5

Pathology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

DONE BY

Abdulrahem

CONTRIBUTED IN THE SCIENTIFIC CORRECTION

لينا عبد الهادي

CONTRIBUTED IN THE GRAMMATICAL CORRECTION

لينا عبد الهادي

DOCTOR

Dr.Manar Hajeer

In the last lecture we talked about apoptosis, its definition ,types, as well as the differences between apoptosis and necrosis.

❖ The mechanisms of apoptosis:

Two distinct pathways converge on **caspase activation**, which is executive apoptotic enzyme that activates the process of apoptosis: **the mitochondrial pathway** and **the death receptor pathway.**

1) The mitochondrial (intrinsic) pathway seems to be responsible for apoptosis in the most of the physiological and pathological situations.
2) The death receptor pathway (extrinsic pathway): used in limited number of scenarios.

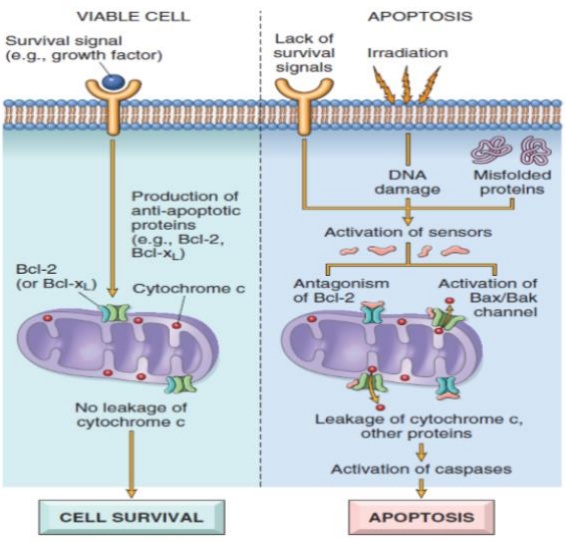
……

✓ The mitochondrial pathway:

- There're many **triggers for cell to die by mitochondrial pathway** of apoptosis, such as:
  1) DNA damage.
  2) Accumulation of misfolded proteins.
  3) Decrease of survival signals (hormonal and growth signals) that reach the cell to maintain it alive.
- When one or more of these triggers happen, a group of sensors inside the cell called **Bcl-2 family proteins** will be activated, but what are these proteins?
- Bcl2 family proteins are composed of:
  1) Sensors (**BH3**).
  2) Proapoptotic proteins (proteins that activate apoptosis) that are located in the mitochondrial membrane (**Bax and Bak**).
  3) Anti-apoptotic proteins that prevent apoptosis (**Bcl-2 and Bcl-x**).
- **The mechanism**:

✓ If there're survival signals, Bcl-2 will be activated, preventing the activation of Bax and Bak.

✓ If there's no survival signals or there is cell damage, BH3 sensors are activated, Bax and Bak are activated, then bax and bak will dimerize forming a channel, allowing the leakage of cytochrome C and other pro-apoptotic proteins to the cytosol. cytochrome C will activate caspase 9, which will activate



executive caspases that will activate the process of apoptosis by activating proteases (breakdown the cytoskeleton of the cell) and endonucleases (breakdown the DNA of the cell), finally the cell will make apoptotic bodies and these apoptotic bodies are engulfed by phagocytes.

