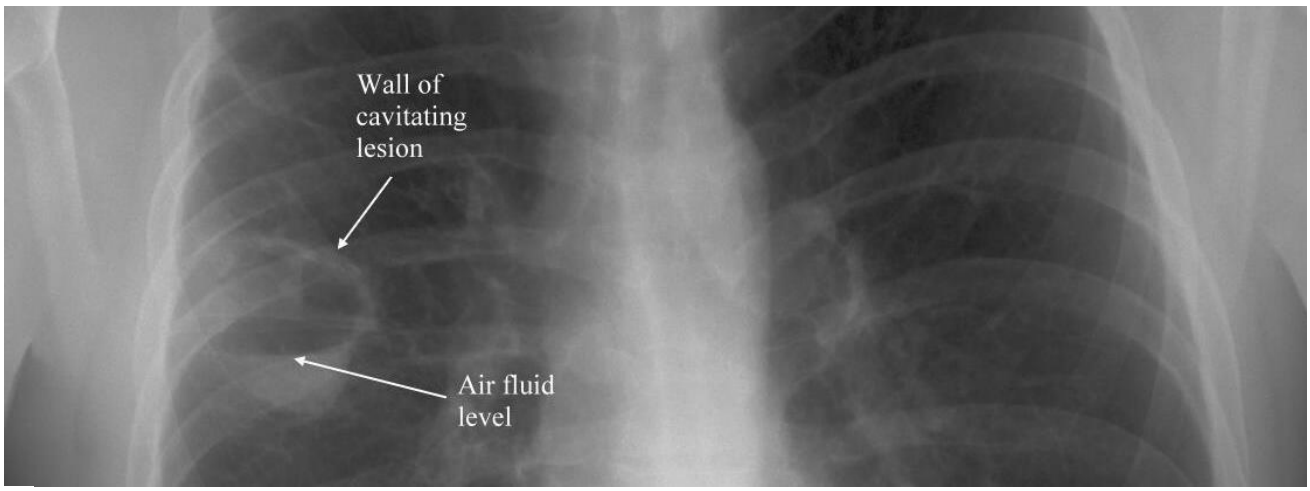
[50] التليف الكبدي
[51] داء ترسب الأصبغة الدموية
[52] فقر الدم المنجلي

Tuberculosis (TB)



[How the body reacts to TB]

Saud is a 19 years old male from Jizan suffering from Fever, Excessive sweating, weight loss and hemoptysis (coughing blood). So what's wrong with him?

Diagnoses: the symptoms shows that he has an **inflammatory condition**, specially that he comes from jizan so the disease is prevalent in that area.
The percentage that the patient has TB (**Tuberculosis**[53]) is **85%** however, we still have to make sure by taking a chest X-ray, **cavitating lesion** in his lung should be present on the picture. A sample of the patient's sputum [54]will show that he has a **mycobacterium** (Tuberculosis bacteria).

[53] السل
[54] المخاط الذي يفرز أثناء الكح من الرئه

Questions

Q1: What is necrosis
Death and degradation of cells from severe environmental insult.

Q2: What is apoptosis?
Programmed cell death.

Q3: What are the six types of necrosis?
Coagulative, Caseous, liquefactive, gangrenous, fibrinoid and fat necrosis.

Q4: What nuclear changes that might take place in necrosis?
1- Pyknosis (Condensation of chromatin).
2- Karyorrhexis (Fragmentation of nucleus).
3- Karyolysis (Lysis of nucleus).

Q5: What are the steps involved in apoptosis?
1- Cell shrinkage.
2- Chromatin condensation.
3- Formation of cytoplasmic blebs and apoptotic bodies.
4- Phagocytosis of apoptotic cells or cell bodies, usually by macrophages.

Q6: What is Steatosis (Fatty Change)?
It is the abnormal accumulation of triglycerides inside parenchymal cells[55].

Q7: What type of necrosis is seen in tuberculosis granulomas?
Caseous necrosis.

Q8: What is pus?
dead cell debris, PMNs, monocyte, lysosomal enzymes in an exudative, purulent soup. It is usually seen in liquefactive necrosis.
PMNs stands for (Polymorphonuclear Neutrophils).

Q9: In which type of necrosis is tissue architecture preserved?
Coagulative necrosis.

Q10: What are the three types of gangrene?
1- Wet gangrene which is associated with liquefactive necrosis.
2- Dry gangrene which is associated with coagulative necrosis.
3- Gas gangrene which is caused by chemical weapons.

Q11: What is the "wear-and-tear" pigment?
Lipofuscin. The breakdown product of lipids which accumulates in the cells of older people as a brown pigment.

Q12: Name three important free radicals.
1- Superoxide O_2 .
2- Hydrogen peroxide (H_2O_2).
3- Hydroxyl group (OH).

Q13: What are the difference between dystrophic and metastatic calcification?
1- Dystrophic: Occurs within diseased tissues, with unknown reason.
2- Metastatic: Occurs within normal tissues because of Hypercalcaemia

[55] The functioning, and important cells of an organ. The main cells.

Q14: How does a free radical cause a cell injury?
By interacting with biochemical reactions within the cell.

Q15:What is the function of melanin?
It gives the skin its dark color and it prevents from UV sun rays damage.

Q16: What is the most common cause of coagulative necrosis?
Ischemia.

Q17: How can you diagnose a patient with myocardial infarction?
1- Increasing in troponin I & T
2- Increasing in CPK-MB

Q18: Where does liquefactive necrosis occur?
In organs that are rich in water.

Q19: Which organ is usually effected by liquefactive necrosis?
The Brain.

Q20: What disease causes caseous necrosis?
Tuberculosis.

Q21: Where does Fibrinoid necrosis take place in?
Blood vessels.

Q22: What enzymes should a physician look for when suspecting pancreatitis?
1-Lipase. 2- Amylase.

Q23: Where does Lipofuscin take place in?
In cardiac muscle, hepatocytes… etc.

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Good Luck!

قال الإمام الشافعي:

"إنما العلم علمان : علم الدين وعلم الدنيا، فالعلم الذي للدين هو الفقه والعلم الذي للدنيا هو الطب"

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