Pathology

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Intracellular accumulations and calcifications

cell injury and adaptations

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INTRACELLULAR ACCUMULATIONS

Intracellular accumulations: The deposition of exogenous or endogenous substances inside the cell. This can be done by many mechanisms that include:

- 1)Inadequate removal of a normal substance (fatty change in the liver)
- 2)Accumulation of an abnormal endogenous proteins due to folding defect (α1-antitrypsin defficiency)
- 3)Failure to degrade a metabolite due to inherited enzyme deficiencies (lysosomal storage diseases and glycogen storage diseases)
- 4)Deposition and accumulation of an abnormal exogenous substance (carbon and selica)

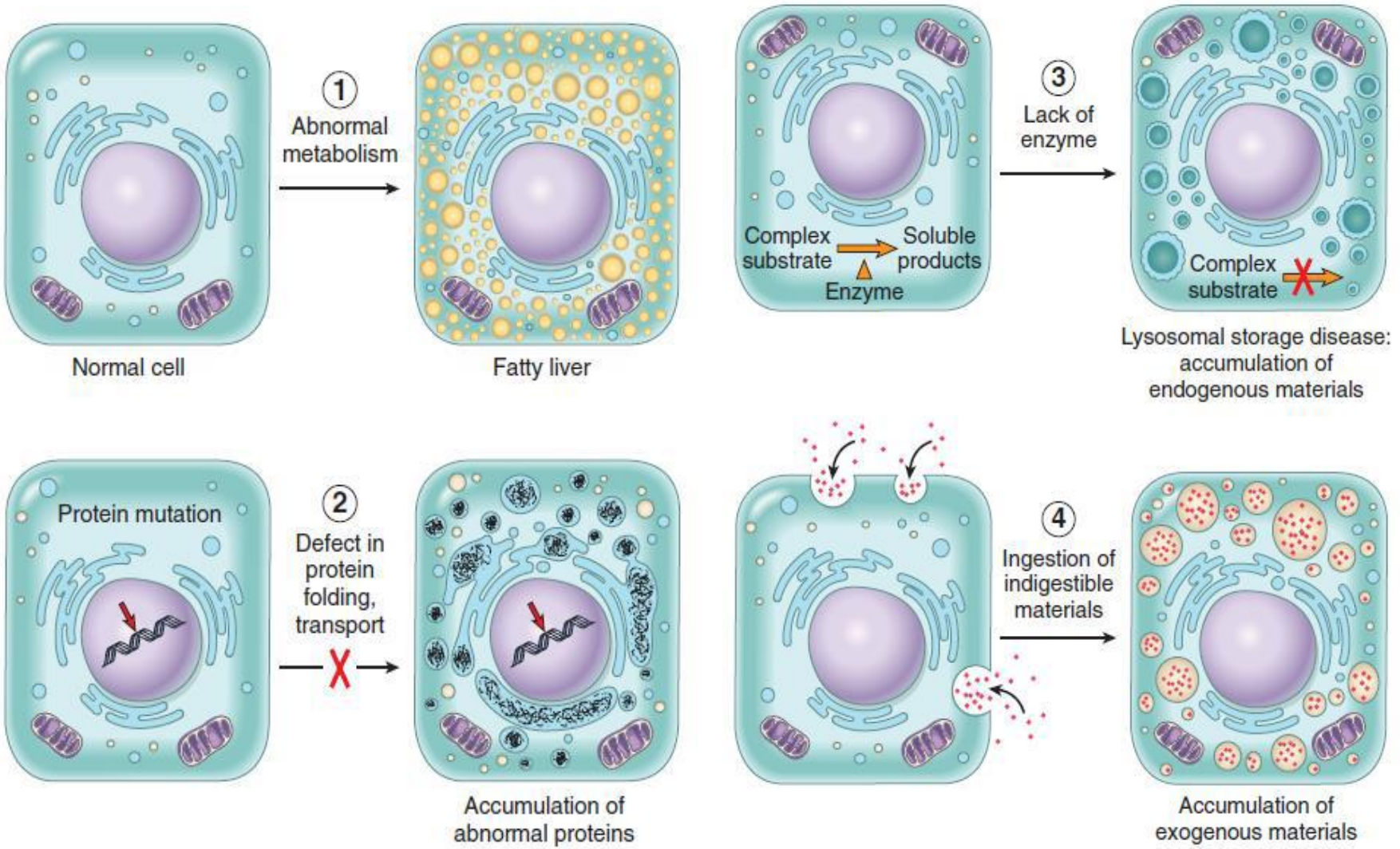
Notes:

1) Fats/ triglycerides are normally produced in the hepatocytes, and when they are not adequately removed they will accumulate in those cells. Triglycerides are normally transported outside the cells by binding to certain proteins, so any defect in those proteins may cause fat accumulation. Figure 1 in the next slide.