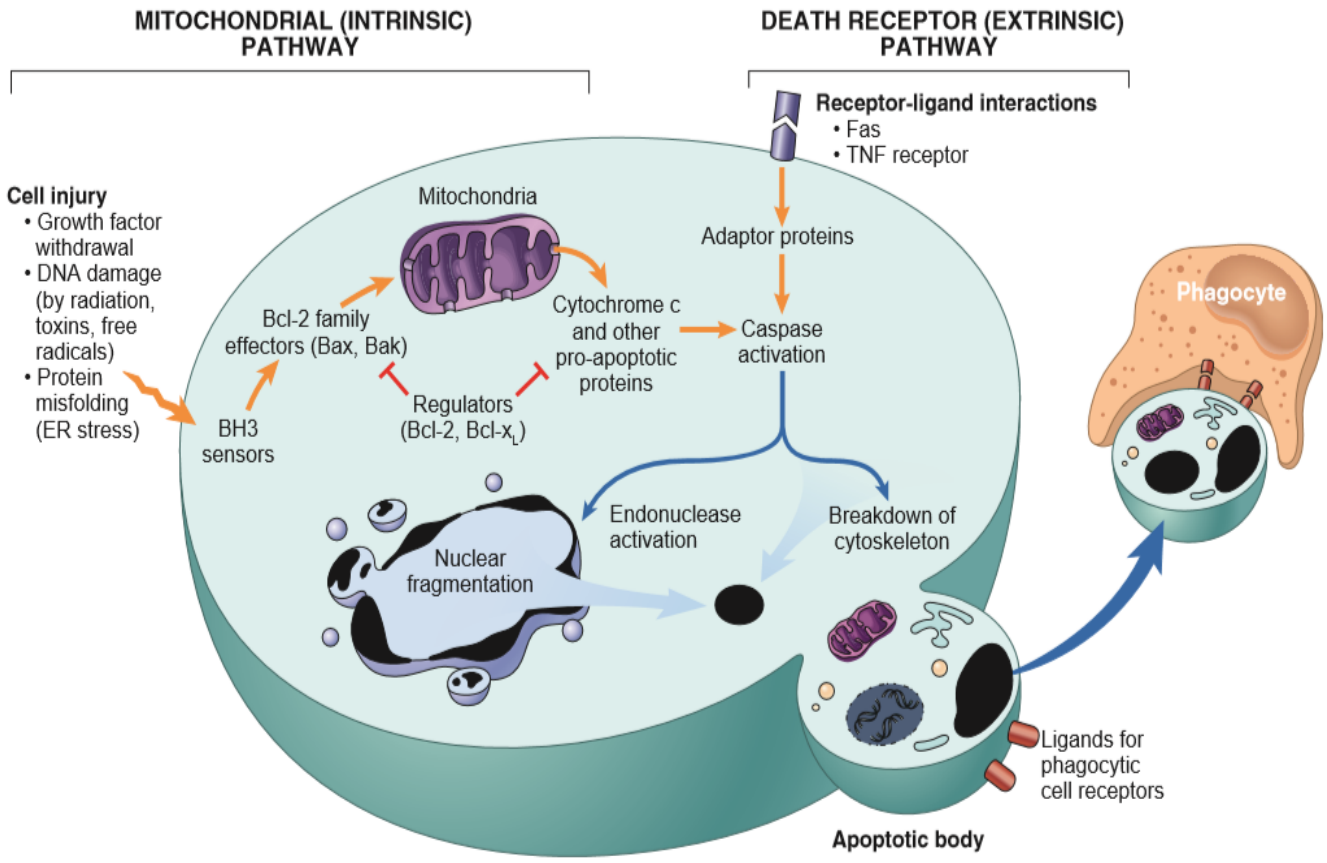


Fig. 2.12 Mechanisms of apoptosis. The two pathways of apoptosis differ in their induction and regulation, and both culminate in the activation of caspases. In the mitochondrial pathway, BH3-only proteins, which are related to members of the Bcl-2 family, sense a lack of survival signals or DNA or protein damage. These BH3-only proteins activate effector molecules that increase mitochondrial permeability. In concert with a deficiency of Bcl-2 and other proteins that maintain mitochondrial permeability, the mitochondria become leaky and various substances, such as cytochrome c, enter the cytosol and activate caspases. Activated caspases induce the changes that culminate in cell death and fragmentation. In the death receptor pathway, signals from plasma membrane receptors lead to the assembly of adaptor proteins into a "death-inducing signaling complex," which activates caspases, and the end result is the same.

