INTRACELLULAR ACCUMULATIONS

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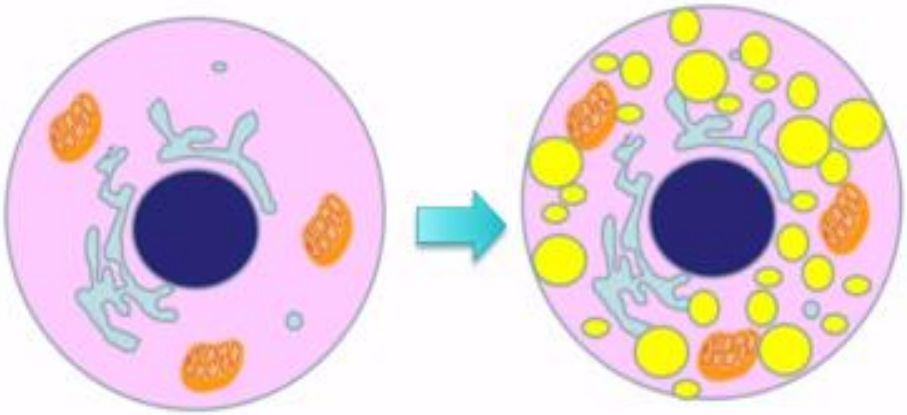
بسم الله الرحمن الرحيم


لاَ يُكَلِّفُ اللهُ نَفْسًا إِلاَّ وُسْعَهَا
ALLAH DOES NOT BURDEN A SOUL BEYOND THAT IT CAN BEAR
Surah Baqarah | Verse 286

Learning objectives:

- By the end of this lecture you should be able;
- To describe intracellular accumulations
- To enumerate different types of intracellular accumulations
- Discuss important intracellular accumulations

What are intracellular accumulations?



INTRACELLULAR ACCUMULATIONS

- Sometimes cells may accumulate abnormal amounts of various substances, which may be harmless or associated with some injury.
- The substances may be located in the cytoplasm or within organelles (typically lysosomes) and nucleus.

- Substance may be synthesized by the affected cells or may be produced elsewhere i.e. may be

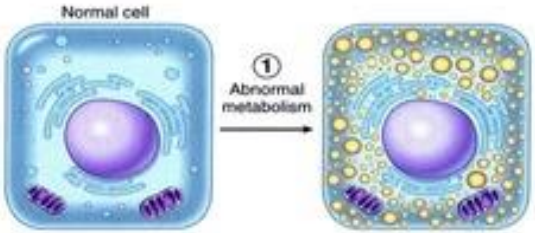
1. Endogenous
2. Exogenous

- Main mechanisms of intracellular accumulations are;

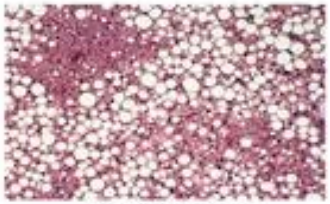
a. Inadequate removal of endogenous substance (defects in packaging and transport)

b. Failure to degrade a metabolite due to inherited enzyme deficiencies (storage diseases)
c. Excessive production of an endogenous substance
d. Deposition of an abnormal exogenous material

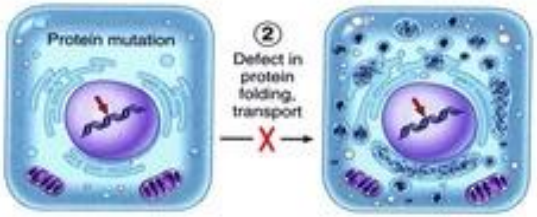
Most accumulations are attributable to four types of abnormalities:



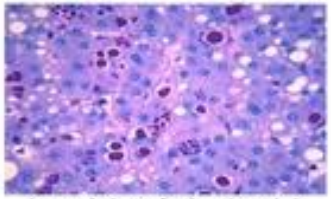
A normal endogenous substance is produced at a normal rate, but the rate of metabolism is inadequate to remove it.
Example: fatty change in the liver.



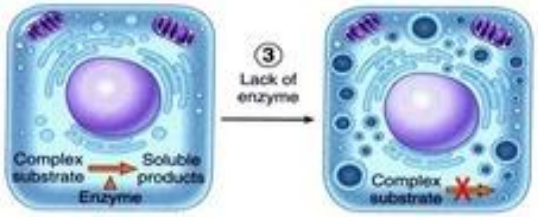
Steatosis (fatty liver)



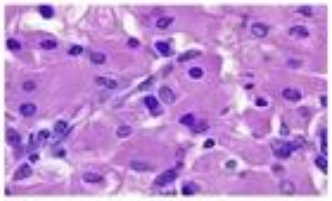
An abnormal endogenous substance, typically the product of a mutated gene, accumulates because of defects in protein folding and transport and an inability to degrade the abnormal protein efficiently.
Example: accumulation of mutated α1-antitrypsin in liver cells.



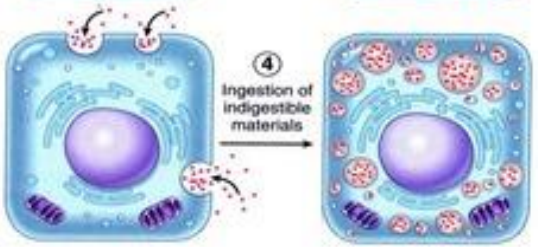
Accumulations of α-1-antitrypsin in liver cells



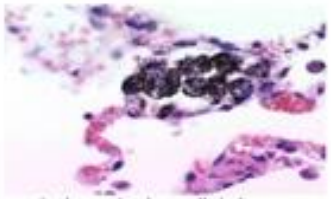
A normal endogenous substance accumulates because of defects, usually inherited, in enzymes that are required for the metabolism of the substance.
Example: lysosomal storage disease.



Gaucher disease



An abnormal exogenous substance is deposited and accumulates because the cell does not have the machinery to degrade it.
Example: accumulation of carbon particles, accumulation of silica or asbestos particles.



Anthracosis: dust cells in lung

- Selected intracellular accumulations include;

A. Endogenous accumulations:

1. Triglycerides
2. Cholesterol esters
3. Proteins
4. Pigments
5. Glycogen
6. Hemosiderin and Ferritin

B. Exogenous accumulations:

1. Anthracotic pigment (Coal or carbon pigment)
2. Lead

1. Triglyceride accumulation (Fatty change):

- Fatty change or steatosis is accumulation of triglycerides/neutral fats within cells of an organ. Especially common in liver but can occur in other organs like

  a. Heart

  b. Skeletal muscles

  c. Kidneys

- Men and women equally affected.
- Steatosis is associated with hepatitis and future development of liver cirrhosis.
- Steatosis may be Alcoholic or non-Alcoholic.
- Risk factor for alcoholic steatosis is alcohol consumption.
- While risk factors for non-alcoholic steatosis are:

1. Toxins in form of Carbon tetrachloride (CCl_4)
2. Protein malnutrition
3. Obesity
4. Diabetes/ Insulin resistance
5. Hypoxia
6. Hyperlipidemias or Dyslipidemias

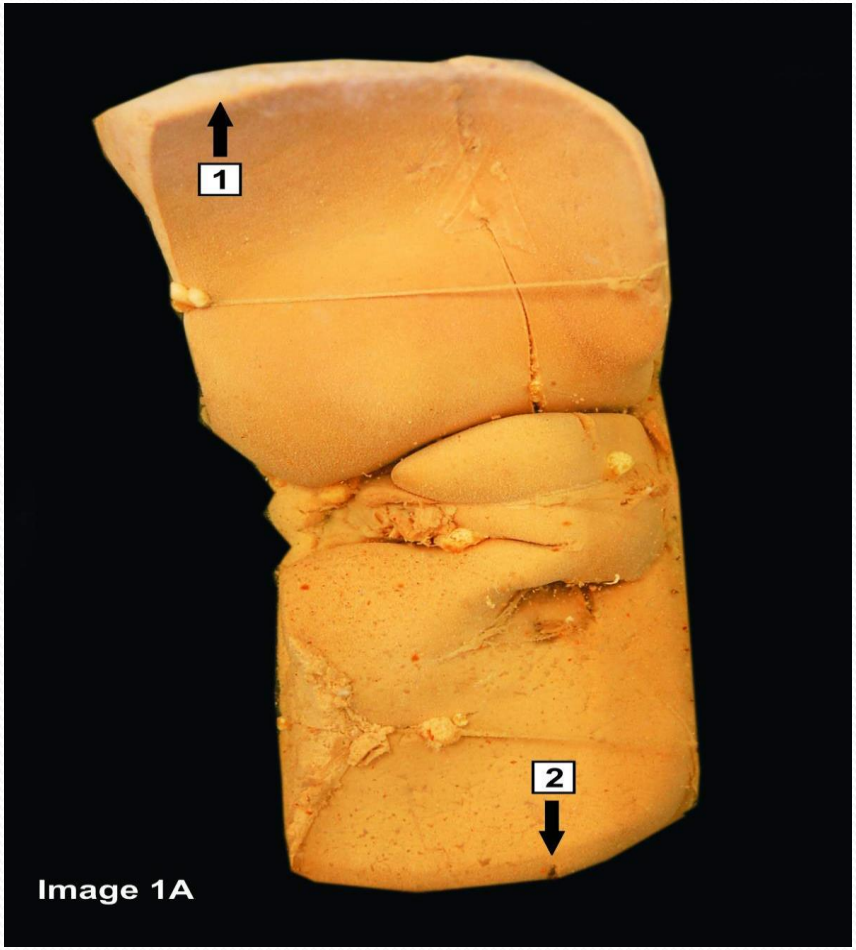
- **Morphology:**
- **Grossly** organ (liver) is larger than normal.
- Losses it sharp margins
- Becomes pale yellow
- Greasy on touch
- **Histologically** two patterns of fats deposition are seen.