2) In order to secrete the α1-antitrypsin enzyme outside the cell, certain folding processes are needed because the enzyme should be in a certain configuration. If this folding process is defective or the cell is unable to fold this protein, it will accumulate inside the cell in its abnormal configuration. A deficiency of this enzyme can be noted in peripheral blood or tissue because it isn't being secreted. Figure 2

3) A deficiency in the enzymes needed to degrade certain substances can cause cell accumulations. Figure 3

4) These exogenous substances (carbon and silica) are indigestible and will stay inside the cells. They can also give certain colors to the cells they accumulate in. Carbon usually accumulates in the lungs. Figure 4

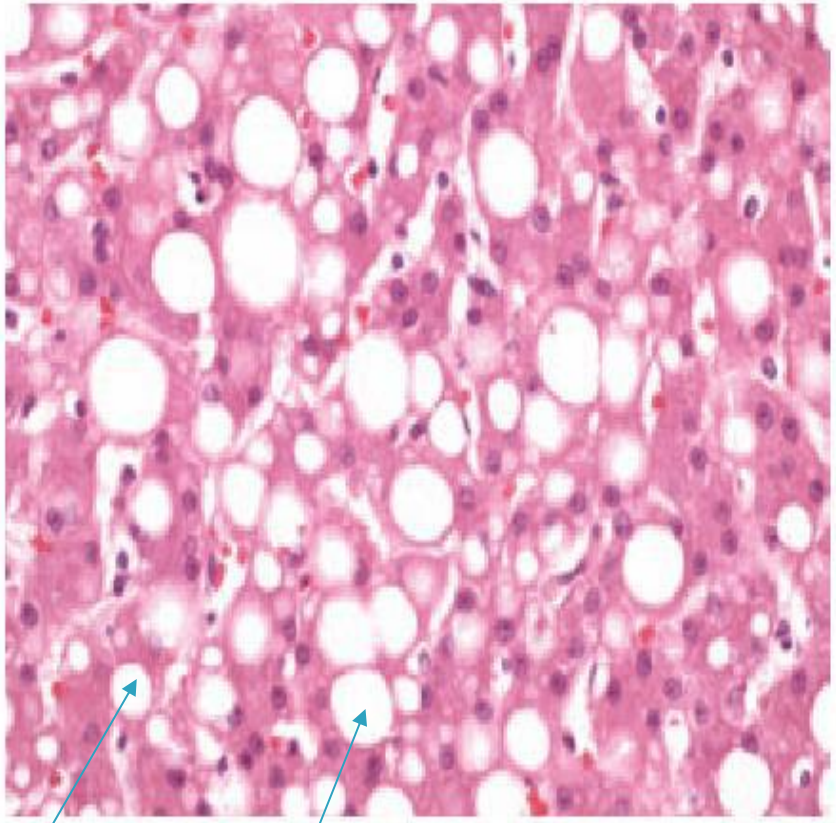

Normal cell
1
Abnormal metabolism
Fatty liver
Complex substrate
Soluble products
Enzyme
3
Lack of enzyme
Complex substrate
Lysosomal storage disease: accumulation of endogenous materials
Protein mutation
2
Defect in protein folding, transport
Accumulation of abnormal proteins
4
Ingestion of indigestible materials
Accumulation of exogenous materials

fatty change: steatosis

Steatosis: clinical term for the deposition of fats in hepatocytes

Because the liver is very important in regards to fat metabolism

- Most common in liver
- Triglycerides
- Also in heart, kidney, muscle
- Causes: toxins, protein malnutrition, DM, obesity, anoxia
- Alcohol abuse and DM+obesity are the most common causes of fatty liver



The triglyceride accumulation is manifested under the microscope by empty whitish vacuoles inside the cells, displacing the nucleus to the periphery and giving an appearance similar to adipose tissue.

Macroscopically, the liver is enlarged and has a yellowish cut surface if there is fat accumulation.

Notes about the causes of steatosis:

1)Toxins: an overdose of acetaminophen (acetaminophen toxicity) will lead to fatty liver change.

2)Protein malnutrition: In order to secrete triglycerides outside the cell, they need to bind to proteins (like apoproteins) as mentioned before. If we have a deficiency in these proteins, the triglycerides will accumulate in the liver.

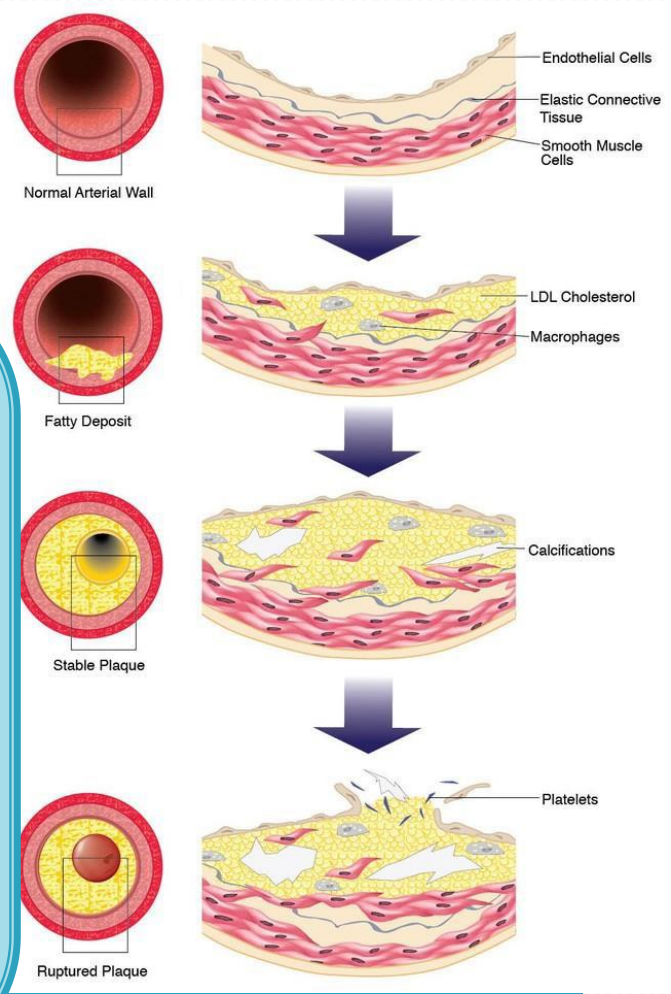
3)The most common causes of fatty liver disease are different according to geographic location. In Western countries for example, alcoholic fatty liver disease is the most common.
In our part of the world, non-alcoholic fatty liver disease is the most common (due to DM + obesity, sometimes called metabolic syndrome).