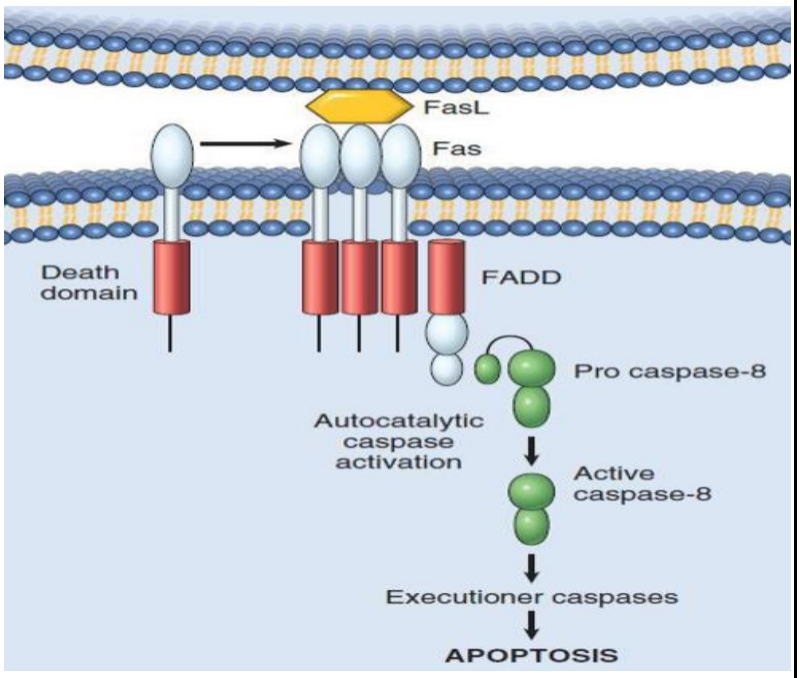
✓ **The death receptor pathway (extrinsic pathway):**

- Family of receptors called **tumor necrosis factor receptors (TNF)** are responsible for this pathway.
- Common examples of these receptors include **type 1 TNF receptor** and **fas**.
- These receptors bind to ligands such as fas ligand (**fas L**) that located on other cells (usually **T cytotoxic lymphocytes**).
- **This pathway is involved in two scenarios:**

1) Self-reacting lymphocytes removal (mentioned in sheet 4).
2) Killing of the target cells by cytotoxic T lymphocytes, these target cells could be virally infected cells or tumor cells (both have fas receptors on their membranes).

- **The mechanism**: when the combination between **fas** (the death receptor) and **fas L** (the ligand) happened, the cytoplasmic **death domain** is activated, then it will activate **caspase 8**.

  Caspase 8 will activate other executive caspases that will activate the breakdown of cytoskeleton (proteases) as well as the breakdown of nucleus (endonucleases).



……

❖ Autophagy:

- Autophagy ("self-eating") refers to lysosomal digestion of the cell's own components.
- It is a survival mechanism in times of nutrient deprivation, so that the starved cell can live by eating its own contents and recycling these contents to provide nutrients and energy.
- When the cell exposes to starvation, it will decrease its size to decrease the consumption of ATP. As a result, the cell will be atrophic.
- It's a survival mechanism(atrophy). If atrophy fails, the cell will die by apoptosis.
- **The mechanism**: a membrane that is derived from the ER engulfs the organelles forming a vacuole called **autophagic vacuole**. This vacuole links to lysosome forming **autophagolysosome** (autophagosome), then the lysosomal

