

CELL INJURY FOR MEDICAL (LECTURE 3)

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Lecture 3 outline

1. **INTRACELLULAR ACCUMULATION** Reversible cellular changes and accumulations:
 - fatty change, hyaline change, accumulations of exogenous pigments (carbon, silica, iron dust, lead and argyria).
 - Accumulations of endogenous pigments: melanin, bilirubin, haemosiderin (haemosiderosis and haemochromatosis), lipofuscin.
2. **PATHOLOGIC CALCIFICATION:** metastatic calcification and dystrophic calcification

Intracellular Accumulations

Some substances can accumulate inside the cell in large amounts and cause problems in the cell and the organ. The substance may accumulate in either the cytoplasm or the nucleus. This is called as intracellular accumulation.

The accumulating substance can be:

- (1) Substance that is present in the cell normally but has accumulated in excess, such as water, lipids, glycogen, proteins, and carbohydrates
- (2) An abnormal substance that is not present in the cell normally. It can be either
 - Exogenous (from outside the body) e.g. a mineral or component of bacteria etc.
 - Endogenous (from inside the body) e.g. a product of abnormal synthesis or metabolism
- (3) Pigments: they can be endogenous or exogenous.

Examples of some of the substances that accumulate in excess in the cell:

A) Water: abnormal accumulation of water in cells is called hydropic change (cellular swelling). It is an early sign of cellular degeneration in response to injury. It is due to the failure of energy-dependent ion pumps present on the plasma membrane and this leads to loss of normal ionic and fluid homeostasis.

B) LIPIDS: All major classes of lipids can accumulate in cells:

- Triglycerides e.g. steatosis (fatty change)
- cholesterol/cholesterol esters (accumulation of cholesterol in the form of intracellular vacuoles can be seen in atherosclerosis in which there is accumulation of cholesterol in the smooth muscle cells and macrophages in the wall of arteries).
- and phospholipids

C) GLYCOGEN:

D) PIGMENTS: exogenous and endogenous

Accumulation of triglycerides: Steatosis (Fatty Change)

Fatty change is the abnormal accumulation of triglycerides inside cells. It is mainly seen in liver, but it is also seen in heart, muscle, and kidney.

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

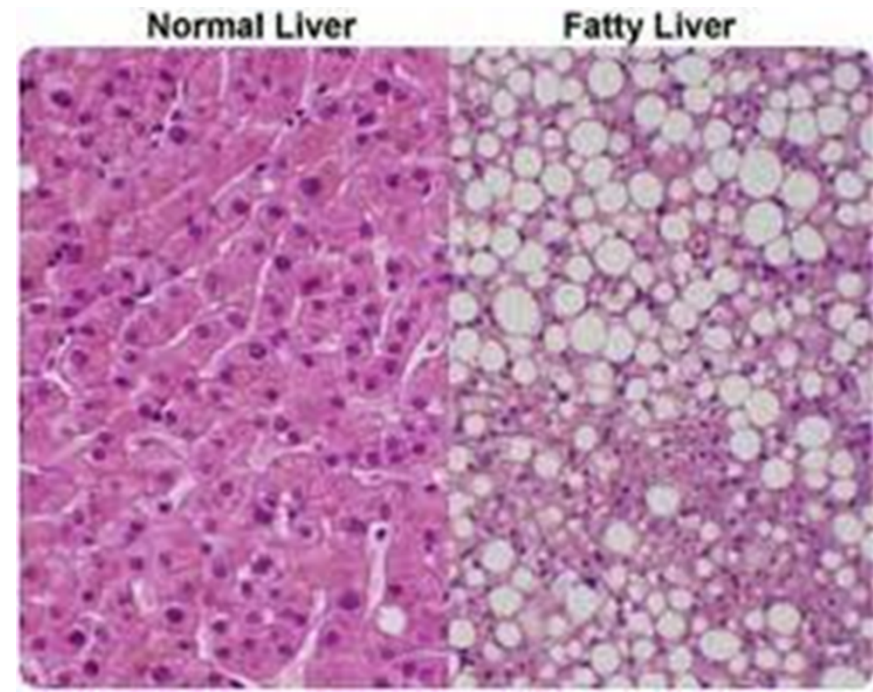
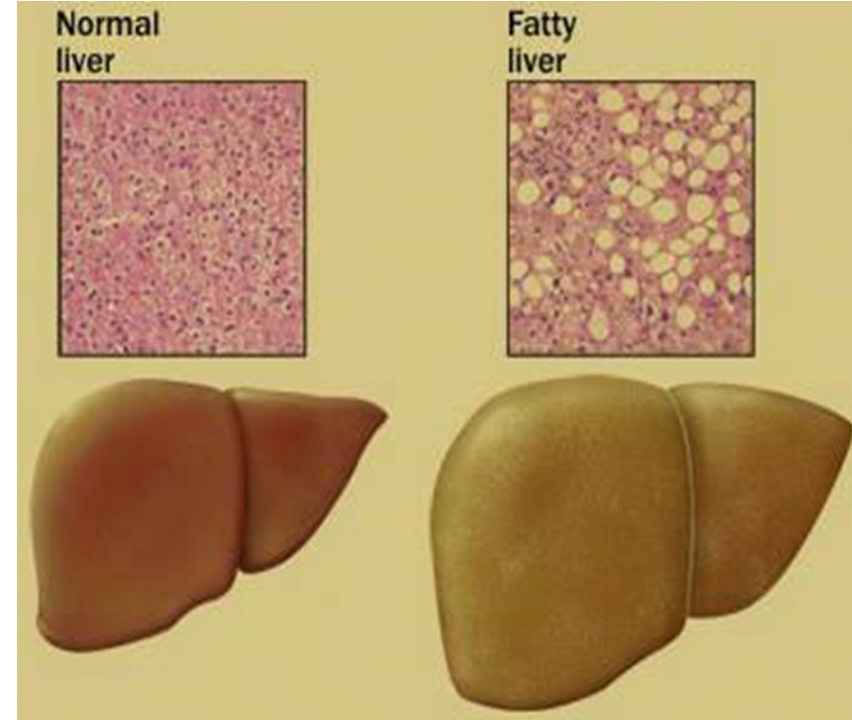
□ The causes of steatosis include:

- Toxins e.g. alcohol abuse
- protein malnutrition,
- diabetes mellitus,
- obesity,
- Anoxia/starvation
- Pregnancy
- Severe anemia

Steatosis (Fatty Change)

Morphology of Steatosis in liver:

- **Gross:** In mild cases liver looks normal. In severe cases liver is enlarged, yellow and greasy.
- **Light microscopy:** clear vacuoles in the cytoplasm displacing the nucleus to the periphery of the cell. Occasionally, cells rupture, and the fat globules merge, producing a so-called fatty cysts. The lipid stains orange-red with Sudan IV or Oil Red-O stains



ACCUMULATION OF GLYCOGEN

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

ACCUMULATION OF PIGMENTS

PIGMENTS are colored substances. There are:

- Endogenous pigments: synthesized within the body itself. Some endogenous pigments are normal constituents of cells (e.g. melanin) and others are not normal constituents of cells.

Examples of endogenous pigments:

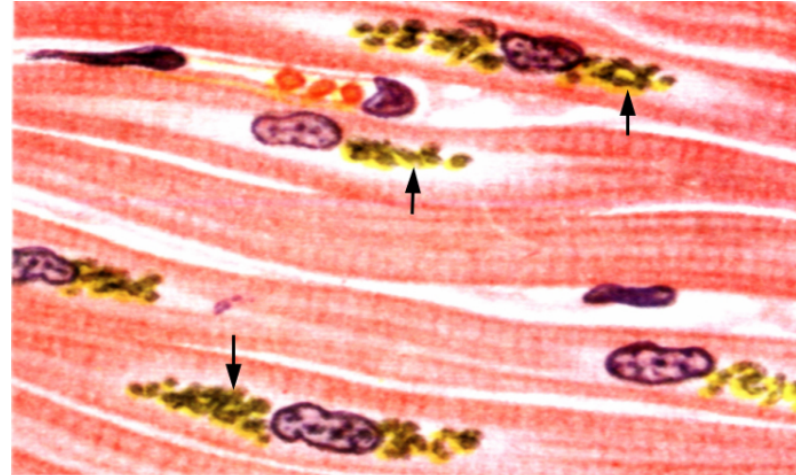
- Lipofuscin
 - Melanin
 - Bilirubin
 - Hemosiderin
- Exogenous pigments: they are not synthesized within the body itself and are coming from outside the body.

Endogenous Pigments

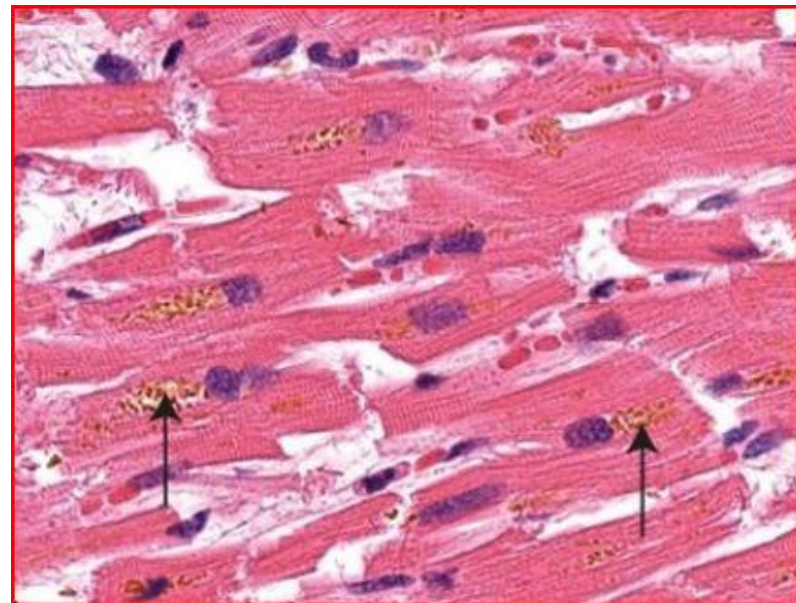
A) Lipofuscin is also known as wear-and-tear or aging pigment. Lipofuscin is endogenous and causes no damage to cells.

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

The figures are of heart muscle cells.