Cholesterol and Cholesteryl Esters

- Phagocytic cells become overloaded with lipid (triglycerides, cholesterol, and cholesteryl esters)
- Due to Increased intake or decreased catabolism
- Atherosclerosis

- The best example is the deposition of these lipids in the walls of blood vessels in diabetic or elderly patients

- **(in the picture)** The yellow material, called the atheroma, starts to accumulate in the blood vessel wall. With time, the blood vessel's lumen will become narrower and this can be complicated with the formation of an overlying/superimposed thrombus which can lead to total occlusion of the vessel and result in infraction.



Proteins

- Much less common than lipid accumulations
- Either excess external or internal synthesis

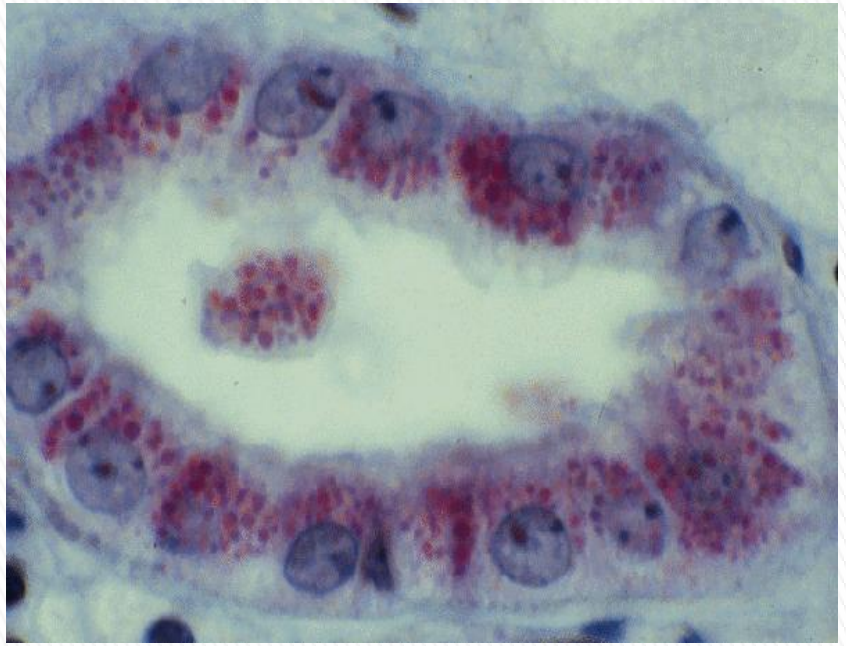
Examples of protein accumulations:

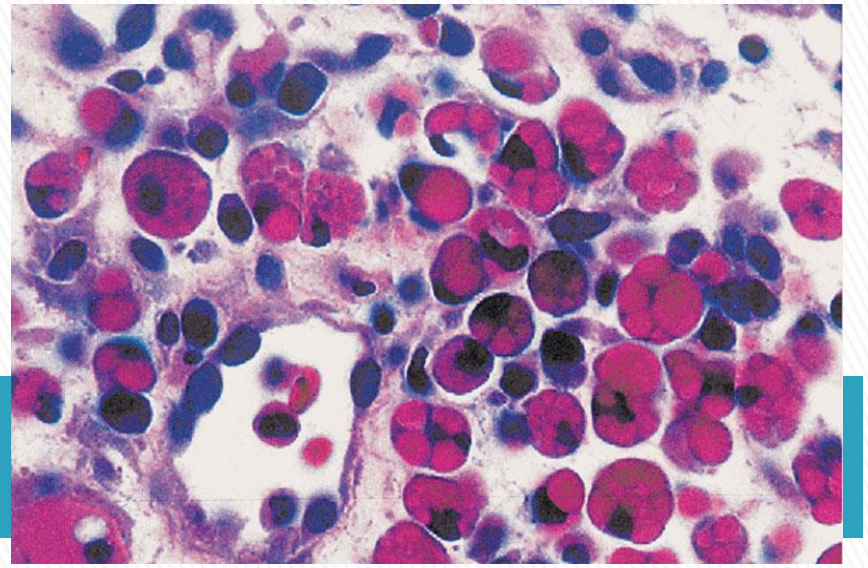
- Proximal renal tubules in nephrotic syndrome
- Russell bodies in plasma cells.
- Alcoholic hyaline in liver.

