PATHOLOGY

CHAPTER: CELL INJURY

(for first year medical students in 3 lectures)

[Topics in 3 lectures: cell injury, free radical injury, necrosis and apoptosis, cellular accumulations, pathological calcification, adaptation to cell injuries]

(LECTURE 3)

Dr. Sufia Husain
Associate Prof & Consultant
Department of Pathology
College of Medicine
KSU, Riyadh

1st October 2020

Reference: Robbins & Cotran Pathology and Rubin's Pathology

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. **EXTRACELLULAR ACCUMULATION:** amyloidosis *(additional information)*
3. **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 these cells belong to. This is called as **intracellular accumulation.** The substance may accumulate in either the cytoplasm or the nucleus. The accumulating substance can be:

(1) A substance that is always present in a normal cell but has accumulated in excess e.g. 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) A pigment: it can be an endogenous or an exogenous pigment.

Examples of 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 (note: it is due to the failure of energy-dependent ion pumps on the plasma membrane → resulting in abnormal ion-fluid homeostasis).

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

- Accumulation of triglycerides → steatosis (fatty change)
- Accumulation of cholesterol and cholesterol esters → seen in atherosclerosis (in atherosclerosis there is accumulation of cholesterol in the wall of arteries).
- Accumulation of phospholipids

C) GLYCOGEN:

D) PIGMENTS: exogenous and endogenous

ACCUMULATION OF LIPIDS:

e.g. Steatosis/Fatty Change (accumulation of triglycerides)

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.

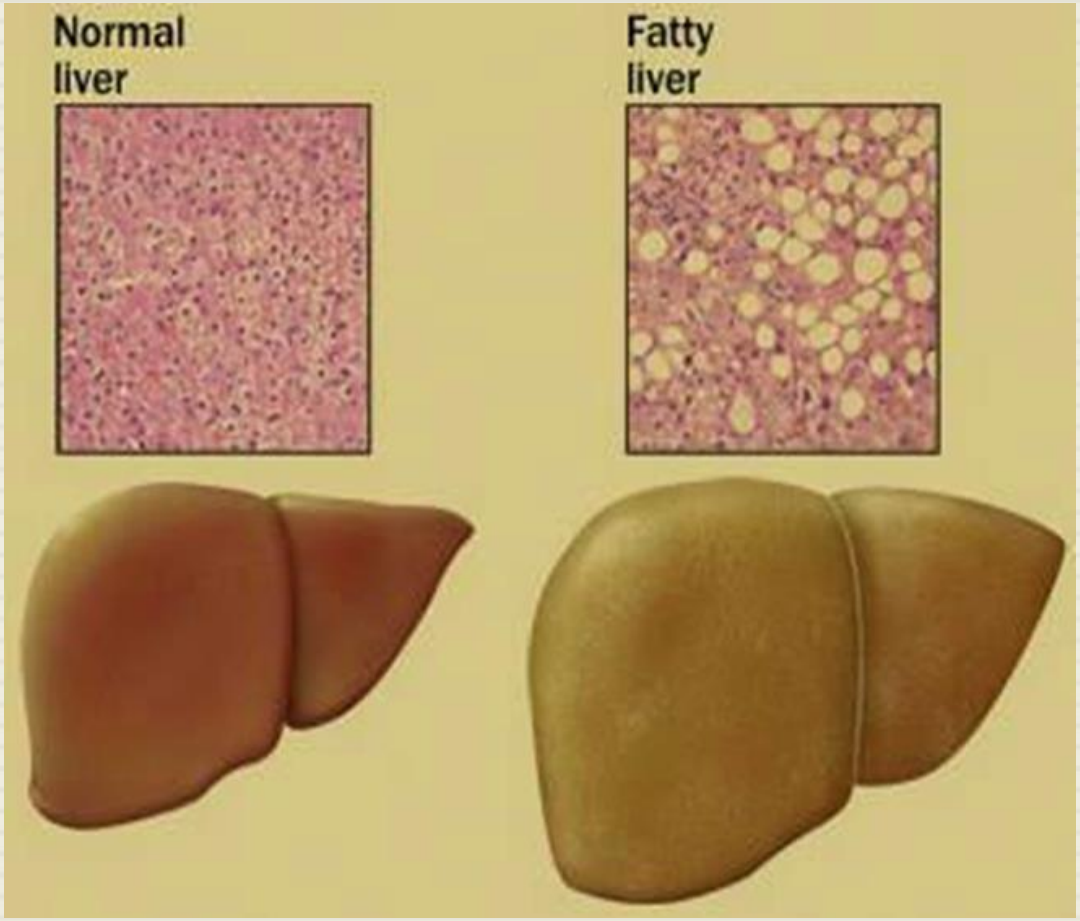
Excess accumulation of triglycerides within the hepatocytes occurs when there is an imbalance between the uptake, utilization, & secretion of fat by the affected cell.

- The causes of steatosis include:
  - Toxins e.g. alcohol abuse
  - protein malnutrition,
  - diabetes mellitus,
  - obesity,
  - Anoxia/starvation
  - Pregnancy
  - Severe anemia

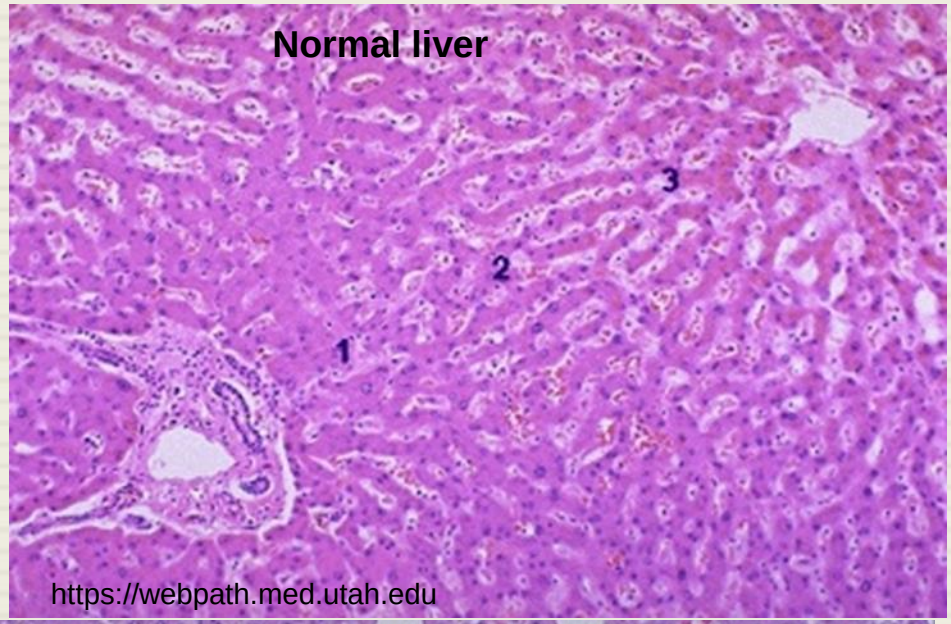
Steatosis (Fatty Change)

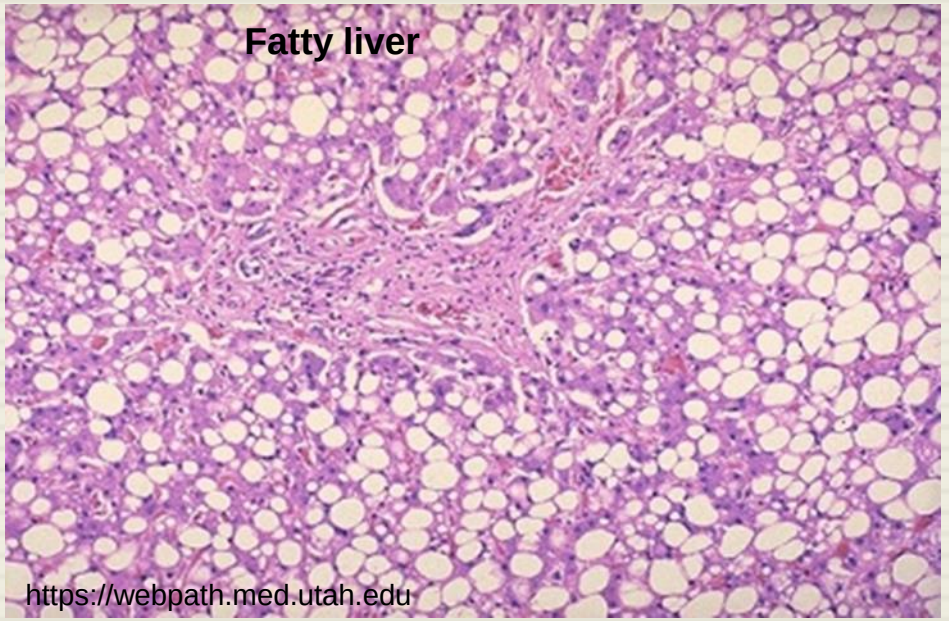
Morphology of Steatosis in liver:

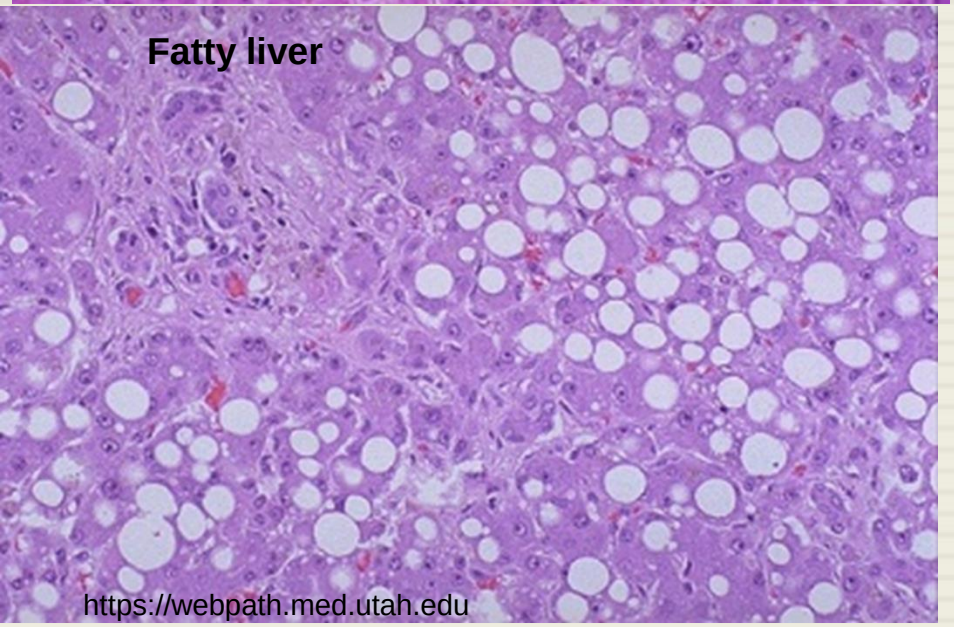
- **Gross:** In mild cases liver looks normal. In severe cases liver is enlarged, yellow and greasy.
- **Light microscopy:** clear vacuoles in the cytoplasm displacing the nucleus to the periphery of the cell. Occasionally, cells rupture, and the fat globules merge, producing a so-called fatty cysts.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



Steatosis (Fatty Change)







ACCUMULATION OF GLYCOGEN

- Glucose is the main source of fuel for cells. Excess glucose is stored in the liver and muscles in the form of glycogen. Glycogen is stored in the cell cytoplasm.
- Excessive intracellular deposits of glycogen can be seen in patients with abnormality in the glucose or glycogen metabolism.
- Glycogen appears as clear vacuoles within the cell cytoplasm. Glycogen stains pink/violet with periodic acid schiff (PAS) stain.
- Glycogen accumulation is seen in:
  - Diabetes mellitus: it is a disorder of glucose metabolism. In this disease, glycogen accumulates in the kidney (proximal convoluted tubules), liver, pancreas (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 and there can be abnormal accumulation of glycogen in the liver, muscle and other tissues.

ACCUMULATION OF PIGMENTS

PIGMENTS are colored substances. Pigments can be:

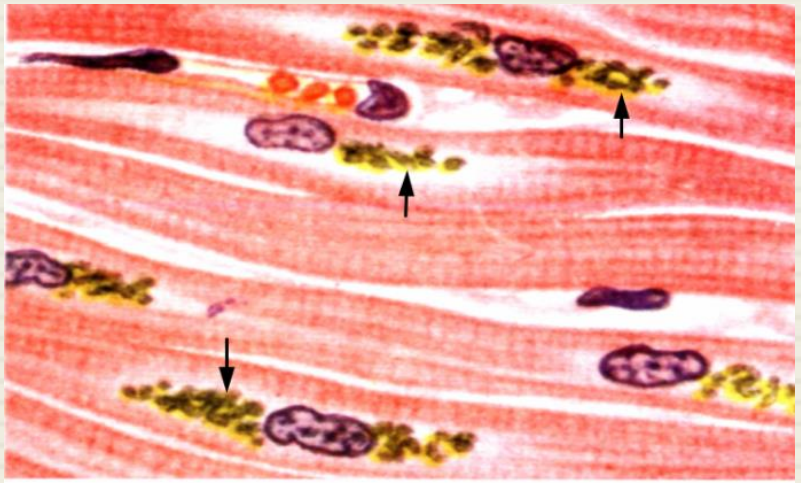
- Endogenous pigments: synthesized within the body itself. Some endogenous pigments are normal constituents of cells (e.g. melanin) and others are not normal constituents of cells. Examples of endogenous pigments:
  - Lipofuscin
  - Melanin
  - Bilirubin
  - Hemosiderin
- Exogenous pigments: they are not synthesized within the body itself and are coming from outside the body.

Endogenous Pigments

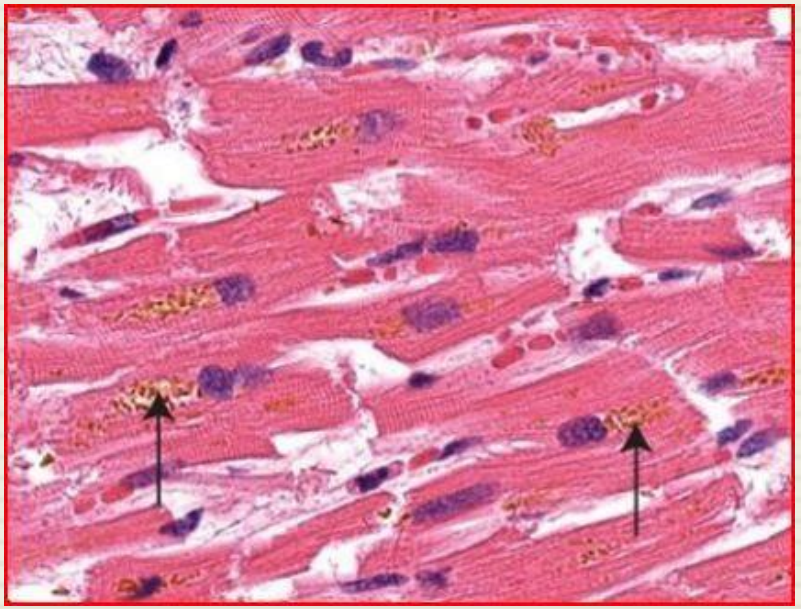
A) Lipofuscin is also known as "wear-and-tear" or "aging" pigment. Lipofuscin is endogenous and causes no damage to cells.

- Presence of lipofuscin pigment indicates past free radical injury (lipid peroxidation).
- It is golden yellow-brown, granular intra-cytoplasmic pigment
- It is prominent in the liver and heart of aging patients, in atrophic tissue, in patients with severe malnutrition and cancer cachexia.

(The figures are of heart muscle cells/cardiomyocytes.)