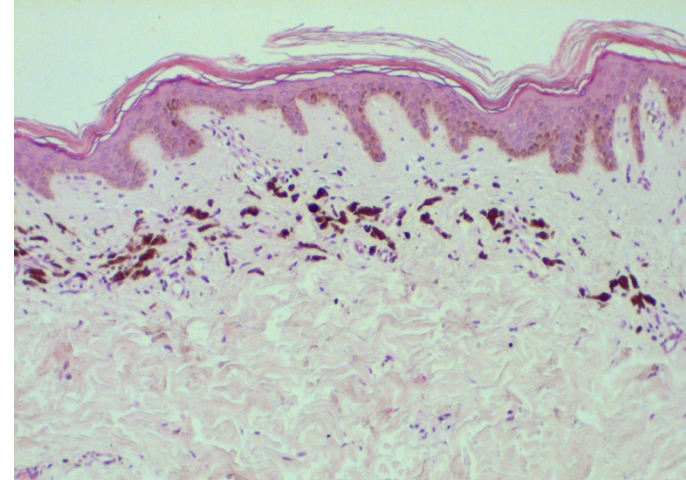
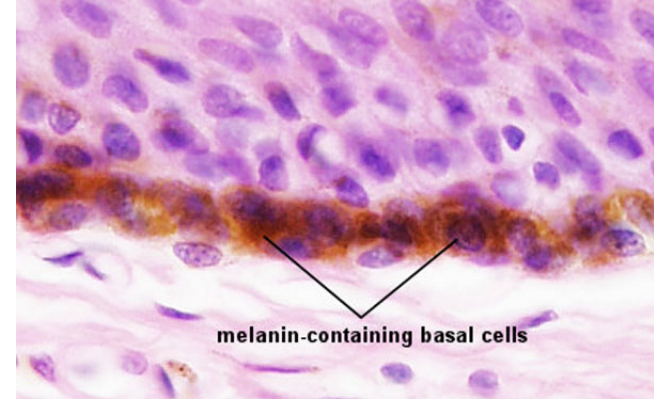
lipofuscin in cardiac cells



Endogenous Pigments cont.

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

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



Top 2 figures: normal skin with basal melanin.

Bottom figure: post inflammatory hyperpigmentation

Endogenous Pigments cont.

C) Bilirubin is a yellowish pigment found in bile, a fluid made by the liver.

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



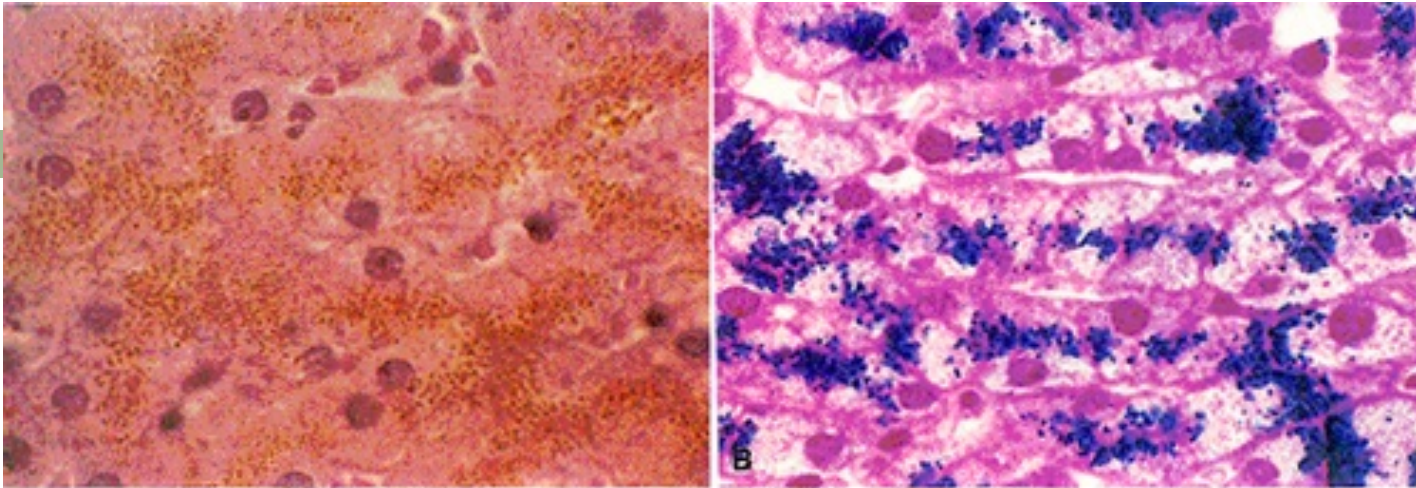
Endogenous Pigments cont.

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

□ Excess accumulation of hemosiderin can be seen in 2 main conditions:

1. **Hemosiderosis:** accumulation of hemosiderin mainly in macrophages. Here the pigment does not cause tissue damage. It can be:
 - localized hemosiderosis (e.g. common bruise: there is lysis of rbc's, release of hemoglobin and the iron in it is converted to hemosiderin)
 - systemic hemosiderosis.
2. **Hemochromatosis;** a more extensive accumulation of hemosiderin, often in parenchymal cells in various organs, with associated tissue damage, scarring & organ dysfunction. It can result in liver fibrosis, heart failure, diabetes mellitus and skin discoloration (bronzed diabetes).

Endogenous Pigments cont.



