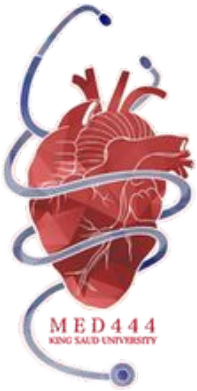


PATHOLOGY TEAMWORK

MED444

Cellular accumulation and pathological calcification

Editing File :

Color index:

Main text (Black)

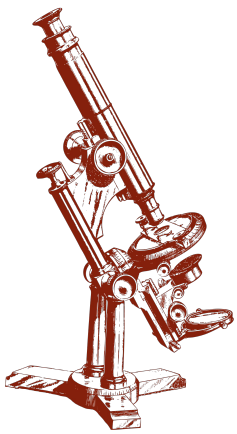
Female slides (pink)

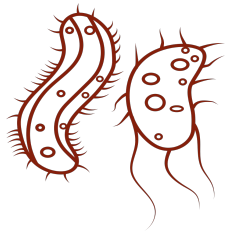
Male slides (blue)

Important (red)

Dr's note (green)

Extra Info (grey)





Objectives

- Intracellular accumulations: Reversible cellular changes and accumulations:
- fatty change, hyaline change, etc.
- Accumulations of endogenous pigments: melanin, bilirubin, hemosiderin (hemosiderosis and hemochromatosis), lipofuscin.
- Accumulations of exogenous pigments (carbon, silica, iron dust, lead and argyria).
- Extracellular accumulations: Amyloidosis.
- Pathologic calcifications: metastatic calcification and dystrophic calcification

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Intracellular accumulation

Under some circumstances, cells may accumulate abnormal amounts of various substances, which may be harmless or may cause varying degrees of injury. Some substances accumulate inside the cell in large amounts and cause problems in the cell and the organ these cells are in. This is called as intracellular accumulation.

The substance may be located/accumulated in the cytoplasm, within organelles (typically lysosomes), or in the nucleus, and it may be synthesized by the affected cells or it may be produced elsewhere. The main pathways of abnormal intracellular accumulations are inadequate removal and degradation or excessive production of an endogenous substance, or deposition of an abnormal exogenous material

The accumulating substance may be:

- A substance that is always present in a normal cell but has accumulated in excess
  - e.g. water, lipids, glycogen, proteins and carbohydrates.
- An abnormal substance that is not present in the cell normally.
  - 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
- A pigment
  - it can be an endogenous or an exogenous pigment

Examples of substances that accumulate in excess in the cell:

1-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).

2-Lipids

All major classes of lipids can accumulate in cells:
1-Accumulation of triglycerides steatosis (fatty change)
2-Accumulation of cholesterol and cholesteryl esters seen in atherosclerosis (in atherosclerosis there is accumulation of cholesterol in the wall of arteries).
3-Accumulation of phospholipids

3-Pigments

exogenous and endogenous

4-Glycogen

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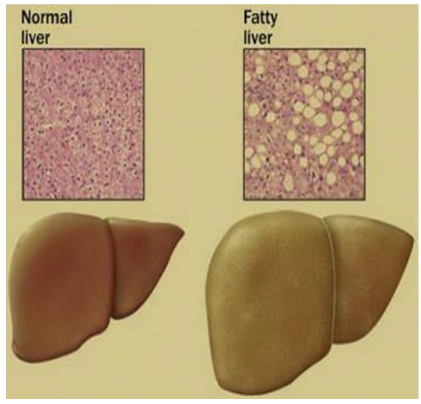
ACCUMULATION OF LIPIDS: e.g. Steatosis/Fatty Change (accumulation of triglycerides)

Fatty change, also called steatosis, refers to any/abnormal accumulation of triglycerides within parenchymal cells/inside cells. It is most often seen in the liver, since this is the major organ involved in fat metabolism, but also may occur in heart, skeletal muscle, kidney, and other organs.
Excess accumulation of triglycerides within the hepatocytes occurs when there is an imbalance between the uptake, utilization, & secretion of fat by the affected cell.

