

# Cellular accumulation and Pathological calcification

Editing File

Objectives:

- 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.
- EXTRACELLULAR ACCUMULATION: amyloidosis (additional information)
- PATHOLOGIC CALCIFICATION: metastatic calcification and dystrophic calcification

Color Code:

Female's Notes

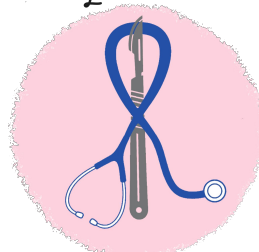
Male's Notes

Important

Extra

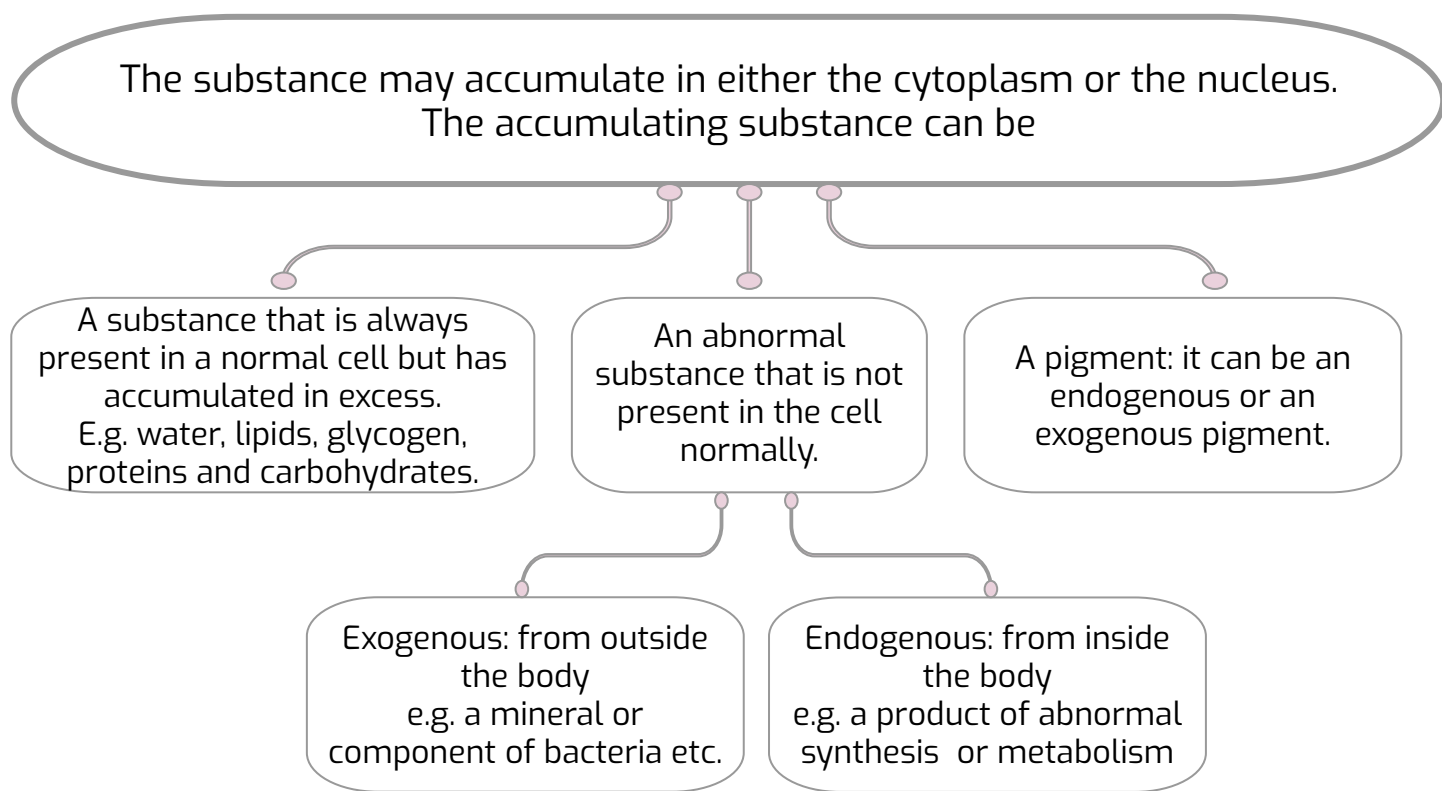


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# Intracellular accumulation

**Intracellular accumulation:** Substance can be accumulate inside the cell in large amounts and cause problems in the cells and the organs these cells belong to.