hemosiderin granules in liver cells

Left: HE stain, Right: Prussian blue stain

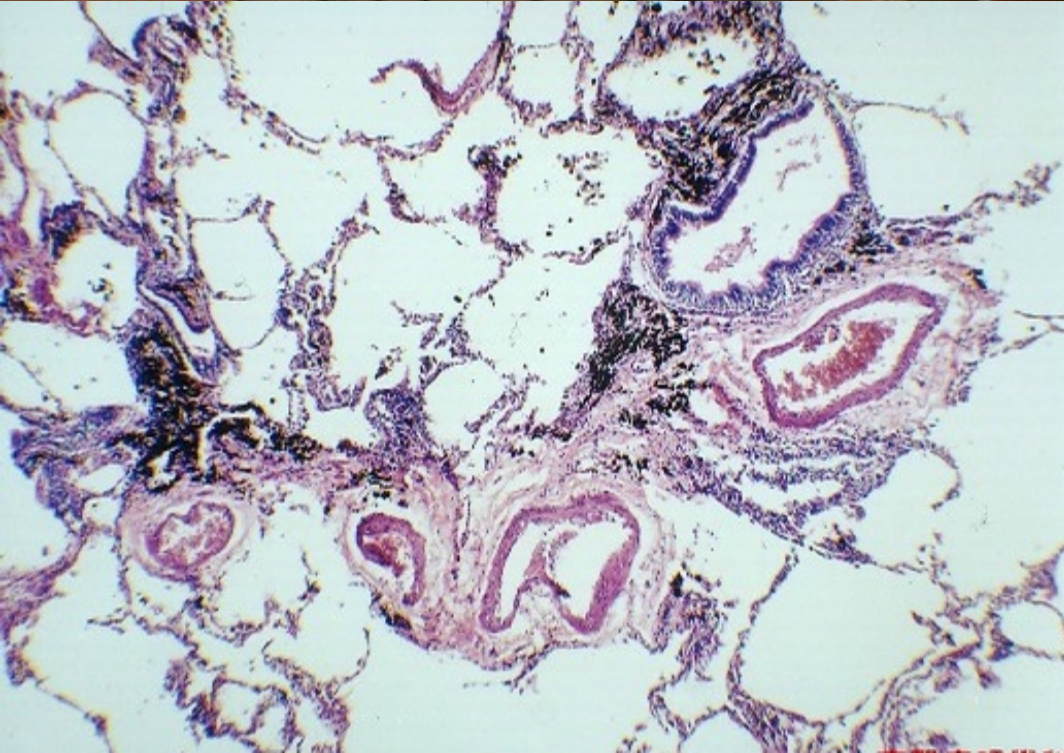
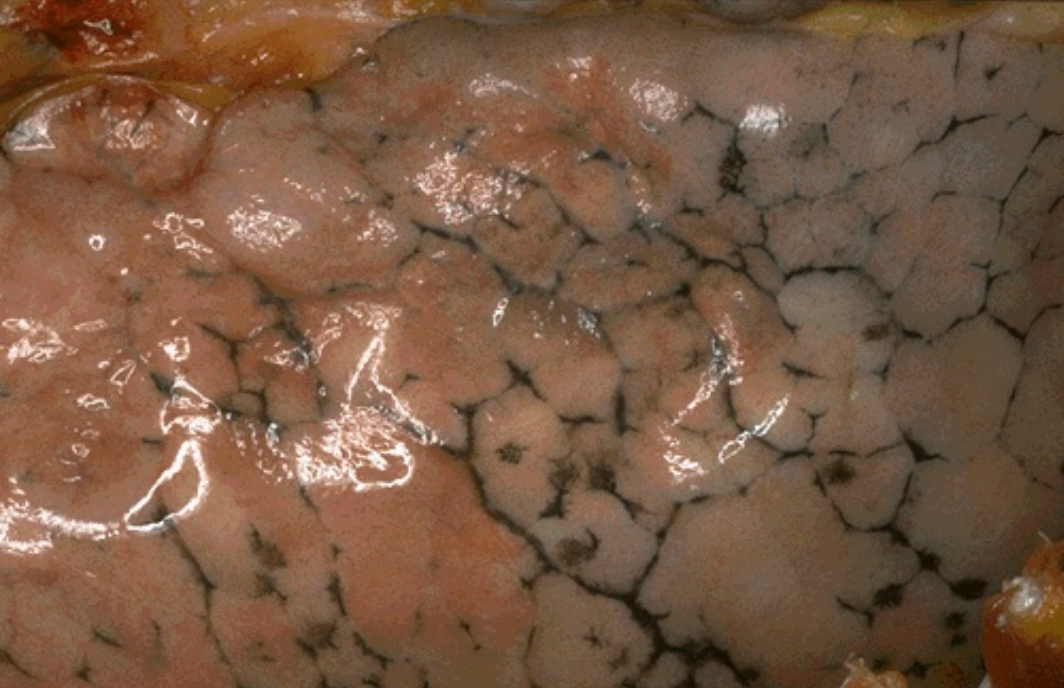
- The causes of excess systemic iron are:
 1. increased absorption of dietary iron,
 2. impaired use of iron,
 3. hemolytic anemias,
 4. Exogenous iron from blood transfusions.

