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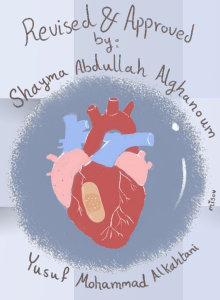


MED439
KING SAUD UNIVERSITY

CELL INJURY

Lecture 3

{ عَلَّمَ الْإِنسَانَ مَا لَمْ يَعْلَمْ }

Objectives:

- Understand the causes of and pathologic changes occurring in fatty change (steatosis), accumulations of exogenous and endogenous pigments (carbon, silica, iron, melanin, bilirubin and lipofuscin).
- Understand the causes of and differences between dystrophic and metastatic calcifications.

Color Index:
Girl's Slides
Important
Male's Notes
Female's Notes
Extra information

pathology
MED 439

Intracellular Accumulation:

Substance accumulate inside the cell in large amounts and cause problems in the cell and the organ it's called intracellular accumulation.

The substance may accumulate in either the cytoplasm or nucleus. And can be:

A **substance that's always present** in normal cell but has accumulated excess e.g. water, lipids, glycogen, protein, carbohydrates

An **abnormal substance not present** in the cell normally.

It can be:

Exogenous (from outside the body) e.g. a mineral or component of bacteria.

Endogenous (from inside the body) e.g. a product of abnormal synthesis or metabolism.

A pigment: it can be an endogenous or an exogenous.

Examples of substances that accumulate in excess in the cell:

A) water: abnormal accumulation of water in the cells is called hydropic change (cellular swelling). It's an early sign of cellular degeneration in response to injury (note: it's due to the failure of energy-dependent ion pump on the plasma membrane → leading to loss of normal ion & fluid homeostasis).

B) Lipids: all major classes of lipids can accumulate in cells:
- Accumulation of triglycerides → steatosis (Fatty change)
- Accumulation of cholesterol → seen in the Atherosclerosis. (in which there is accumulation of cholesterol in the smooth muscle cells and macrophages in the wall of arteries).
- Accumulation of phospholipids.

C) Pigments: exogenous and endogenous.

D) Glycogen

Accumulation of lipids e.g. triglycerides (called Steatosis, fatty change)

Fatty change is abnormal accumulation of triglycerides inside cells. It is mainly seen in the liver,but it is also in the heart,muscle,kidney. Excess accumulation of triglycerides within the hepatocytes occurs when there is imbalance between the uptake,utilization, secretion of the fat by affected cell. (metabolism)

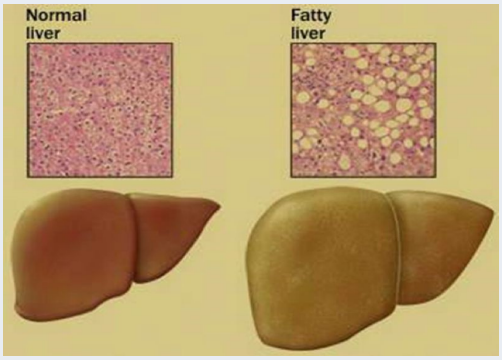
The cause of steatosis include:

- toxins e.g. alcohol abuse
- Protein malnutrition
- Diabetes mellitus
- Obesity
- Anoxia /starvation
- Pregnancy
- Severe anemia

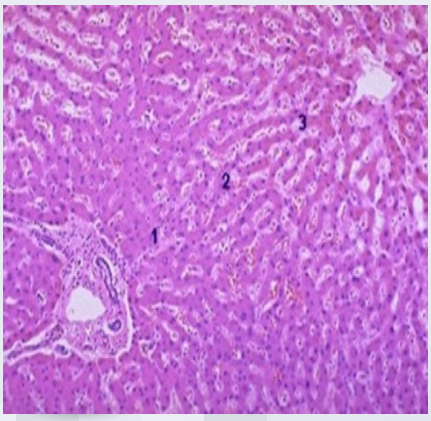
Morphology of steatosis in liver:

Gross: in mild cases liver looks normal, in severe liver looks yellow and greasy.

