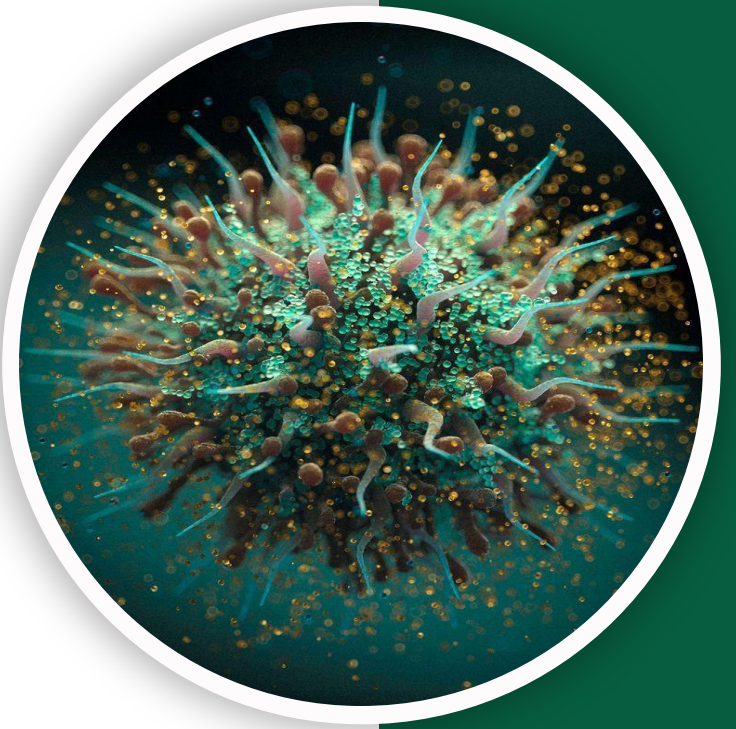
بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pathology | Lecture 5

Intracellular Accumulations and Calcifications



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Intracellular accumulations and calcifications

cell injury and adaptations

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INTRACELLULAR ACCUMALATIONS

It means the deposition & buildup of a material inside the cells

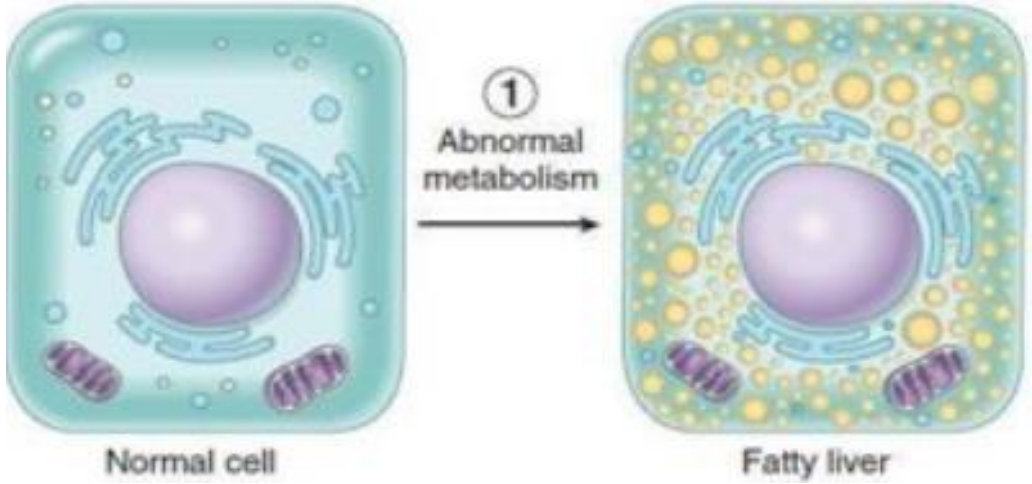
This material could be endogenous or exogenous.

Deposition mechanisms:

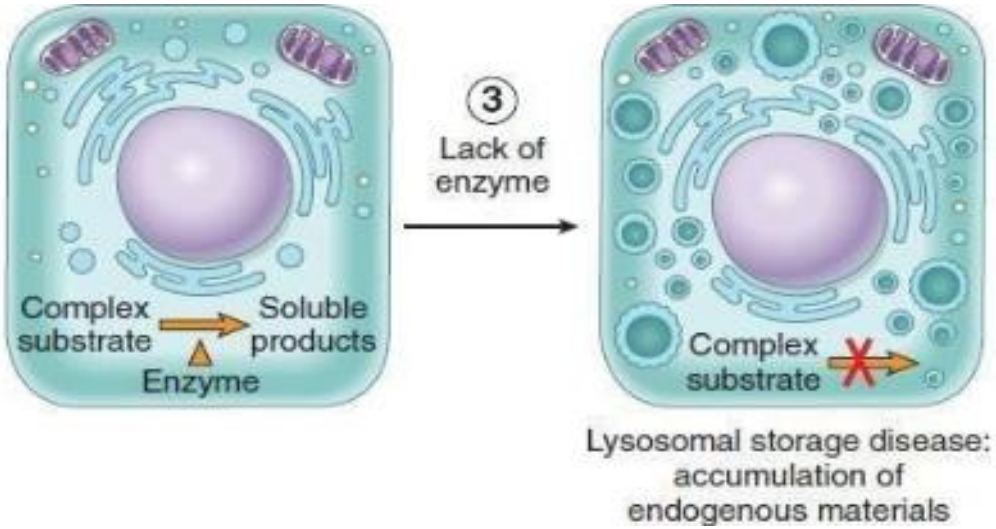
- 1)Inadequate removal of a normal substance (fatty change in the liver)
  Fats are normally stored in the hepatocytes
  They will build up inside the liver cells upon inadequate removal, Example : fatty liver disease.
- 2)Accumulation of an abnormal endogenous proteins due to folding defect

  (α1-antitrypsin deficiency) When alpha-1-antitrypsin is abnormally folded, it accumulates inside the cytoplasm instead of being secreted out of the cell. This results in a deficiency of this **plasma protein**.
- 3)Failure to degrade a metabolite
  due to inherited enzyme deficiencies(lysosomal storage diseases and glycogen storage diseases)