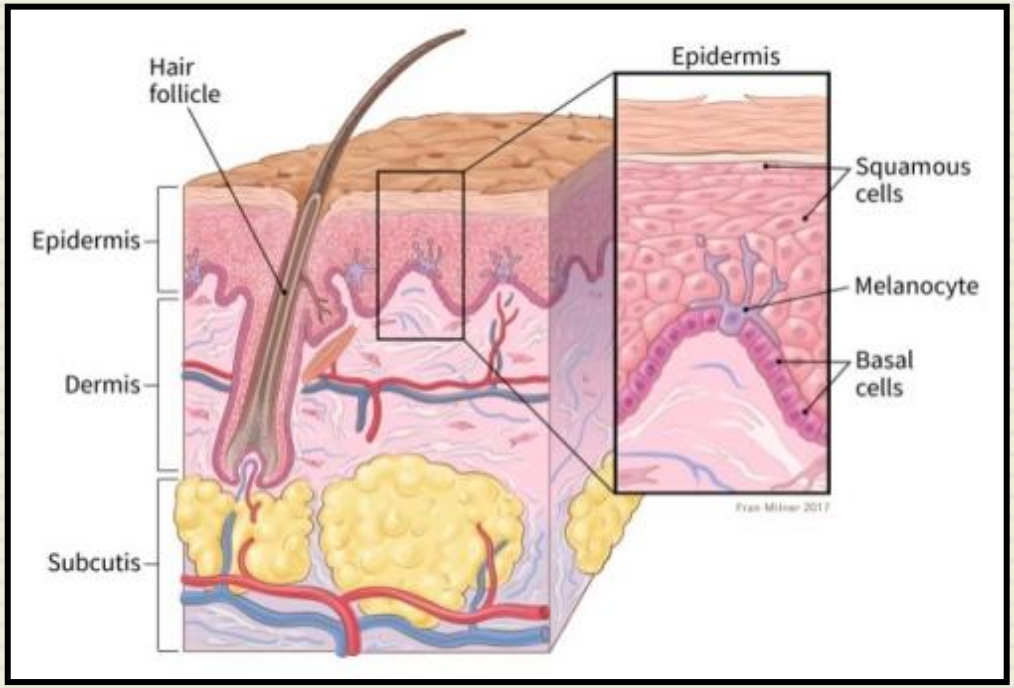
lipofuscin in cardiac cells



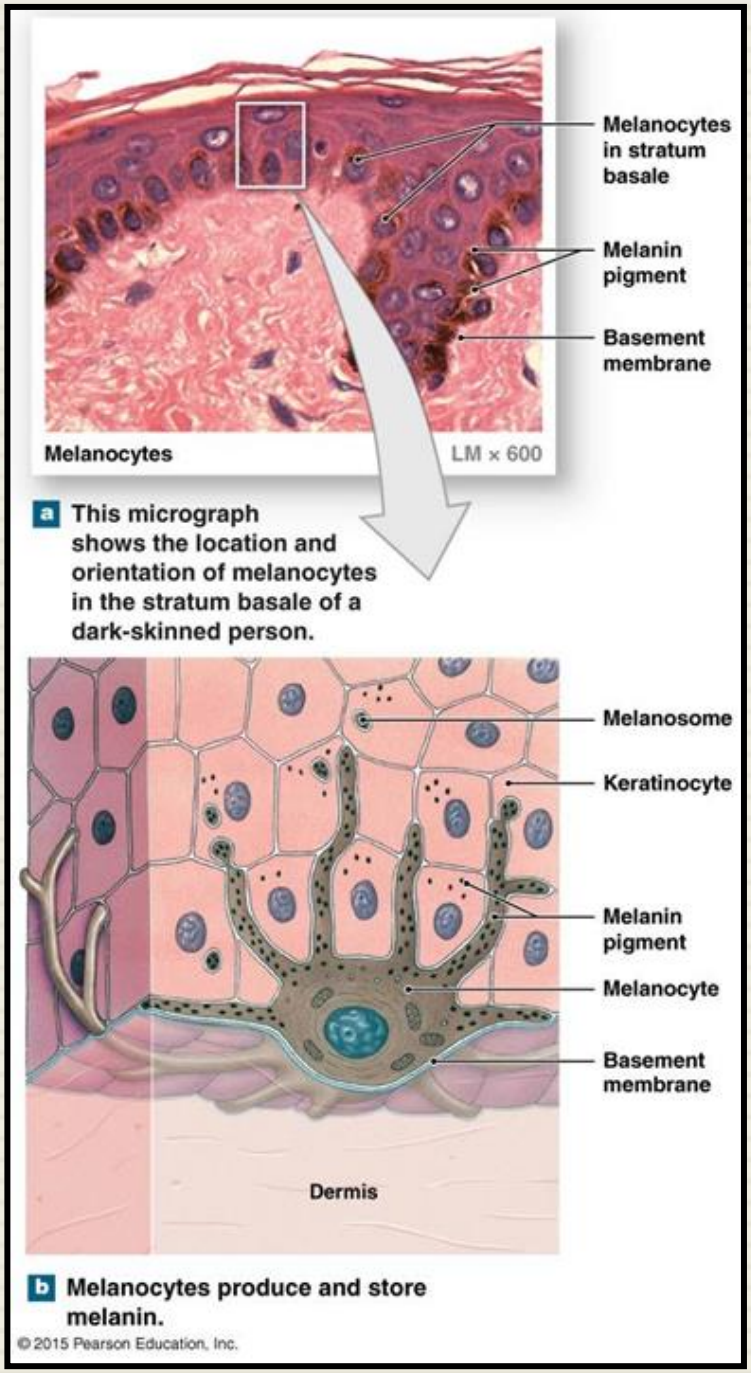
B) Melanin:

background information

The skin is made up of epidermis, dermis etc. Melanocytes are the pigment cells present in the basal layer of the epidermis and they produce melanin pigment. Melanin is responsible for the color of our skin. Melanin is stored in lysosomes of the melanocytes (melanosomes). Melanosomes and melanin granules are transferred from melanocytes to the cytoplasm of adjacent epidermal cells/ keratinocytes. Melanin protects from the harmful effects of UV light.



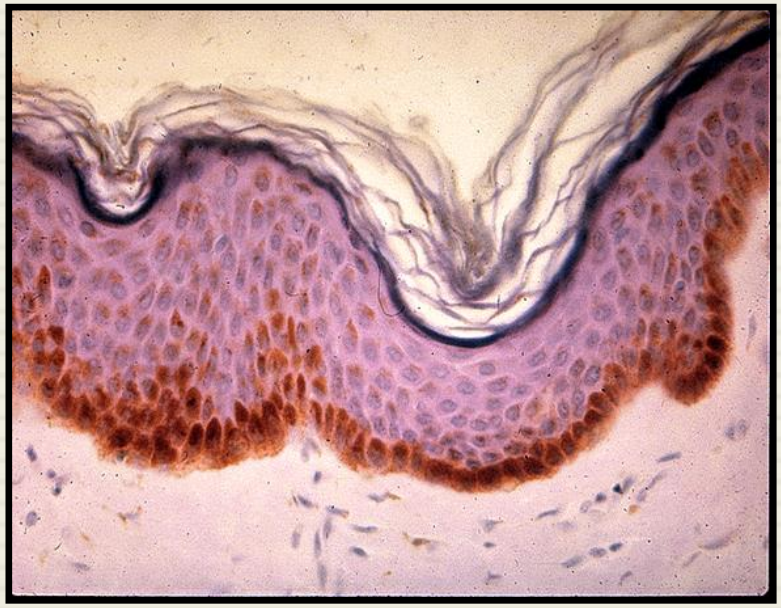
https://www.cancer.org/cancer/melanoma-skin-cancer

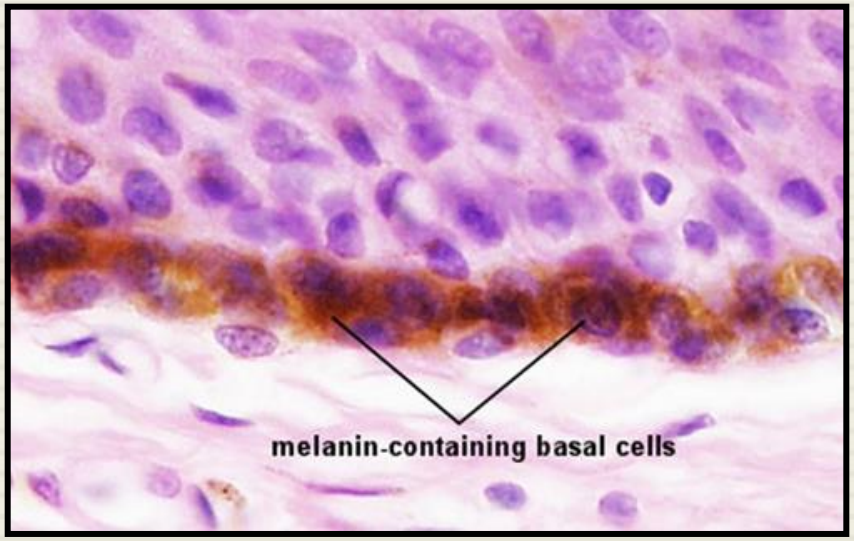


B) Melanin:

background information

normal skin with basal melanin.