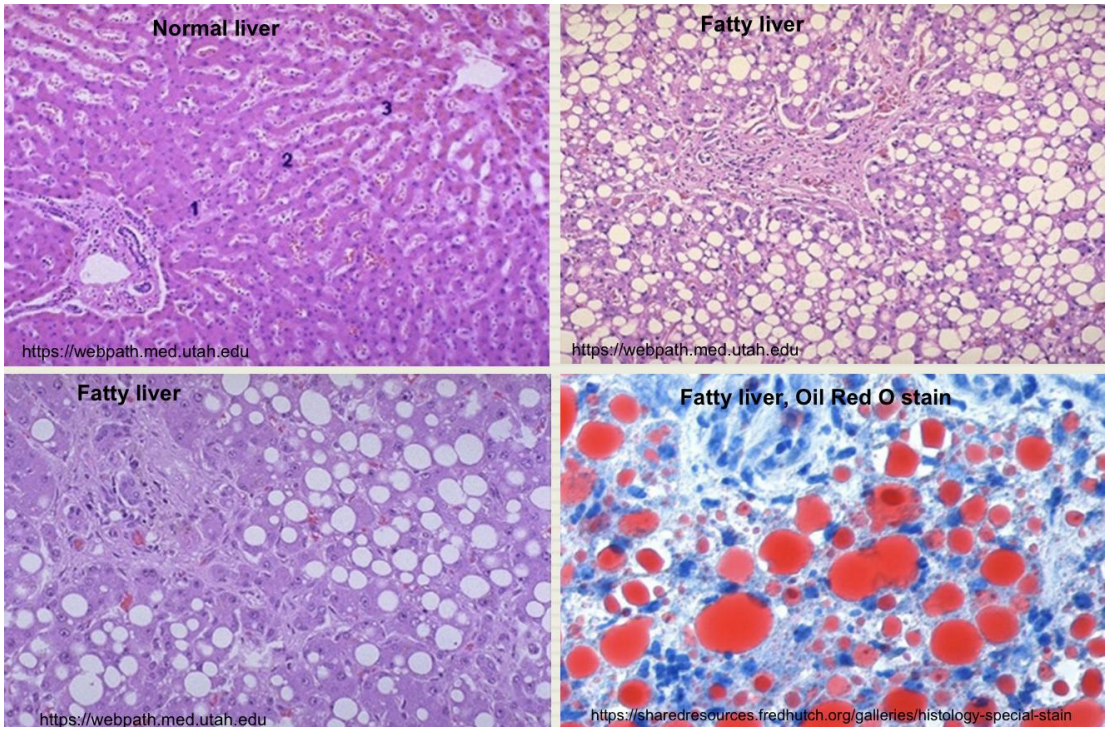
The causes of steatosis include:

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

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/colors orange-red with special stains like **Sudan IV and Oil Red-O**.



Normal liver and fatty liver under light microscope:



ACCUMULATION OF LIPIDS: Cholesterol and Cholesteryl Esters: (Males' slides only)

-Cellular cholesterol metabolism is tightly regulated to ensure normal generation of cell membranes (in which cholesterol is a key component) without significant intracellular accumulation.
-However, phagocytic cells may become overloaded with lipid (triglycerides, cholesterol, and cholesteryl esters) in several different pathologic processes, mostly characterized by increased intake or decreased catabolism of lipids.

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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.

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IN MALES' SLIDES ONLY

Protein accumulation

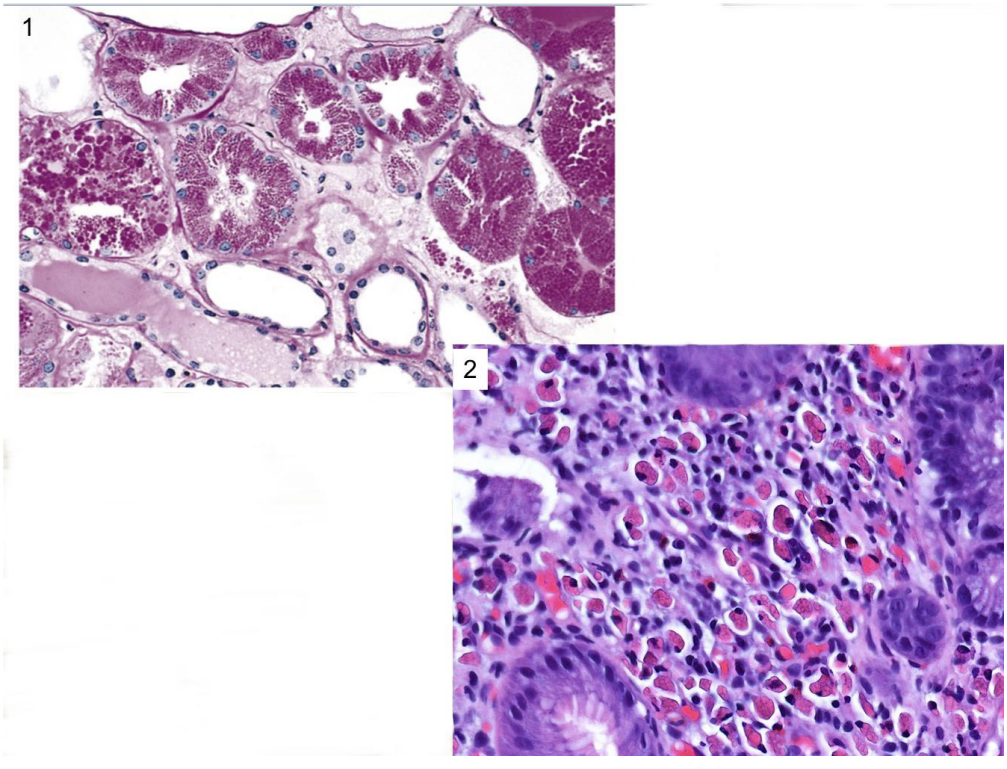
-They may occur when excesses are presented to the cells or if the cells synthesize excessive amounts.