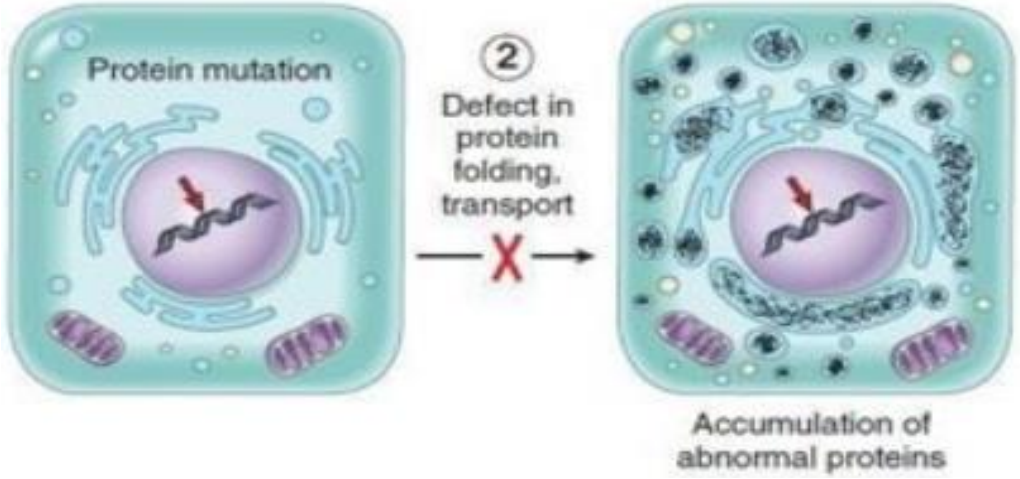
- 4)Deposition and accumulation of an abnormal exogenous substance
  (carbon and silica) Carbon deposition is normally in the lungs & lymph nodes.



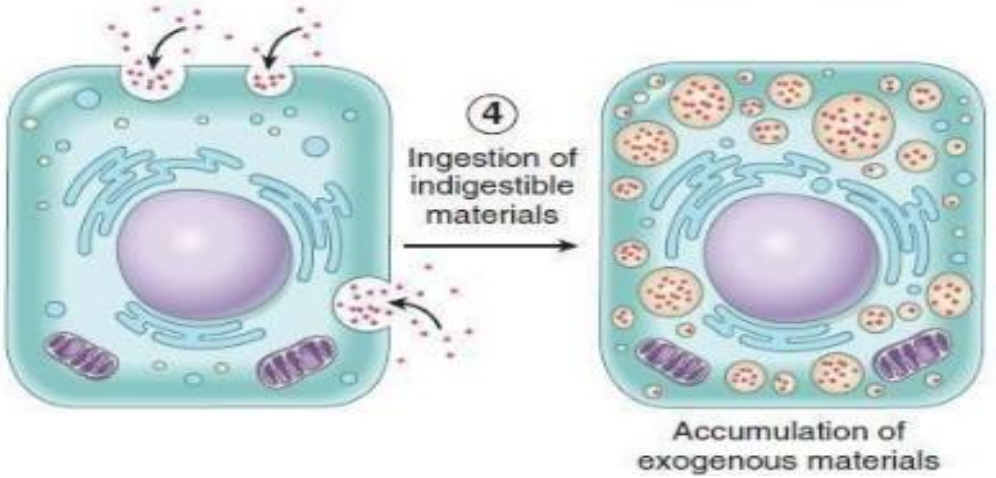
Fatty liver disease due to accumulation of a normal substance (Fat) in hepatocytes
Fatty content is represented with yellow droplets.



Lack of enzymes to degrade certain substances, leading to substrate accumulation, as seen in lysosomal storage diseases and glycogen storage diseases.



Protein folding defect, causing deposition & accumulation of abnormal endogenous proteins
Like in α1-antitrypsin deficiency.

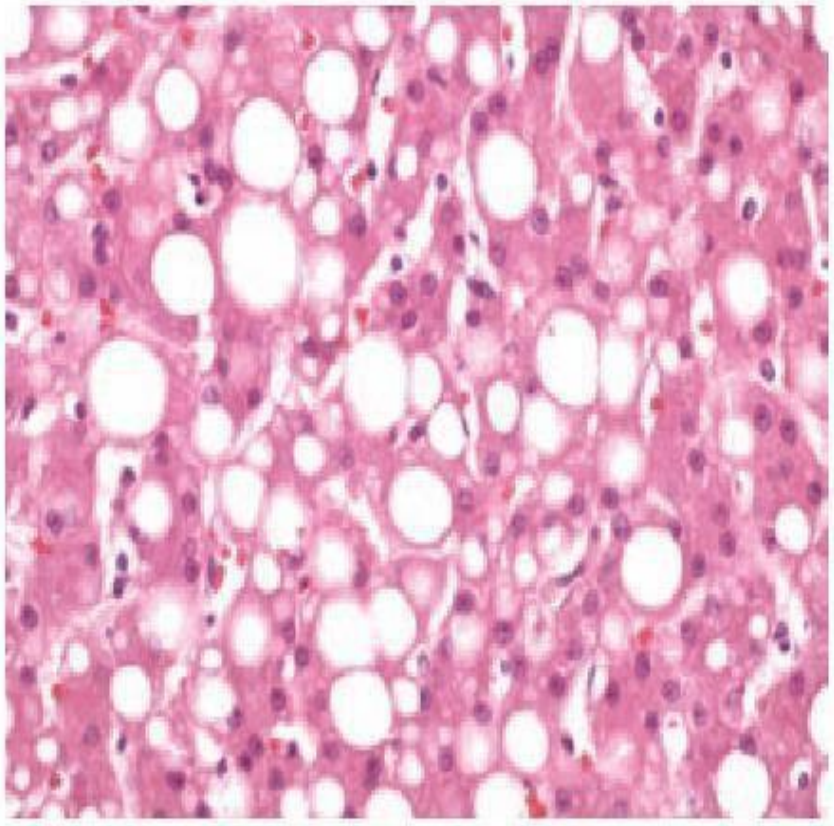


Ingestion of an exogenous substance, which is usually indigestible, such as carbon (represented by the red dots), causing intracellular accumulation.

fatty change: steatosis

Clinical or pathologic term for the deposition of fat inside hepatocytes

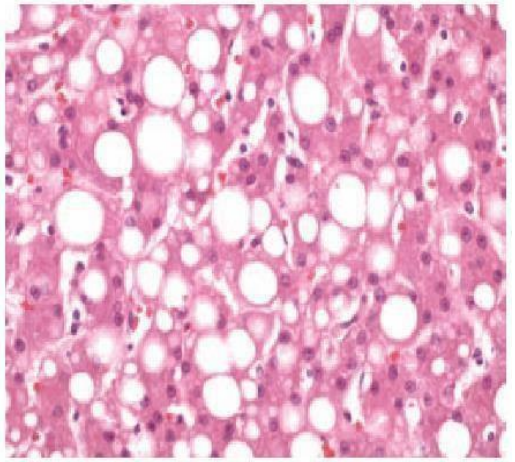
- Most common in liver — Due to its role in fat metabolism
- Triglycerides, the form fat is deposited in.
- Also in heart, kidney, muscle
- Causes: Toxins, protein malnutrition, DM (diabetes mellitus), obesity, anoxia
- Alcohol abuse and DM+obesity are the most common causes of fatty liver



Toxins: like an overdose of acetaminophen or CCl_3
Anoxia: Loss of oxygen supply (not decreased but totally lost)

In western countries alcoholic fatty liver disease is the most common type, and in our region it's the non-alcoholic fatty liver disease

Why do TAGs accumulate in the liver?
Because TAGs need to be bound to apoproteins to be secreted into the bloodstream and transported successfully.
In cases of deficiency or decreased synthesis of these proteins (which is why protein malnutrition is a cause), TAGs accumulate inside the liver, usually manifested by:



1. Enlarged liver

2. Macroscopic appearance: Yellowish cut surface

3. Microscopic appearance: appearance of empty white vacuoles/spots in hepatocytes that displace the nuclei to the periphery, giving an appearance similar to that of adipose tissue.