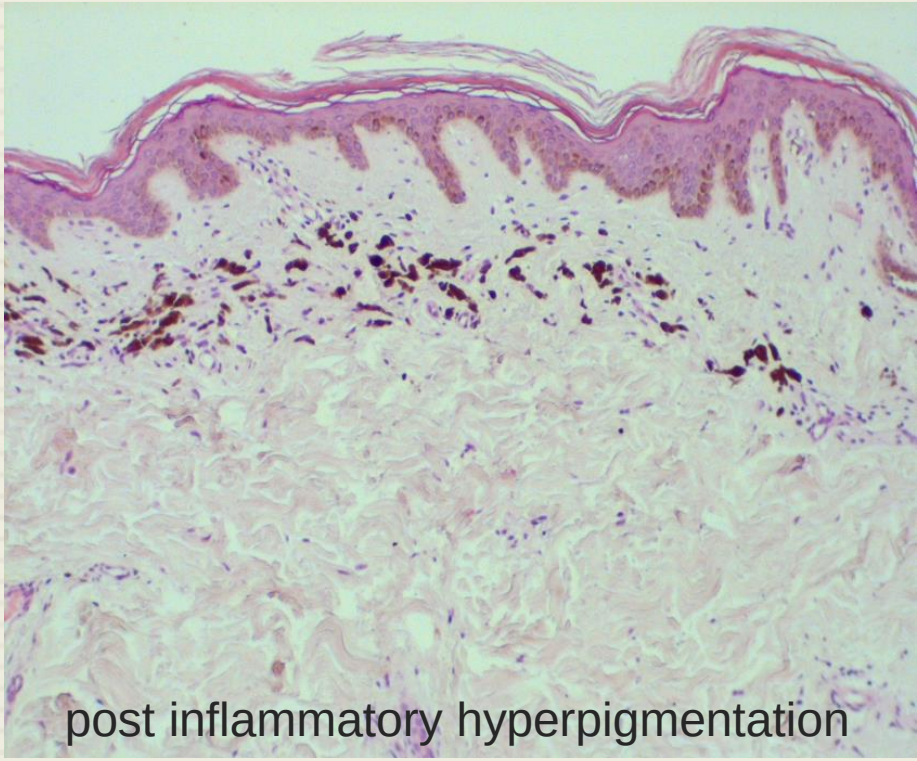




Endogenous Pigments cont.

B) Melanin: an endogenous, non-hemoglobin, brown-black pigment normally present in the melanocytes.

- It accumulates in excess in benign and malignant melanocytic tumors.
- Also, in inflammatory conditions of the skin it travels from epidermis into the underlying dermis where it is stored in the macrophages, resulting in the formation of dark spots. This is called as "post inflammatory hyperpigmentation" of the skin.
- Masson-Fontana stain is used to identify melanin.

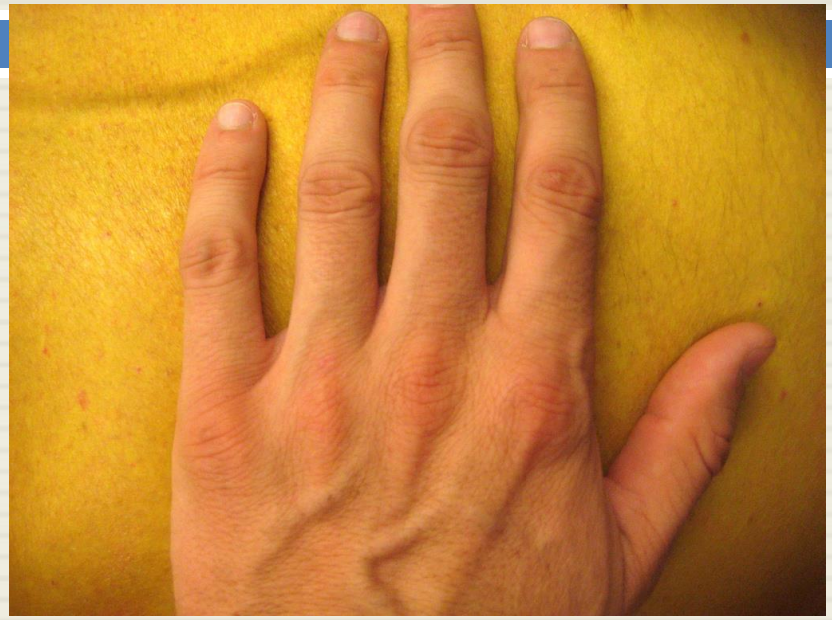


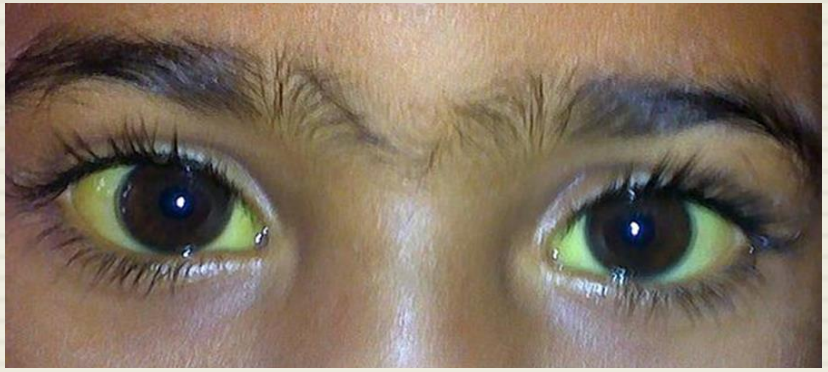
post inflammatory hyperpigmentation

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 (i.e. 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.



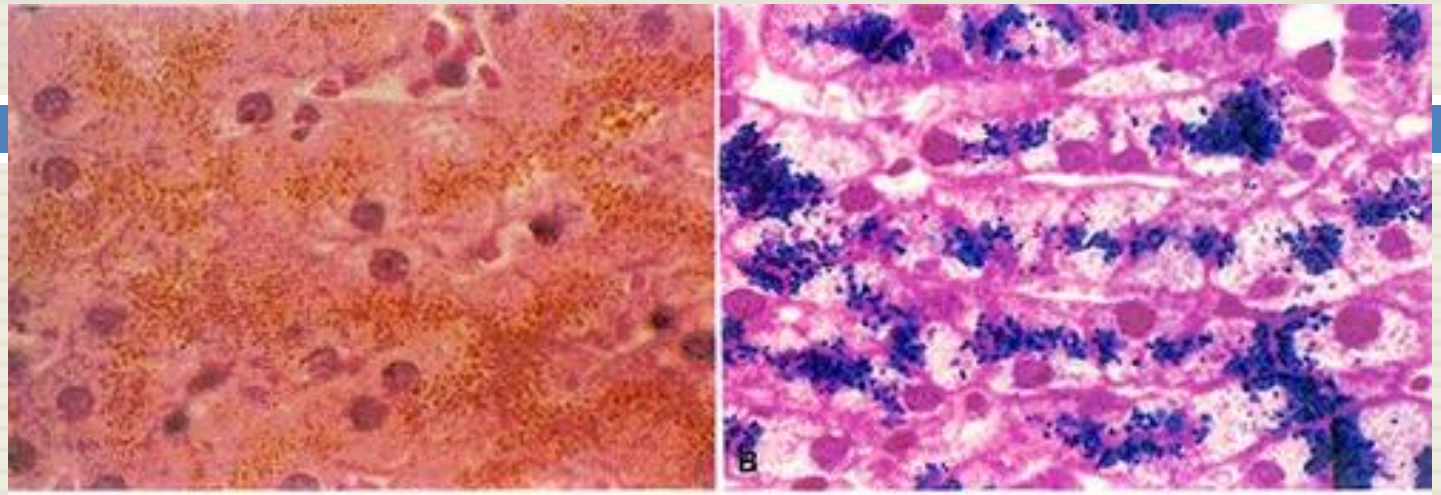


Endogenous Pigments cont.

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

- Excess accumulation of hemosiderin can be seen in 2 main conditions:
  1. **Hemosiderosis:** in it there is accumulation of hemosiderin in macrophages mainly. Here the pigment does not cause significant tissue damage. It can be:
     - localized hemosiderosis (e.g. common bruise: there is lysis of rbcs, release of hemoglobin and the iron in it is converted to hemosiderin)
     - systemic hemosiderosis: there is systemic overload of iron.
  2. **Hemochromatosis:** in it there is a more extensive systemic overload/ accumulation of iron and hemosiderin, often in parenchymal cells of various organs with associated tissue damage, scarring & dysfunction of that organ. It can result in liver fibrosis, heart failure, diabetes mellitus and skin discoloration (bronzed diabetes).
- The causes of excess systemic iron are:
  1. increased absorption of dietary iron,
  2. impaired utilization of iron,
  3. hemolytic anemias
  4. from blood transfusions (the transfused red cells provide an exogenous load of iron)

Endogenous Pigments cont.