-In the kidney, for example, trace amounts of albumin filtered through the glomerulus are normally reabsorbed by pinocytosis in the proximal convoluted tubules.

-However, in disorders with heavy protein leakage across the glomerular filter (e.g., nephrotic syndrome), much more of the protein is reabsorbed, and vesicles containing this protein accumulate, giving the histologic appearance
of pink, hyaline cytoplasmic droplets.

-The process is reversible: if the proteinuria abates, the protein droplets are metabolized and disappear.

-Another example is the marked accumulation of newly synthesized immunoglobulins that may occur in the RER of some plasma cells, forming rounded, eosinophilic Russell bodies.



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Accumulation of pigments

Pigments are colored substances, they 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.

- Lipofuscin
- Melanin
- Bilirubin
- Hemosiderin

Exogenous pigments

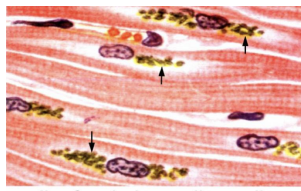
they are not synthesized within the body itself and are coming from outside the body.

1-Lipofuscin

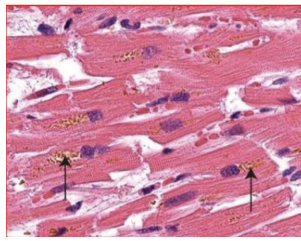
Definition

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 a golden yellow-brown, granular intra-cytoplasmic pigment. (It is an insoluble brownish-yellow granular intracellular material that accumulates in a variety of tissues.)
<u>Particularly accumulated in (prominent):</u>
-liver, heart, and brain (with aging/atrophy)
-atrophic tissue
-in patients with severe malnutrition
-cancer cachexia
The brown pigment when present in large amounts, imparts an appearance to the tissue that is called brown atrophy.



lipofuscin in cardiac cells



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2-Melanin

Definition

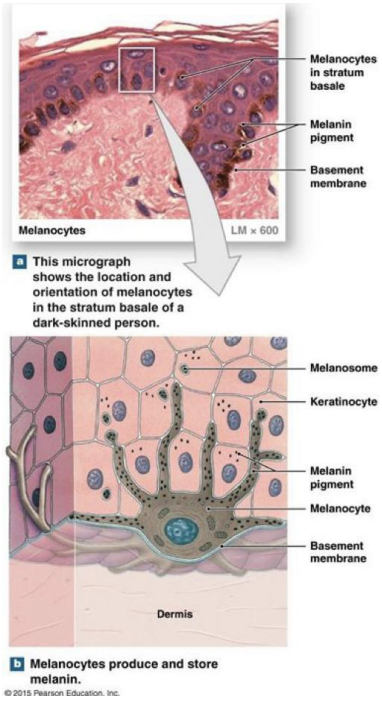
-It is an endogenous, non-hemoglobin, brown-black pigment normally present in the melanocytes.

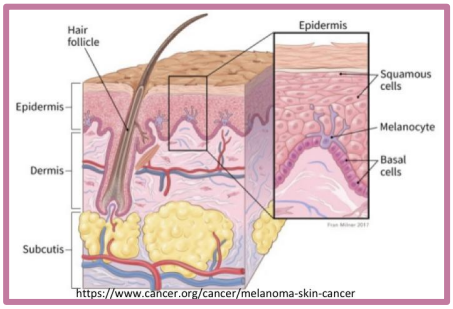
-It accumulates in excess in benign and malignant melanocytic tumors.

-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.