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

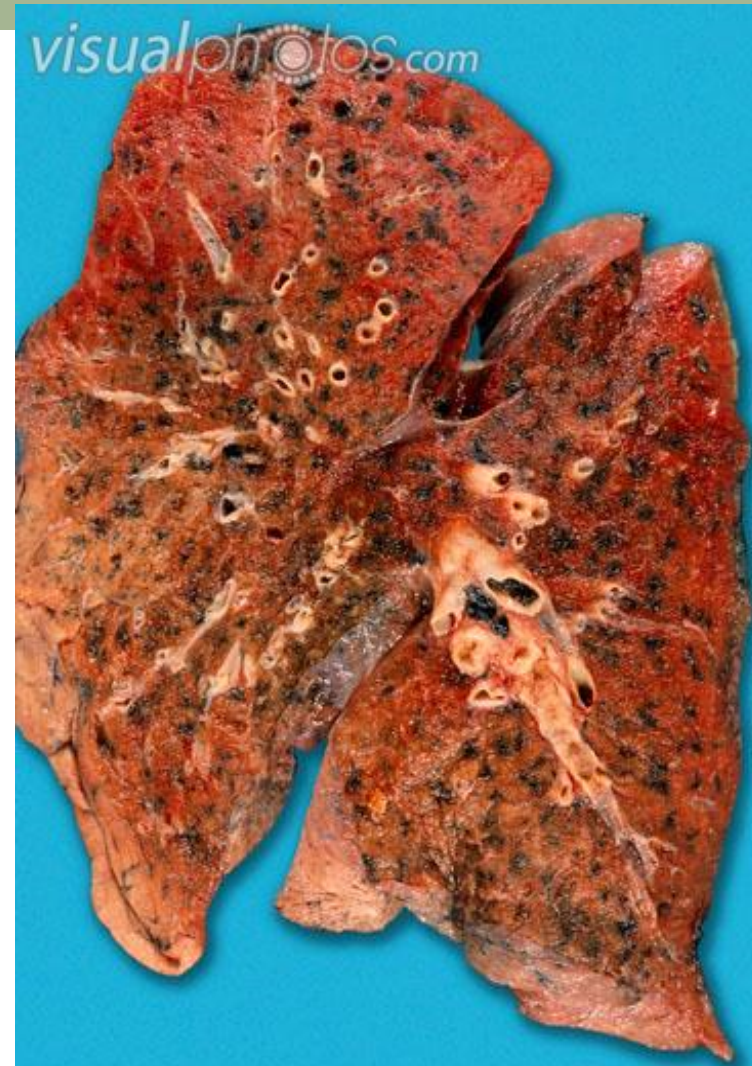
Exogenous Pigments

- **Anthracosis:** the most common *exogenous pigment* is *carbon pigment* or coal dust, which is an air pollutant. When breathing dirty polluted air, it is picked up by macrophages in the lung alveoli and also transported to the neighboring lymph nodes. Accumulation of this pigment blackens the lungs (*anthracosis*) and the draining lymph nodes. Smokers have the most pronounced anthracosis. The anthracotic pigment looks bad, but it causes no major organ dysfunction.
- But in the coal mining industry, there is too much carbon dust in the lung of coal miners, which leads to lung disease known as **coal worker's pneumoconiosis**.
- Other exogenous pigments that can be harmful when they accumulate in large amounts are silica, lead, iron dust and silver.
- **Plumbism** is **lead** poisoning and **argyria** is silver poisoning. In both cases there may be permanent grey discoloration of skin and conjunctivae.
- **Tattooing** is a form of localized, exogenous pigmentation of the skin. The pigments inoculated are phagocytosed by dermal macrophages.

Anthracosis lung



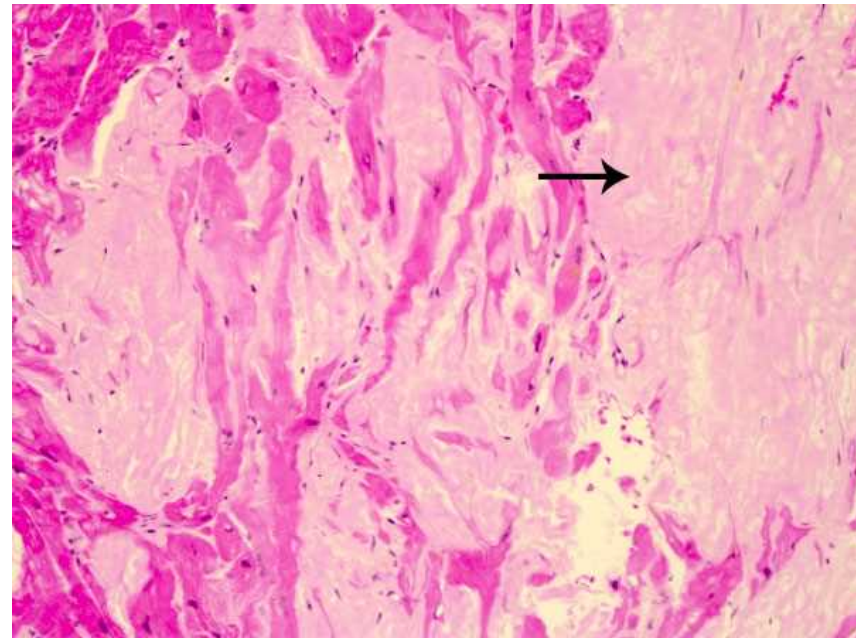
visualphotos.com



Amyloid Deposition (additional information)

- **Amyloidosis** is an **extracellular deposition** of fibrillary amyloid protein in various organs (kidney, liver, blood vessels, heart etc.) leading to organ damage.
- It is associated with a number of inherited and inflammatory disorders.
- Amyloidosis is a disorder of protein mis-folding. Amyloid is composed of non-branching fibrils of β -pleated sheets.
- There are 2 main clinical forms of amyloidosis

1. **Primary amyloidosis:** is associated with plasma cell abnormality e.g. multiple myeloma. In it the “AL” type amyloid is deposited.
2. **Secondary amyloidosis:** it is secondary to chronic inflammatory or autoimmune diseases (osteomyelitis, tuberculosis, rheumatoid arthritis etc). In it “AA” type (amyloid associated protein) amyloid is deposited.