hemosiderin granules in liver cells

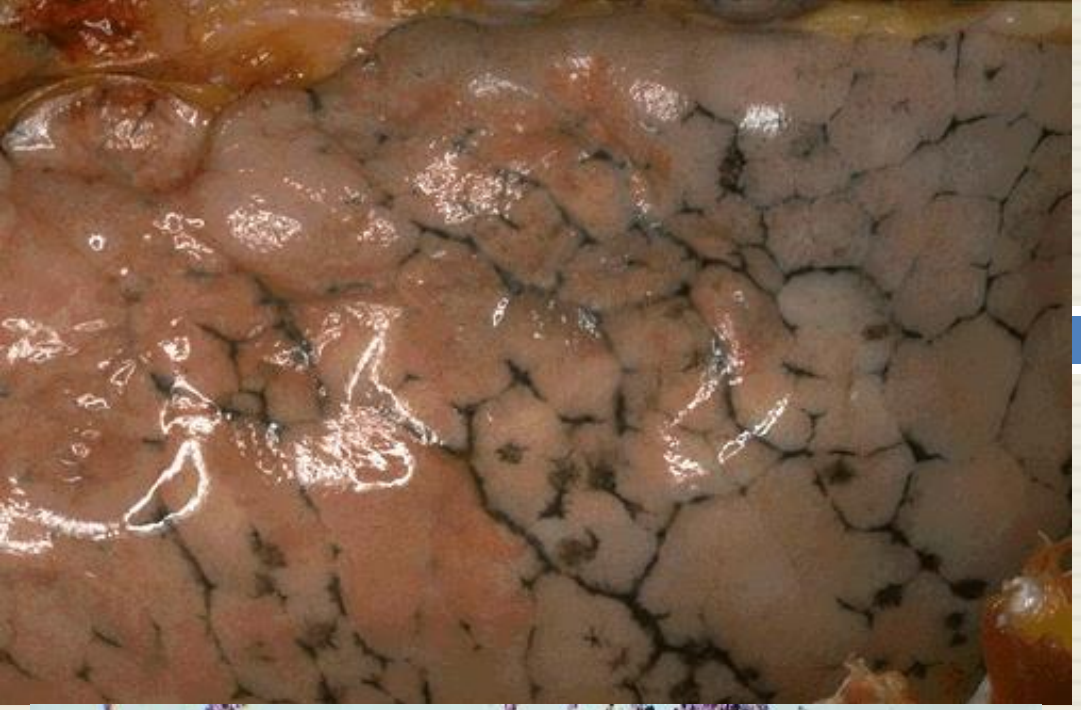
Left: HE stain, Right: Prussian blue stain

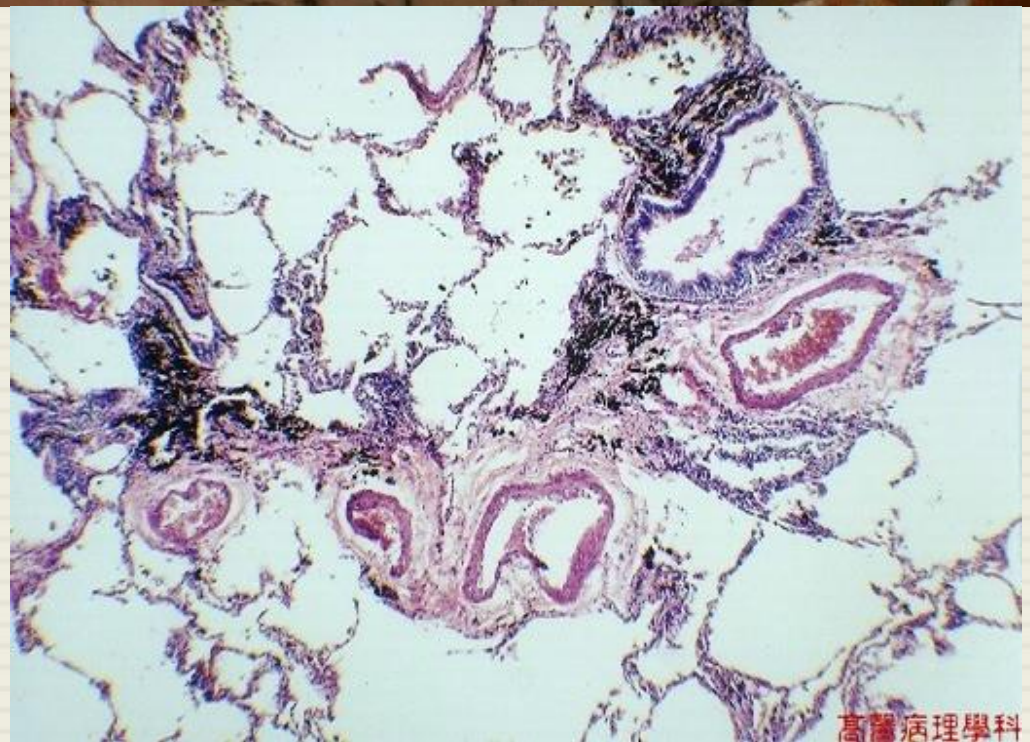
Morphology: Iron pigment is golden and granular in the cytoplasm of cells e.g. macrophages, cells of the liver (hepatocytes), cells of pancreas, heart etc. It appears blue-black with Pearl Prussian blue stain.

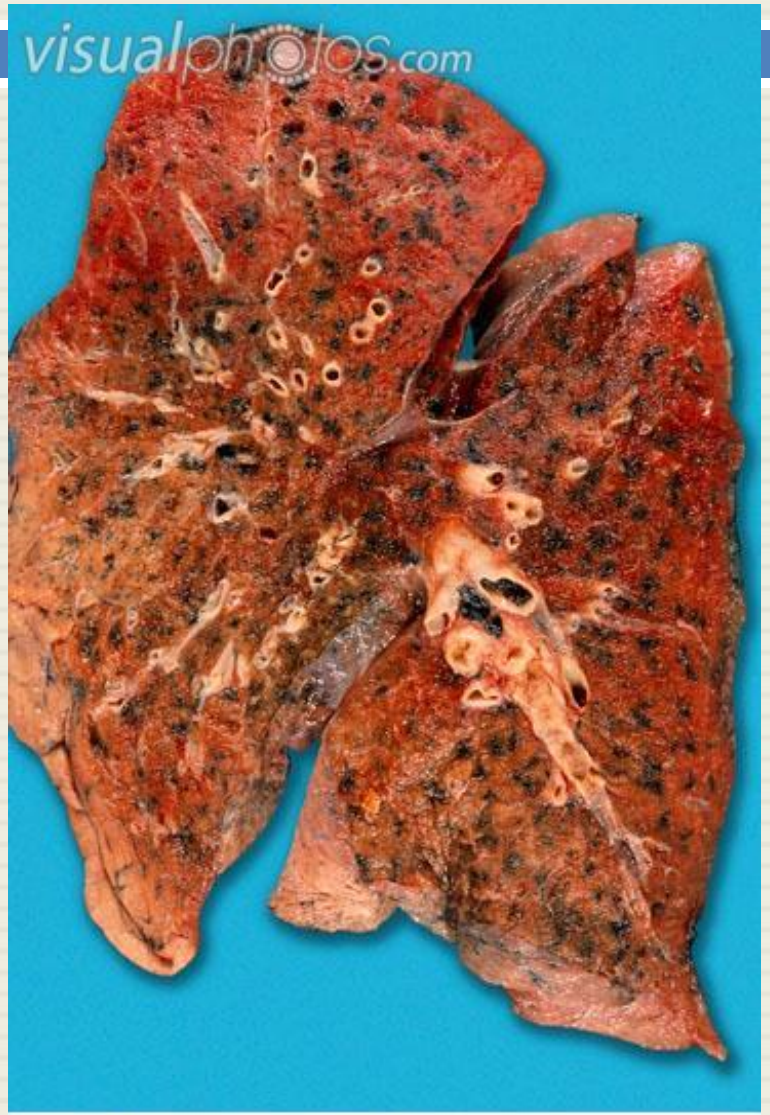
Exogenous Pigments

- **Anthracosis:** the most common *exogenous pigment* is *carbon pigment* or coal dust, which is an air pollutant. The dirty polluted air is breathed in and the carbon particles are 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 marked anthracosis. The anthracosis does not cause any major organ dysfunction.
- **Coal worker's pneumoconiosis:** in the coal mining industry, there is too much carbon dust in the lung of coal miners and it leads to a lung disease known as coal worker's pneumoconiosis.

Anthracosis lung







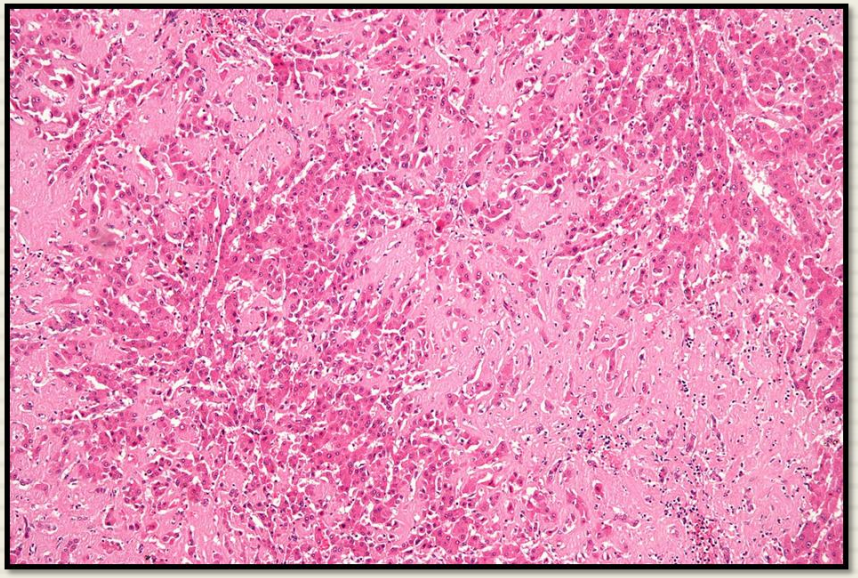
Exogenous Pigments

- 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.