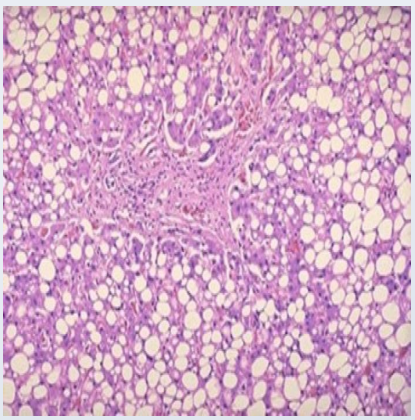
Light microscope: clear vacuoles in the cytoplasm displacing the nucleus to periphery of the cell. Occasionally,cells rupture,and fat globules merge, producing a so- called fatty cysts. The lipid stains orange-red with Sudan IV (4) or Oil Red-O stains.



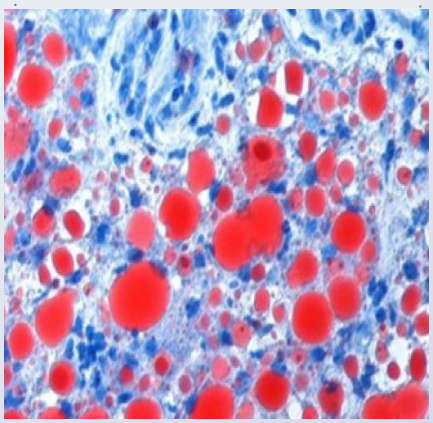
Confirms this is lipids because it turns to orange



Normal liver



Fatty liver



Fatty liver with Oil Red O stain

Accumulation of Glycogen

Glucose is the main source of fuel for cells. Excess glucose is stored in the liver or muscles in the form of Glycogen.

Excessive intracellular deposits of Glycogen can be seen in patient with abnormally glucose or glycogen metabolism.

Glycogen is stored in the cell cytoplasm.

Glycogen appears as clear vacuoles with the cell cytoplasm

Glycogen stains pink/violet with periodic acid schiff(PAS).

Glycogen accumulation is seen in:

Diabetes mellitus: it is disorder of glucose metabolism. In this disease glycogen is found in the proximal convoluted tubules of kidney,liver,the beta cells of islets of langerhans,heart muscle cell etc.

Glycogen storage disorders: it is 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 substance it can be:

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

Examples:

- Lipofuscin
- Melanin
- Bilirubin
- Hemosiderin

Exogenous pigments: they are not synthesized within the body itself, it's from outside the body.

Endogenous pigments:

1-Lipofuscin

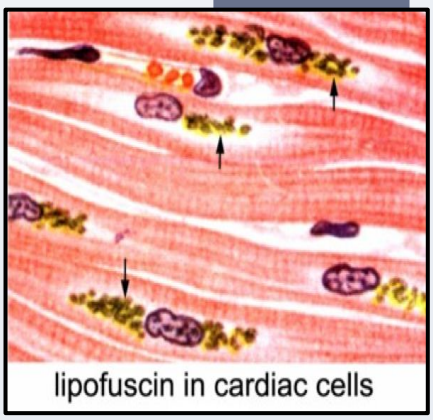
also known as wear and tear, aging pigment, lipofuscin causes no damage to cells.

Presence of lipofuscin indicates past free radical injury (peroxidation)

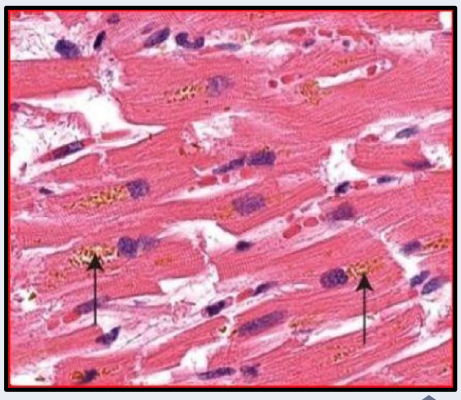
It's golden yellow brown, granular intra-cytoplasmic pigment

It's prominent in the liver and heart of aging patients, in atrophic tissue,severe malnutrition and cancer cachexia