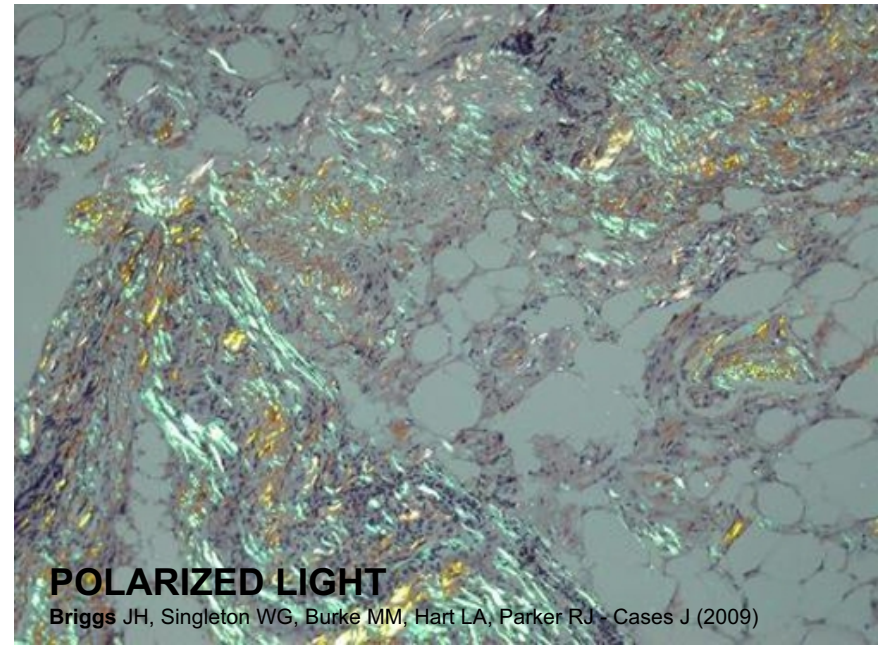
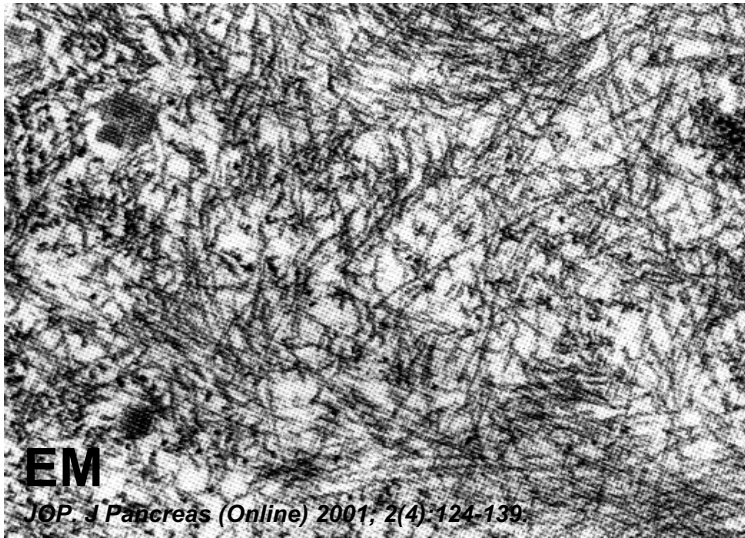
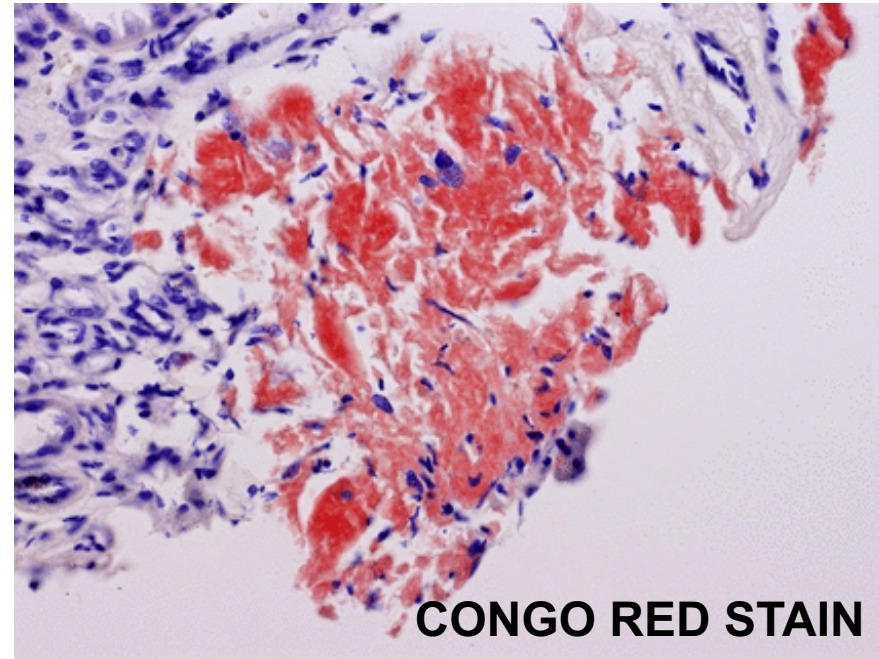


Light microscopy H&E stain

Pathpedia.com

Morphology of amyloid

- **Light microscopy:** it is pink eosinophilic material. With Congo red stain: it appears bright orange. And when the congo red stained tissue is exposed to polarized light it produces an apple-green birefringence.
- **Electron microscopy:** amyloid deposits are composed of non-branching fibrils, 7.5 to 10 nanomicon in diameter.
- **Diagnosis:** can be made with biopsy of organs like the kidney, rectum, gingiva and skin.



Pathologic Calcification

Pathologic calcification is the abnormal tissue deposition of calcium salts. There are two forms of pathologic calcification.

1. *dystrophic calcification*: is the deposition of calcium in dead or dying tissues; here the serum calcium levels are normal and calcium metabolism is normal.
2. *metastatic calcification*: is the deposition of calcium in normal and healthy tissue; it is seen in hypercalcemia. The serum calcium levels are elevated and the calcium metabolism is abnormal

Pathologic Calcification

Dystrophic calcification:

Seen in areas of necrosis or damage e.g.