- Alcoholic hyaline liver: Pink material deposited in the liver in cases of alcoholic liver disease

- Neurofibrillary tangles in neurons

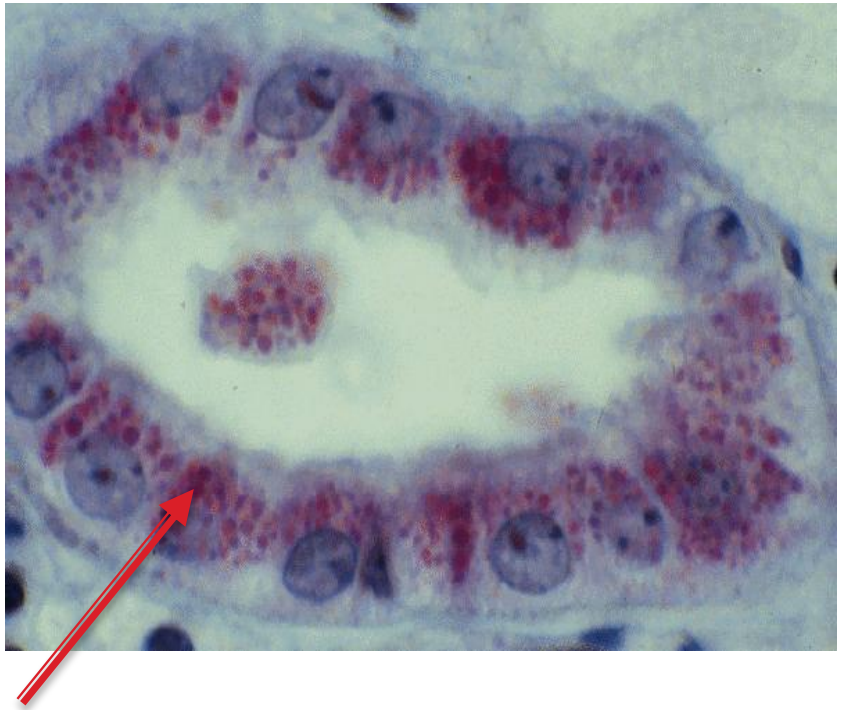
Neurofibrillary tangles: We see these in the neurons of the cerebral cortex in patients with Alzheimer's disease





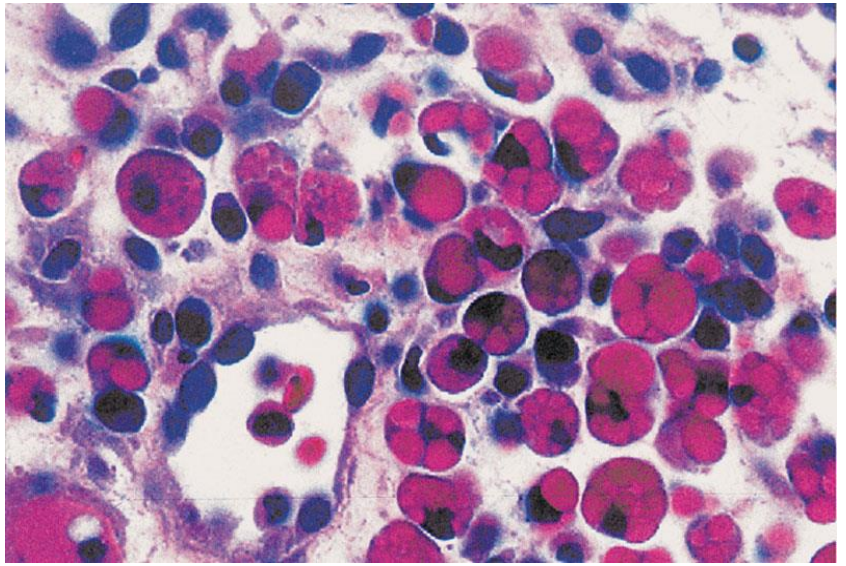
Proximal renal tubules in nephrotic syndrome:

The proteins (the pink granules in the cytoplasm of the renal tubules in the first picture) are reabsorbed proteins from the urine. The reabsorption happens because these patients suffer from a high rate of protein (Albumin) loss due to increased kidney permeability for proteins. As a response, the renal tubules will try to conserve as much protein as possible by reabsorbing these proteins, and the reabsorbed proteins accumulate in the cytoplasm



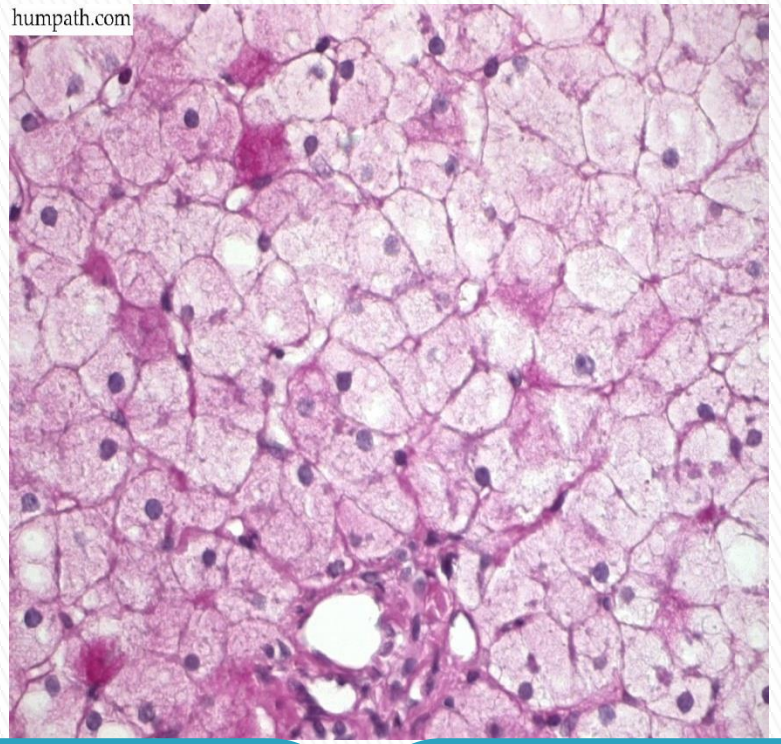
Russell bodies in plasma cells:

The second picture shows antibodies in the endoplasmic reticulum of plasma cells. Plasma cells are the cells responsible for antibody production. When excessive amounts of antibodies are produced, they will accumulate in the form of droplets called Russell bodies. (The heavy pinkish appearance is due to the Russel bodies. The dark blue bodies are nuclei).



Glycogen

- Abnormality in glucose or glycogen metabolism
- **DM** (in renal tubules, heart, B cells of pancreas).
- **Glycogen storage diseases**



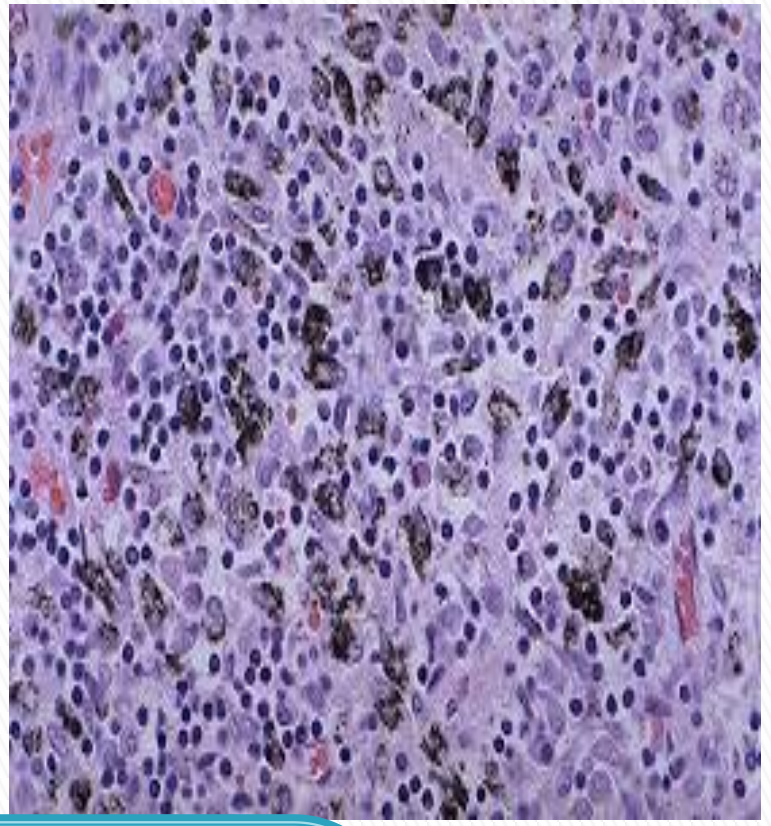
In glycogen storage disease, there is a deficiency of the enzyme needed for glycogen catabolism, and this is usually an inherited genetic disease.

- This picture shows hepatocytes which are loaded with large amounts of glycogen due to its excessive accumulation, giving the cells a bubbly appearance

Sometimes we can detect the accumulation of glycogen by certain special stains like the periodic acid-Schiff (PAS) stain

Pigments

- **Exogenous**
- Most common exogenous, **carbon** (coal dust, air pollution)
- Alveolar macrophages → lymphatic channels → tracheobronchial LN
- *Anthracosis*



- Pigments are ANY COLORED MATERIAL that can be DEPOSITED in the cytoplasm of the cell, these pigments could be of exogenous source or endogenous source produced inside the body

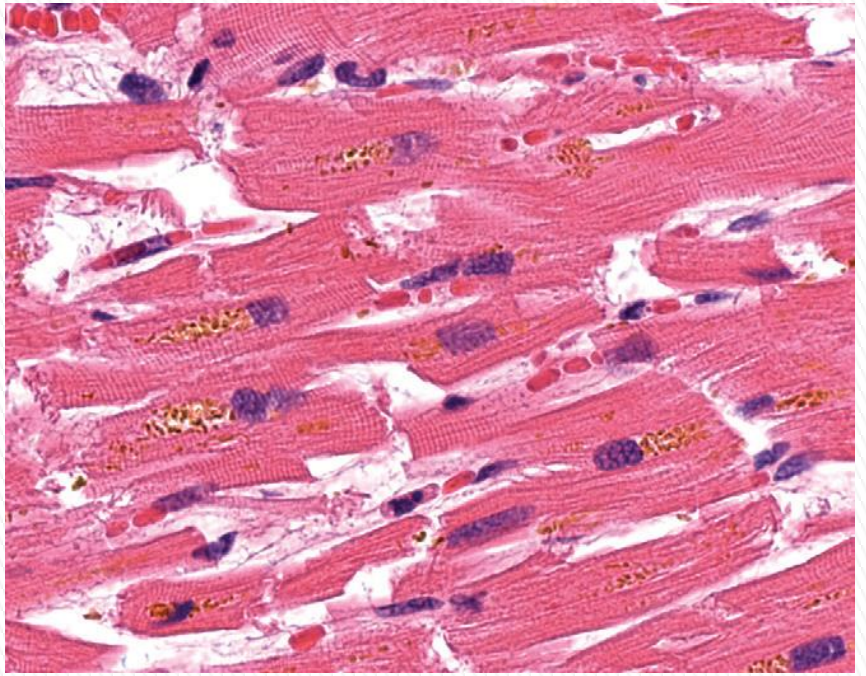
- Carbon usually deposited in patients who are smokers, exposed to air pollution