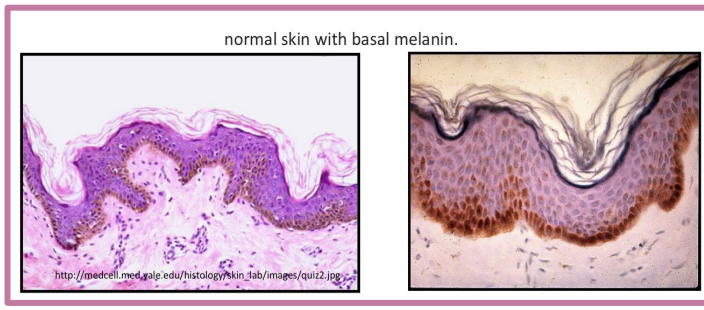
-Melanin is responsible for the color of our skin. Melanin is stored in lysosomes of the melanocytes (melanosomes). Melanosomes are produced by melanocytes

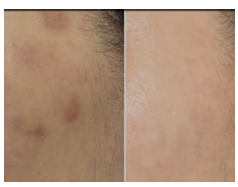
-Melanosomes and melanin granules are transferred from melanocytes to the cytoplasm of adjacent epidermal cells/ keratinocytes. Melanin protects from the harmful effects of UV light.

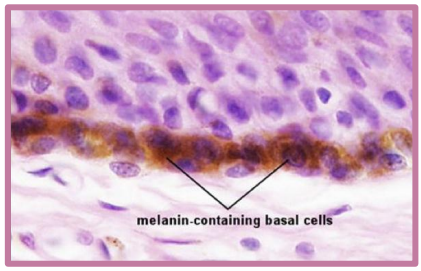




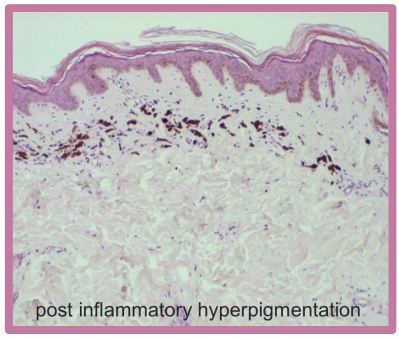
in inflammatory conditions of the skin it travels from epidermis into the underlying dermis where it is stored in the macrophages, resulting in the formation of dark spots. This is called as "**post inflammatory hyperpigmentation**" of the skin.







Masson-Fontana stain is used to identify melanin.



3- Bilirubin

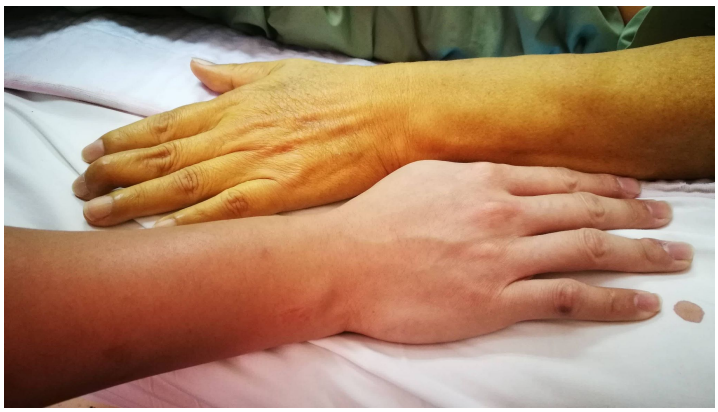
DEFINITION

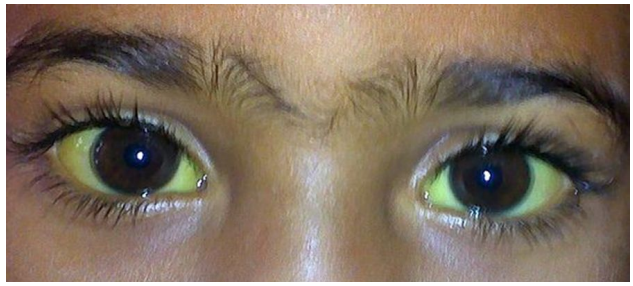
it is a yellowish pigment found in bile, a fluid made by the liver.

- Bilirubin is a breakdown product of heme catabolism (i.e. from the breakdown 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 yellow 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 of biliary tract.





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4- Hemosiderin

DEFINITION

it 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.

TYPES

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

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).