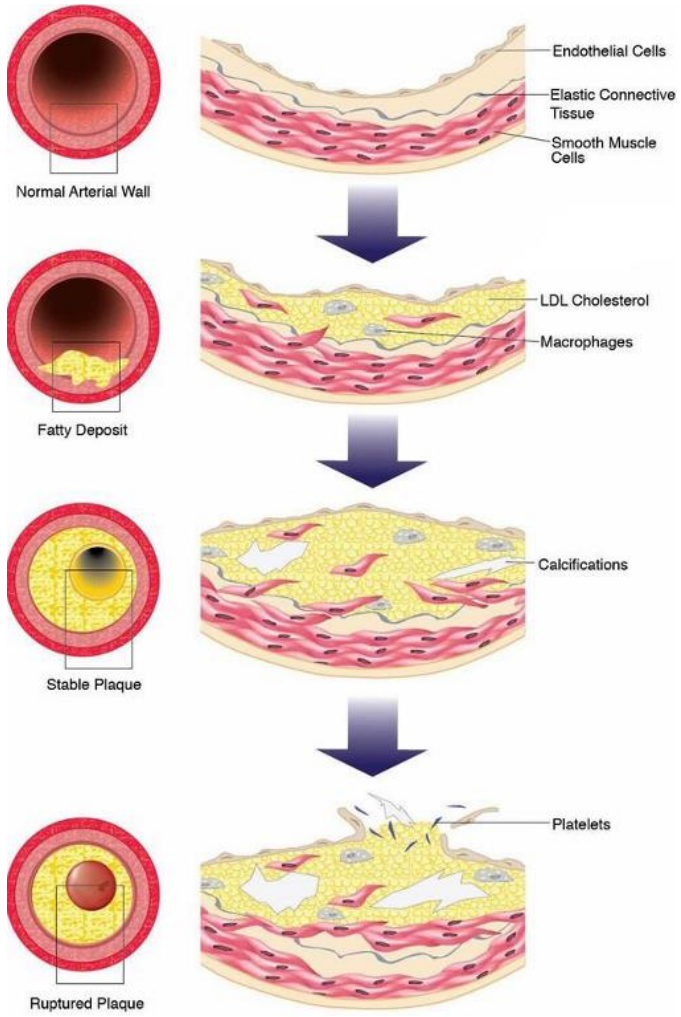
Cholesterol and Cholesteryl Esters

- Phagocytic (macrophages) cells become overloaded with lipid (triglycerides, cholesterol, and cholesteryl esters)

The best-known example is the deposition of cholesterol and cholesteryl esters in the walls of blood vessels, commonly seen in diabetic patients and the elderly.

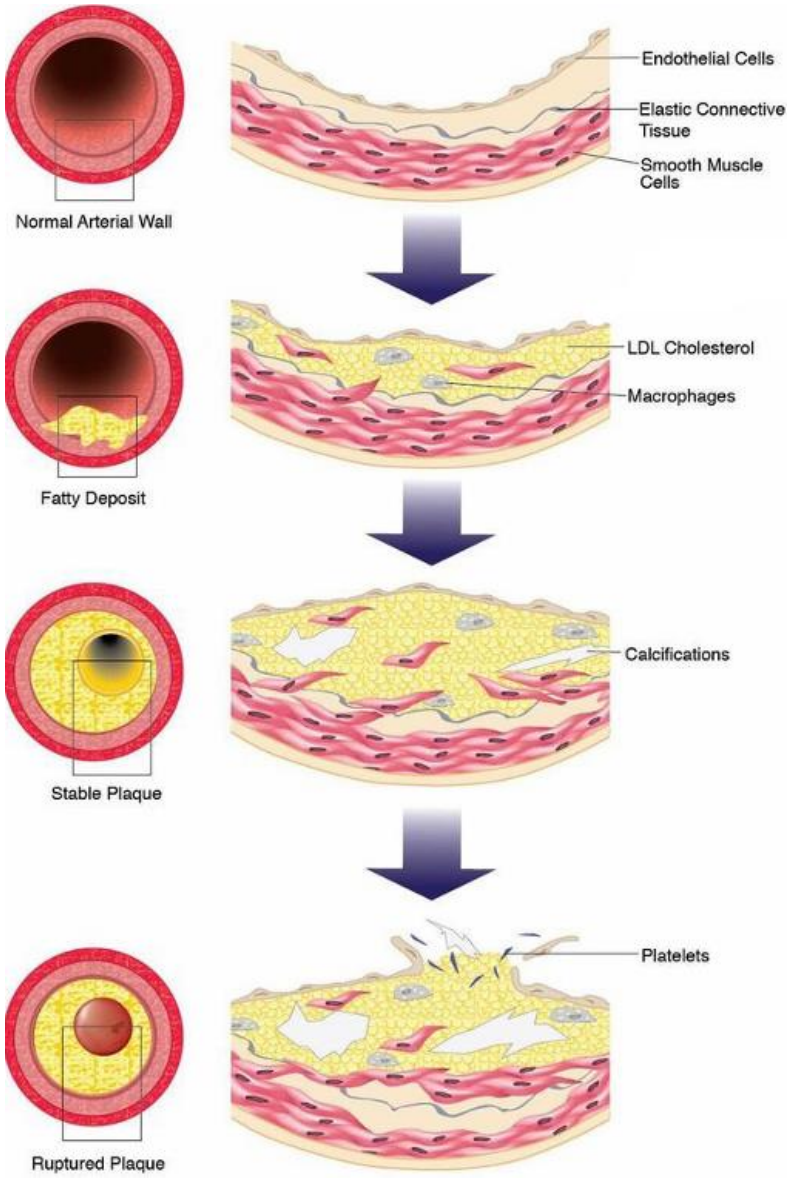
- Due to Increased intake or decreased catabolism of cholesterol

- Atherosclerosis



Atherosclerosis: Atheroma begins to accumulate in the walls of blood vessels, and over time, narrowing of the lumen occurs. This can lead to obstruction of the vessel and may result in the formation of a superimposed thrombus, which might cause total occlusion of the vessel and potentially lead to infarction.