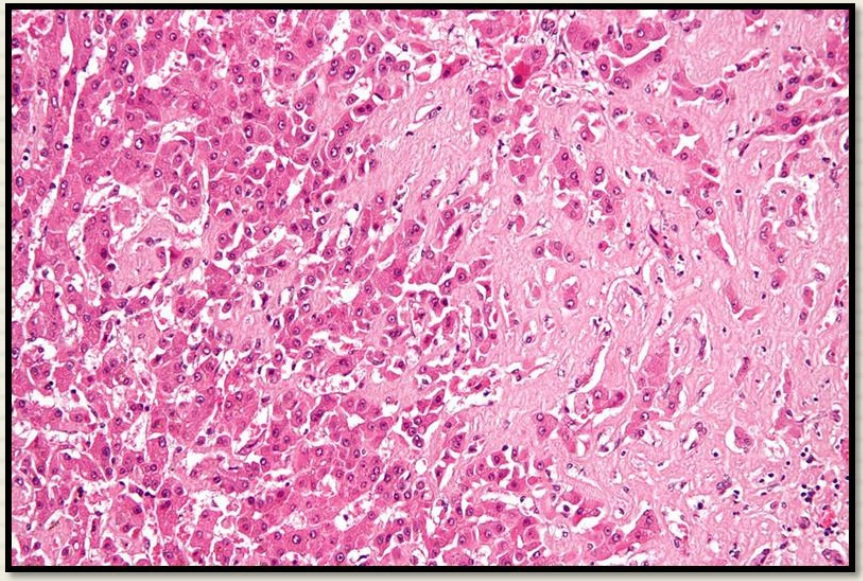
EXTRACELLULAR ACCUMULATION: Amyloidosis

(additional information)

- **Amyloidosis** is a disorder of protein mis-folding, which results in the **extracellular deposition and accumulation** of a fibrillary protein called amyloid.
- Amyloid is composed of non-branching fibrils of β-pleated sheets.
- It is deposited in various organs (kidney, liver, blood vessels, heart etc.) leading to damage of that organ.
- Amyloidosis is associated with a number of inherited and inflammatory disorders.
- There are 2 main clinical forms of amyloidosis:
  - **Primary:** associated with plasma cell abnormalities e.g. multiple myeloma; has "AL" type of amyloid.
  - **Secondary:** is secondary to chronic inflammatory or autoimmune diseases e.g. tuberculosis, rheumatoid arthritis etc.; has "AA" type of amyloid associated protein.



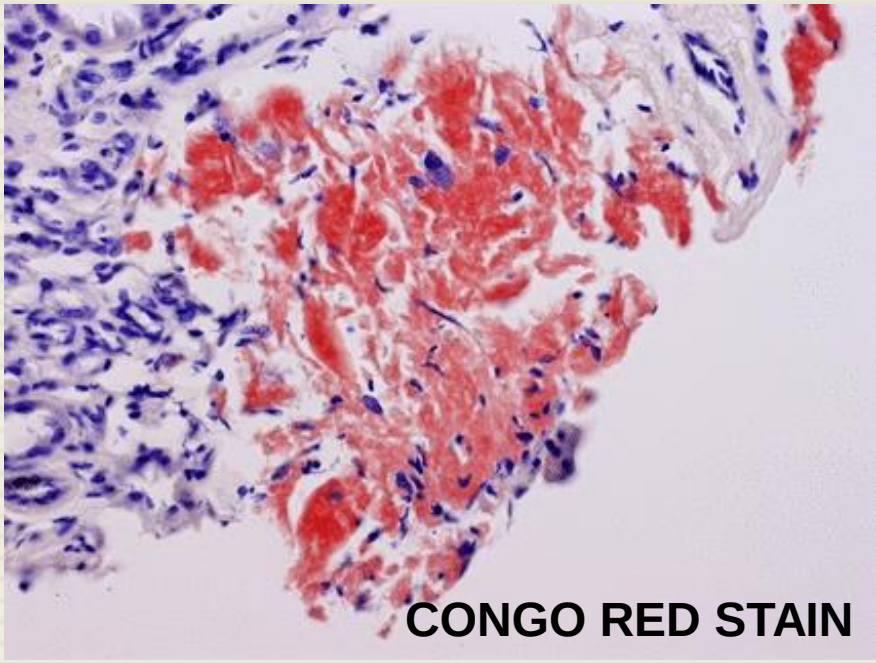
Amyloidosis of liver, H&E stain

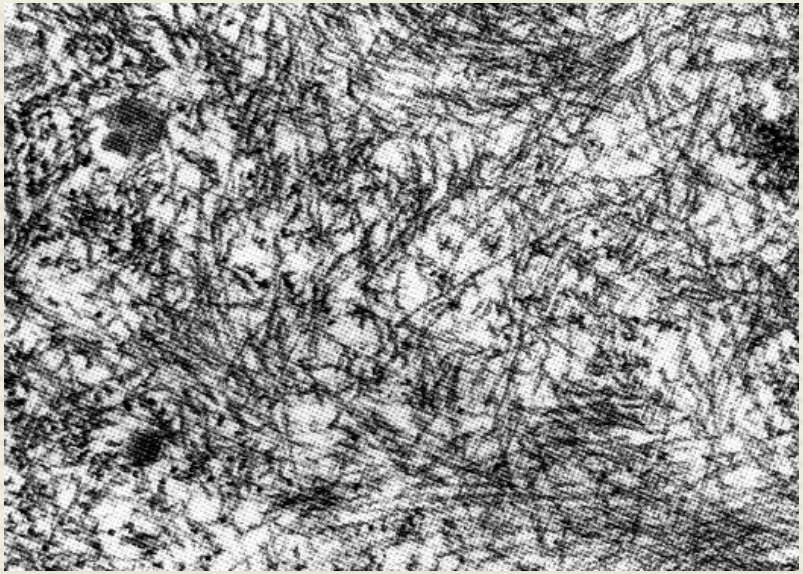


Morphology of amyloid

(additional information)

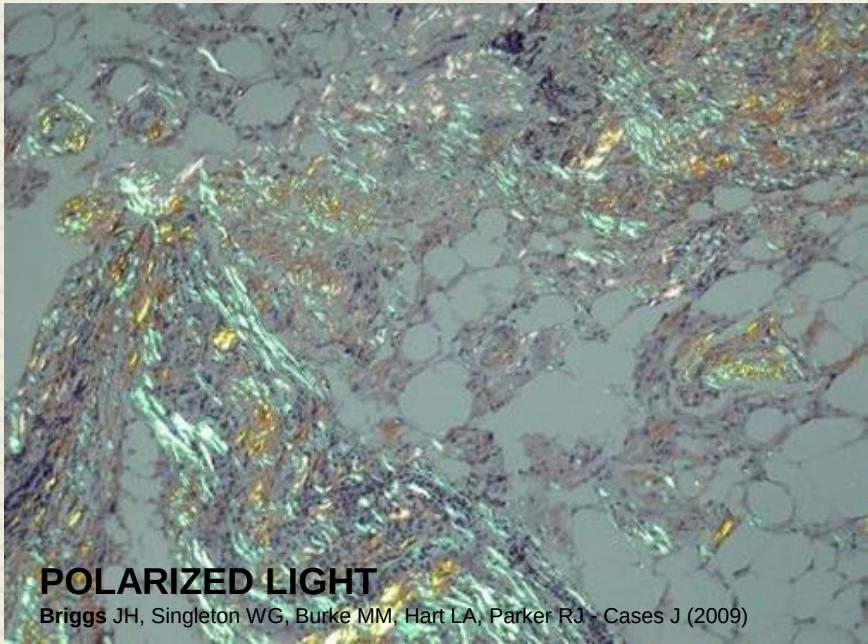
- **Light microscopy:** it is pink eosinophilic material. With Congo red stain → it looks bright orange. And when the congo red stained tissue is exposed to polarized light → it produces an apple-green birefringence.
- **Electron microscopy:** amyloid deposits are composed of non-branching fibrils, 7.5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





Electron microscopy

JOP. J Pancreas (Online) 2001; 2(4):124-139.



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.