- 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

- Accumulation of triglyceride → 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.

3

## Pigment:

Endogenous and exogenous

4

## Glycogen

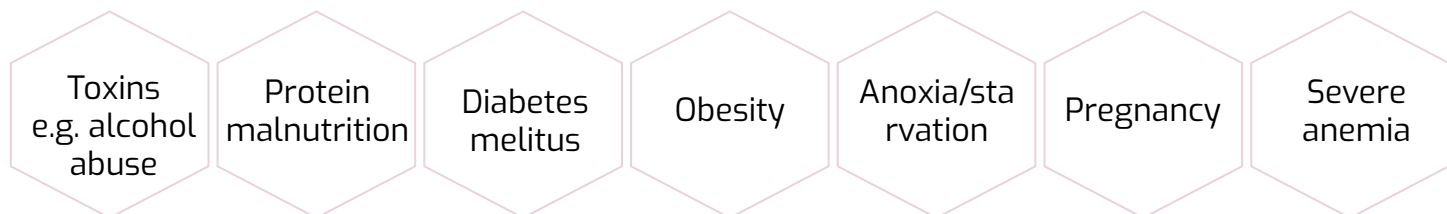
# Accumulation of lipids:

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 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, and secretion of fat by the affected cell.

- The causes of steatosis include:



## Morphology of steatosis in liver

### Gross

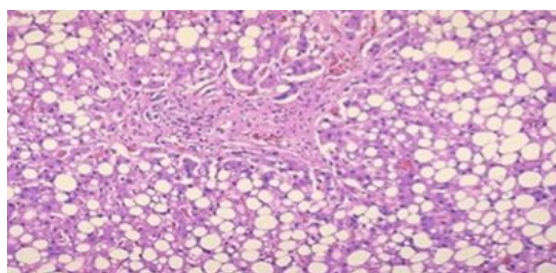
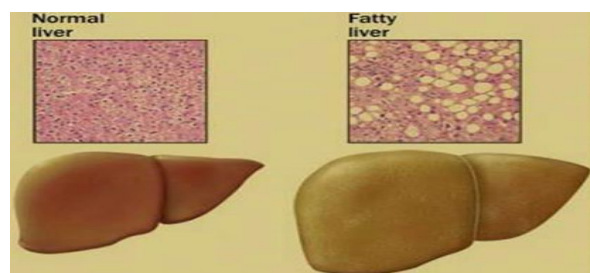
In mild cases: liver looks normal.

In severe cases: liver is enlarged yellow and greasy

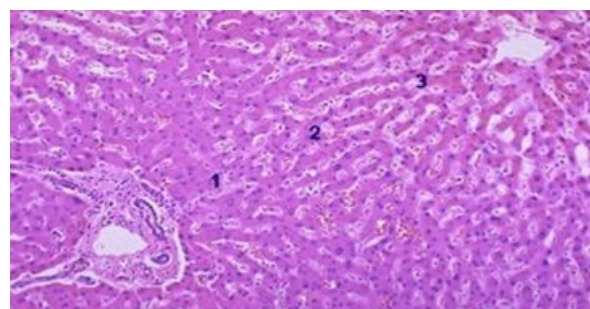
### Light microscope

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

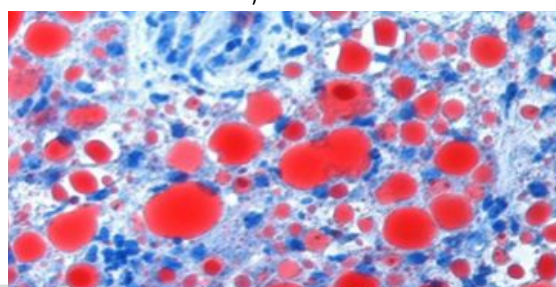
The lipid stains orange-red with sudan IV or Oil red-O stains.



fatty liver



Normal liver



fatty liver, Oil Red O stain

# Accumulation of glycogen

- Glucose is the main sources 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 patient 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 diseases glycogen accumulation in the kidney (proximal convoluted tubules), liver,pancreas, ( $\beta$  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 of glycogen in the liver, muscle and other tissue.

# Accumulation of pigment

Pigments are colored substance.

Pigments can be

Endogenous

Synthesized within the body itself. Some endogenous are normal constituent of cells (e.g. melanin) and other are not normal constituent of cells.