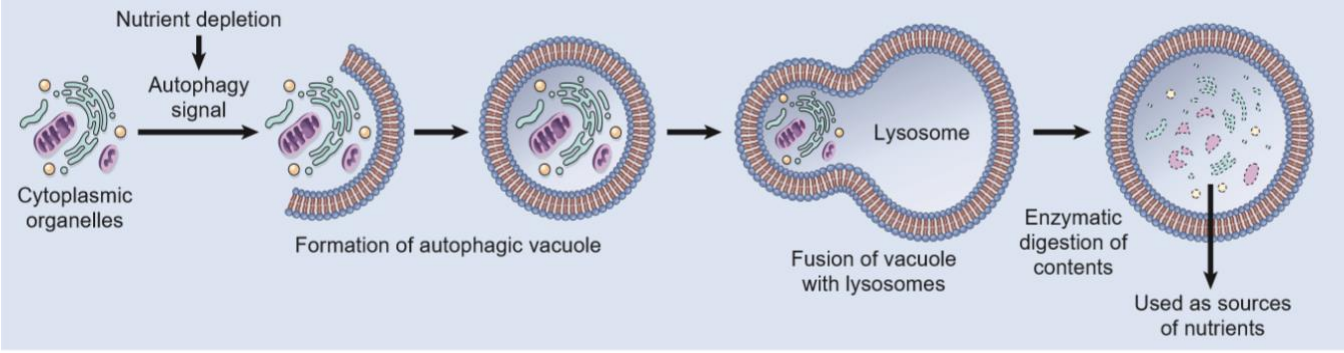


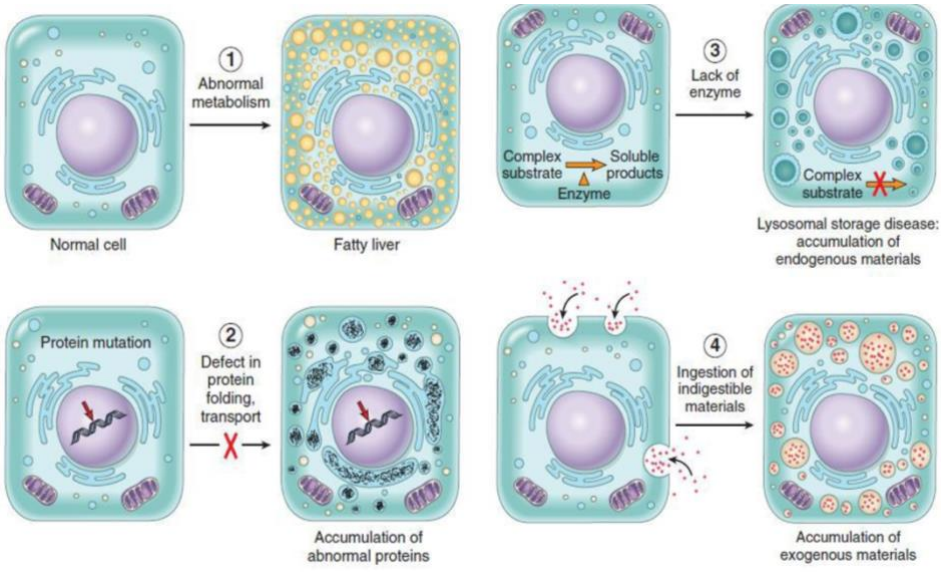
Fig. 2.14 Autophagy. Cellular stresses, such as nutrient deprivation, activate autophagy genes, which initiate the formation of membrane-bound vesicles in which cellular organelles are sequestered. These vesicles fuse with lysosomes, in which the organelles are digested, and the products are used to provide nutrients for the cell. The same process can trigger apoptosis by mechanisms that are not well defined.

enzymes will digest the contents of the cell degrading them. As a result, the cell will shrink, and its size will decrease.

❖ ***Intracellular accumulations:***

- Accumulation and deposition of a material that could be **endogenous** or **exogenous** inside the cell.
- This process gives the cell different appearance and color under the microscope, or even under the naked eye when it happens in certain organs such as skin and sclera of the eye.
- This process happens in four ways:

1) **Inadequate removal of a normal substance**, in this case there's material that normally exists inside the cell, but it accumulates more than usual.
   Example: liver cells secrete the lipids to the outside by linking them to apoproteins, if these apoproteins are absent (e.g. cell injury), deposition of lipids inside the liver cells will happen, this case called **fatty change**.
2) **Accumulation of an abnormal endogenous substance**.
   Example: **alpha1-antitrypsin deficiency disease**: alpha1-antitrypsin is an enzyme normally present inside the cell. In pathological cases, it will be misfolded (abnormal), so it will accumulate inside the cell.
3) **Failure to degrade a metabolite due to inherited enzyme deficiencies**.
   Example: **storage diseases** that could be:
   a) Glycogen storage diseases: glycogen accumulation when there's deficiency in glycogen metabolizing enzymes.
   b) Lysosomal storage diseases: lysosomal enzymes are deficient, so substrates will accumulate inside the cytoplasm.
4) **Deposition and accumulation of an abnormal exogenous substance** (carbon and selica).
   Example: **carbon deposition in the lungs**, especially with smokers and people who are exposed to air pollution. Carbon enters to the body by breathing then it

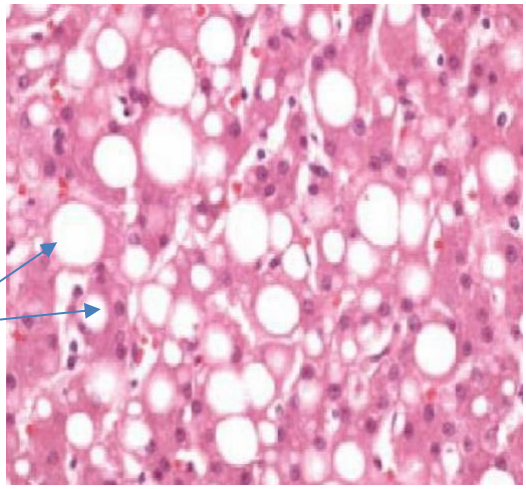


will accumulate inside the lungs.