Not found in the babies, sign of oxidative injury



lipofuscin in cardiac cells

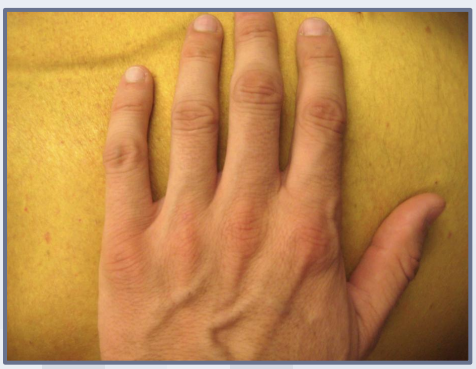


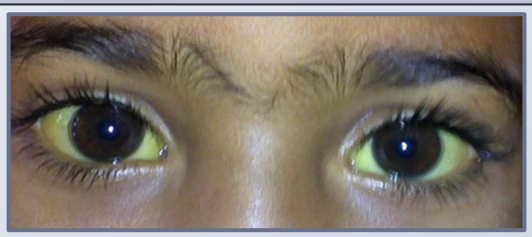
2-Bilirubin

Is a yellowish pigment found in the bile , a fluid made by liver. It is a breakdown product of heme catabolism (from the breakdown of hemoglobin)

High bilirubin → **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.





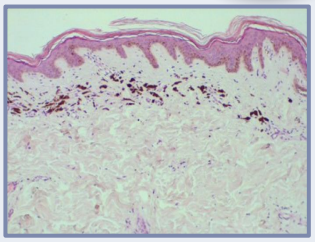
3-Melanin

Click

More melanin = darker skin

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.



Melanine: is a non-hemoglobin, brown-black pigment normally present in the melanocytes, responsible for the color of our skin

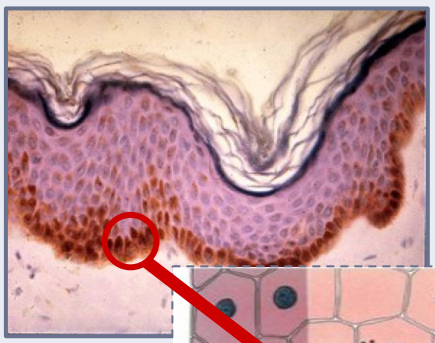
Function of Melanin: protects from the harmful effects of UV light.

Melanin is stored in the cytoplasm of the melanocytes (in the melanosome). Melanosome and melanin granules are transferred from melanocytes to the cytoplasm of adjacent epidermal cells/ keratinocytes.

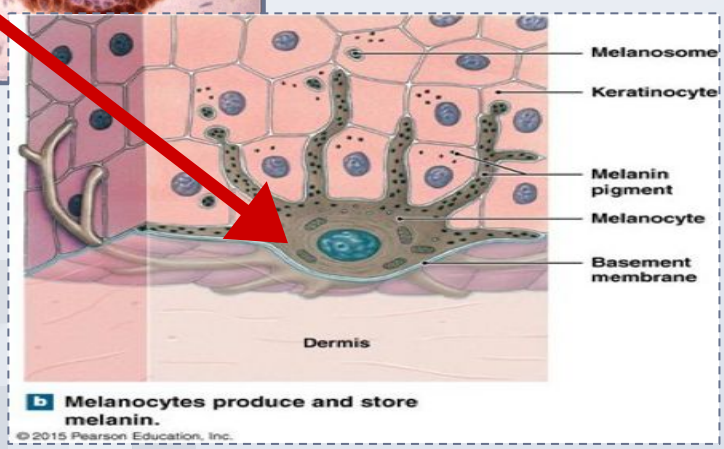
It accumulates in large amounts in benign and malignant melanocytic tumors. (UV light stimulates melanocyte to produce more melanin)

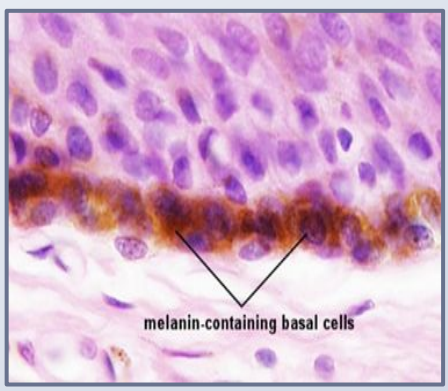
In inflammatory conditions of the skin it spreads from epidermis into underlying dermis where it is stored in the macrophages and it's called "post inflammatory hyperpigmentation" of the skin.