Hemosiderosis

In it there is accumulation of hemosiderin in macrophages mainly. Here the pigment does not cause significant tissue damage. It can be:

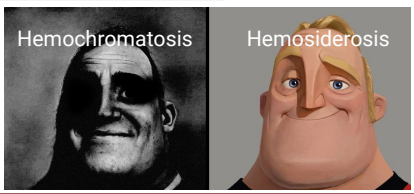
systemic

there is systemic overload of iron.

localized

كدمة

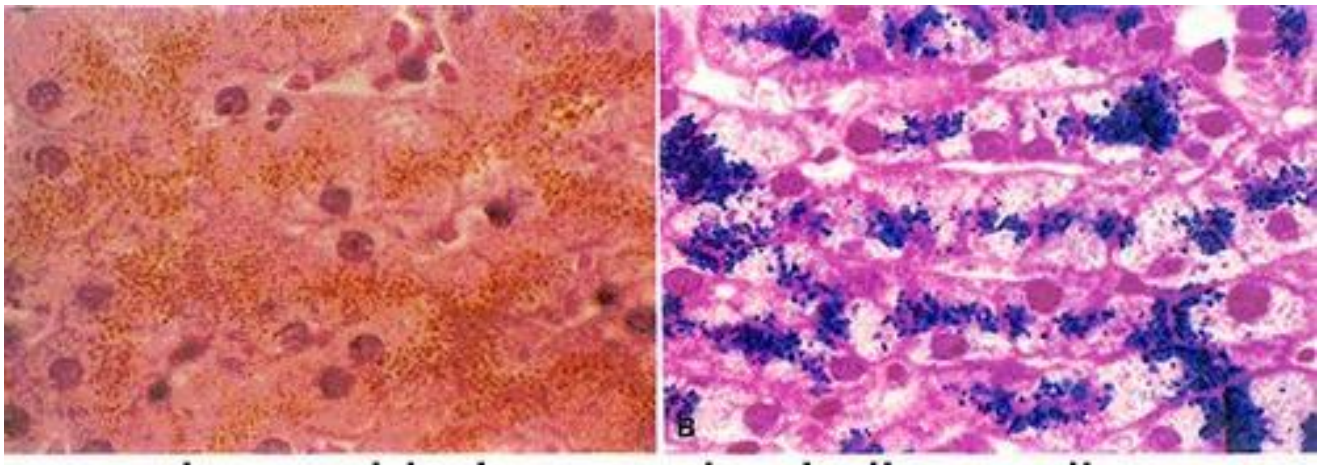
(e.g. common bruise : there is lysis of RBCs, release of hemoglobin and the iron in it is converted to hemosiderin)



The causes of excess systemic iron are:

1. increased absorption of dietary iron (Hereditary hemochromatosis).
2. impaired utilization of iron (myelodysplastic syndrome). (مثل كبار السن)
3. hemolytic anemias.
4. from blood transfusions (the transfused red cells provide an exogenous load of iron).

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.



hemosiderin granules in liver cells

Left: HE stain, Right: Prussian blue stain

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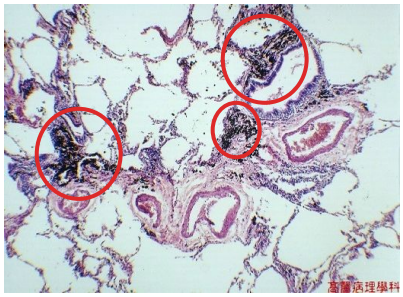
Exogenous pigments

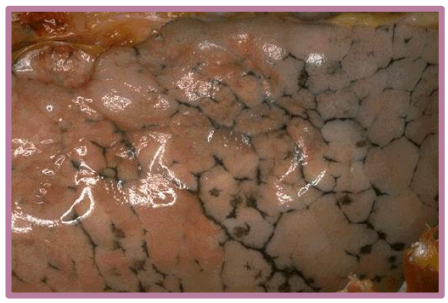
Anthracosis: الجمرة الخبيثة

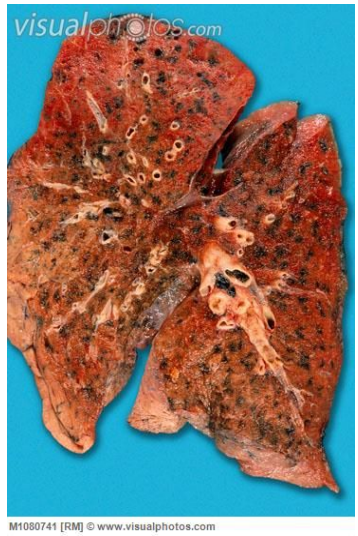
the most common exogenous pigment is carbon pigment or coal dust, which is an air pollutant. The dirty polluted air is breathed in and the carbon particles are picked up by macrophages in the lung alveoli and also transported to the neighboring lymph nodes. Accumulation of this pigment blackens the lungs (anthracosis) and the draining lymph nodes. Smokers have marked anthracosis. The anthracosis does not cause any major organ dysfunction.

Coal worker's pneumoconiosis: تغبر الرئة

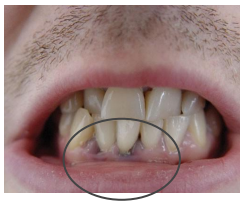
in the coal mining industry, there is too much carbon dust in the lung of coal miners and it leads to a lung disease known as coal worker's pneumoconiosis.