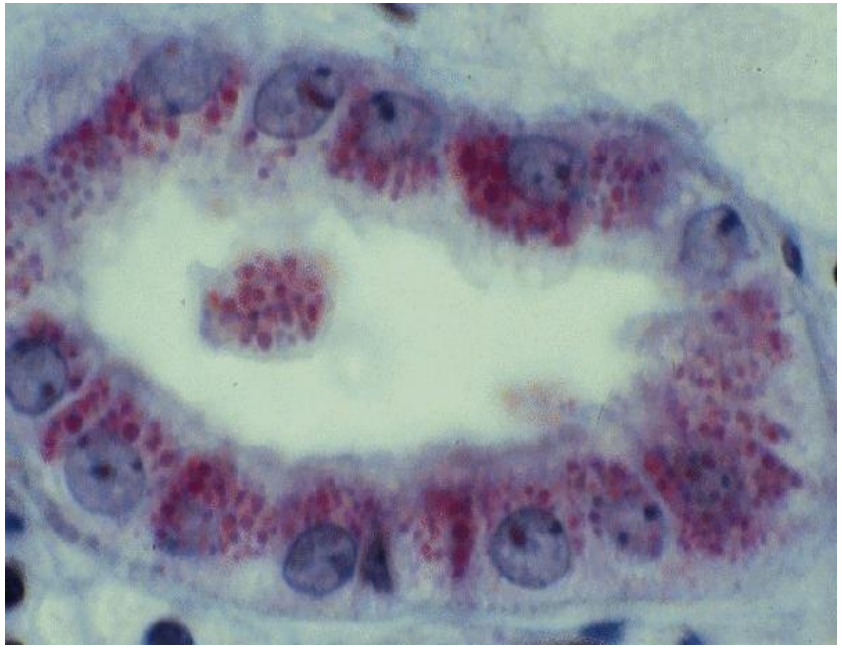
Cholesterol, a normally present substance in the body, contributes significantly to this process when found in high amounts. Its accumulation within arterial walls promotes atherosclerosis, leading to luminal narrowing that may result in ischemia, myocardial infarction, and other cardiovascular complications.