❖ **Examples on intracellular accumulations**:

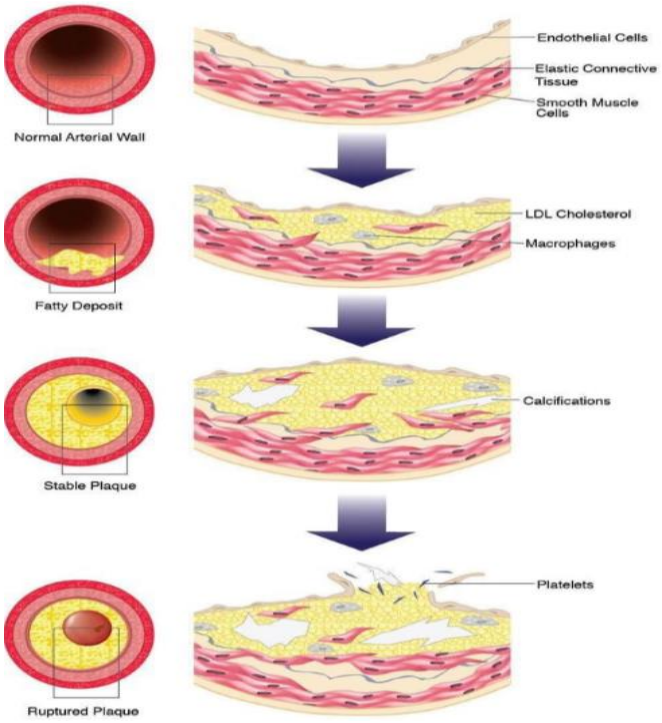
1) **Fatty change (steatosis)**:

- fat is deposited (when there's deficient in its transport) in the organs that do fat metabolism like liver (most common), heart, kidney, and muscle.
- According to its cause, fatty change is divided into alcoholic (by alcohol consumption especially in large amounts), and non-alcoholic (by toxins, protein malnutrition, DM (diabetes mellitus), obesity, anoxia).
- Deposited fat (triglycerides) appears under the microscope as clear vacuoles.
- According to its degree (mild, moderate, and severe), the appearance of the liver under the microscope may be as the appearance of adipose tissue.

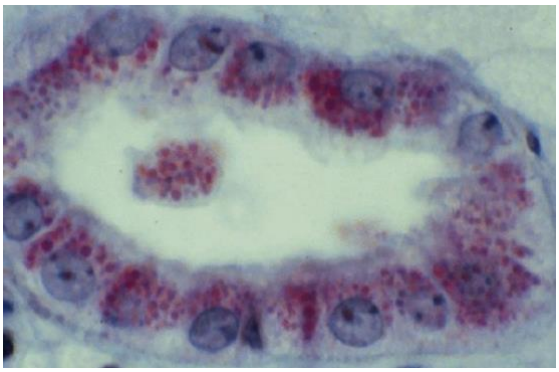


2) **Cholesterol and cholesteryl esters accumulation**:

- The best example is deposition of cholesterol in the wall of the blood vessels (atherosclerosis).
- phagocytic cells may become overloaded with lipid (triglycerides, cholesterol, and cholesteryl esters) in several different pathological processes, mostly characterized by increased intake or decreased catabolism of lipids.



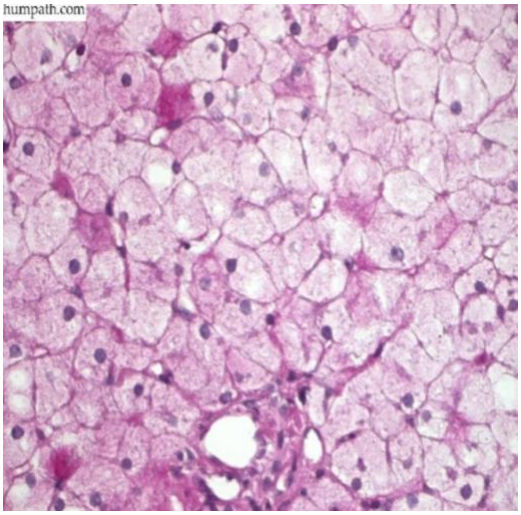
3) **Protein accumulation**: Either excess external or internal synthesis.