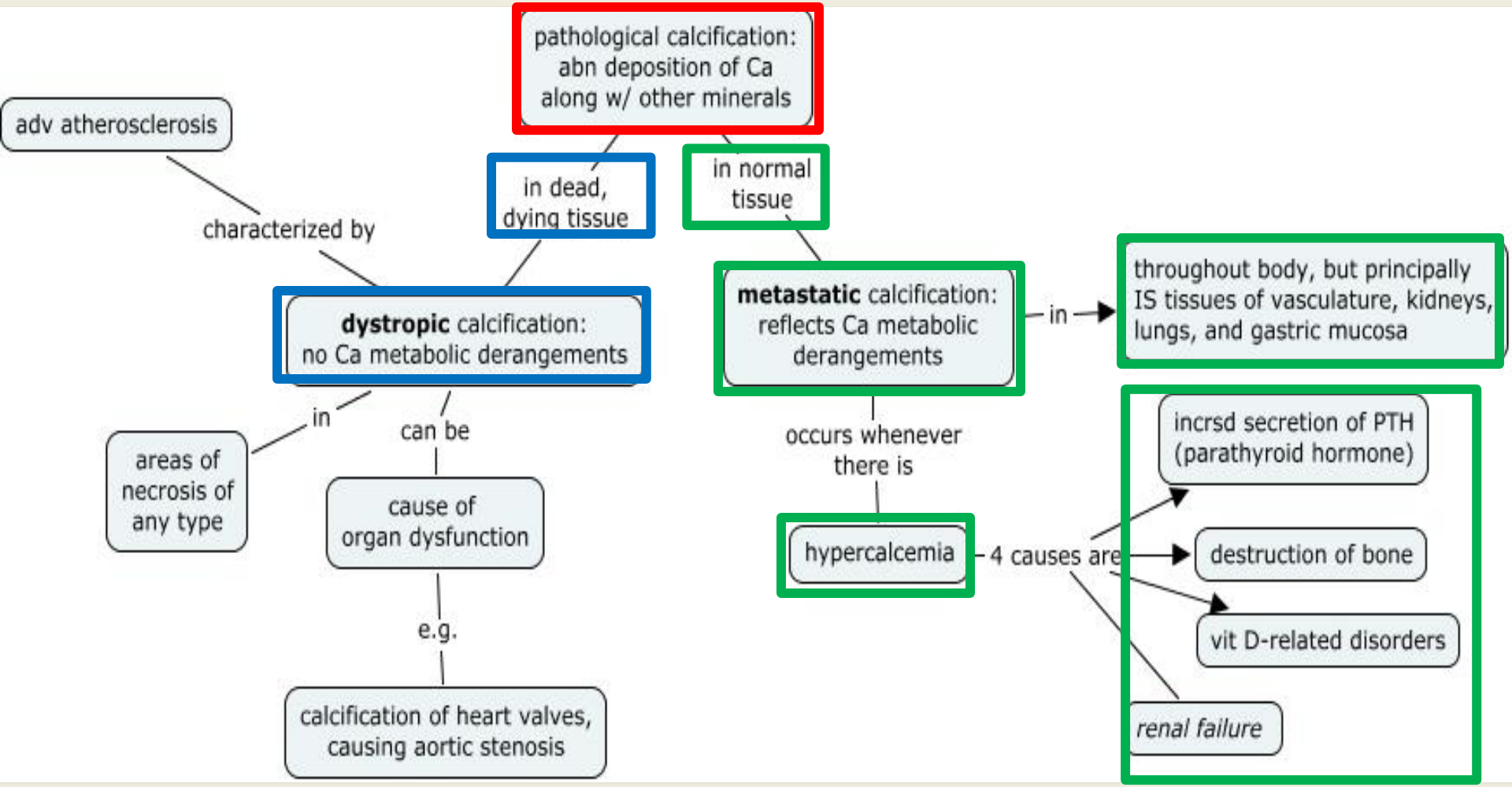
- Blood vessels: in the atheromas of advanced atherosclerosis
- Heart: in aging or damaged/scarred heart valves.
- A tuberculous lymph node can be converted to stone by the calcium.
- In fat necrosis.
- Psammoma body (see later)
- Areas of trauma

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)

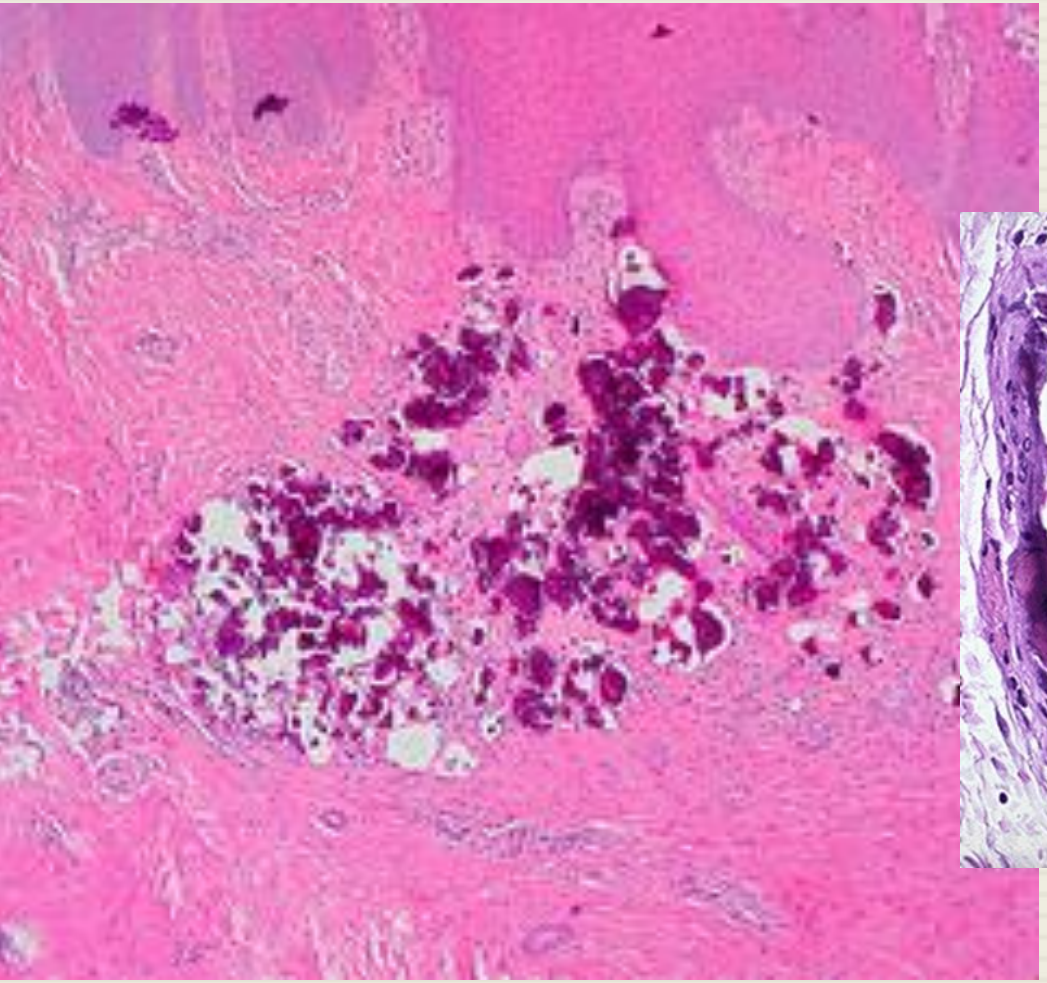
Pathologic Calcification: summary

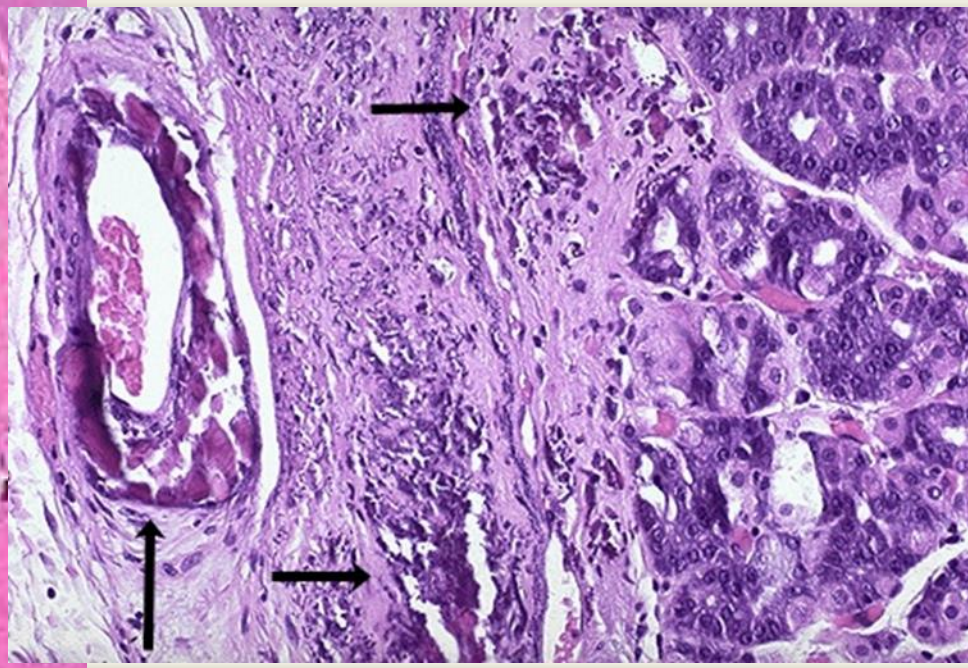


Morphology of pathologic calcification
(dystrophic or metastatic, both look the same)