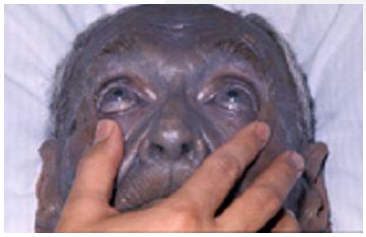




Other exogenous pigments that can be harmful when they accumulate in large amounts are silica ,lead, iron dust and silver.



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.

Amyloidosis

- it 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.

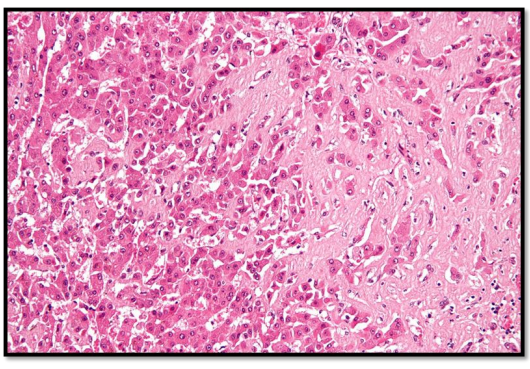
★ There are 2 main clinical forms of amyloidosis:

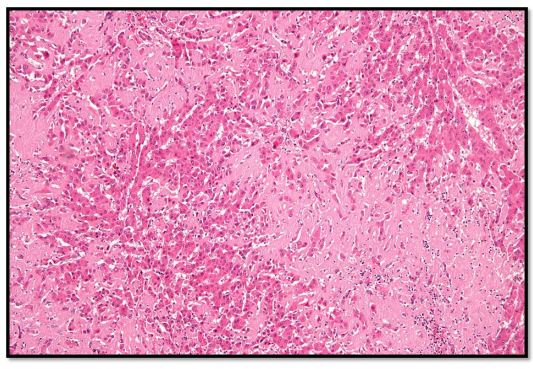
primary

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.





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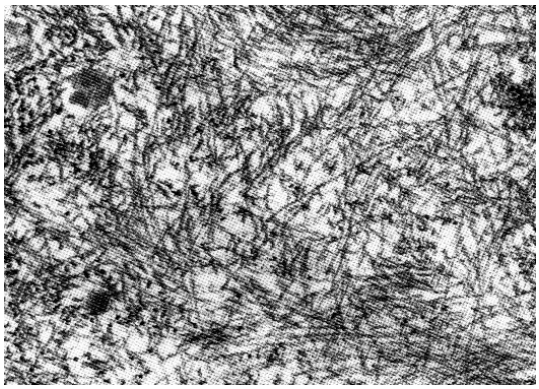
females' slides only

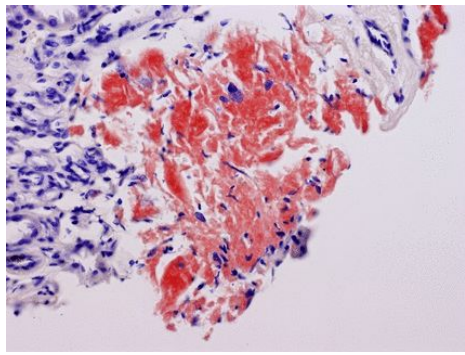
Morphology of amyloid

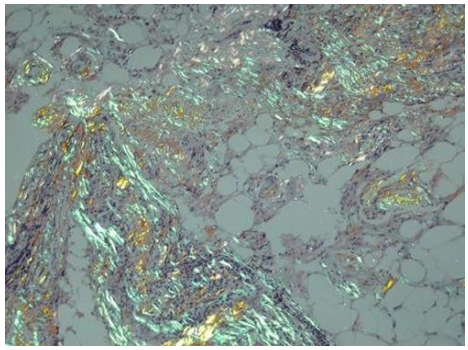
Light microscopy: it is pink eosinophilic material. With Congo red stain it looks bright orange. And when the congo red stained tissue is exposed to polarized light it produces an apple-green birefringence.

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.







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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.