- **Nephrotic syndrome**: in this case kidney starts to secrete proteins in the urine, then the body tries to absorb them by kidney tubules, causing protein accumulation (pinkish droplets) in these tubules.
- **Russel bodies**: droplets of proteins (immunoglobulins) inside plasma cells form when there's inflammation or infection.
- Hyaline protein material is deposited in the liver cells (**Alcoholic hyaline in liver**).
- **Neurofibrillary tangles in neurons** (in the case of ischemia).

  *** details aren't required.**

4) **Glycogen accumulation**:

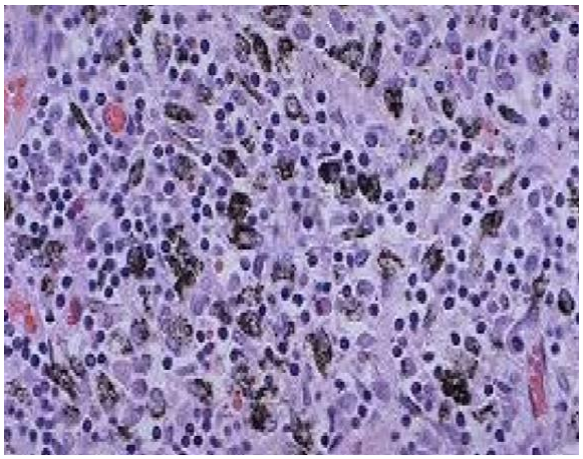


- It's an example of **glycogen storage diseases**.
- Lead to dysfunction of hepatocytes.
- Abnormality in glucose or glycogen metabolism.
- The best example is diabetes mellitus (**DM**).
- It could be in liver, renal tubules, heart, and B cells of pancreas.
- This picture is from the liver, in the picture hepatocytes are less pinkish and swollen.
- If we use a special stain, we will notice the deposited glycogen inside the cells better.

5) **Pigments accumulation**:

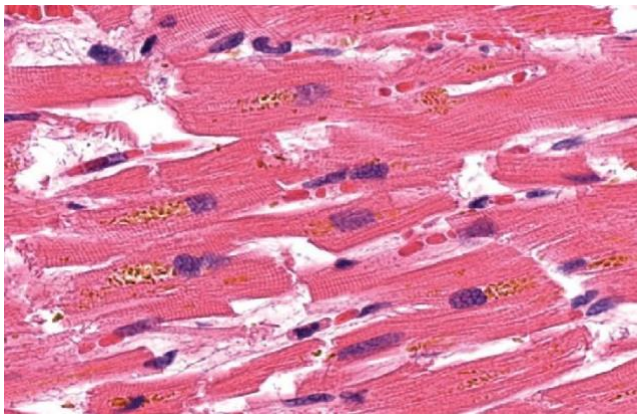
- Pigments could be exogenous or endogenous.

A. **Carbon accumulation (anthracosis)**:



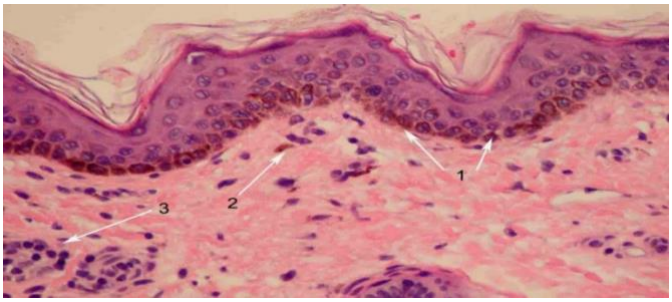
- The most common example of **exogenous** is carbon (coal dust, air pollution) that is inhaled by **smokers** or people who are exposed to polluted air.
- carbon enters the lungs, then it is engulfed by **macrophages** and go to **lymphatics** which will deposit carbon in the **lymph nodes**. (Alveolar macrophages → lymphatic channels → tracheobronchial LN).
- Hence in the picture, There's black discoloration due to carbon deposition.