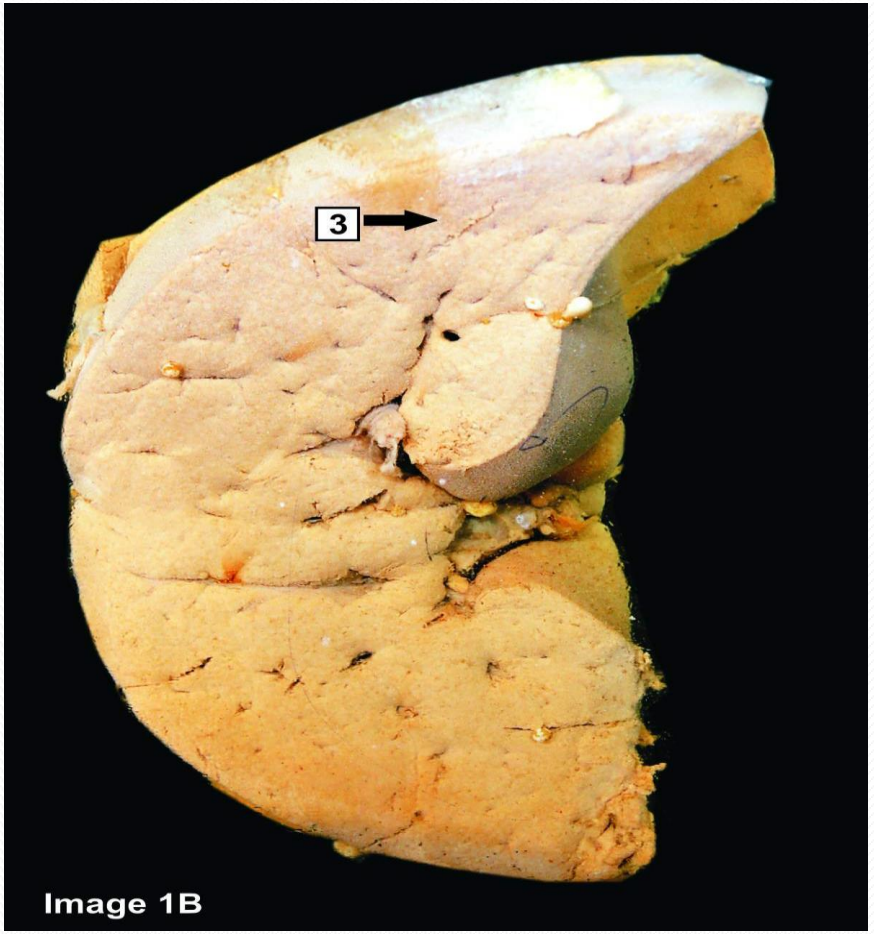
1. At the beginning, the hepatocytes contain small fat vacuoles (liposomes) around the nucleus **(microvesicular) fatty change.**

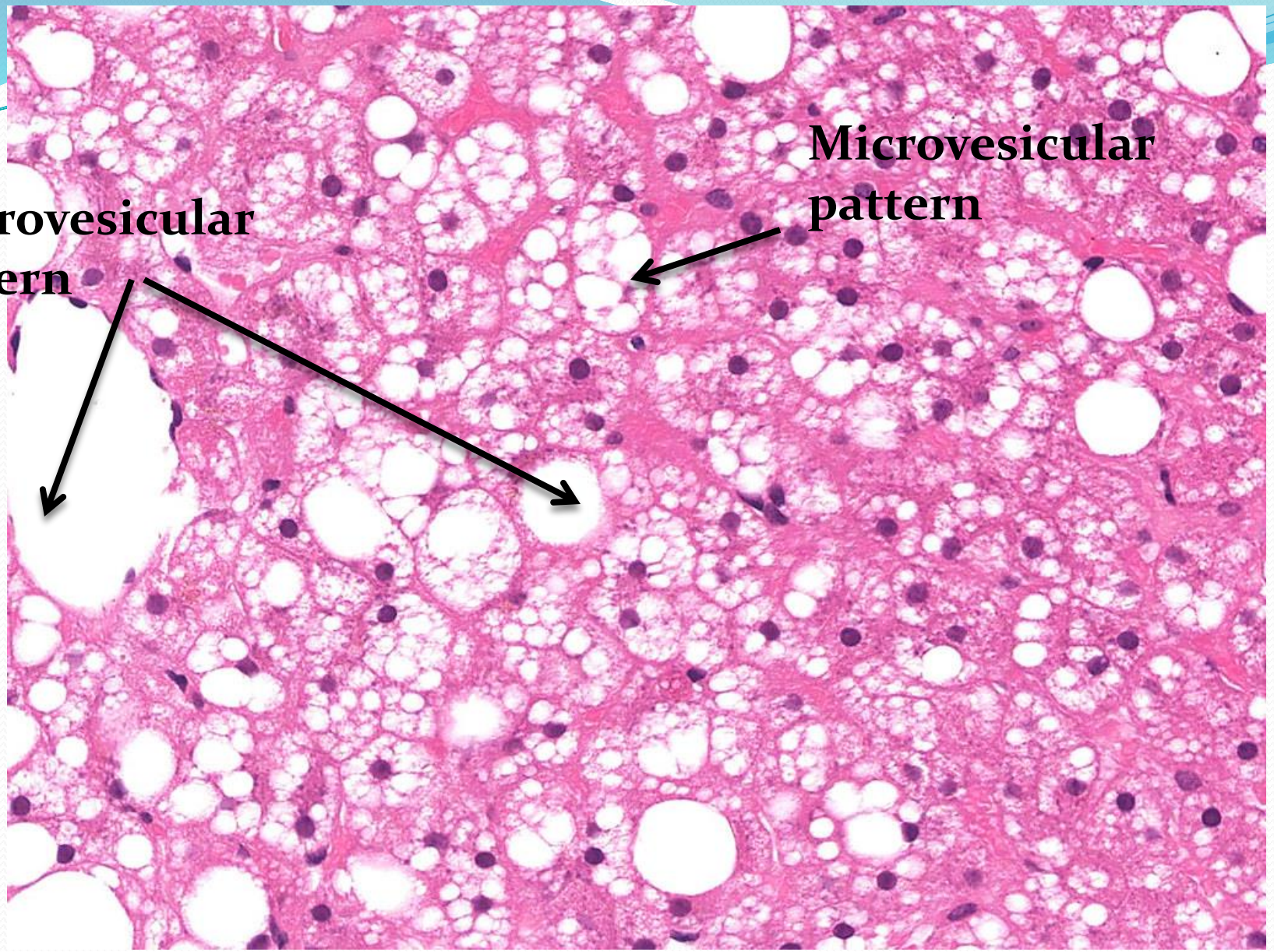
2. In the late stages, the size of the vacuoles increases pushing the nucleus to the periphery of the cell giving characteristic signet ring appearance (macrovesicular) fatty change.

Fatty liver:

The organ is enlarged (normal weight M: 1400-1600 gm, F 1200-1400 gm). There are(1) rounded margins (2) and pale yellow colour. (3) greasy to touch.