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
- Areas of trauma

Metastatic calcification: It is seen mainly in

- kidneys
- lung
- stomach

It is associated with hypercalcemia. There are four principal causes of hypercalcemia:

Destruction of bone in bone tumors e.g. multiple myeloma, leukemia and metastatic cancer in bone	**Hyperparathyroidism** increased secretion of parathyroid hormone
Renal failure causes retention of phosphate leading to secondary hyperparathyroidism	**Vitamin D intoxication /hypervitaminosis D**

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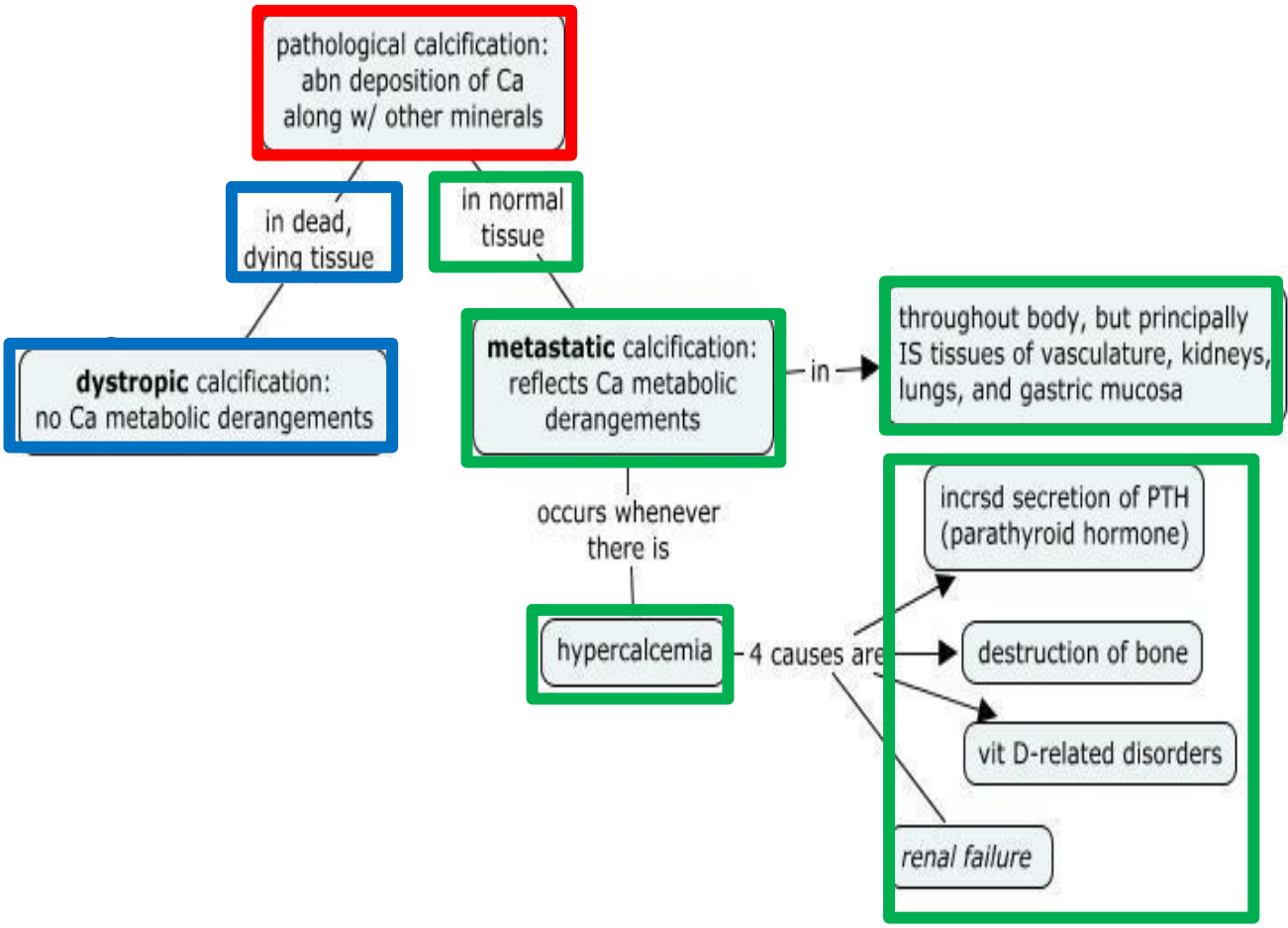
Pathologic Calcification summary:



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.