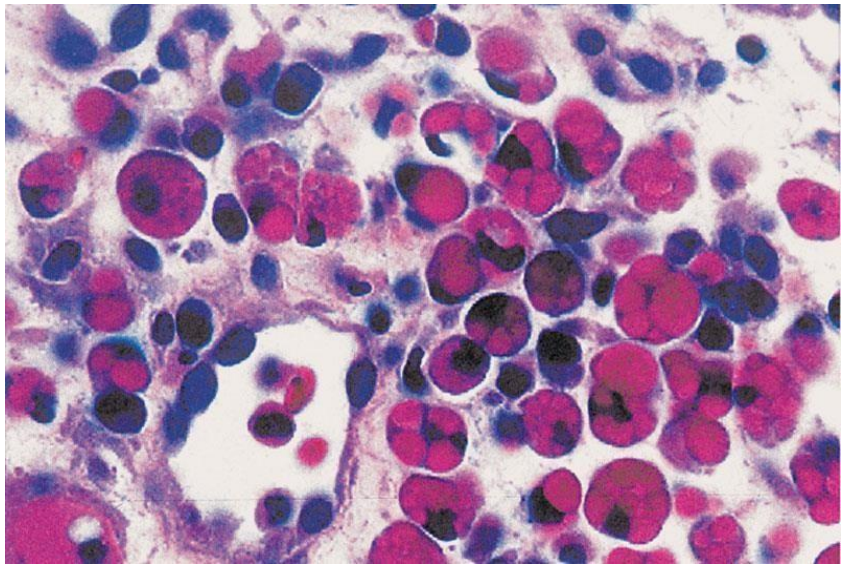


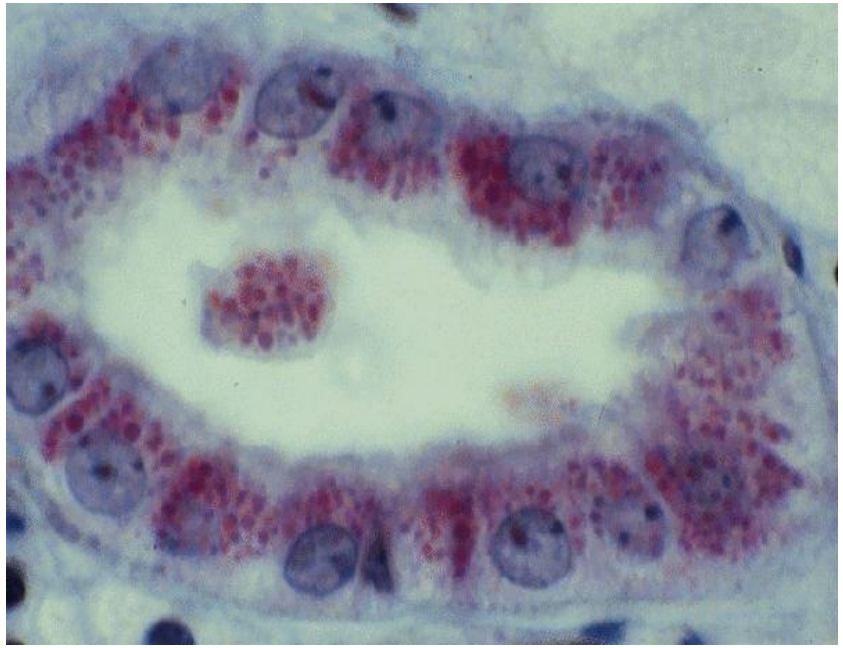
This yellow material is called Atheroma

Proteins

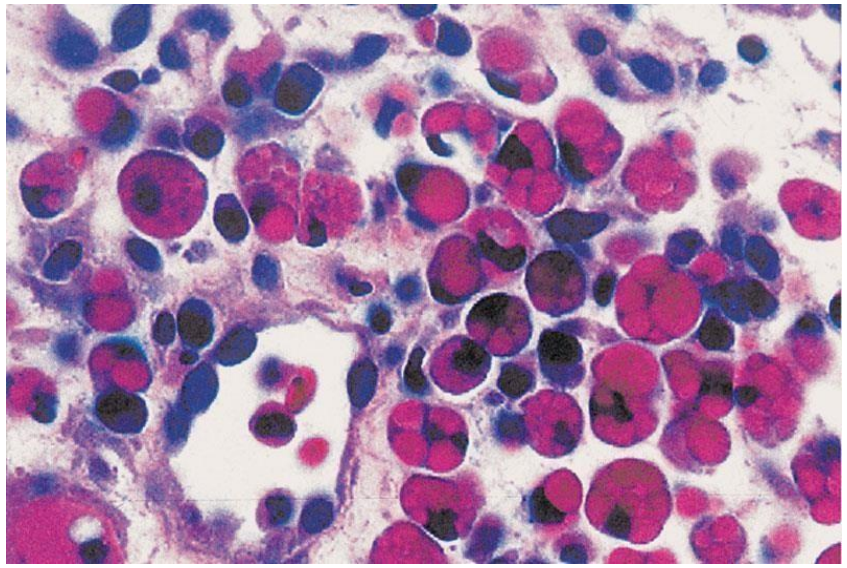
- Much less common than lipid accumulations
- Either excess external intake of proteins or internal synthesis of proteins
- Proximal renal tubules in nephrotic syndrome
- Russell bodies in plasma cells.
- Alcoholic hyaline in liver Hyaline is a pink (eosinophilic) material that can be deposited in the liver in cases of alcoholic fatty liver disease.
- Neurofibrillary tangles in neurons seen in neurons of the cerebral cortex in patients with Alzheimer's disease.







- In patients with nephrotic syndrome, excess proteins (albumin mainly) filtered into the urine are reabsorbed by renal tubular epithelial cells. Because the kidney has high permeability for albumin, these reabsorbed proteins accumulate and are deposited inside the tubular epithelium.
- This slide shows renal tubules in nephrotic syndrome. Proteins appear as pink granules in the cytoplasm of renal tubular epithelial cells.



- Accumulation of immunoglobulins in the endoplasmic reticulum of plasma cells.
- Plasma cells are responsible for antibody production, so when large amounts are produced, they accumulate as droplets called Russell bodies.

They appear as pink deposits within the cytoplasm of plasma cells

A general rule :

Anywhere excessive plasma cells are existing; there must be a lot of antibodies

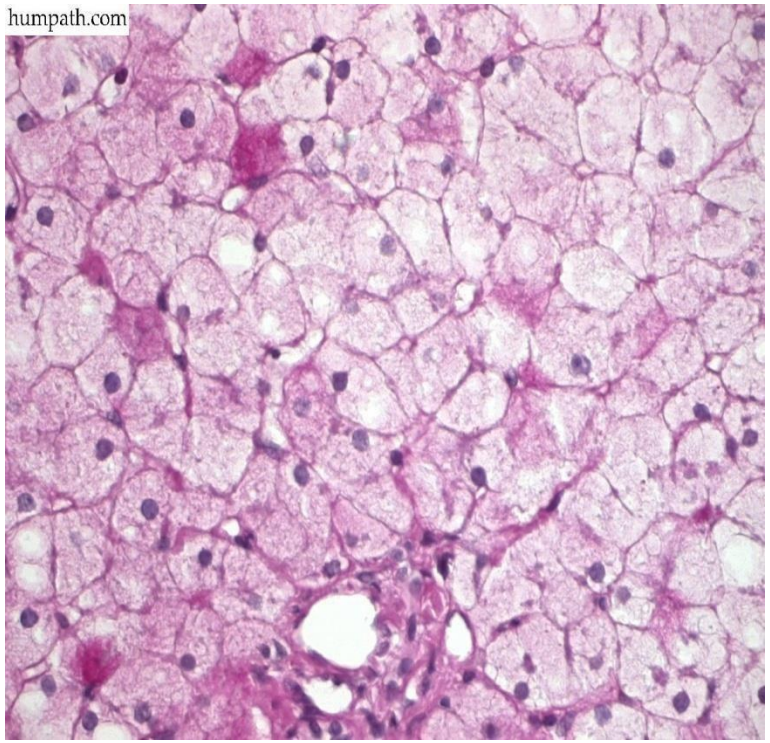
Glycogen

- Abnormality in glucose or glycogen metabolism

- **DM** (glycogen excessive deposition in in renal tubules, heart, (beta) B cells of pancreas)

- **Glycogen storage diseases** It is a deficiency of the enzyme responsible for glycogen catabolism, and it is usually an inherited disease.

• People who have diabetes also suffer from glycogen accumulation and deficiency in glycogen metabolism

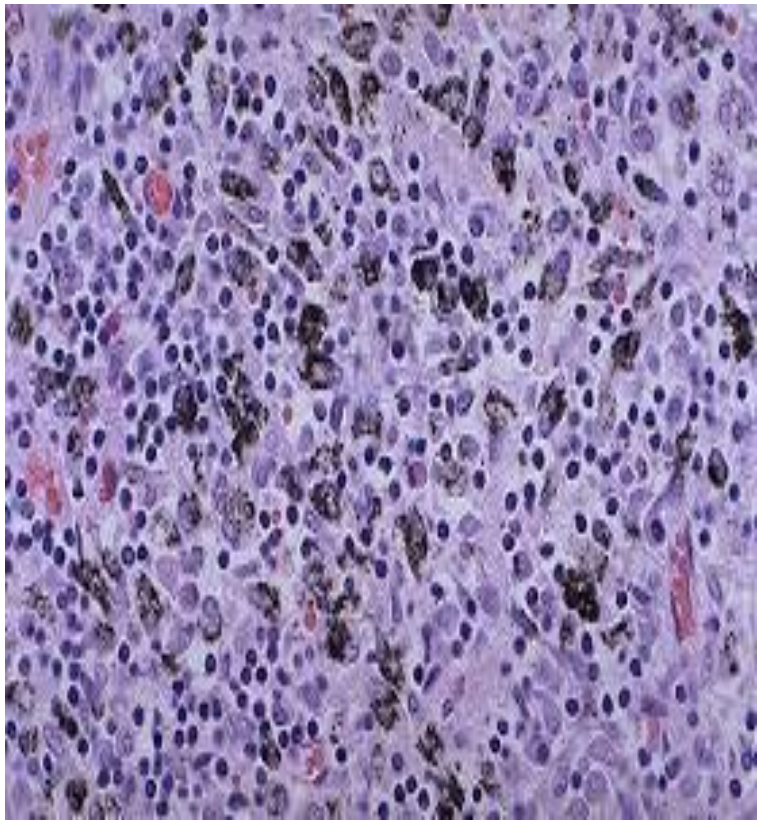


H&E Section from the liver. Hepatocytes are loaded with large amounts of glycogen, giving the cells a bubbly appearance. PAS stain is a special stain used to detect this glycogen accumulation.