Masson-Fontana stain is used to identify melanin.



melanosis coli (melanin like pigment) seen in people who have constipation and use laxatives excessively in the lamina propria (CT between the glands)
Often discovered through colonoscopy (type of endoscopy)





4-Hemosiderin

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

Excess accumulation hemosiderin

1 Hemosiderosis

accumulation of hemosiderin is mainly in macrophages. 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.

**Deposits in macrophages all over blood

2 Hemochromatosis*

*more severe version of iron accumulation

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).

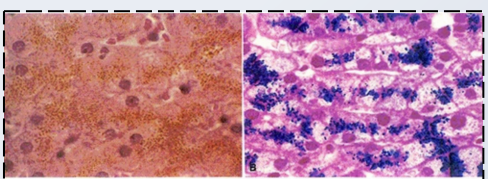
1st degree hemochromatosis (haemochromatosis) is genetic

Sickle shaped RBC (shrivel-shaped RBC) might go into necrosis

Note: when something deposits in macrophages it doesn't cause damage/injury to cells, the trouble starts when it begins depositing in cells, occupying space and not allowing cells to function properly

The causes of excess systemic iron are:

1. increased absorption of dietary iron
2. impaired utilization of iron I.e. Iron is not being used, only stored
3. hemolytic anemias excess abnormal hemolysis of RBC
4. from blood transfusions (the transfused red cells provide an exogenous load of iron



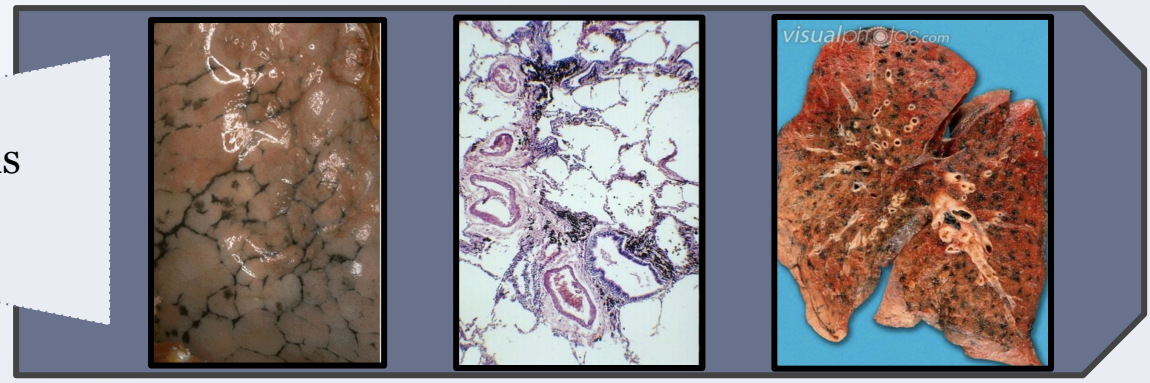
hemosiderin granules in liver cells
Left: HE stain, Right: Prussian blue stain

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 Perl's 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 (which can't digest it) 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 (as long as it's in macrophages).

Anthracosis - lung



Coal workers' pneumoconiosis: in the coal mining industry, there is too much carbon dust in the lung of coal miners, it gets deposited in lung cells and it leads to a lung disease known as coal workers' 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 conjunctiva.

Tattooing is a form of localized, exogenous pigmentation of the skin. Tattoo ink (India ink) is Injected underneath the dermis of the skin. The ink is a foreign body (antigen) and causes inflammatory reaction, it is then phagocytosed by macrophages but they cannot digest it

EXTRACELLULAR ACCUMULATION: Amyloidosis

Amyloidosis is a disorder of protein misfolding, which results in the **extracellular deposition and accumulation** of a fibrillary protein called amyloid*.

*When it accumulate outside cells, it starts crushing them.

Amyloid is composed of non-branching fibrils of β-pleated sheets.

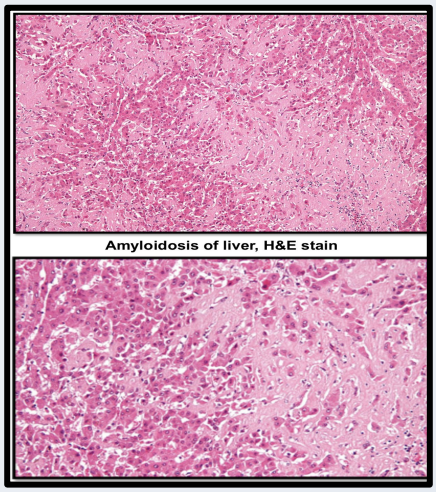
It is deposited in various organs (kidney, liver, blood vessels, heart, tongue, intestine, lymph etc.) leading to damage of that organ.