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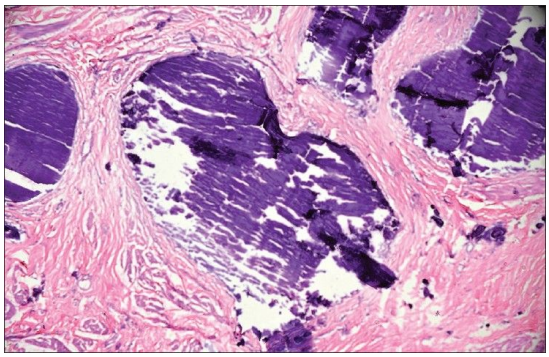
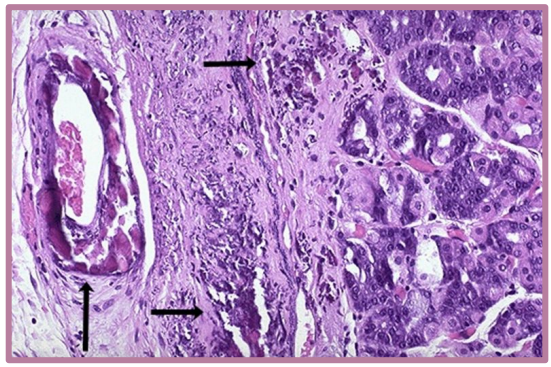
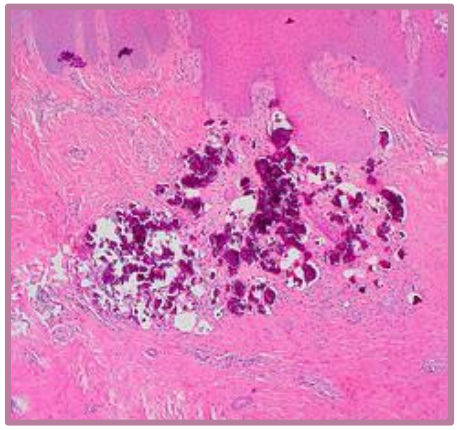
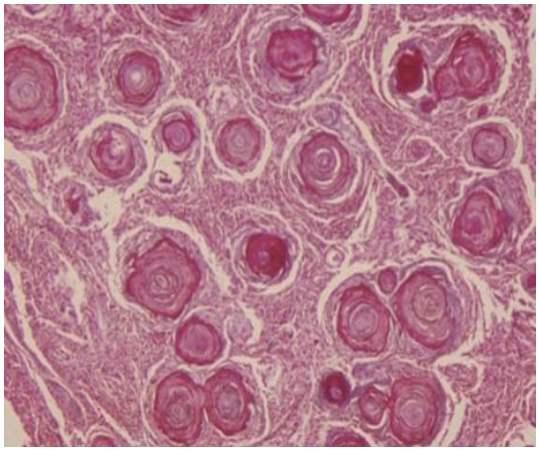
Pathologic Calcification

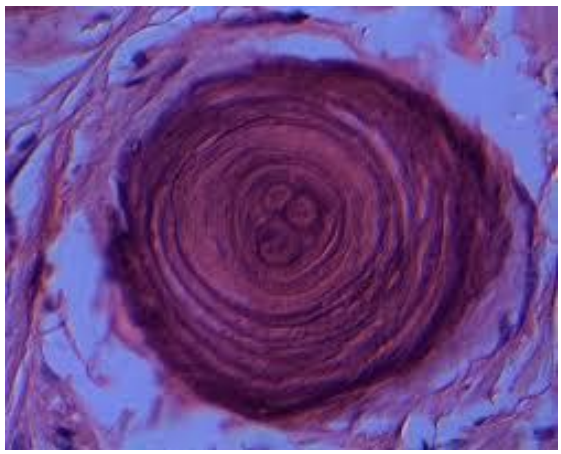






Psammoma bodies





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MCQs

1. In secondary amyloidosis, Amyloid has "....." type of Amyloid associated proteins

A. AS | B. AP | C. AA

2. Stain that identifies Steatosis:

A. Oil Red-O stain | B. Congo Red stain | C. Masson-fontana

3. Which pigment accumulation can be seen as golden yellow brown?

A. Bilirubin | B. Melanin | C. Lipofuscin

4. jaundice is high level of:

A. Glycogen | B. Lipids | C. Bilirubin

1	2	3	4
C	A	C	C

5 **Glycogen accumulation due to a disorder of glucose metabolism, seen in:**

A. Glycogen storage diseases

B. Diabetes mellitus

C. Hemosiderosis

6 **Anthracosis is an accumulation of:**

A. Carbon

B. Coal

C. Both

7 **Pearl Prussian blue stain identifies:**

A. Hemosiderin

B. Bilirubin

C. Protein accumulation

8 **it is a special type of dystrophic calcification made up of concentric lamellated calcified structures:**

A. metastatic calcification

B. hypercalcemia

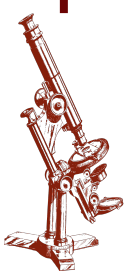
C. Psammoma body

9 **A pregnant woman is susceptible to:**

A. Anthracosis

B. Hemochromatosis

C. Steatosis



5	6	7	8	9
B	C	A	C	C

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Pathology Team

PATHOLOGY TEAMWORK
MED444

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