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

Metastatic calcification:

It is seen mainly in kidneys, lung and stomach. It is associated with hypercalcemia. There are four principal causes of hypercalcemia:

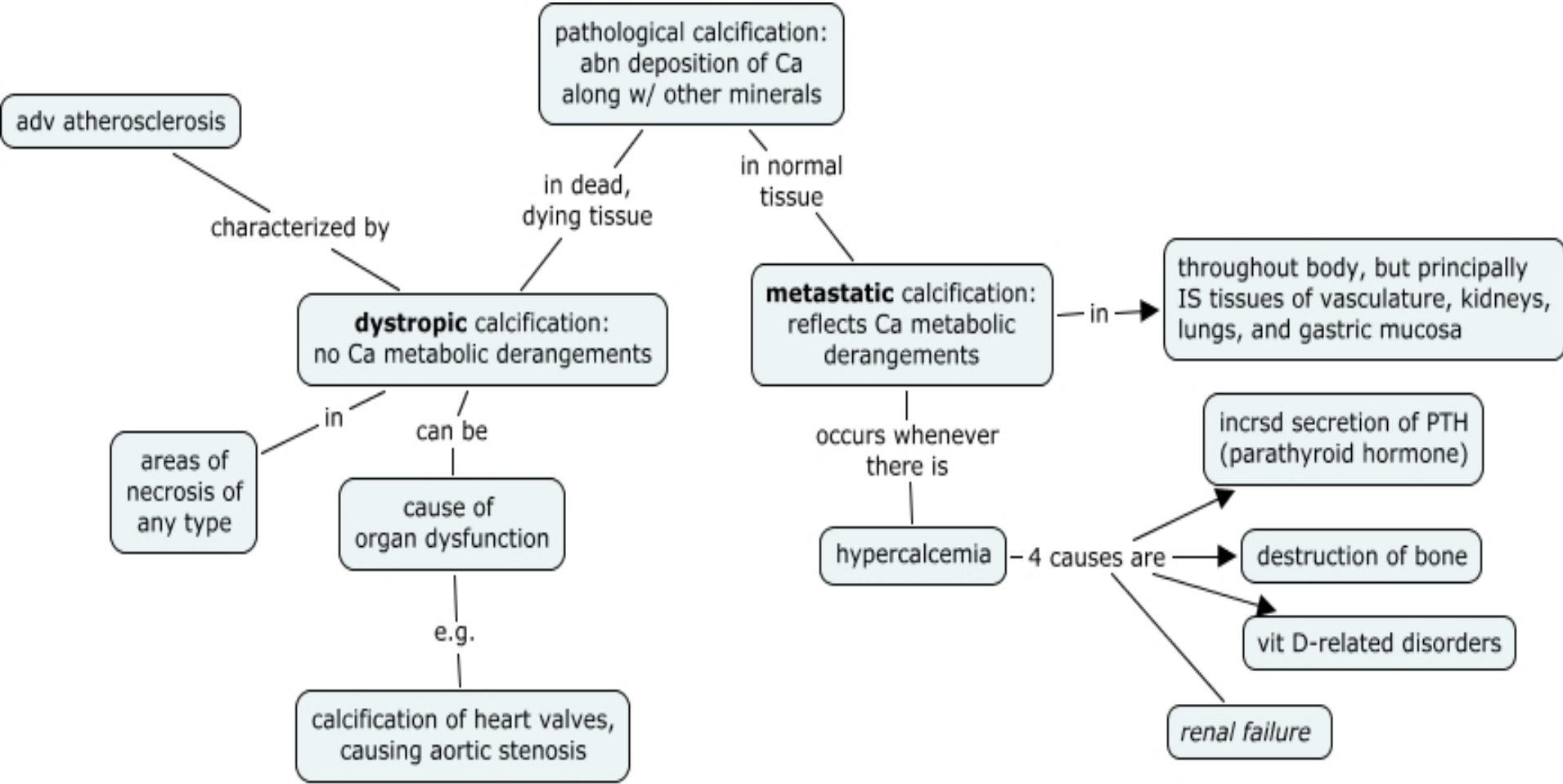
- a) Hyperparathyroidism: increased secretion of parathyroid hormone
- b) Destruction of bone in bone tumors e.g. multiple myeloma, leukemia and metastatic cancer in bone
- c) Vitamin D intoxication/hypervitaminosis D.
- d) Renal failure (causes retention of phosphate leading to secondary hyperparathyroidism)