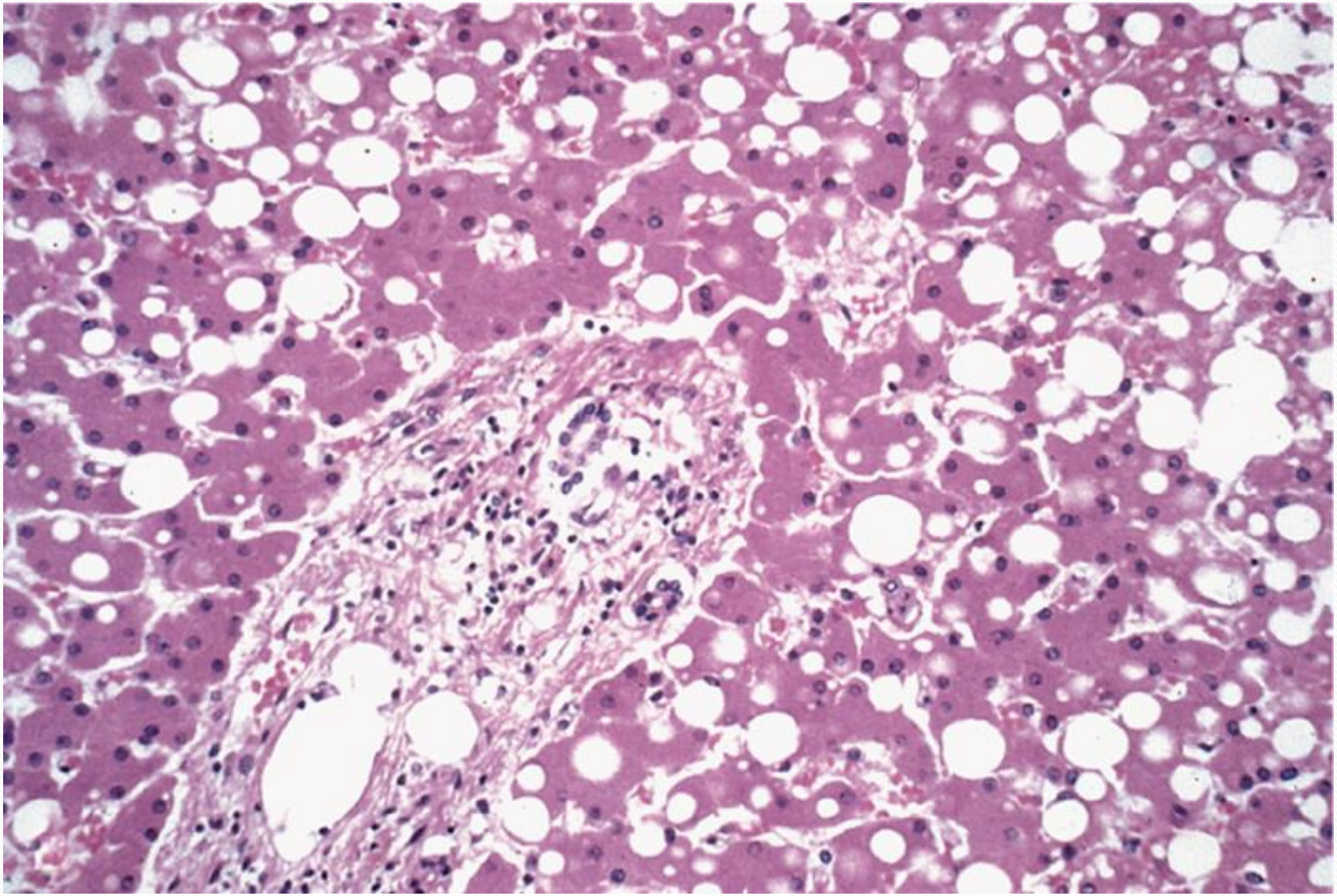


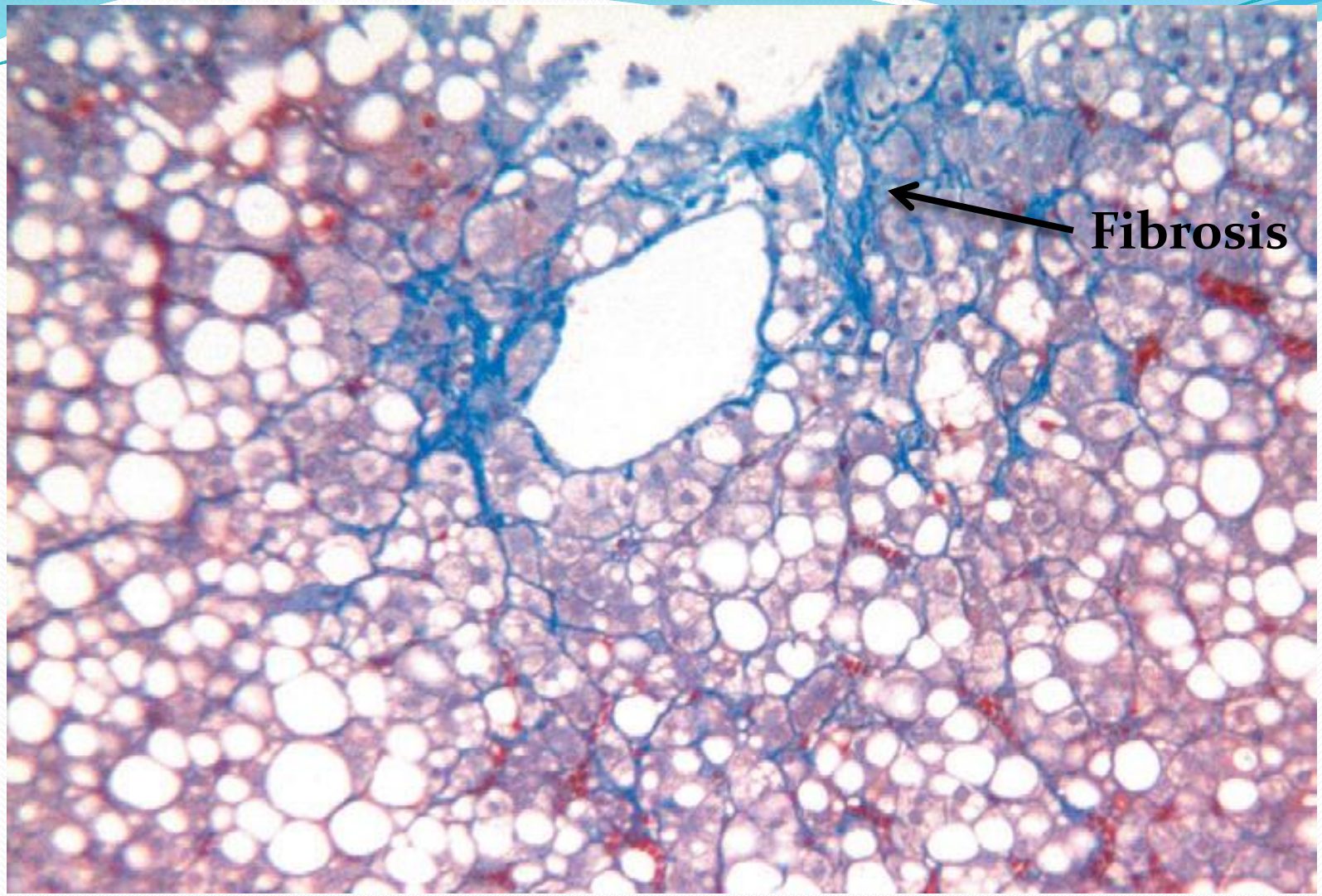




Microvesicular and Macrovesicular Steatosis

Fatty change liver showing adipocytes turned into fat vacuoles. Nuclei pushed to side giving signet ring appearance to the cells



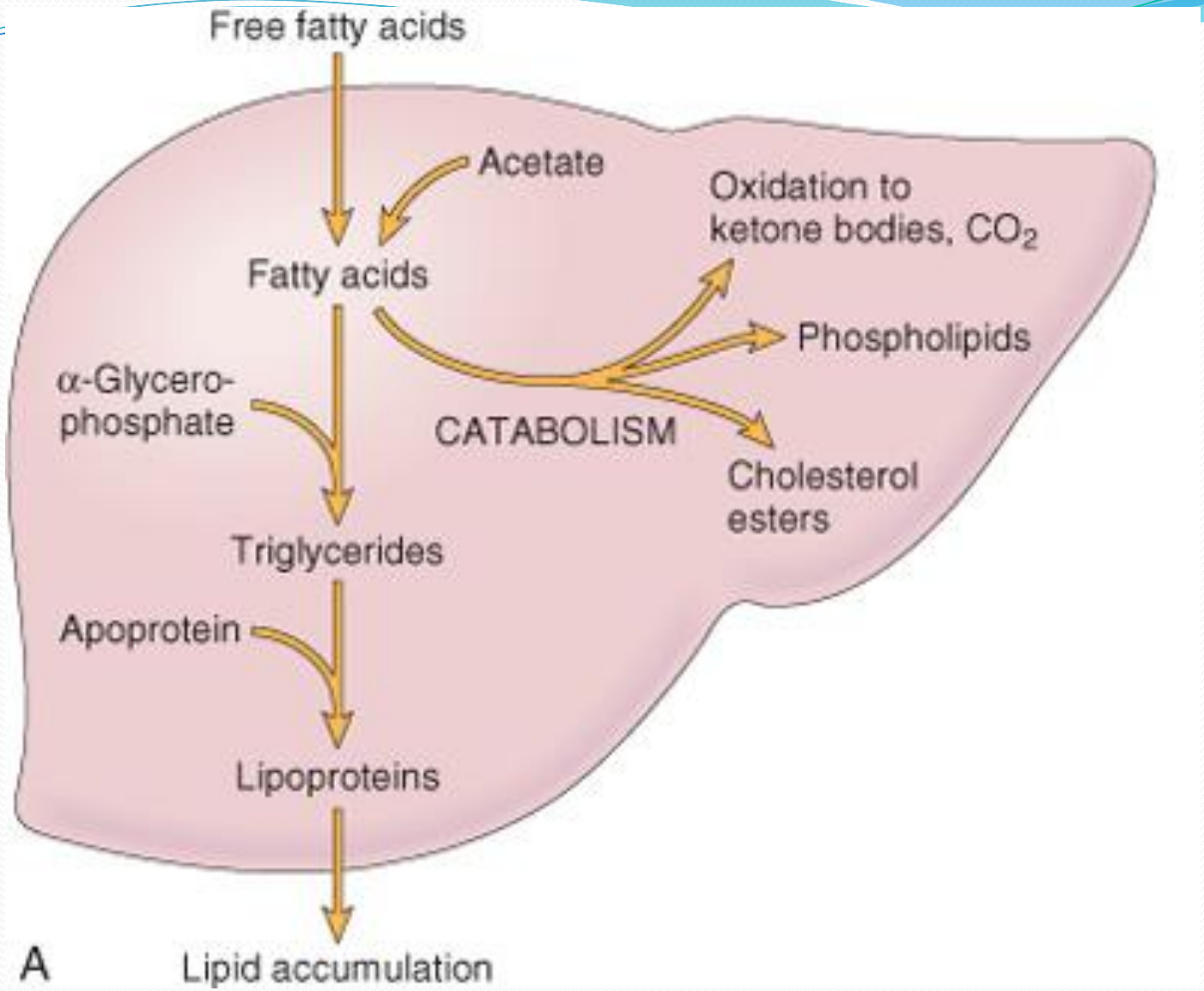


Macrovesicular steatosis

Pathogenesis:

- Defects in fat metabolism are responsible for pathogenesis of FLD. Free fatty acids from adipose tissue or ingested fats are transported to hepatocytes where they are converted into

1. Cholesterol esters
2. Phospholipids
3. Triglycerides
4. Ketone bodies after oxidation


Free fatty acids
Acetate
Oxidation to ketone bodies, CO_2
Fatty acids
Phospholipids
α-Glycero-phosphate
CATABOLISM
Cholesterol esters
Triglycerides
Apoprotein
Lipoproteins
A
Lipid accumulation

- Some FFA is synthesized from acetate in the hepatocytes.

  Triglycerides then bind with apoproteins to form lipoproteins which then leave the hepatocytes.

  Excess accumulation of triglycerides occurs due to defect at any step from entry of FFA to the exit of triglycerides.

1. If we look at the causes of fatty change

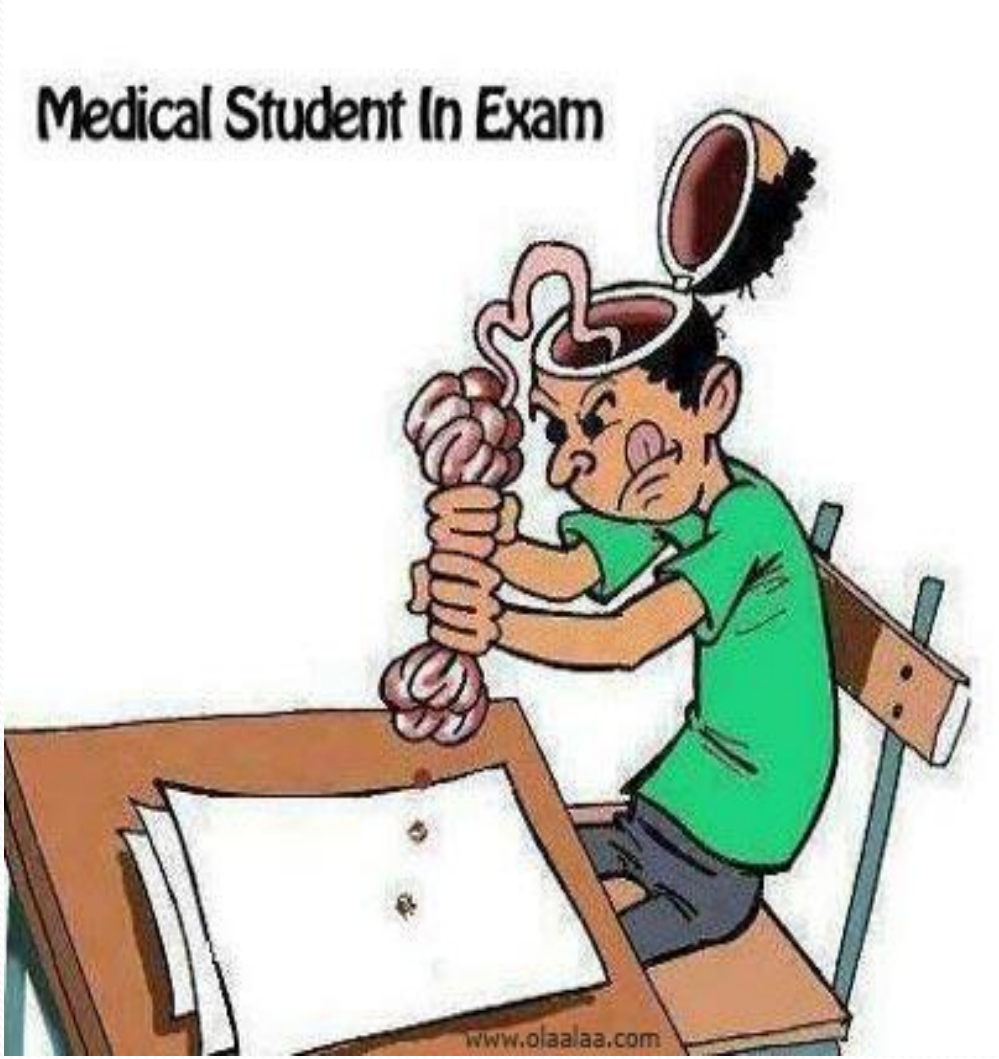
   Alcohol inhibits fatty acid oxidation and favors their synthesis thus leads to fat accumulation.

2. Protein malnutrition decreases the synthesis of apoproteins.
3. CCl_4 inhibits apoprotein synthesis.
4. Hypoxia inhibits fatty acid oxidation

5. Diabetes and insulin resistance associated with high level of triglycerides.

- It is supposed that both these conditions cause increased mobilization of fatty acids and glucose to liver.