Pigments

colored materials that can be deposited in the cytoplasm of cells, and they may originate from either endogenous or exogenous sources.

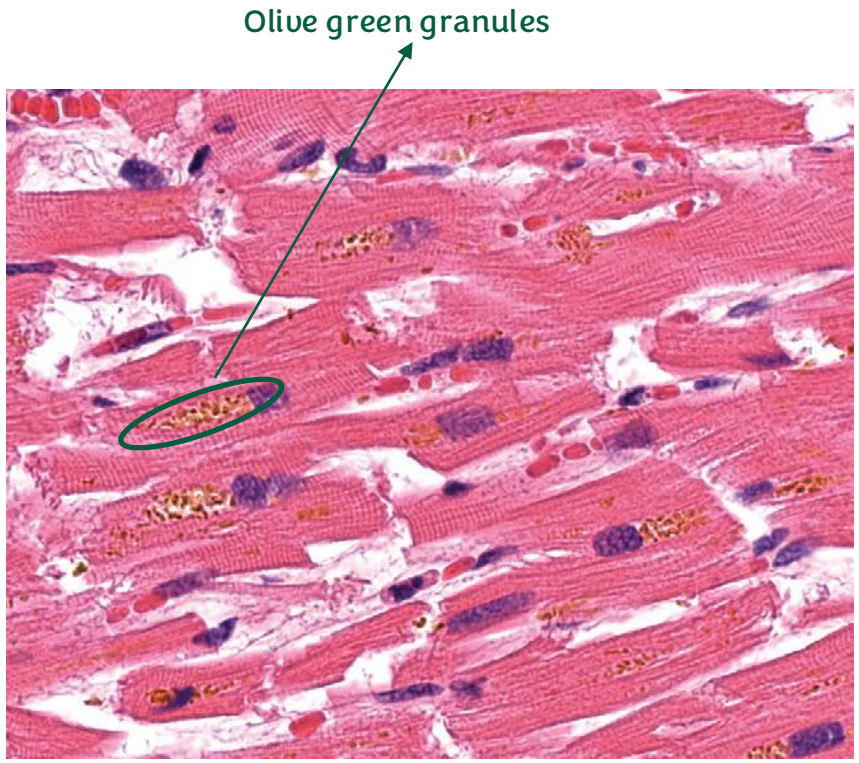
- Exogenous
- Most common exogenous, **carbon** (coal dust, air pollution) **& smoking**
- Alveolar macrophages→ lymphatic channels→ tracheobronchial LN
- *Anthracosis* pathologic term indicating carbon deposition in the lungs, specifically the accumulation of carbon pigment.



Alveolar macrophages engulf the carbon in their cytoplasm. This indigestible carbon then travels through the lymphatic channels, eventually reaching the tracheobronchial lymph nodes. The accumulation of carbon gives a black discoloration in the lungs and lymph nodes, which can be seen even with the naked eye during a biopsy.

Pigments

- **Endogenous**
- **Lipofuscin** its presence doesn't cause any harm (Innocent pigment)
- "wear-and-tear pigment"
- Age/atrophy seen in aged cells and in cases of atrophic tissues
- It is seen in Heart, liver, and brain
- Lipid and protein



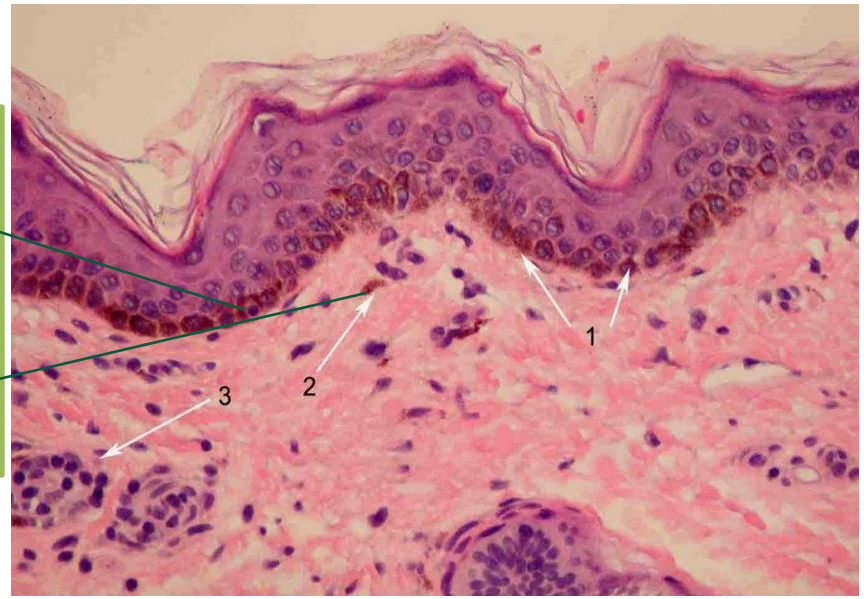
Section from heart muscle

Derived from the damaged lipids and proteins in the cell and organelles membranes

- Marker of past free radical injury
- Called *brown atrophy* when it is deposited in excessive amounts in the atrophic tissue giving it a brown color.

Pigments

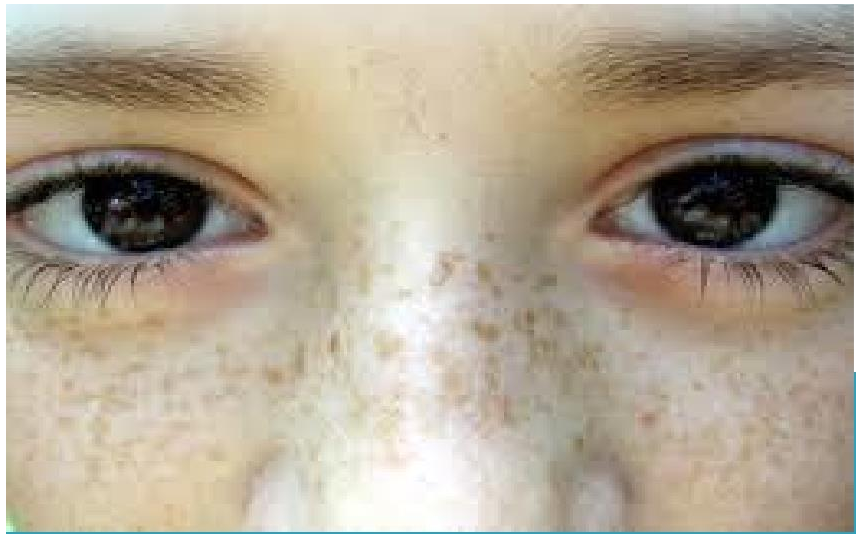
- Not all these brown cells are melanocytes; some are keratinocytes taking the pigment
- Pigment can be seen in macrophages of the dermis