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.

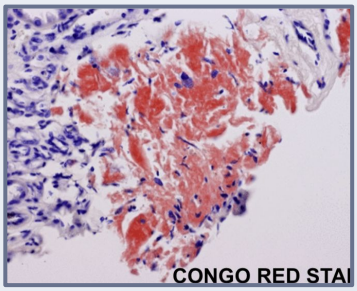
Secondary: is secondary to chronic inflammatory or autoimmune diseases e.g. tuberculosis, rheumatoid arthritis etc.; has "AA" type of amyloid associated protein.

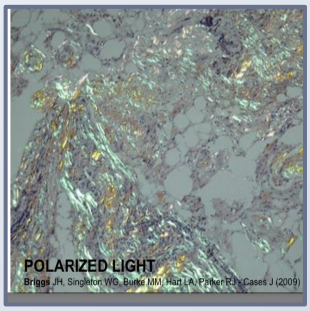

Amyloidosis of liver, H&E stain

Morphology of amyloid

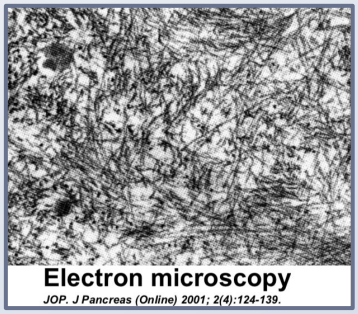
Light Microscopy: it is pink eosinophilic material.

With Congo red stain ➡ bright orange.
And when the congo red stained tissue is exposed to polarized light ➡ an apple-green birefringence.





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

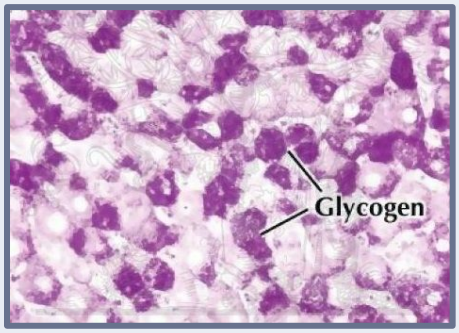


Diagnosis: can be made with biopsy from organs like the kidney, rectum, gingiva and skin.

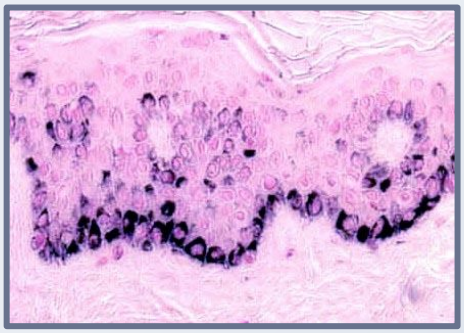
⋆Summary of Substances & Stains

substance	stain	Stain colour
Lipids (steatosis)	Sudan IV / Oil Red-O stain	Orange-Red
Glycogen	Periodic acid schiff (PAS)	pink/violet
melanin	Masson-fontana	black
Iron (hemosiderin)	Perl's prussian blue stain	blue-black
amyloid	Congo Red stain	Bright red
	Congo Red stain + exposed to polarized light	Apple-green birefringence

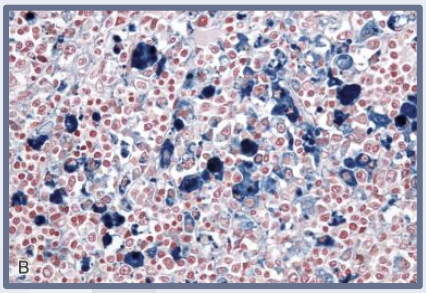
Sudan IV



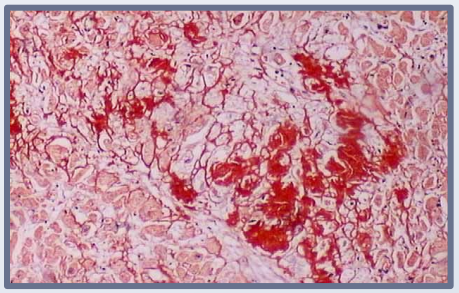
Periodic acid schiff (PAS)