5. Obesity is associated with hypertriglyceridaemia. Shares almost same mechanism responsible for diabetes.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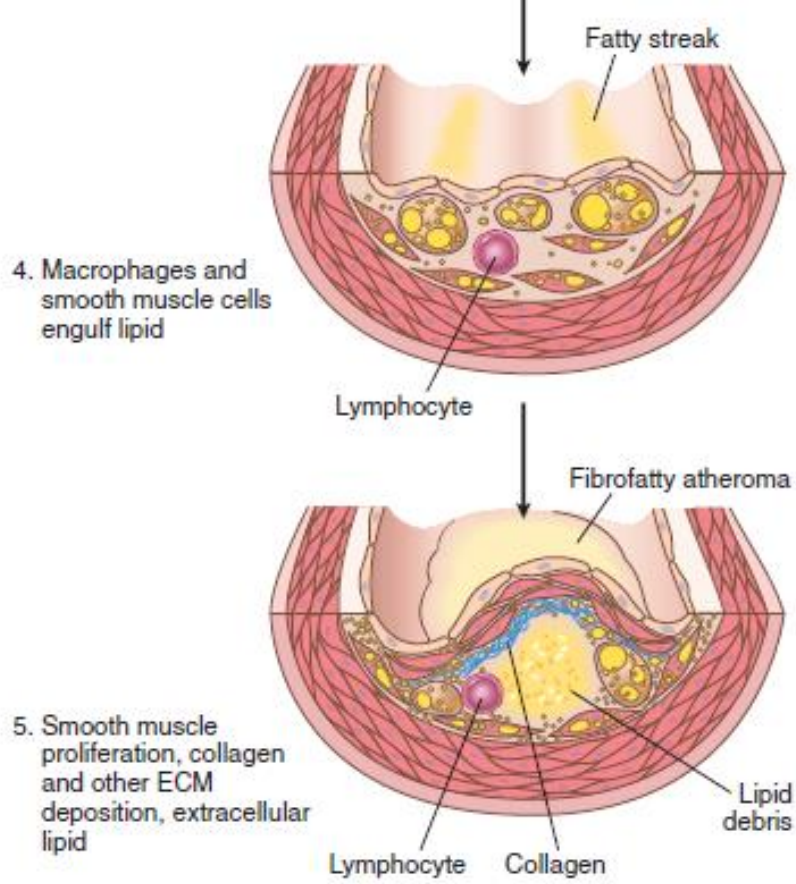
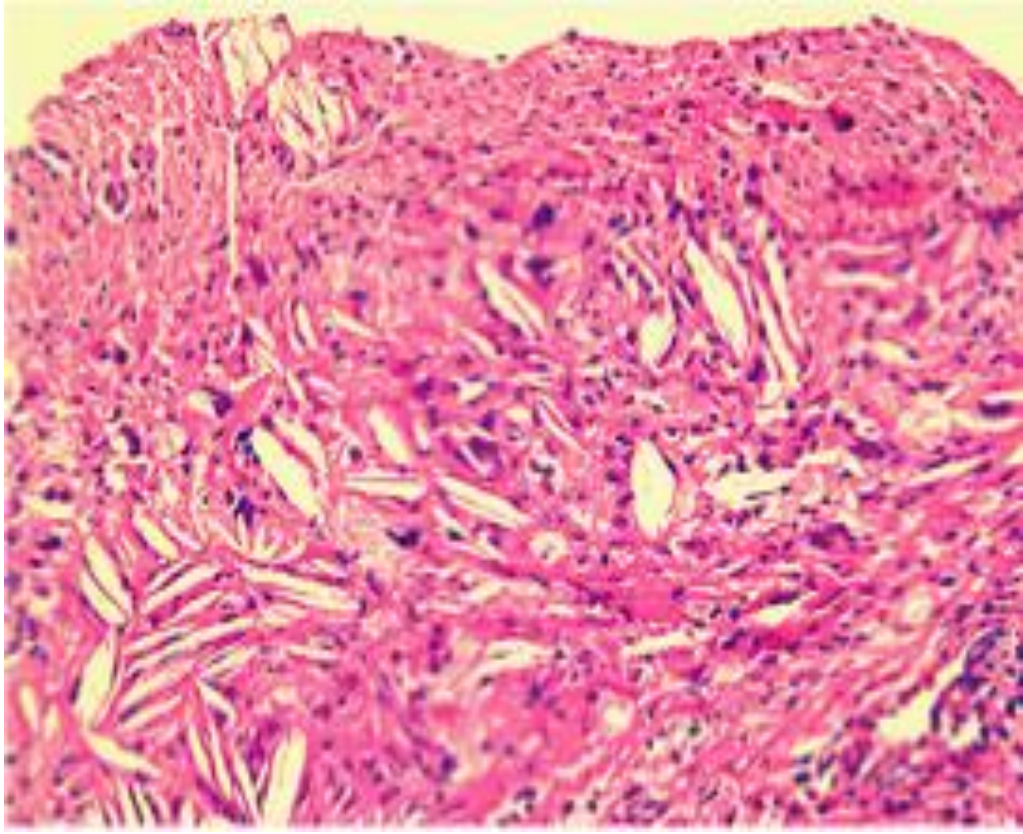
2. Cholesterol and cholesterol esters:

- Normally cholesterol is used to synthesize cell membrane and not deposited in the cell.
- Macrophages may become overloaded with cholesterol in different conditions.
- These cholesterol loaded macrophages give a foamy appearance to their cytoplasm (*foam cells*).

a. In atherosclerosis, smooth muscle cells and macrophages (foam cells) together form atherosclerotic fatty streaks and plaques (yellow color lesions).

- Some foam cells rupture and release cholesterol in extracellular space.
- The extracellular cholesterol esters may crystallize in form of long needles, producing clefts.





Abnormal cholesterol accumulation in an atherosclerotic plaque.

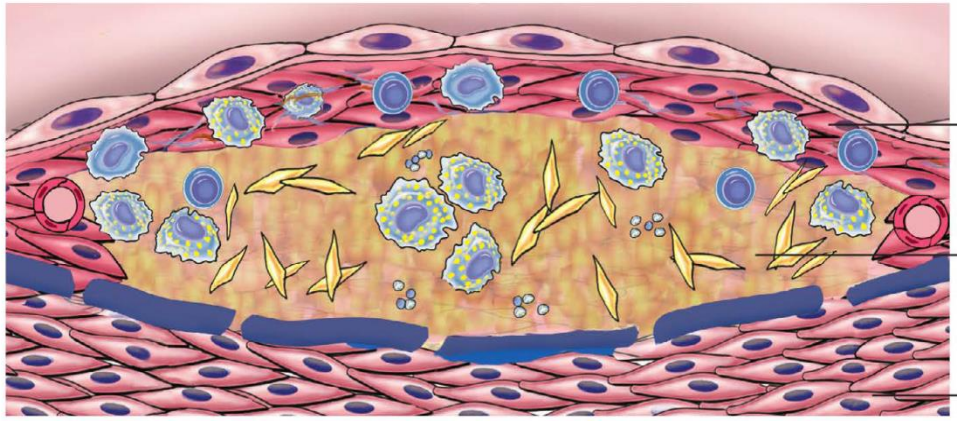


Figure 11-7 Basic structure of an atherosclerotic plaque. Note that atherosclerosis is an intimal-based process.

b. When present in the sub-epithelial connective tissue of skin or in tendons, clusters of these macrophages form masses called xanthomas.

- Cholesterol deposited in sub-epithelial tissue of eyelids or around eyelids is called Xanthalesma.
- Often said to be a subtype of Xanthoma.