- **Endogenous**
- **Melanin**
- Source: melanocytes in the skin
- Melanin offers UV protection

  Upon exposure to the sun, the production of melanin increases especially in fair skinned people
- Accumulates in dermal macrophages and adjacent keratinocytes

Melanin is produced in melanocytes, but it can be taken by adjacent keratinocytes in the basil layer of the epidermis

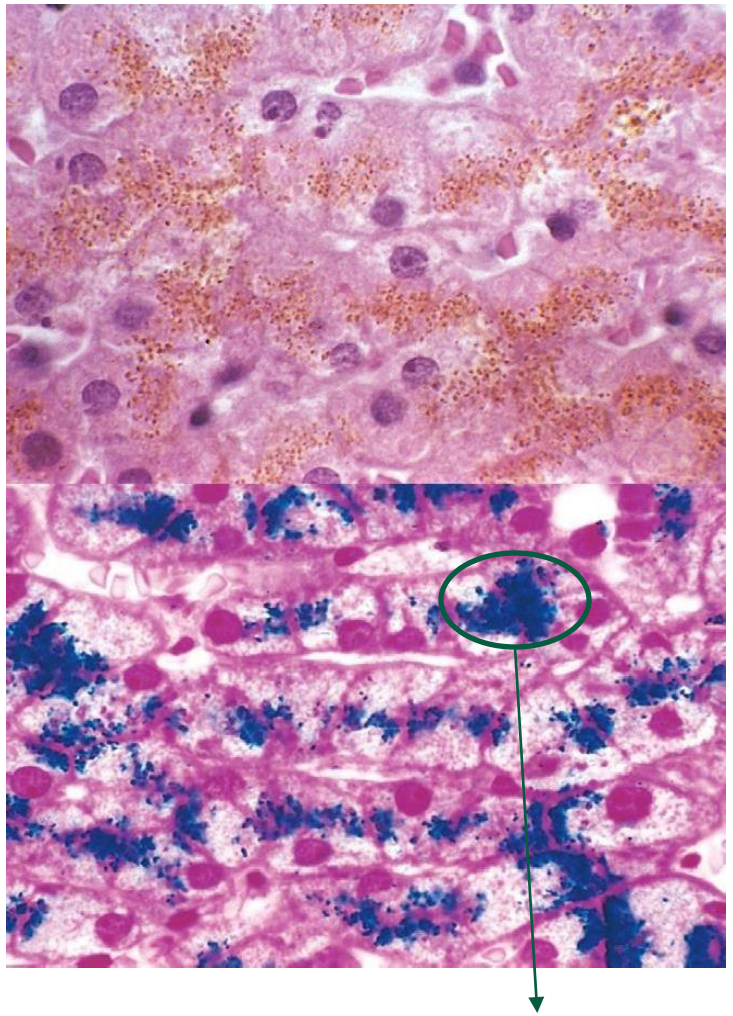


- Freckles

Freckles are the brownish spots appearing on this face.
They can appear on the dorsum of hands (sun exposed skin).

pigments

- **Hemosiderin**
- Hb-derived granular pigment (derived from iron)
- Granular brownish granules
- Iron + apoferritin==ferritin micelles (normally)
- When iron is deposited in excessive amount, much more ferritin micelles accumulate inside the cells, giving these brownish granules.
- Special stains are used such as prussian blue stain to distinguish this pigment from other brownish pigments like lipofuscin



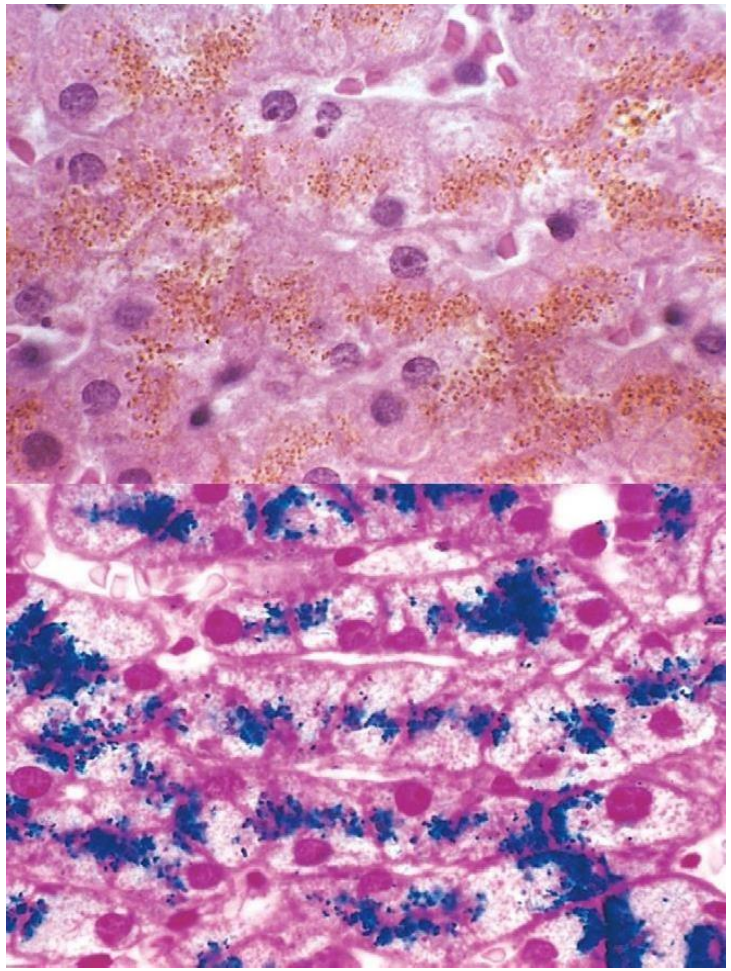
Prussian blue | Iron deposition

Blue granules appear only in hemosiderin pigment, not in lipofuscin or melanin because they can't take the stain

•Physiologic deposition: in the mononuclear phagocytes or macrophages of the BM (bone marrow), spleen, and liver, from RBC turnover

•Bruise: local pathologic deposition from hemorrhage red → blue → yellow due to iron accumulation

•Hemosiderosis: systemic pathologic deposition of hemosiderin (hemochromatosis (genetically inherited disease in which iron is deposited in many organs in the body like in liver, spleen, heart and skin), hemolytic anemias (rapid RBC turnover in sickle cell anemia or spherocytosis) , repeated blood transfusions (Thalassemia))