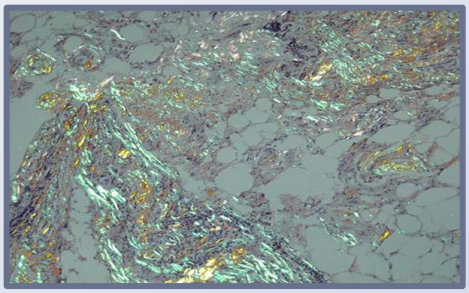
Masson-fontana



Perl's prussian blue stain



Congo Red stain



Congo Red stain + exposed to polarized light

Pathologic Calcification

Is the abnormal tissue deposition of calcium salts

⋆Include 2 types

Remember: Dystrophic is Deposition in Dead/Dying tissue

	Dystrophic	metastatic
Location of calcium deposition	In dead or dying tissue	Normal & healthy tissues
Serum calcium levels	normal	elevated
Calcium metabolism	normal	abnormal
Seen in	Areas of necrosis or damage	kidney, lung, stomach

Metastatic calcification is associated with or seen in **hypercalcemia**

Causes of Hypercalcemia

1. **Hyperparathyroidism**
   increased secretion of parathyroid hormone (PTH)
2. **Vitamin D intoxication**
   known as hypervitaminosis D.
3. **Destruction of bone* in bone tumors**
   e.g.multiple myeloma, leukemia and metastatic cancer in bone.
   *The destruction releases calcium into blood
4. **Renal Failure**
   causes retention of phosphate leading to secondary hyperparathyroidism
5. **Milk alkali syndrome**
   people who drink a lot of milk (its rare)
6. **Old age**
   Mild hypercalcemia can be found in old people
7. **Metastatic Malignant tumors**

Examples of dystrophic calcification

- **Blood vessels** → **in the atheromas of advanced atherosclerosis**
- **In fat necrosis**
- **heart** → **in aging or damaged/ scarred heart valves*.**
- **Psammoma body**

*due to previous myocardial infarction.

- **tuberculous lymph node** → **converted to stone by the calcium.**
- **Areas of trauma**

More examples:

1- Aortic valve malformation (two cusps)
Calcium calcification on the valve because of the congenital abnormality associated with
dystrophic calcification

2- Microcalcification in the breast
Caused by trauma. Trauma caused rapture in the blood vessel, rapture in blood vessel make the blood come to the tissue, the blood carries with it enzymes, these enzymes do fat necrosis, fat necrosis attracts calcium salt, then dystrophic calcification breast mass. (Dystrophic calcification in breast caused by trauma)

3- **Pancreatic enzymes** are released to the peritoneal cavity because there is cell injury and inflammation. These enzymes are lipolytic. It causes fat necrosis in the fat of abdomen. The fatty acids then complex with calcium to form soaps.

Morphology of Pathologic calcification

Calcium deposition occur anywhere in the body. E.g.

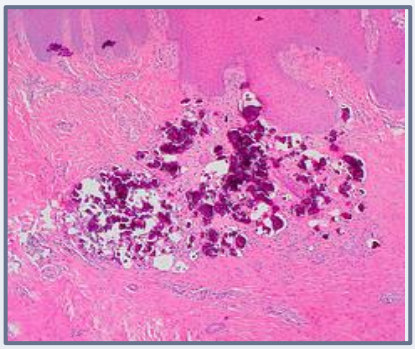
Wall of blood vessels | Kidney | Stomach | lung | skin

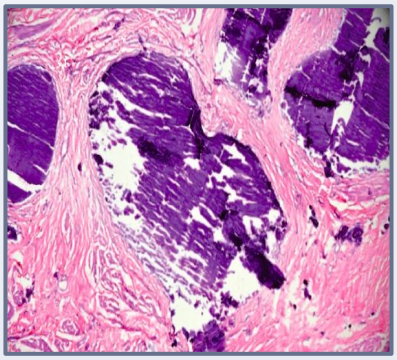
Whatever the site of deposition, the calcium salts appear <u>macroscopically</u> as fine, white granules or clumps, often felt as gritty deposits.