- If deposited in alveoli, the macrophages in the lung engulf this carbon which will give black discolorations to the cytoplasm of macrophage then travels to → lymphatic channels → tracheobronchial lymph nodes and it gives black discolorations in the lymph node in addition to the lung.
- Carbon is an indigestible substance, that appears as black deposits.
- Anthracosis = carbon deposition in the lung.

Pigments

- **Endogenous**
- **Lipofuscin**
- "wear-and-tear pigment"
- Age/atrophy
- Heart, liver, and brain
- Lipid and protein
- Marker of past free radical injury
- *brown atrophy*

- Its deposition indicates aging, atrophy, or previous cell injury mostly mediated by free radicals

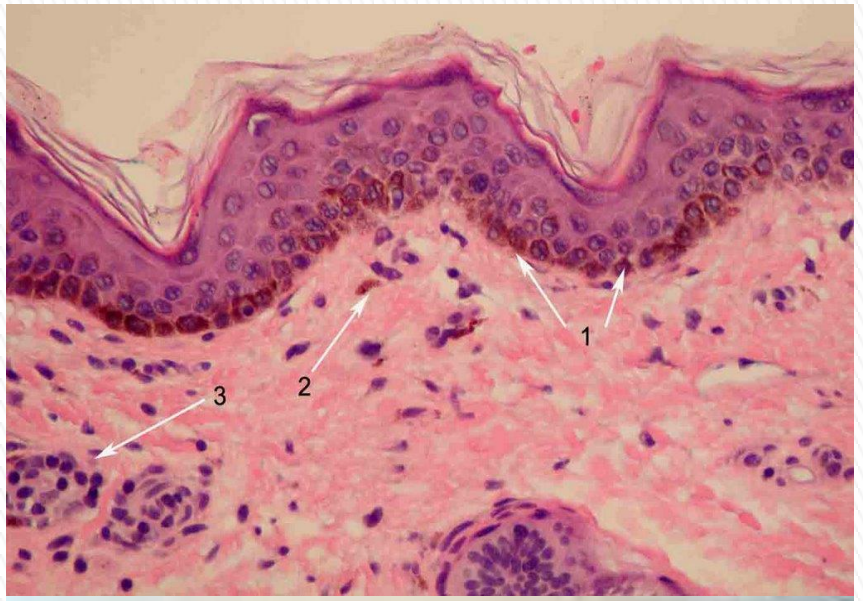


- It is an innocent pigments(doesn't cause any harm).
- It is a lipid and protein-derived (composition): mostly due to the membrane damage or organelles damage in the cell.
- Tissues affected: heart, liver , brain and skeletal muscles.
- When the tissue is severely atrophied, and it turns brown, due to lipofuscin atrophy, it appears as 'BROWN ATROPHY'

- the pic taken from a cardiac muscle and we can see olive green colored granules in the cytoplasm of the cardiac myocyte

Pigments

- **Endogenous**
- **Melanin**
- Source: melanocytes
- UV protection
- Accumulates in dermal macrophages and adjacent keratinocytes
- Freckles



- It produced in melanocytes in the skin
- In cases of increased exposure to sun, especially fair-skinned people,they develop excessive production of melanin, which can also be taken by adjacent keratinocytes in the skin at the basal layer of epidermis (as shown in the arrow) Note that brown-colored cells are NOT only melanocytes, it is also keratinocytes which take the pigment and we can see pigment in the dermal macrophages.
- FRECKELS, which are brown dots