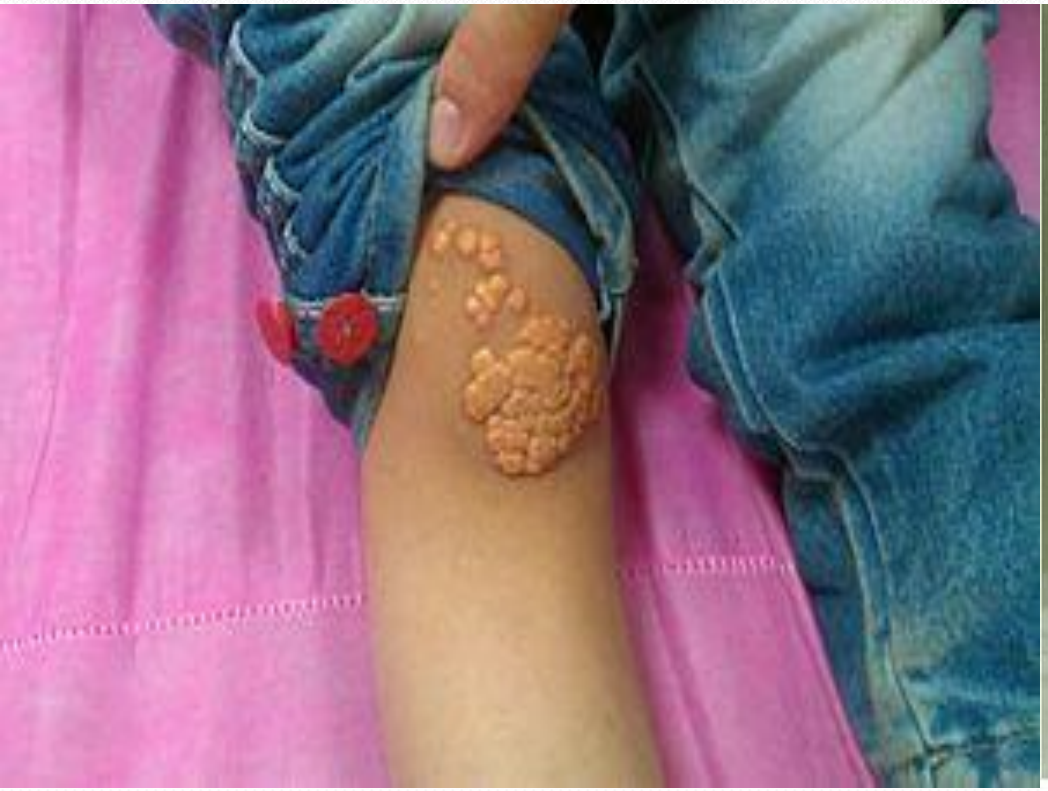
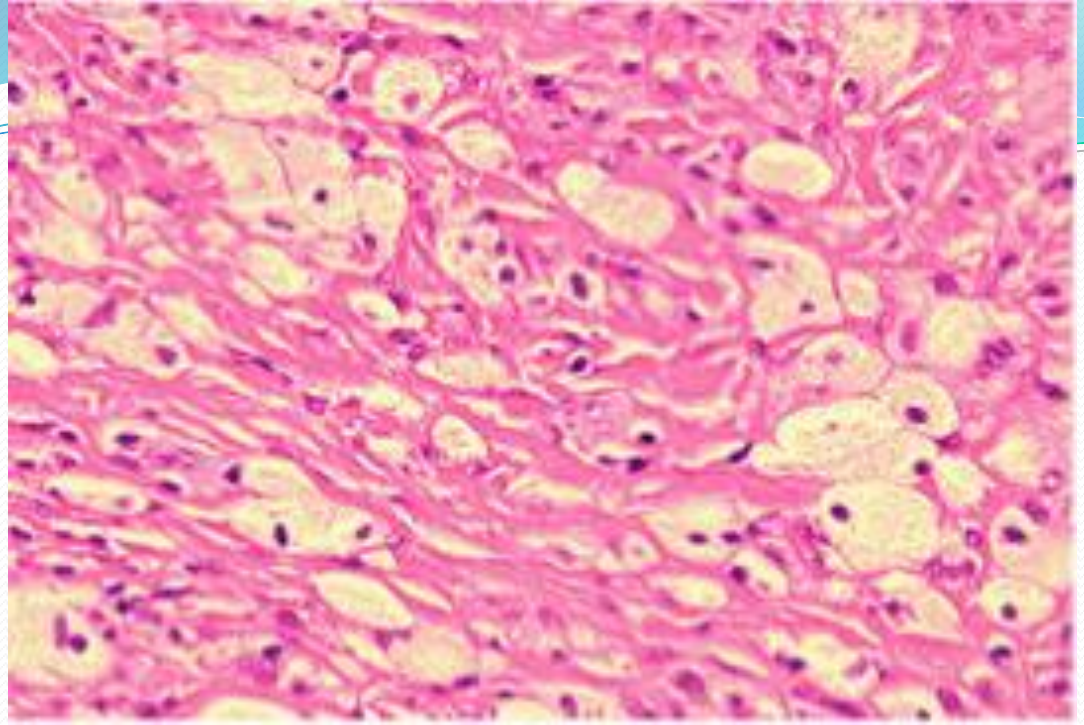
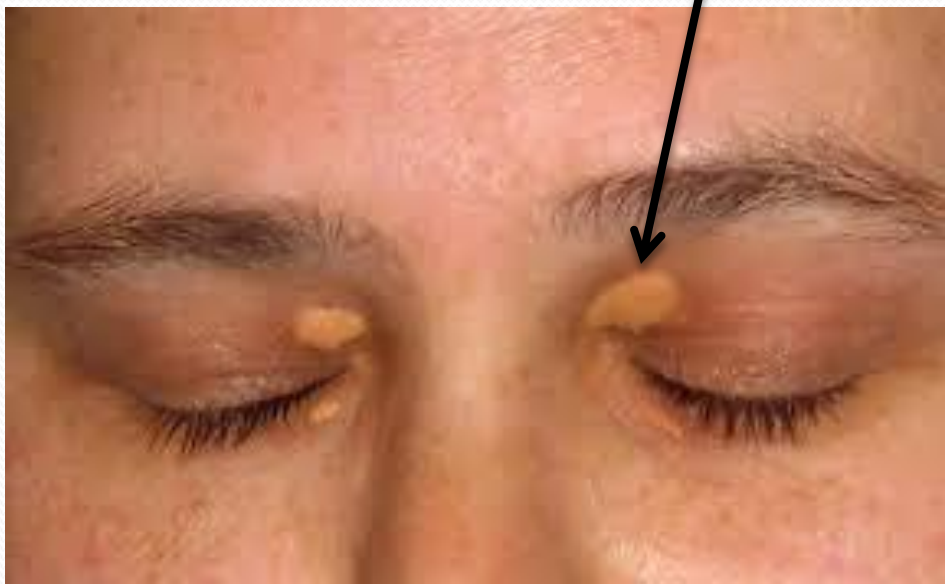


Figure1: Bilateral Achilles Tendon Xanthomas



Xanthalesma

Cholesterol accumulation in macrophages in a cutaneous xanthoma.



c. Niemann-Pick disease, type C.

- A lysosomal storage disease.
- Cholesterol accumulation in multiple organs

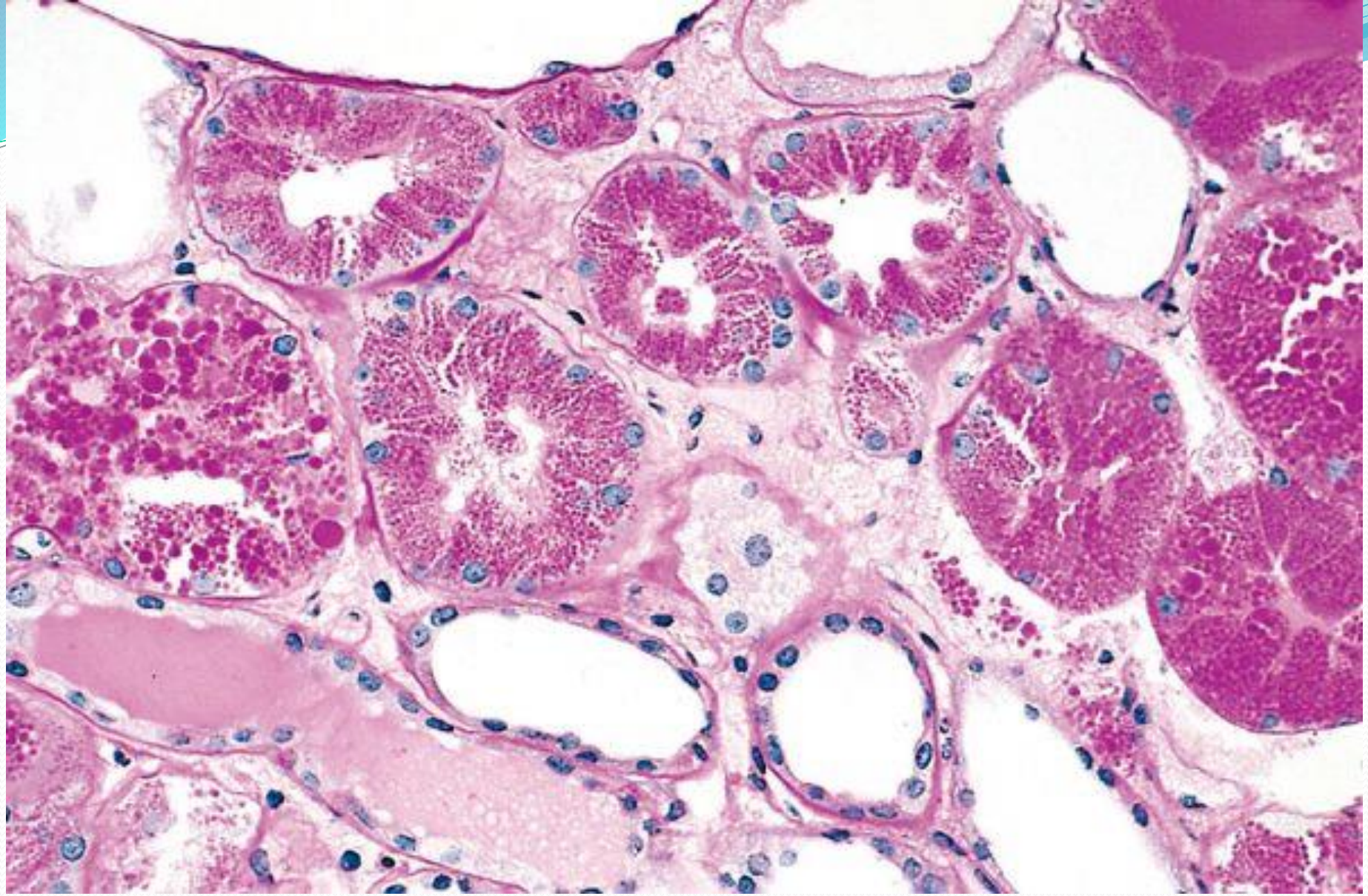
d. Cholesterolosis is focal accumulation of cholesterol-laden macrophages in lamina propria of gallbladder.

- Exact mechanism unknown

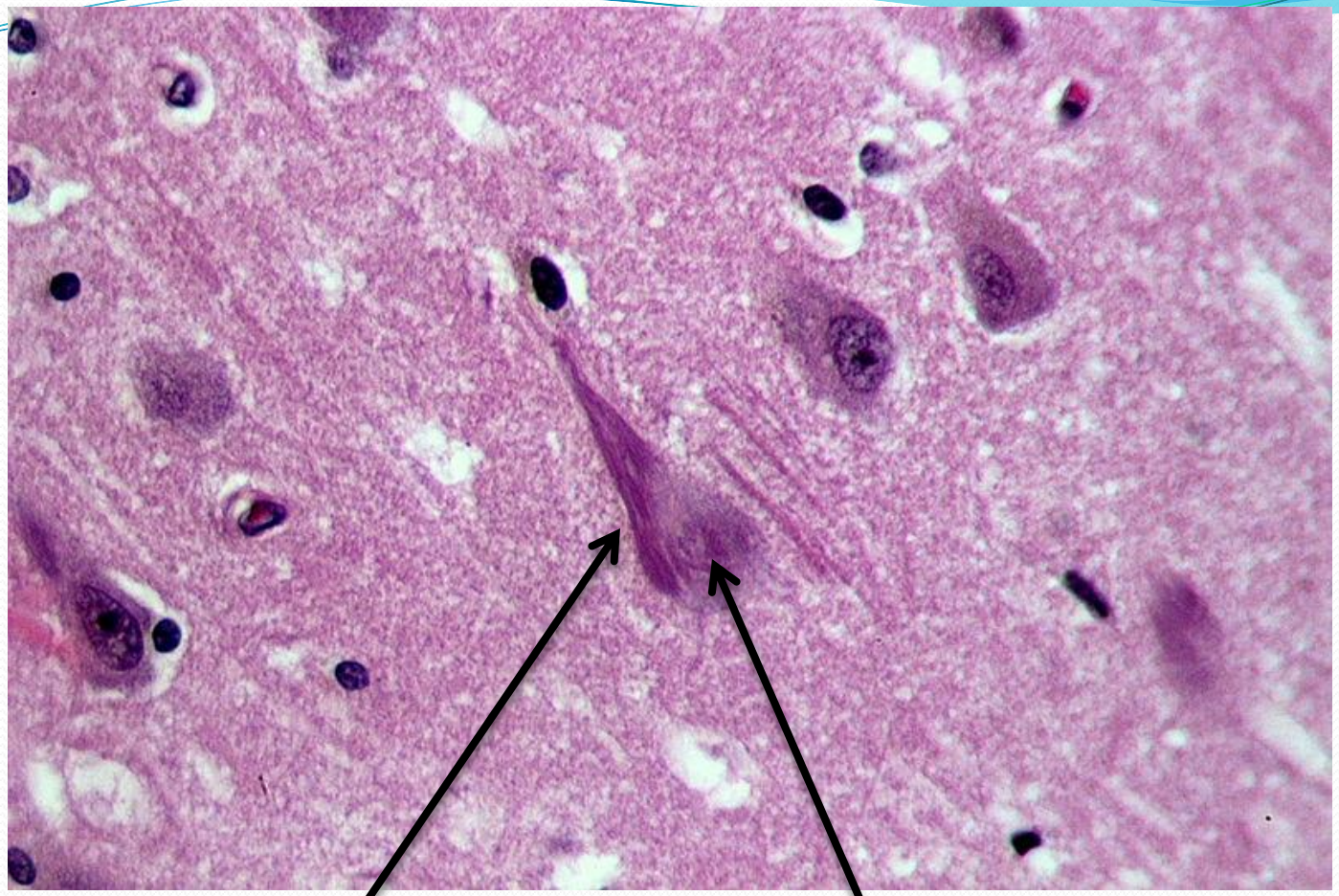
3. Protein

- Less common than lipid accumulations.
- In kidney, small amounts of albumin are filtered through glomerulus and reabsorbed in the proximal convoluted tubules.
- In disorders with heavy protein leakage (proteinuria) e.g. Nephrotic syndrome there is a much larger loss and re-absorption of protein.