<u>Histologically</u>, calcium salts are:

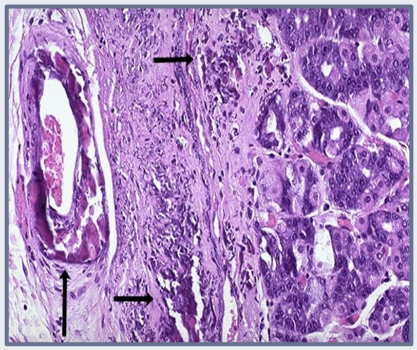
basophilic, amorphous, granular.

Can be intracellular, extracellular or both.





Calcium looks like crushed chalk under the microscope



Calcium looks the same in dystrophic & metastatic calcification so tests need to be done to check for calcium levels & metabolism in blood

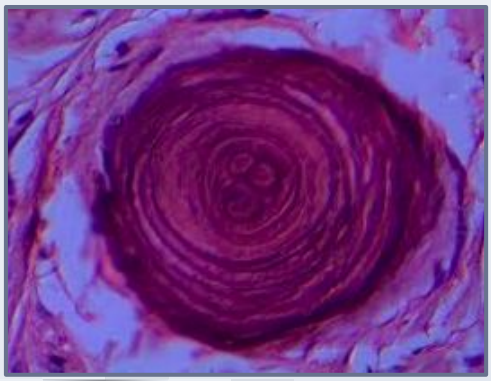
Psammoma body

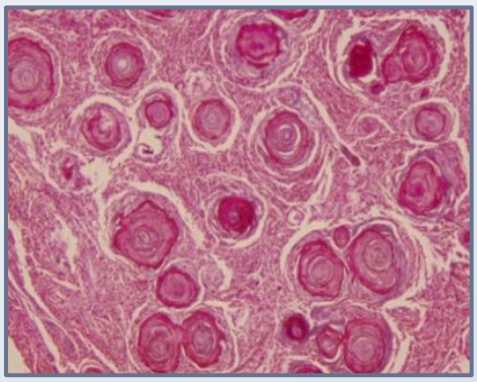
Is a special type of <u>dystrophic calcification</u>

made up of concentric lamellated calcified structures.

<u>Seen in papillary cancers in the body. E. g.</u>

- Thyroid
- Ovary
- Kidney
- In the meningioma* of the brain





*__meningioma__ is a tumor that forms on membranes that cover the brain and spinal cord

1-D 2-B 3-A

MCQs

Q1- Accumulation of ..... could be an early sign of cellular degeneration			
A) Water	B) Lipids	C) Glycogen	D) Pigments
Q2- Accumulation of carbon pigment causes:			
A) atherosclerosis	B) Melanosome granule	C) Anthracosis	D) Yellowish pigment
Q3- In secondary amyloidosis, Amyloid has "....." type of Amyloid associated proteins			
A) AS	B) AP	C) AA	D) AL
Q4- Stain that identifies Steatosis:			
A) Masson-fontana	B) Congo Red stain	C) Sudan IV stain with Yellow-Black color	D) Oil Red-O stain with Orange-Red color
Q5: Psammoma bodies can be found in Papillary cancer of :			
A) Heart	B) Kidney	C) Liver	D) Both B & C
Q6: Which pigment accumulation can be seen as golden yellow brown?			
A) Lipofuscin	B) Bilirubin	C) Melanin	D) Hemosiderin

SAQs

Q1: Name some of the accumulating substances and the stain used to identify them.

Q2: Name examples of Dystrophic calcification.

Q3: The causes of excess systemic iron are?

Q4: What are the differences between Dystrophic and metastatic calcification?

1- Slides 10
2- Slide 12
3- Slide 7
4- Slide 11

الحمد لله على الانتهاء بجزء من العمل :
حُسن ظنّكم بنا، ودعواتكم لنا، هي وقودنا للاستمرار .. والاجتهاد..
العمل من أجل الدفعة، والدفعة تتعاون لأجل العمل، فخرًا بهذه الجامعة العريقة..

نتمنّى لكم خير الطريق والتوفيق <3

-Pathology Team leader
Majed Alaskar

- غادة العثمان
- ماجد العسكر

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