Morphology of pathologic calcification

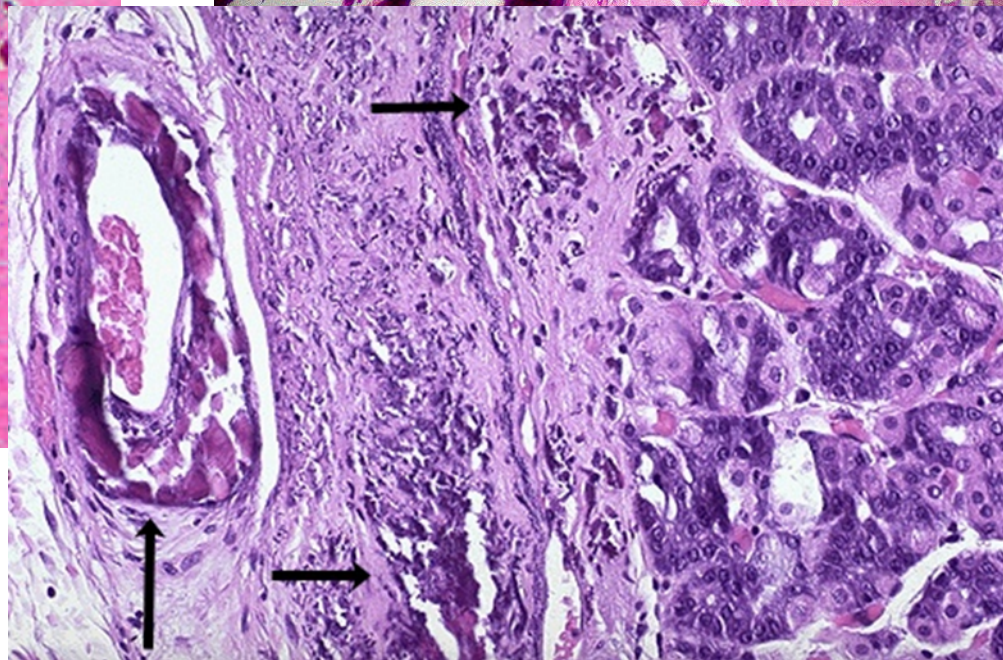
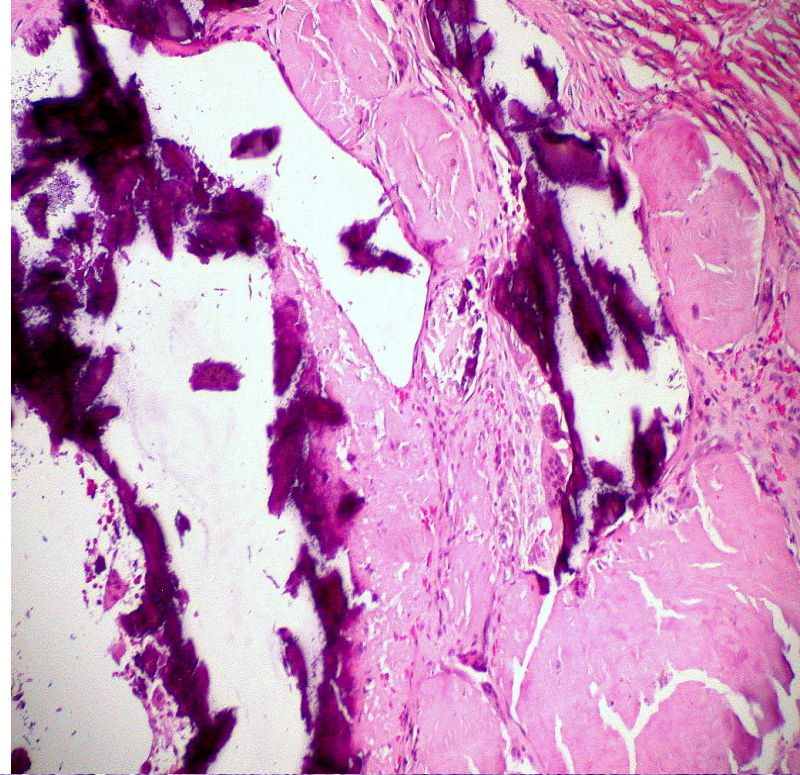
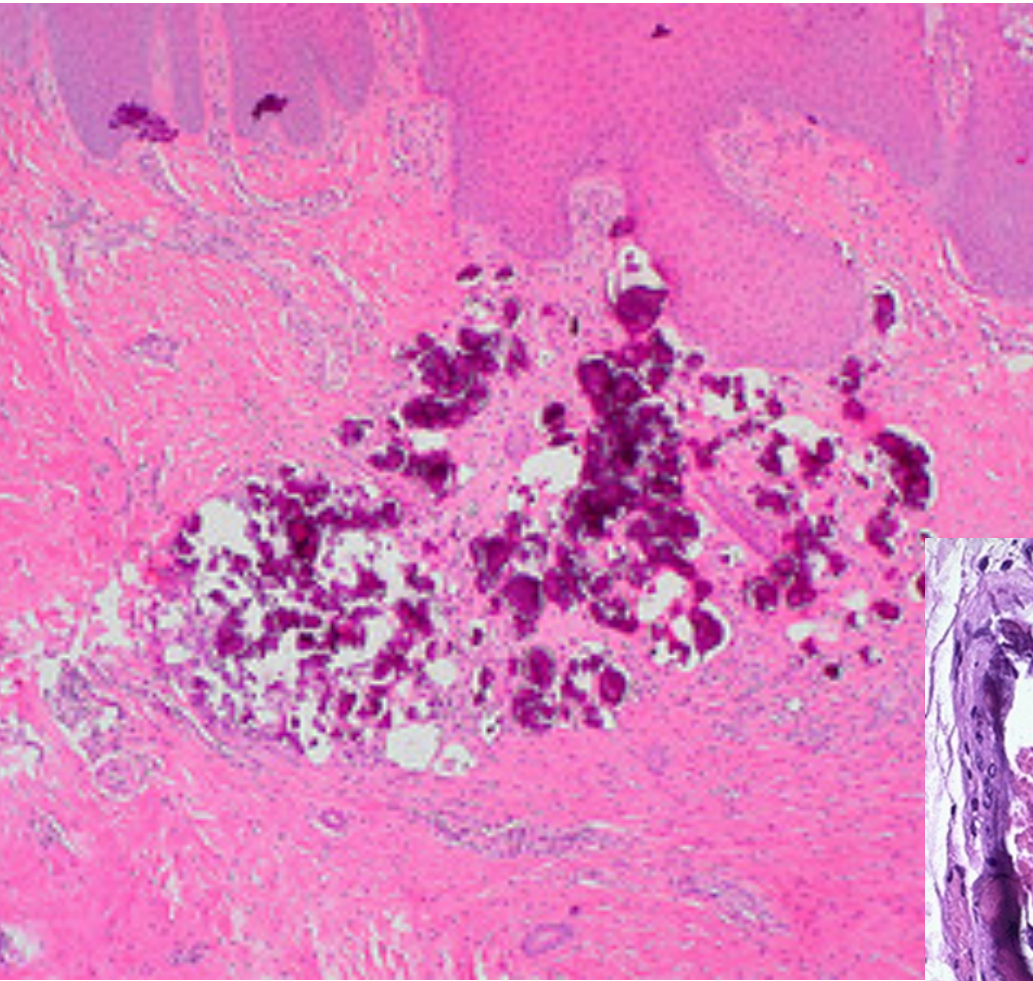
(dystrophic or metastatic, both look the same)

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

Pathologic Calcification



Pathologic Calcification



Psammoma bodies