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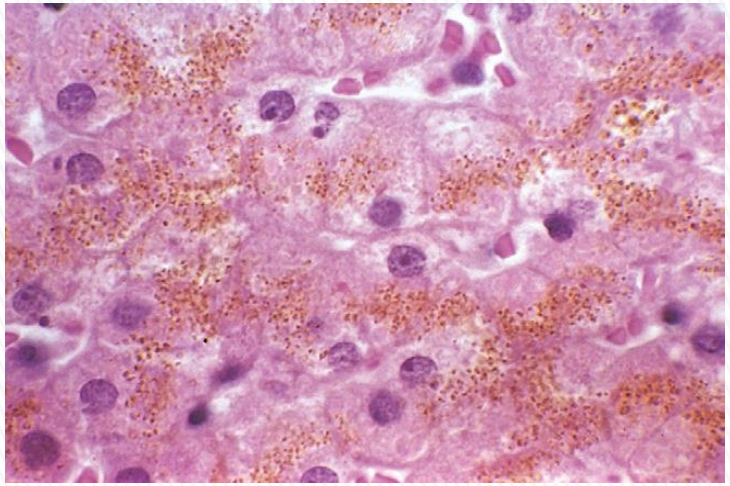
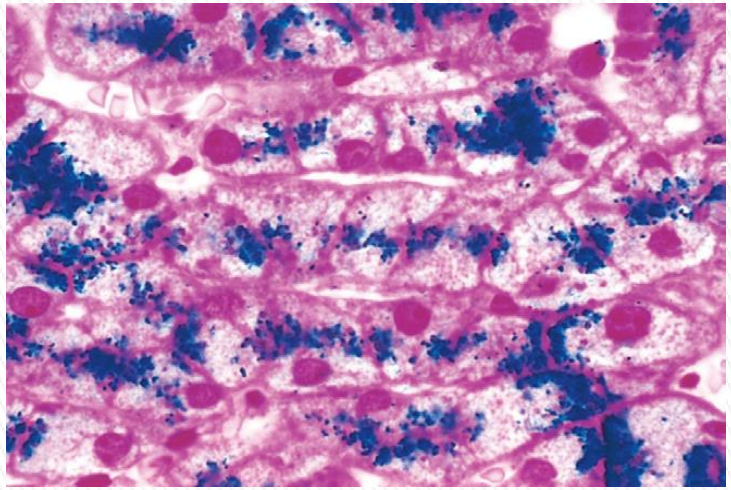
pigments

Hemosiderin

- Hb-derived granular pigment
- Iron +apoferritin==ferritin micelles
- Physiologic in the mononuclear phagocytes of the BM, spleen, and liver, from RBC turnover
- Bruise: local pathologic deposition from hemorrhage
- Hemosiderosis: systemic pathologic deposition of hemosiderin (hemochromatosis, hemolytic anemias, repeated blood transfusions)





- Hb-derived iron pigment (produced from hemoglobin degradation).
- it is granular brownish pigment.
- Iron in cells usually binds to ferritin (protein), to give ferritin micelles (the brownish colered granules).

- How can we make sure that the brown pigment is an iron pigment, not lipofuscin pigment or melanin pigment for example?
- We use Prussian blue stain (special stain), Prussian blue stain gives these granules the blue color if it contains iron, but if it is lipofuscin or melanin it will not take the stain.
- Deposition of Iron can be physiologic or pathologic
- 1.Physiologic in organs or tissues that have frequent RBCs turnover activity such as:bone marrow,spleen and liver so we can see accumulation of hemosiderin in macrophages or the phagocytes of these organs.
- 2. Pathological in localized depositions such as bruises, these bruises will change the color from red or red blue color finally to yellow.
- hemosiderosis: generalized systemic pathologic deposition of hemosiderin can result from hemochromatosis, hemolytic anemias and repeated blood transfusion.
- Pathologic deposition can be generalized, systemic ,everywhere(skin, heart ,liver, muscles).

- There are different causes of hemosederosis:
- 1.HEMOLYTIC ANEMIA –Sickle Cell Anemia,Thalassemia
- *Any condition that increases RBCs destruction is hemolytic anemia,and it can cause general deposition of Iron.
- *Hemolytic anemia patients were found to have a deeply brownish skin.
- 2.HEMOCHROMATOSIS Autosomal dominant condition that causes high Iron deposition in different organs in the body, for example deposition is the heart may lead to heart failure, deposition in the pancreas may lead to Diabetes and so on
- 3.REPEATED BLOOD TRANSFUSIONS e.g:thalassemia,leukemia
- –Patients with thalassemia receive blood transfusions approximately every 3 months, so you can imagine how much Iron will get deposited in their bodies

PATHOLOGIC CALCIFICATION

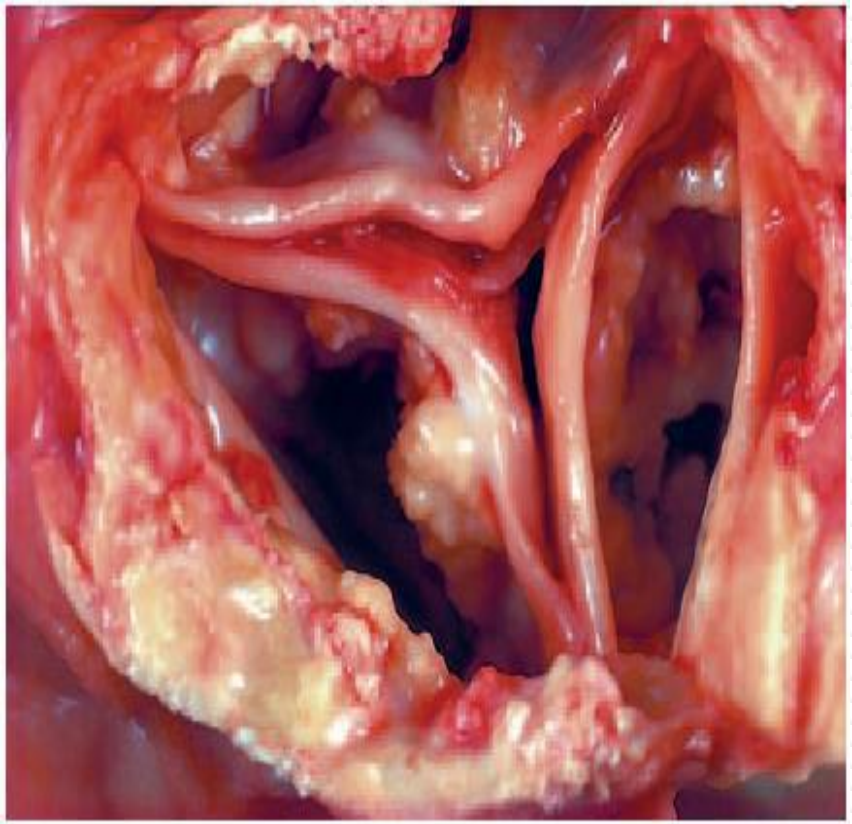
- Abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other mineral