- Heavy re-absorption ⟶ accumulation in tubular cells.
- Process is reversible.
- If proteinuria diminishes, the protein droplets are metabolized and disappear.
- The accumulation of aggregated form of a microtubule-associated protein known as tau is found in the brain in Alzheimer disease.



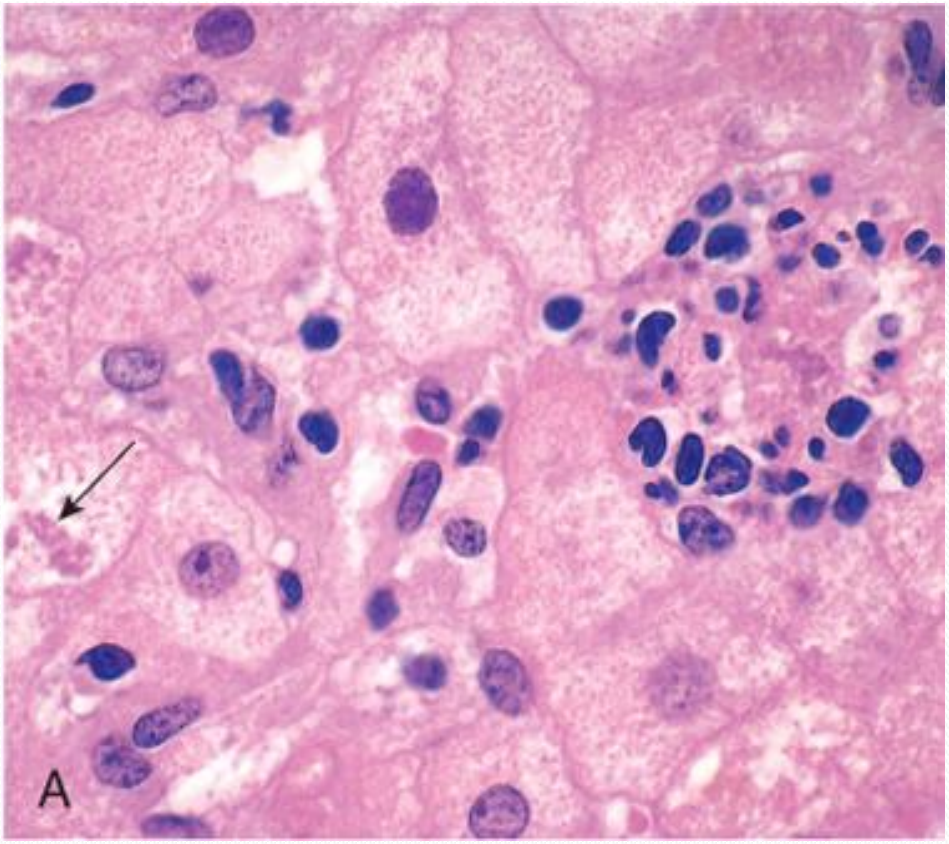
Protein re-absorption droplets in the renal tubular epithelium.



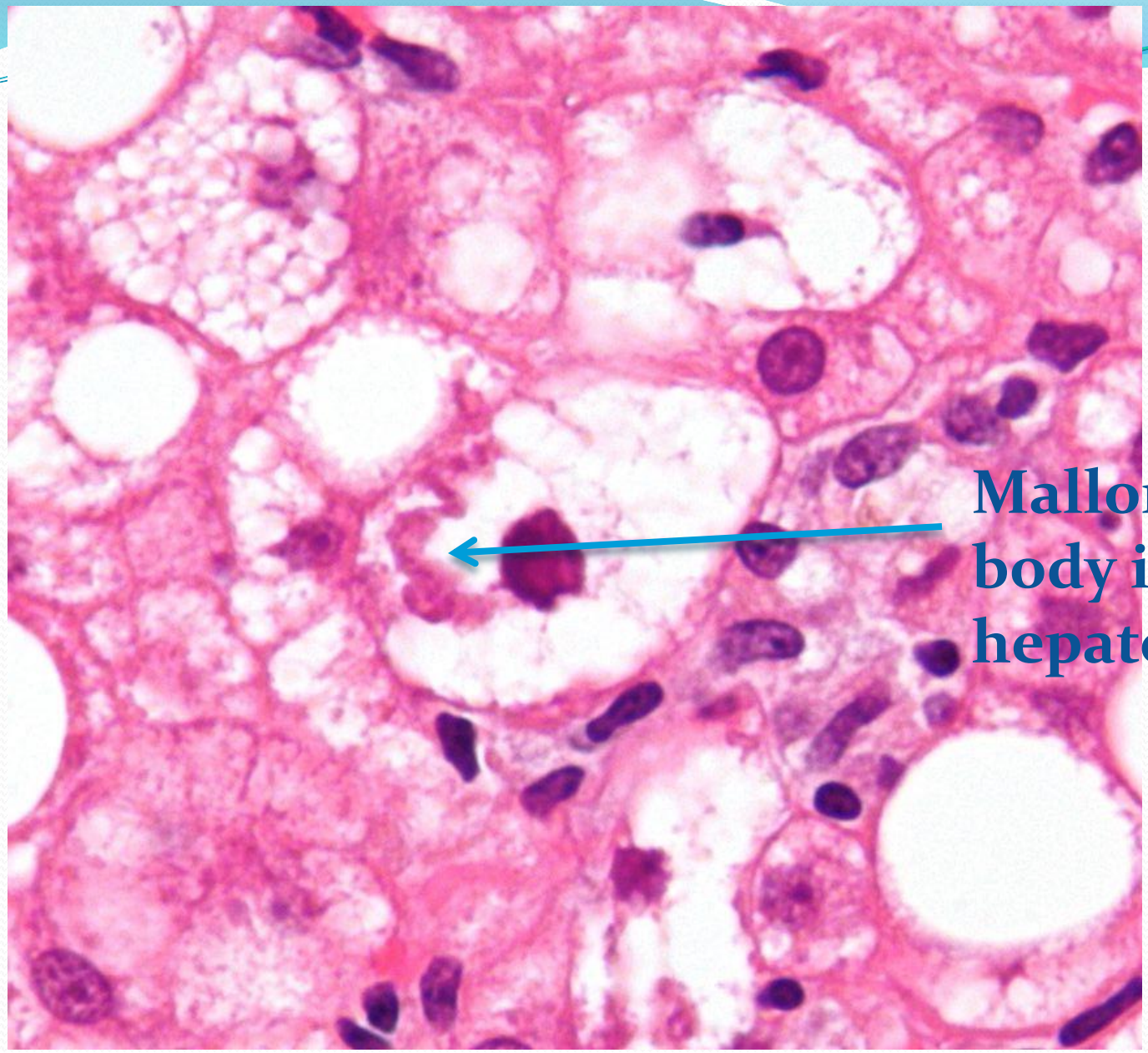
Neurofibrillary tangle (aggregate of tau protein) is present within neuron

- The Mallory body is an eosinophilic protein found in liver cells in case of alcoholic liver disease.

Also called alcoholic hyaline or mallory hyaline

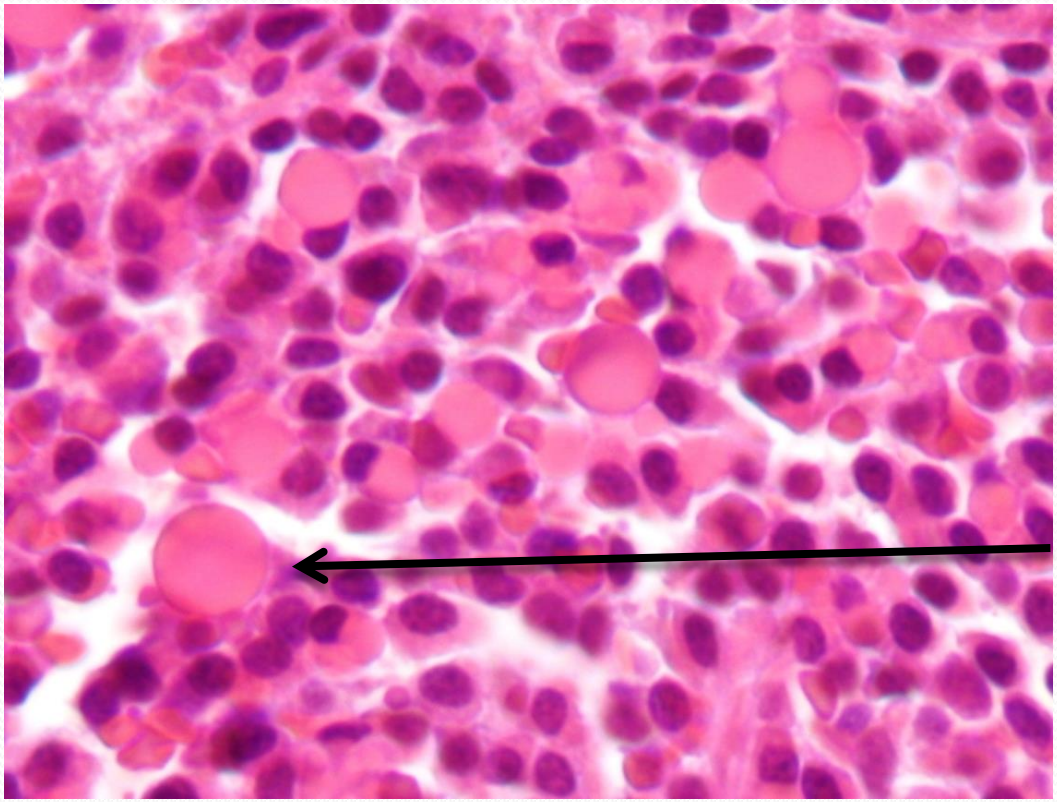


Mallory body (damaged intermediate filaments) **is present in hepatocyte (arrow).**