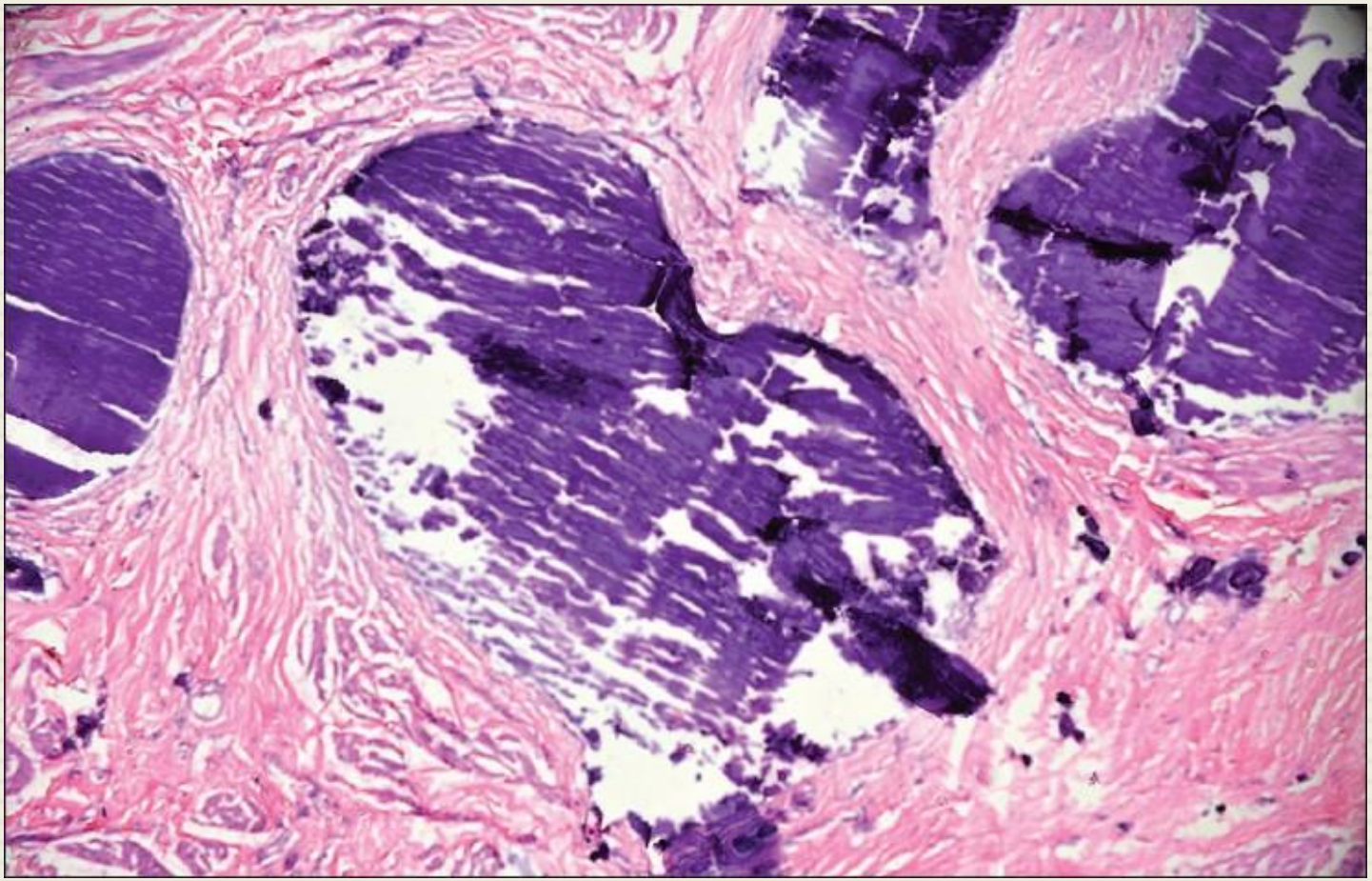
- Ca deposition occurs anywhere in the body e.g. in wall of blood vessels, kidneys, lungs, stomach, skin etc.
- Whatever the site of deposition, the calcium salts appear macroscopically as fine, white granules or clumps, often felt as gritty deposits.
- Histologically, calcium salts are basophilic, amorphous 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



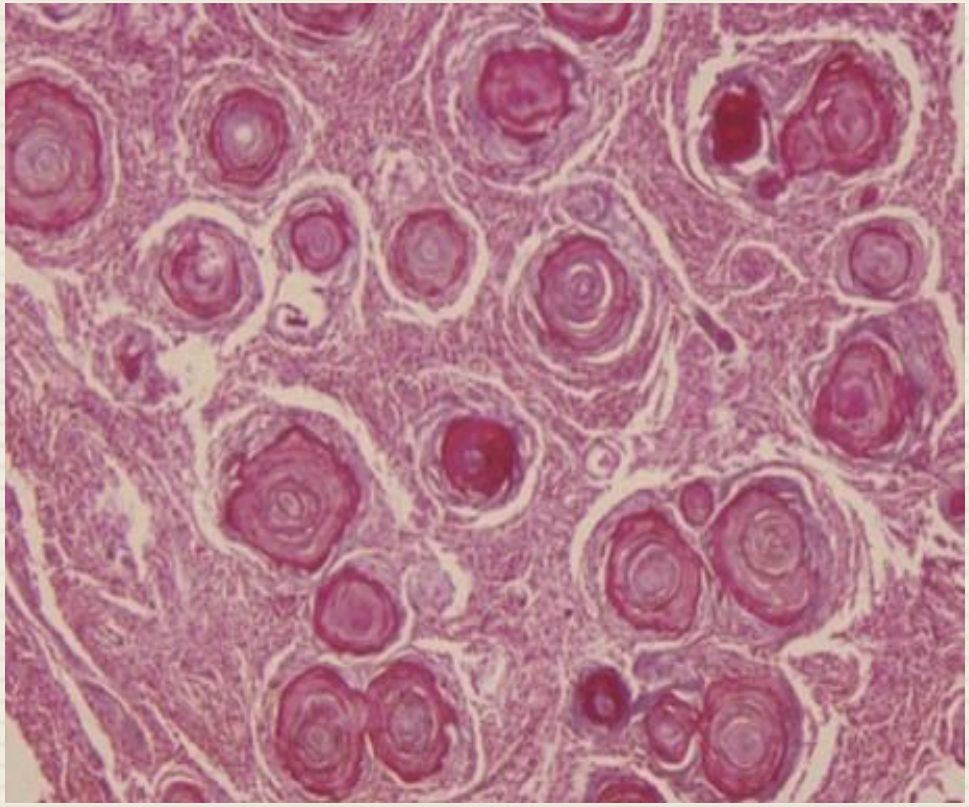


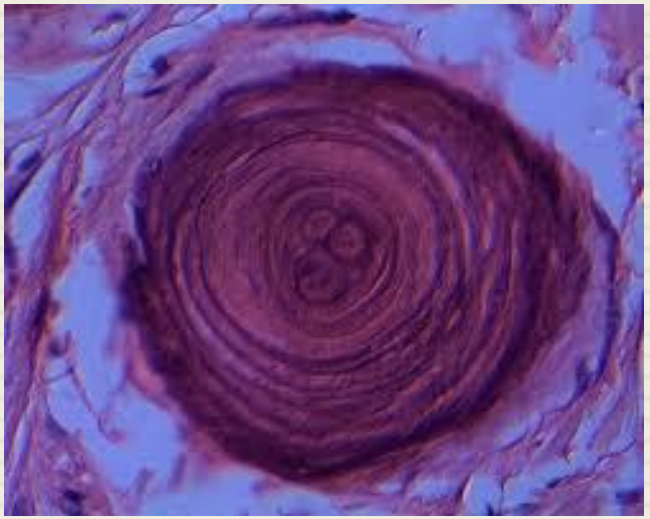
Pathologic Calcification



http://www.njssjournal.org/articles/2014/24/1/images/NigerJSurgSci_2014_24_1_23_134536_f3.jpg

Psammoma bodies





THE END