Examples:

- Lipofuscin
- Melanin
- Bilirubin
- Hemosiderin

Exogenous

They are not synthesized within the body itself and are coming from outside the body



# Endogenous pigments

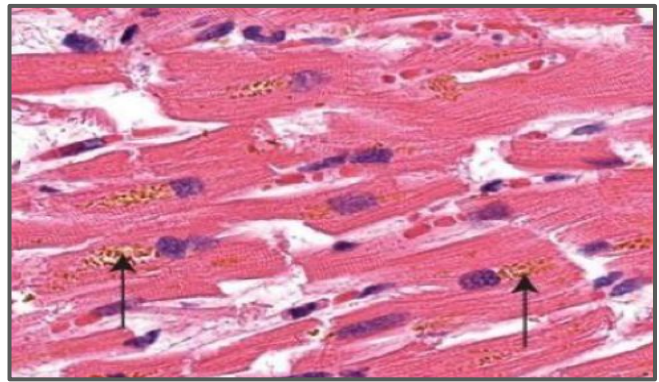
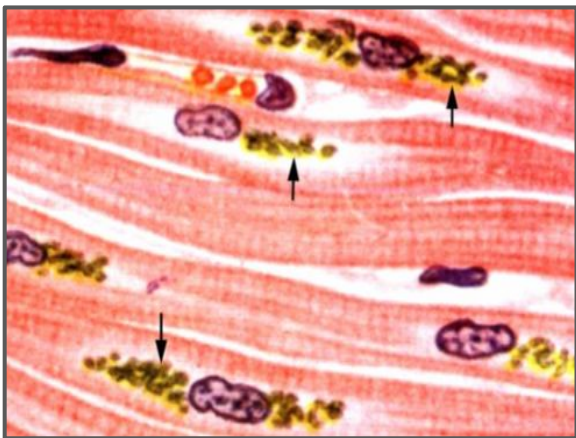
## 1) Lipofuscin :

Also known as “wear-and-tear” or “aging” pigment. Lipofuscin causes no damage to cells.

Presence of lipofuscin pigment indicate past free radical injury ( lipid peroxidation).

It is golden yellow-brown, granular intracytoplasmic pigment.

It is prominent if the liver and the heart of aging patients, in atrophic tissue in patients with severe malnutrition and cancer cachexia.

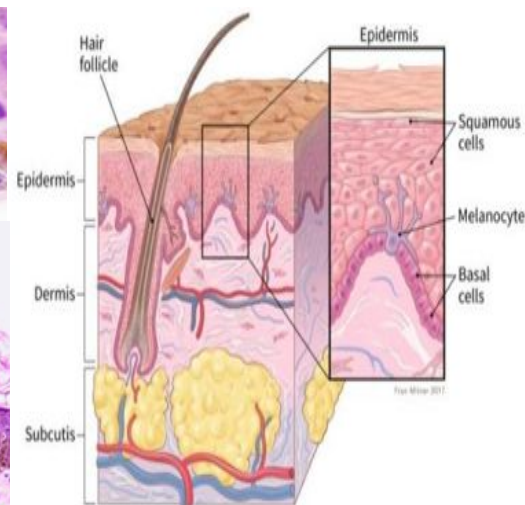
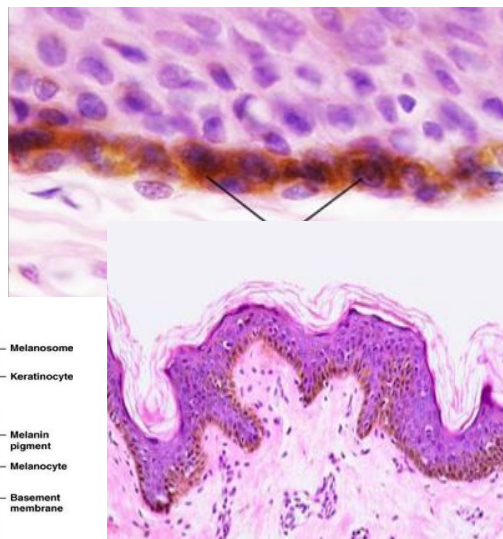
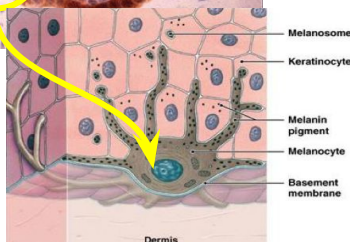
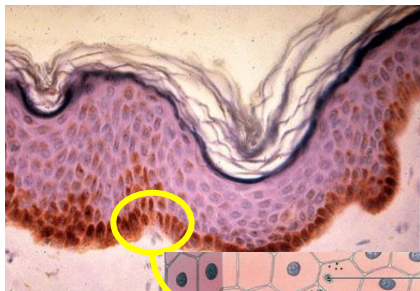


Lipofuscin in cardiac cell

## 2) 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.
- Function of melanin: protect from the harmful effects of UV light.