Mallory body with the characteristic *twisted-rope* appearance

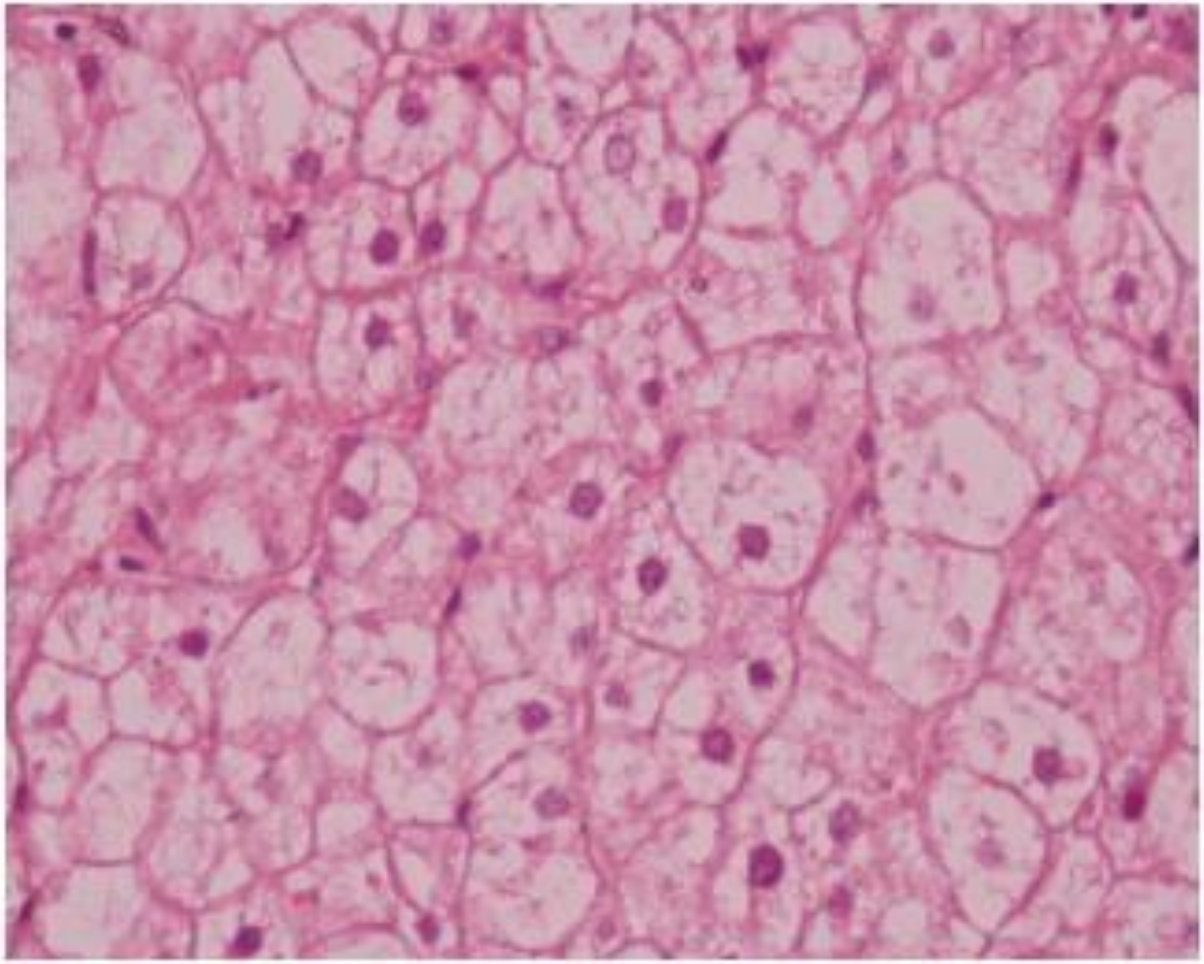
- Another example of protein accumulation is marked accumulation of newly synthesized immunoglobulins in some plasma cells (Multiple myeloma), forming rounded, eosinophilic (Pinkish) “Russell bodies”.



4. Glycogen :

- Either glucose or glycogen metabolic disorder causes deposition of excessive glycogen.
- In poorly controlled diabetes mellitus, glycogen accumulates in renal tubular epithelium, cardiac myocytes, and β cells of the islets of Langerhans.

- Glycogen also accumulates within cells in a group of genetic disorders referred to as glycogen storage diseases (glycogenoses).



Liver in Glycogen storage disease

Question By A STUDENT !!

If A Single Teacher Can't Teach Us All The Subjects, Then..

How Could You Expect A Single Student To Learn All Subjects??

https://www.facebook.com/MedicalJokes

5. Pigments:

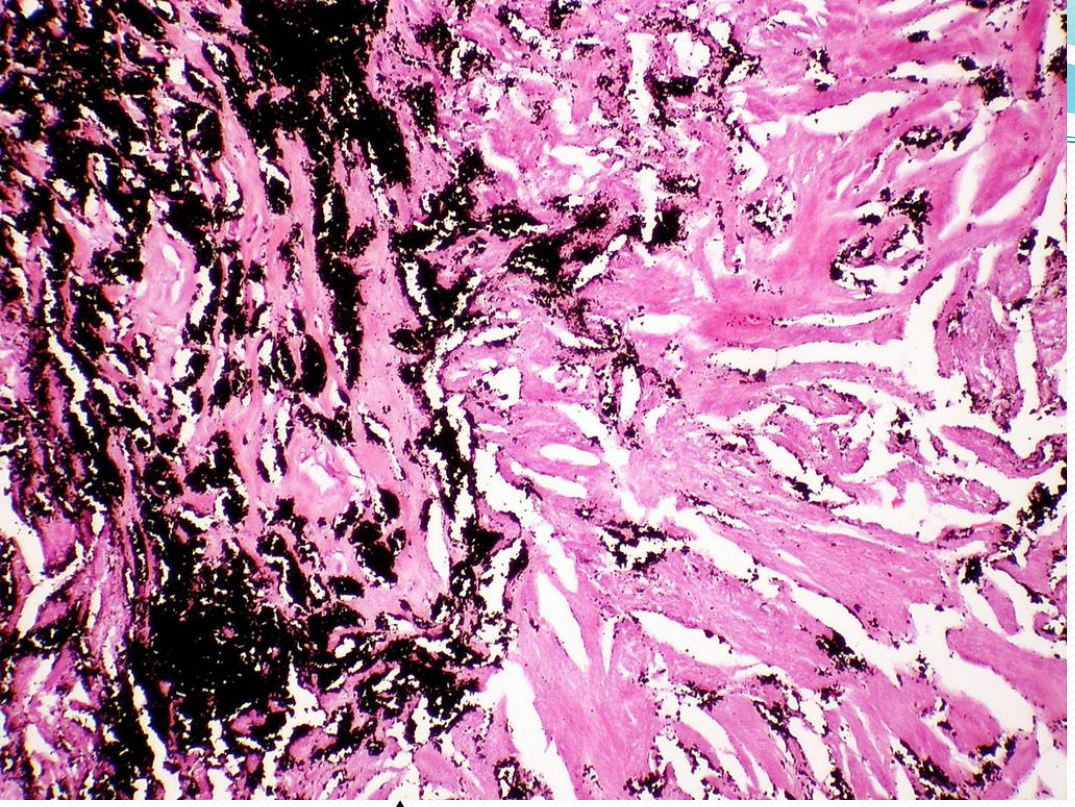
- They are Colored substances which may be

a. Exogenous b. Endogenous

a. Exogenous Pigments:

- The most common exogenous pigment is carbon (coal dust).
- In coal miners aggregates of carbon dust cause a serious lung disease, coal worker's pneumoconiosis.

- Tattooing is a form of localized, exogenous pigmentation of the skin.
- The pigments are phagocytosed by dermal macrophages, in which they reside for the rest of the life.



Coal worker's pneumoconiosis

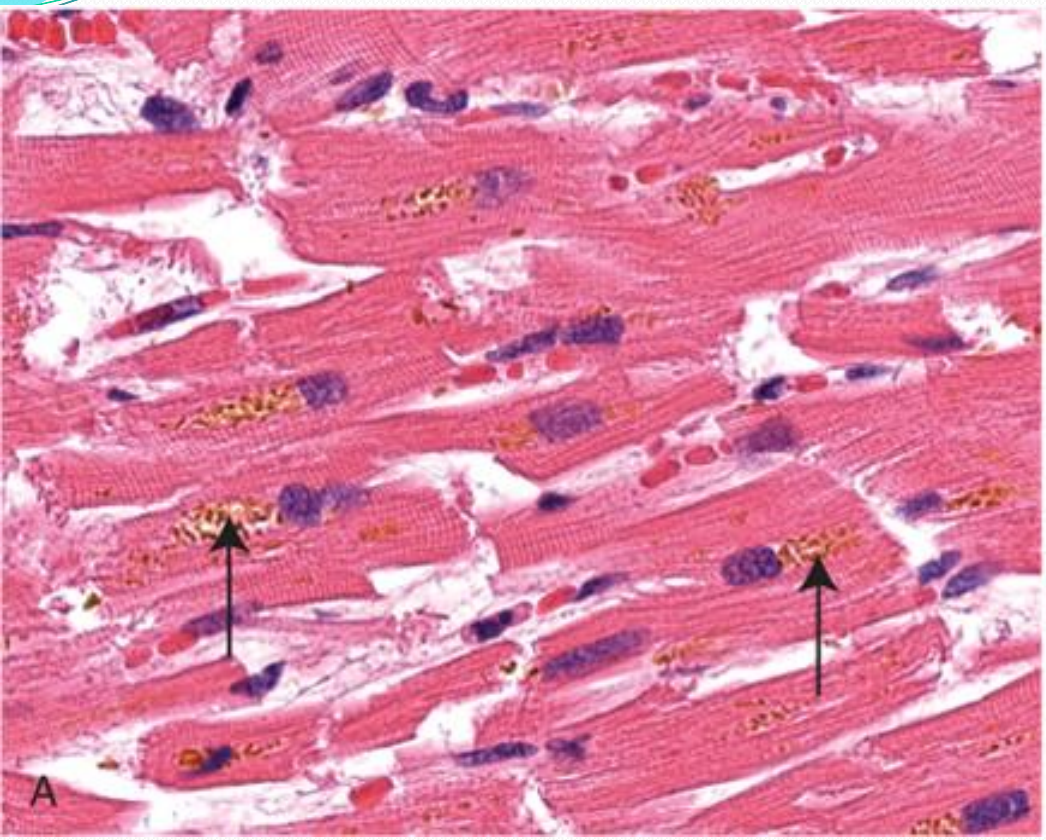
- Endogenous Pigments:

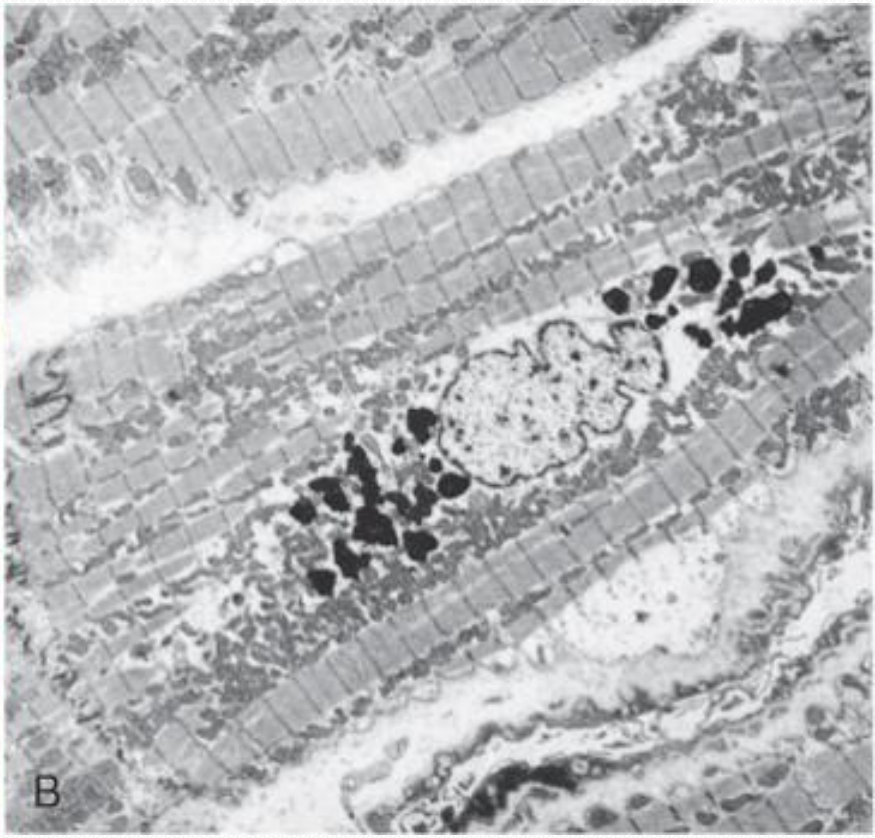
1. Lipofuscin is an insoluble pigment, also known as wear-and-tear pigment (lipochrome).

- Lipofuscin is composed of polymers of lipids and phospholipids in combination with protein
- Lipofuscin not injurious to the cell or its functions.

- In tissue sections it appears as a yellow-brown, granular cytoplasmic pigment.
- The term is derived from the Latin Lipo-fuscus
- Lipo meaning lipid and fuscus meaning brown i.e. Brown lipid.

- It is seen particularly in the liver and heart of aging patients or patients with severe malnutrition and cancer cachexia.

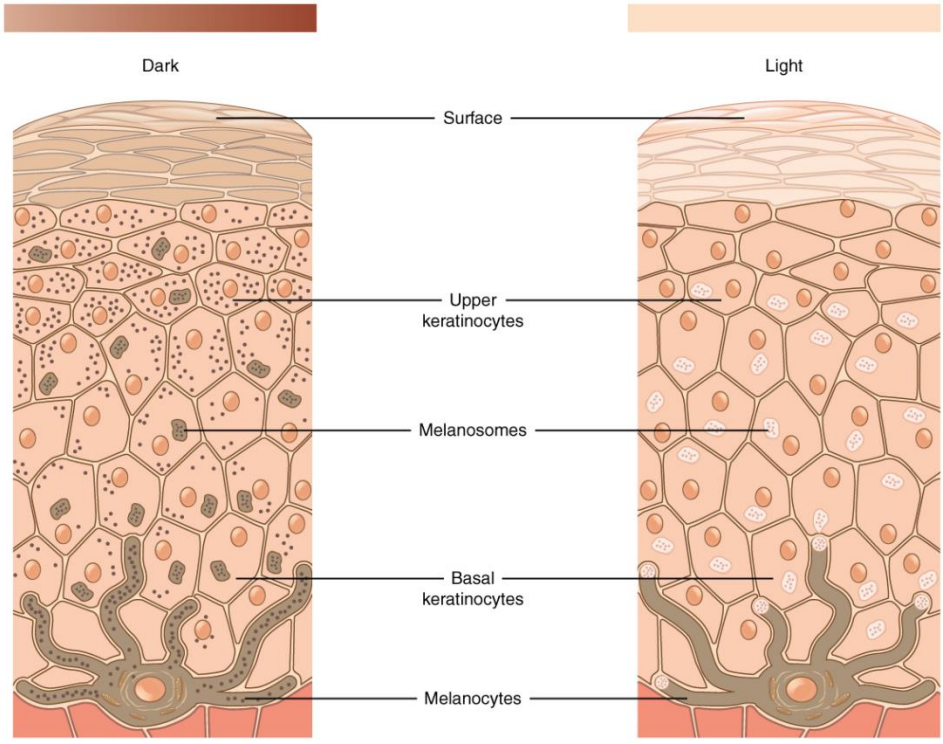




Lipofuscin granules in a cardiac myocyte shown by (A) light microscopy (deposits indicated by arrows), and (B) electron microscopy

2. Melanin, derived from the Greek (melas, black), is a brown-black pigment.

- Synthesized exclusively by melanocytes located in the epidermis and acts as a screen against harmful ultraviolet radiation.

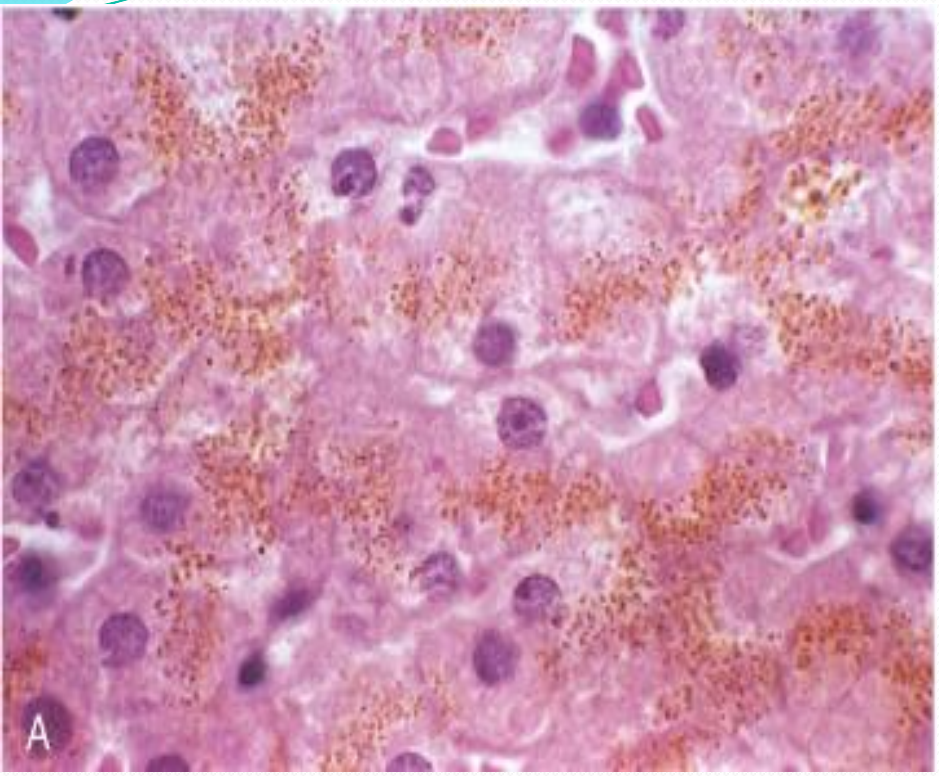


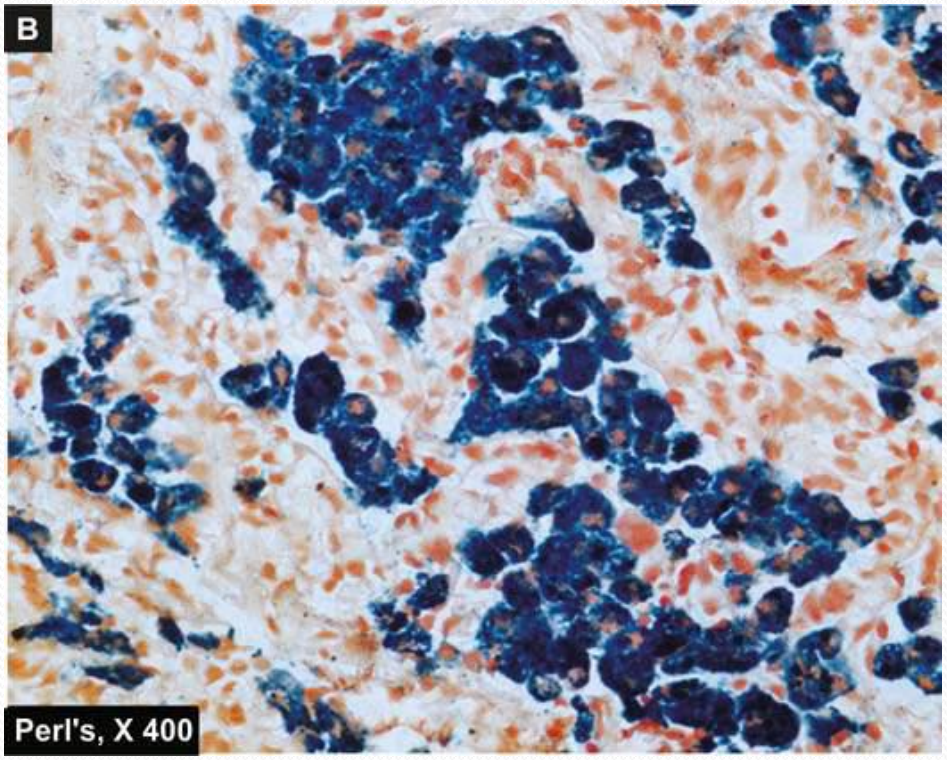
3.Hemosiderin is a hemoglobin-derived, fine golden yellow to-golden brown, granular pigment.

- One of the storage forms of iron.
- Iron normally stored in form of ferritin.
- When there is a local (Skin and soft tissue hemorrhage) or systemic excess of iron, ferritin particles unite together to form hemosiderin granules.

- Hemosiderosis is excessive collection of hemosiderin in tissues due to systemic overload of iron.
- Main causes of hemosiderosis are

1. Increased absorption of dietary iron due to an inborn error of metabolism called **hemochromatosis.**
2. Hemolytic anemias.
3. Repeated blood transfusions.





A. Hemosiderin granules in liver cells showing golden-brown, finely granular pigment.

B. Hemosiderin deposits as seen on staining with Perl’s Prussian blue satin.

- A 58-year-old man has a history of chronic alcohol abuse. He is still able to perform work at his job. He has had no major illnesses. On physical examination, there are no significant findings. Laboratory findings are not remarkable. Which of the following microscopic findings in his liver is most likely to be present?

a. Cholestasis
b. Fatty change
c. Hemochromatosis
d. Hypertrophy of smooth endoplasmic reticulum
e. Coagulative necrosis


Jazak Allahu Khair
جزاك اللهُ خيراً
May Allâh reward
you [with] goodness.