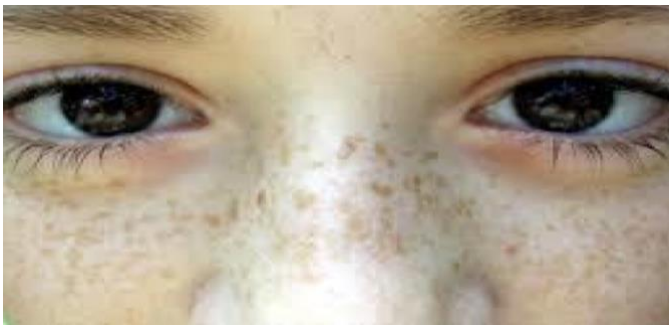
B. **Lipofuscin**: (wear and tear pigment)



- It is an **Endogenous** pigment happens when there's previous damage, especially free radical induced damage (Marker of past free radical injury).
- This previous damage leads to damage in lipids and proteins of the cell membrane converting them to lipofuscin pigment (brown).
- It is deposited also in the case of atrophy, so we call it "**brown atrophy**".
- If there's high deposition, the whole organ will be brown.
- Any previous insult to the cell (e.g. atrophy or injury) induced the deposition of its lipids and proteins will lead to appearance of lipofuscin pigment.
- It can be deposited in **heart**, **liver**, **brain**, and **skeletal muscle** (as in the picture).
- When we see brown pigment, we should know its type because there is more than one pigment gives me brown color such as **lipofuscin** and **iron**.
- It doesn't affect the function of the tissue (there's not clinically significant) except when it is accompanied by **atrophy**.

C. **Melanin**:

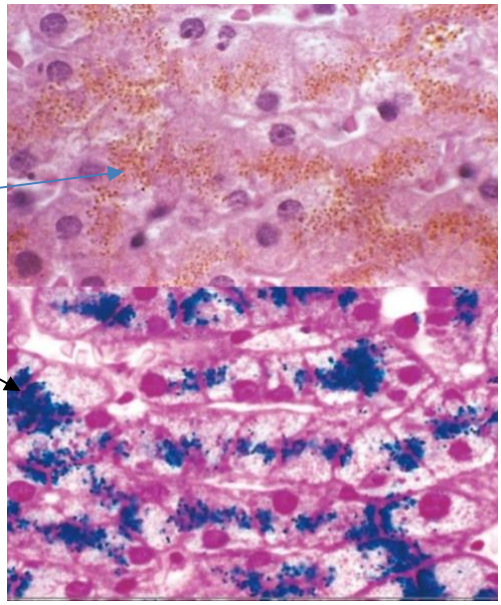




- It is a pigment that is produced by **melanocytes** in the skin. Sometimes, with fair skin people, deposition of melanin in higher amounts happens, resulting in the appearance of **freckles** especially on the face and dorsal of hands.
- Freckles: sun-mediated skin injury, appears as small dark spots on the sun exposed skin due to increase melanin production in the skin.

D. **Hemosiderin (iron deposition)**:

- It is derived from hemoglobin.
- If there's destruction in RBCs (in hemoglobin), there will be deposition of iron.
- It could be **physiological** in some organs that are active in the turnover of RBCs such as **spleen**, **liver**, and **bone marrow**.
- Iron +apoferritin==ferritin micelles.



- There's permanent deposition of iron in the bone marrow (because some cells are dying before they escape), this iron is removed by phagocytes, so the body uses it again to produce hemoglobin.
- Under the microscope, iron is brown, but if we use special iron stain (Prussian iron stain), it will be blue (to distinguish between iron and lipofuscin).
- It could be **pathological** as in the case of bruises (localized deposition).
  Example: when your arm hits a solid body, its color will change from red to blue, then it will be yellow (or brown) as a result of iron deposition, this yellowish color will disappear when phagocytes ingulf the iron and recycle it.
- **Hemosiderosis**: is a generalized deposition all over the body (liver, pancreas, heart, skin, ……) in diseased cases, where the deposition is so high, and it may lead to organ failure.
  Examples include **hemochromatosis**, **hemolytic anemias**, and **repeated blood transfusions**.