# Endogenous pigments cont

**Melanin:** an endogenous, non-hemoglobin, brown-black pigment normally presents in the melanocytes.

- It accumulation in excess in benign and malignant melanocytic tumors.
- 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 spot. This is called as "**post inflammatory hyperpigmentation**" of the skin.
- **Masson-Fontana stain** is used to identify melanin

## 3) Bilirubin:

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

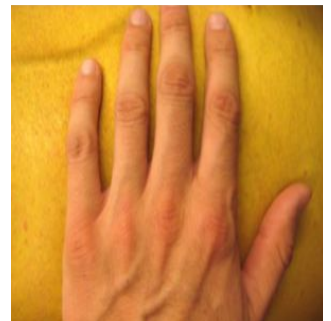
1

It is a yellowish pigmentation of the skin, the conjunctiva, the sclerae (white of the eyes), and other mucous membranes.

Jaundice  
(known as  
icterus)

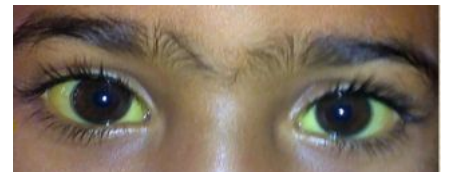
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It is caused by high blood bilirubin levels. Urine is also dark in color. It can also be itching.



3

Jaundice is often seen in liver diseases such as hepatitis or liver cancer or obstruction of the biliary tract by gallstone or tumors.



- It could be due to accumulation of glycogen in body cells (Genetic)
- Appears due to the excess use of Laxatives ( مسهلات )

## 4) Hemosiderin:

It is hemoglobin-derived golden brown **iron containing pigment** and it is a product of hemolysis (breakdown) of red blood cells.

Hemosiderin exists normally in small amount macrophages in bone marrow, liver, and spleen.

Excess accumulation  
of hemosiderin can be  
seen in

### Hemosiderosis

Accumulation of hemosiderin is 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 rbc's, release of hemoglobin and the iron in it is converted to hemosiderin)

Systemic hemosiderosis: there is systemic overload of iron.

### Hemochromatosis

More extensive systemic overload/accumulation of iron and hemosiderin, often parenchymal cells of various organs with associated tissue damage, scarring and dysfunction of that organ.

It can result in liver fibrosis, heart failure, diabetes mellitus and skin discoloration (bronze diabetes).

# Endogenous pigments cont

## The causes of excess systemic iron

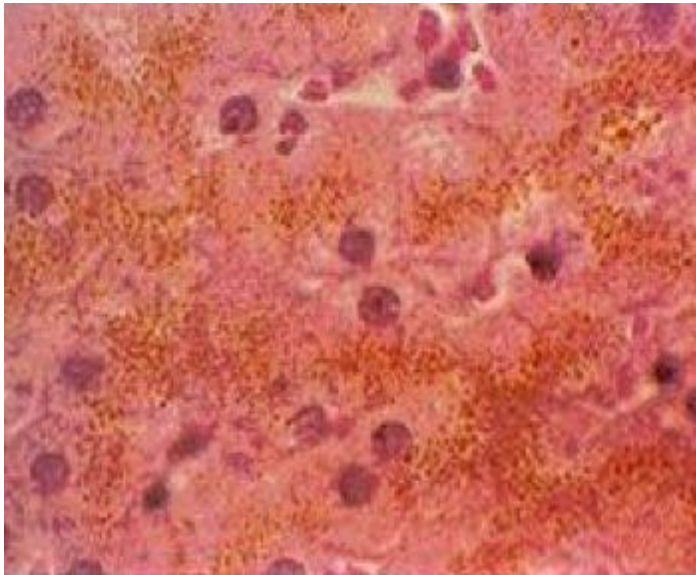
Increases absorption of dietary iron.