- **Dystrophic Calcification**
- Deposition in dead/injured tissues
- Normal Ca2+ metabolism
- Exacerbated by Hypercalcemia

- **Metastatic Calcification**
- Deposition in normal tissues
- Almost always abnormal Ca2+ metabolism (hypercalcemia)

- Dystrophic calcification not associated with Hypercalcemia
- Metastasis the spread of malignancy

Dystrophic calcification



- **Necrosis of any type**
- **Atherosclerosis, aging or damaged heart valves, aortic stenosis, tuberculosis)**
- **Incidental finding indicating insignificant past cell injury**
- **Or May be a cause of organ dysfunction.**

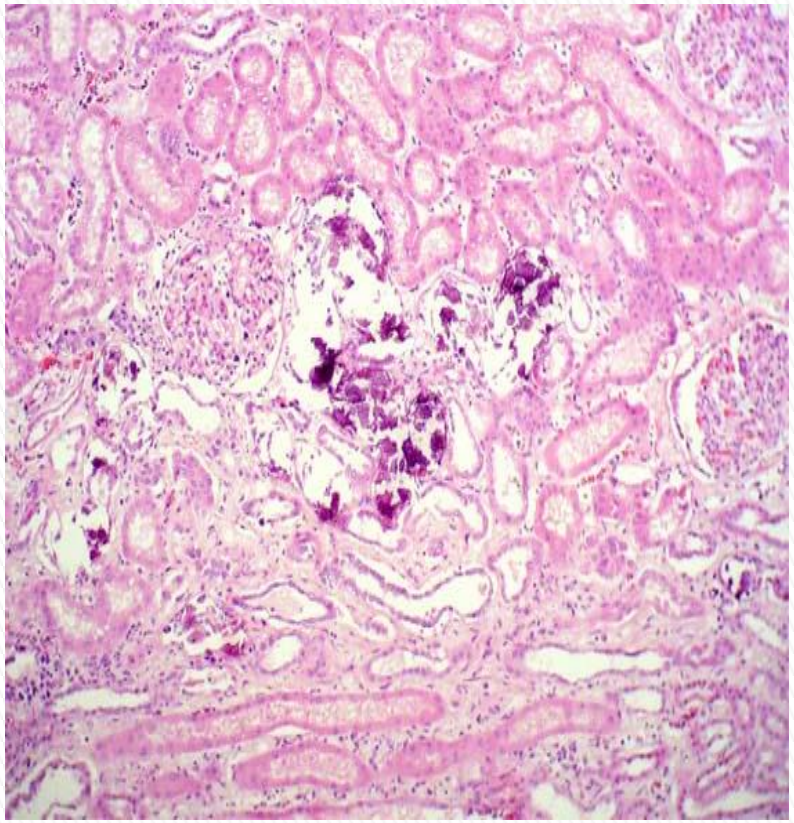
Long-term and excessive calcium accumulation may eventually cause organ dysfunction, but if is a minimal amount it can not be associated with organ dysfunction

-Atherosclerosis has recently been considered an inflammatory reaction,because of macrophages being at the site engulfing lipids in the walls of blood vessels,so atherosclerotic vessels can deposit calcium,thus vessels become more rigid.

-Aging of cells can also lead to calcium accumulation,like aged heart valves that underwent degeneration as a consequence for aging,they show calcium deposition.

-Aortic stenosis,either due to aging or other earlier conditions,can lead to calcium accumulation in aortic heart valves,making them more stiff.

Metastatic Calcification



- Hyperparathyroidism (primary and parathyroid hormone related protein)
- Bone destruction (metastasis, MM, leukemia, Pagets, immobilization)
- Vit-D intoxication,
- Sarcoidosis.
- Renal failure with 2ry hyperparathyroidism.
- **VESSELS, LUNG, KIDNEY**

- under the light microscope calcium can be seen purple and metastatic calcification(the surrounding tissue) is normal(not in injured or aged tissue) but in the aortic valve it gives a whitish chokey color

- the causes of METASTATIC CALCIFICATION are any cause associated with HYPERCALCEMIA
- -Hyperparathyroidism(elevated Parathyroid hormone in the blood,and we know it is the main responsible hormone for calcium balance,so disordered levels of it would induce hypercalcemia)
- Hyperparathyroidism can be primary(problem in the parathyroid itself) or secondary(problem in the hypothalamus) and 2ry is usually associated with renal failure or it could be a tumor (lung cancer as an example) that produces PTH-like proteins in the blood,exerting the same effect of PTH,hypercalcemia.
- Sarcoidosis :autoimmune systemic disease accompanied with
- hypercalcemia

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