PATHOLOGIC CALCIFICATION

- Abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other mineral

Dystrophic Calcification

It is called dystrophic because Deposition occurs in dead/injured tissues

Normal Ca2+ metabolism + normal Ca2+ levels

It is not associated with hypercalcemia but it is Exacerbated by Hypercalcemia

Metastasis is the spread of malignancy (cancer)

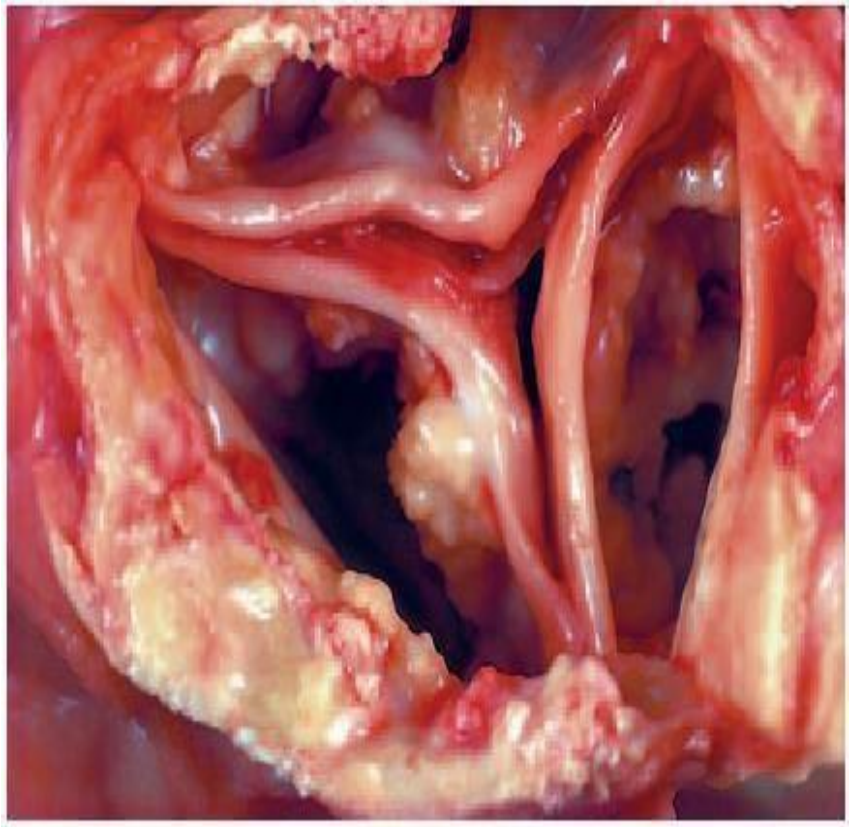
Metastatic Calcification

It is a misnomer because it is not related to metastasis (malignancy)

Deposition in normal tissues

Almost always abnormal Ca2+ metabolism (hypercalcemia)

Dystrophic calcification



Necrosis of any tissue type (e.g. Atherosclerosis, aging or damaged heart valves, aortic stenosis, tuberculosis)

Incidental finding indicating insignificant past cell injury

Or May be a cause of organ dysfunction

Dystrophic calcification

- Dystrophic calcification is the deposition of calcium in necrotic or damaged tissues.
- It occurs in atherosclerotic vessels, damaged or aged heart valves leading to aortic stenosis, and areas of inflammation such as tuberculosis.
- Excessive calcification can cause organ dysfunction.

Metastatic Calcification

Causes: (Any cause associated with hypercalcemia)

- Hyperparathyroidism (primary or secondary and production of parathyroid hormone related protein which occur in certain malignancies)

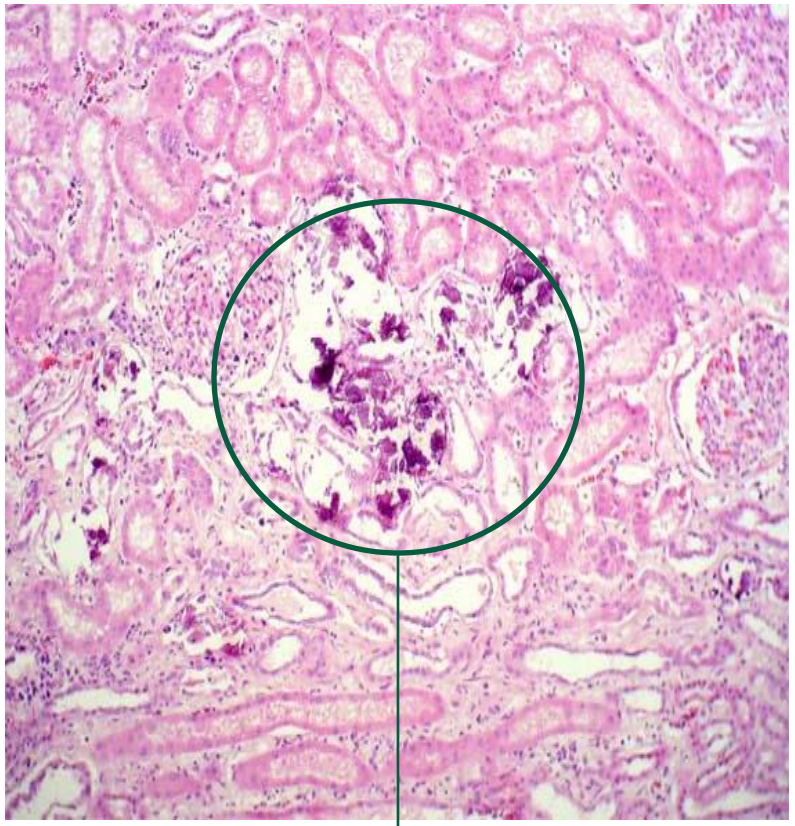
- Bone destruction (metastasis, MM (Multiple myeloma), leukemia, Pagets, immobilization)

Myeloma is a tumor of plasma cells in the bone

- Vit-D intoxication is associated with hypercalcemia
- Sarcoidosis (autoimmune disease associated with hypercalcemia)

- Renal failure with 2ry hyperparathyroidism.

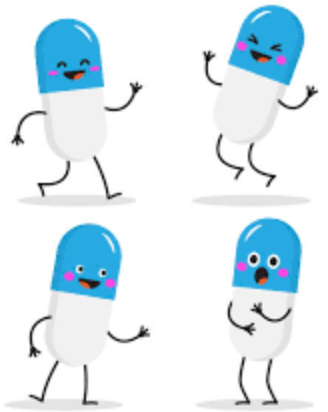
- **VESSELS, LUNG, KIDNEY**



- Microscopically, it appears purple under LM
- Macroscopically, it appears whitish and chalky
- The surrounding tissue is normal

رسالة من الفريق العلمي:

You can be any kind of doctor, just don't be a boring one.



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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			