Impaired utilization of iron.

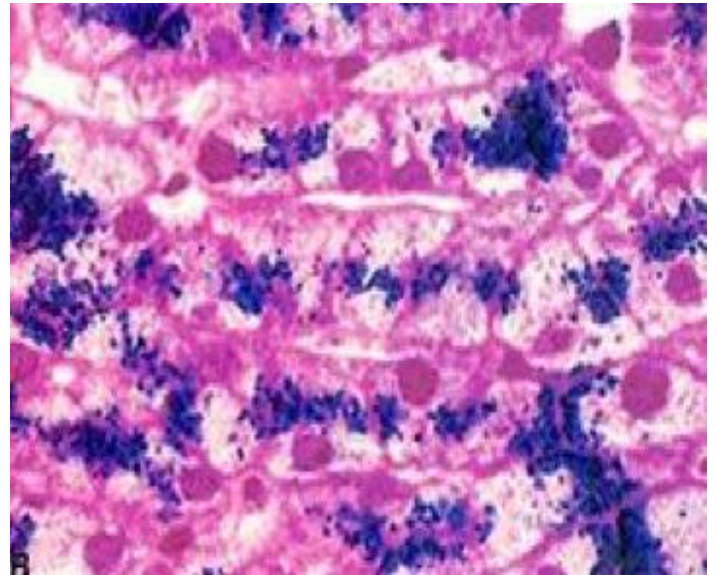
Hemolytic anemias

From blood transfusions (the transfused red cells provide an exogenous load of iron)

## Hemosiderosis granules in liver cells



HE stain



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.

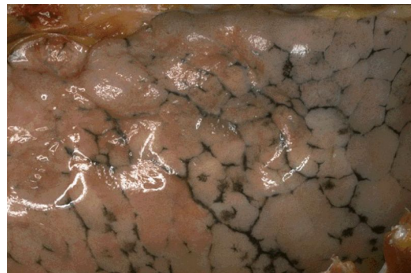
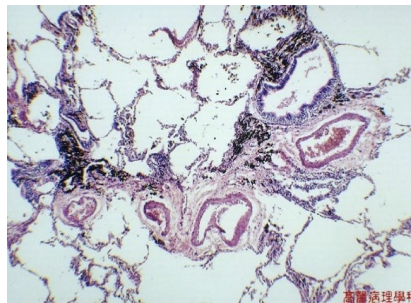
It appears blue-black with **Pearl Prussian blue stain**.



# Exogenous Pigments

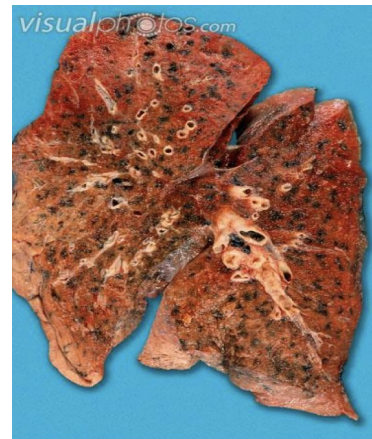
## Anthracosis:

the most common exogenous pigment is **carbon pigment or coal dust**, which is an air pollutant (or in industrial area). The dirty polluted air is breathed in and the carbon particles are picked up by **macrophages** (which can't digest it) in the lung alveoli and also transported to the **neighboring lymph nodes**. Accumulation of this pigment blackens the lungs (it's hard to be removed) (anthracosis) and the draining lymph nodes. **Smokers have marked anthracosis**. **The anthracosis does not cause any major organ dysfunction** (as long it's in the macrophages).



## Coal worker's pneumoconiosis:

in the coal mining industry, there is too much (**excess**) carbon dust in the lung of coal miners (it gets deposited in the lung) and it leads to a lung disease known as coal workers' pneumoconiosis.



**Anthracosis lung**  
It must be for a smoker, note those black dots.

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

Those are minerals: silica, lead, iron, silver

## Plumbism:

- **Plumbism** is lead poisoning
- **Argyria** is silver poisoning.
- In both cases there may be permanent grey discoloration of skin and conjunctiva.

## Tattooing:

Tattooing is a form of localized, exogenous pigmentation of the skin. The pigments inoculated are phagocytosed by dermal macrophages.