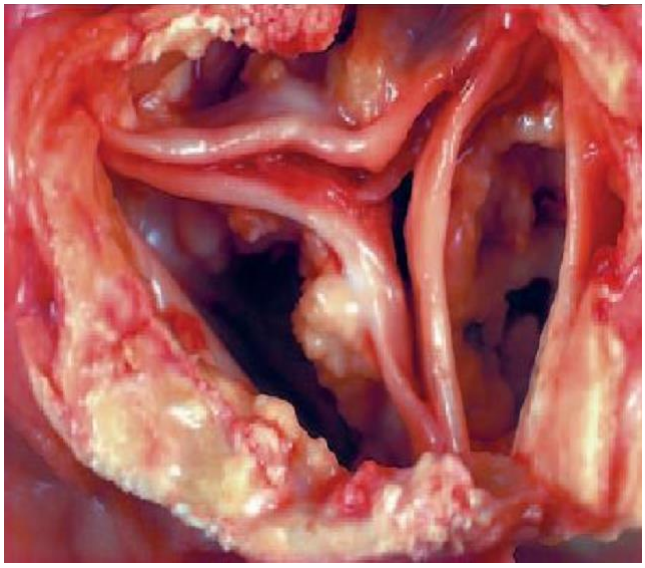
❖ **Pathologic calcification:**

- Abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals.
- Its degree differs according to the amount of calcified calcium.
- It is divided into**:** Dystrophic Calcification and Metastatic Calcification.

1. Dystrophic Calcification:

- Deposition of calcium in dead tissues (due to tissues death!!).
- The degree of calcium in the blood is **usually** normal (there's no hypercalcemia).
- The degree of calcification determines the consequences of it:

- **High**: the patient may get heart failure.
- **Low**: there's previous necrosis responsible for consequences.



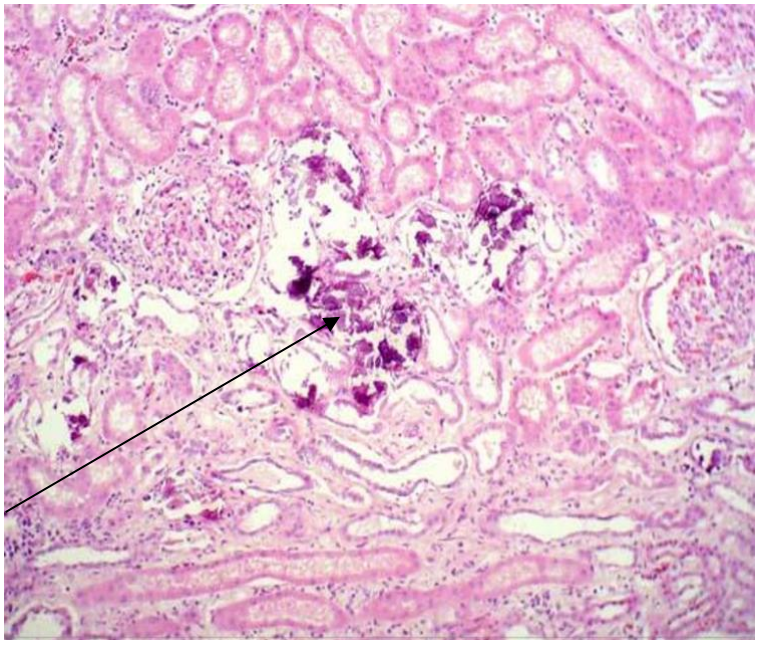
- Examples: **fat necrosis** (in saponification), **atherosclerosis** (calcium is deposited in atherosclerotic blood vessels), **damaged heart valves** (due to aging), **aortic stenosis**, and cases accompanied with inflammation such as **tuberculosis**.

2. Metastatic Calcification:

- This form is associated with hypercalcemia and can occur in normal tissues.
- The most common tissues are blood vessels, kidney (nephrocalcinosis), and lungs.
- Its causes: hyperparathyroidism (primary or secondary (renal failure)), vitamin D intoxication, sarcoidosis, and bone destruction.
- Renal failure gets feedback to parathyroid gland resulting in increasing of parathyroid hormones, leading to secondary hyperparathyroidism.

- bone destruction includes:
  a) **metastasis** to the bone from a malignant tumor anywhere in the body.
  b) **MM**: multiple myeloma.
  c) **Leukemia**.
  d) **Paget's** disease of the bone (benign disease).
  e) **Immobilization**.

  * this picture is from the kidney, calcium appears in purple.



Good luck…