Tattoos are due to the injection of Indian ink to dermis layer



# EXTRACELLULAR ACCUMULATION : Amyloidosis (additional information)

Intracellular فقط للتمييز إن السابق كان  
Extracellular : Amyloidosis وإن فيه  
لكن ما فيه أسئلة عليه في الاختبار

- 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  $\beta$ -pleated sheets.

- It is deposited in various organs (kidney, liver, blood vessels, heart etc.) leading to damage of that organ.

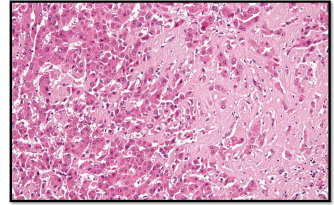
- Diagnosis: can be made with biopsy from organs like the kidney, rectum, gingiva and skin.

- Amyloidosis is associated with a number of inherited and inflammatory disorders.

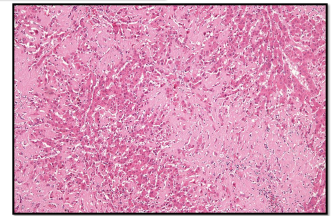
- There are 2 main clinical forms of amyloidosis:

**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.



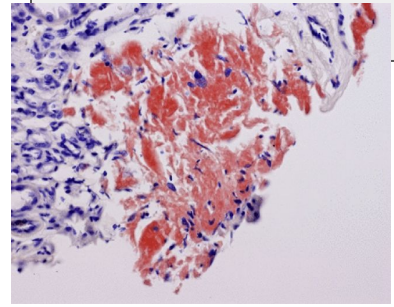
Amyloidosis of liver, H&E stain



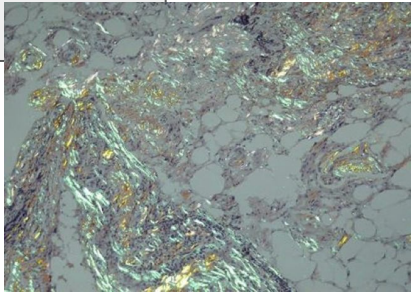
## Morphology of amyloid : (additional information)

**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.

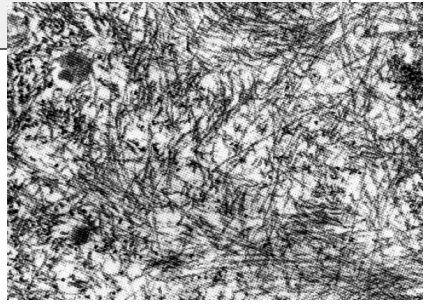
**Electron microscopy:** amyloid deposits are composed of non-branching fibrils, 7.5 to 10 nano-microns in diameter.



CONGO RED STAIN



POLARIZED LIGHT  
Briggs JH, Singleton WG, Burke MM, Hart LA, Parker RJ - Cases J (2009)



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

	dystrophic calcification	metastatic calcification
Location of calcium deposition	in dead or dying tissues	in normal and healthy tissue
Serum calcium levels (if you do a blood test)	normal	elevated
calcium metabolism	normal	abnormal
It is seen in	areas of necrosis or damage	mainly in kidneys, lung and stomach. It is associated with hypercalcemia.

## Dystrophic calcification:

(Calcium is circulating in our blood looking for a place in cells that's empty or injured )

- 1- Blood vessels: in the atheromas of advanced atherosclerosis
- 2- Heart: in aging or damaged/scarred heart valves. ( In this case valve replacement procedure is required )
- 3- A tuberculous lymph node can be converted to stone by the calcium.
- 4- In fat necrosis.
- 5- Psammoma body (see later)
- 6- Areas of trauma

## Metastatic calcification:

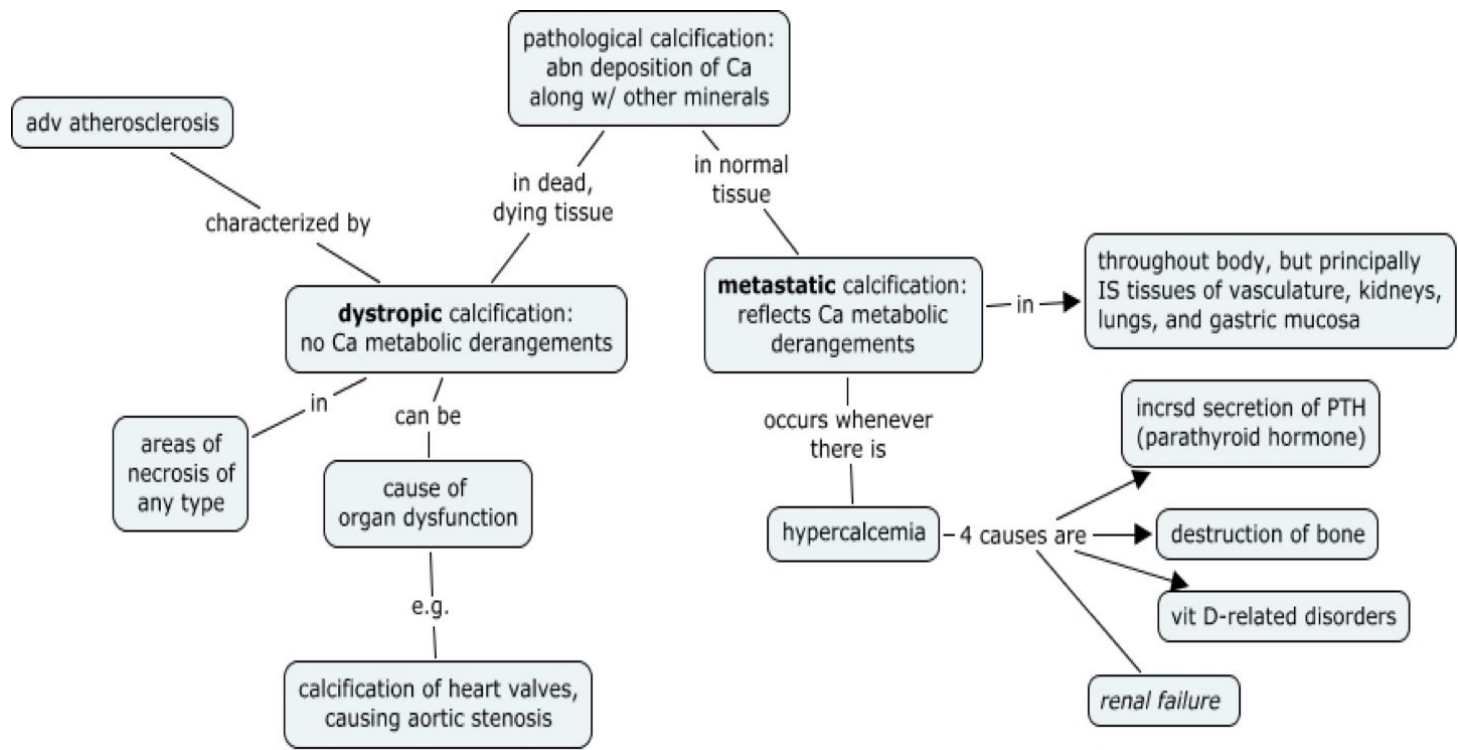
It is associated with hypercalcemia.

### There are four principal causes of hypercalcemia:

- 1- Hyperparathyroidism: increased secretion of parathyroid hormone.
- 2- Destruction of bone in bone tumors e.g. multiple myeloma, leukemia and metastatic cancer in bone( the destruction release calcium into blood).
- 3- Vitamin D intoxication/hypervitaminosis D.
- 4- Renal failure (causes retention of phosphate leading to secondary hyperparathyroidism).

(Dystrophic means something which is dysfunctional or damaged )

# Pathologic Calcification: summary



If the doctor know that the patient had a pathological calcification what should the doctor do to know if it's dystrophic or metastatic ? The doctor must send the patient to blood test to see if the calcium level in the blood is normal or not because both look the same histologically.



# Morphology of pathologic calcification

(dystrophic or metastatic, both look the same, so tests need to be done to check the calcium levels and metabolism in the blood)

Calcium deposition occurs anywhere in the body

in wall of blood vessels

kidneys

lungs

stomach

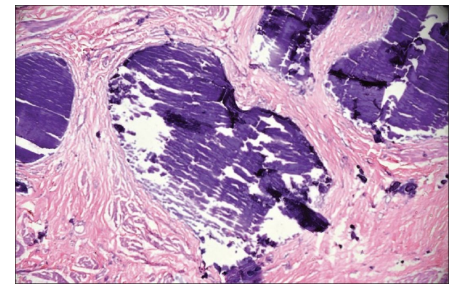
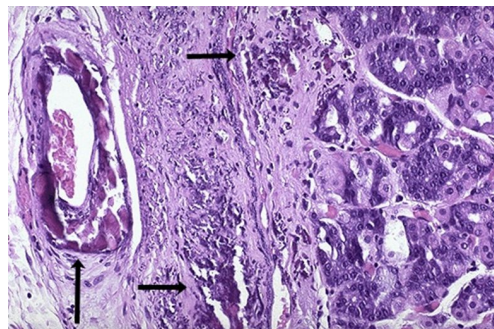
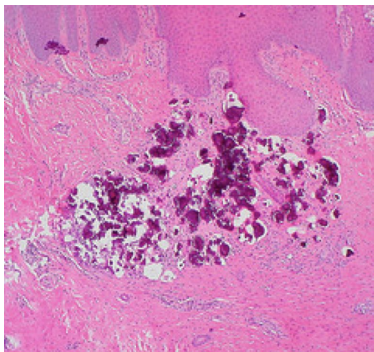
skin etc.

Whatever the site of deposition, the calcium salts appear macroscopically as fine, white granules or clumps, often felt as gritty deposits.

basophilic, amorphous granular.

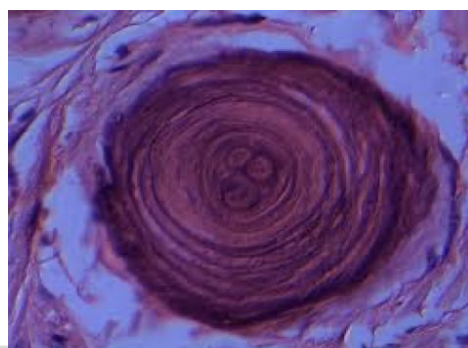
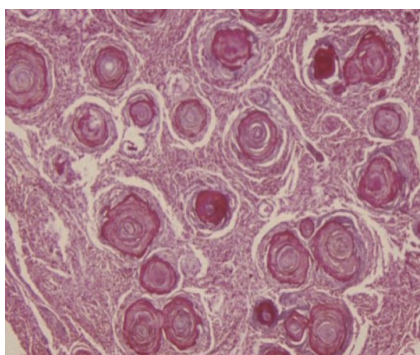
Histologically, calcium salts are:

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.



meningioma\* : is a tumor that forms on membranes that cover the brain and spinal cord just inside the skull.



# MSQs

1) In Tattooing the pigments inoculated are phagocytosed by:	2) Stain that identify melanin:
A- Epidermal macrophages B- Iron pigment. C- Coal dust D- Dermal macrophages	A- Oil Red O stain B- Masson-Fontana C- Prussian blue stain D- Periodic acid schiff (PAS)
3) jaundice is high level of:	4) the cause of steatosis :
A- Bilirubin B- Lipids C- Glycogen D-Hemosiderin	A- Diabetes mellitus B- Glycogen storage diseases C- Hepatitis D- A&B
5) Causes of hypercalcemia:	6) Excess Carbon in lungs may cause :
A-Destruction of bone in bone tumors B- Vitamin C intoxication C- Hyperparathyroidism D- A & C	A- Asthma B- pneumoconiosis C- Calcification D- Renal failure
7) Psammoma body is which type of calcification :	8) Presence of ..... pigment indicate past free radical injury
A-dystrophic B-amyloid C- Endogenous Pigments D-metastatic	A- Bilirubin B- Hemosiderin C- Lipofuscin D- Melanin
9)Hemosiderin exists normally in small amount macrophages in :	10) Argyria is ..... poison
A- Kidney B- Bone marrow C- Skin D- Cardiac muscle	A- Lead B- Silver C- Iron D- Silica

## **Leaders:**

Lama Al-Jamili  
Salem Abokhanjar

## **Sub-Leader:**

Manar Al-Abdullah

## **Organizer:**

Aya Alhossain

## **Members:**

Lama Bin Salamh  
Rahmah Alzahrani  
Noyer Awad  
Rahaf alamri  
Layan Alhelal  
Taif alshehri  
Renad Aldawayan  
laila almeshariy  
Alanoud Albawardi  
Reema Alrashedi  
Shouq Alhathal  
Tarfa albaz  
Jumana AL-qahtani  
Lama Alrumaih  
Ayah Sayed  
Shahad Helmi  
Norah Alsewailem  
Leen Alhadlaq  
Arwa Alenzi  
Reem Al Kulaibi

Mohammed Alwahibi  
Sultan Alosaimi  
Rakan alobaid  
Abdullah Abdulrazaq

