



Amyloidosis. Endogenous and exogenous pigments. Pathological calcification.

I. Microspecimens:

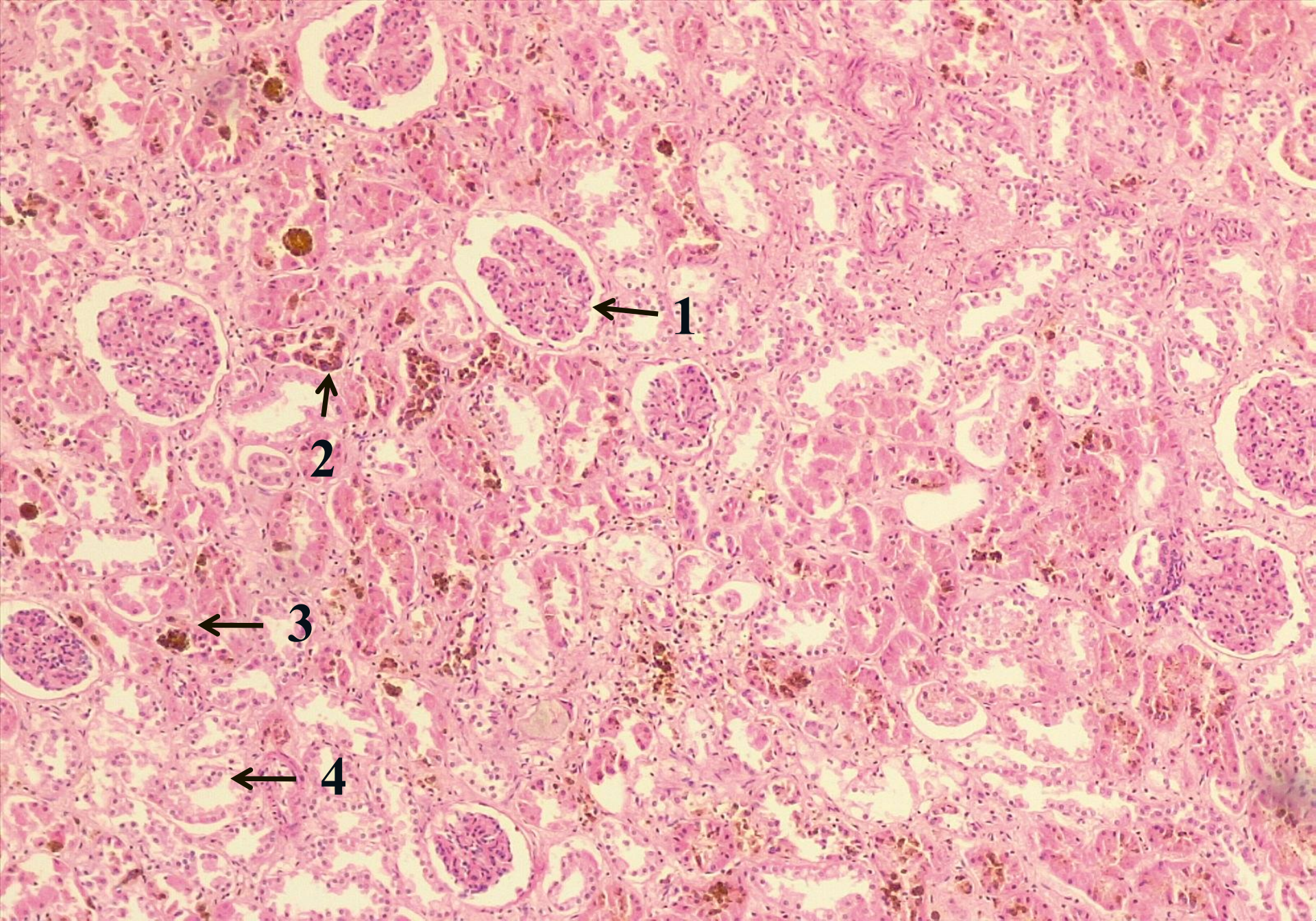
№ 180. Renal hemosiderosis. (*H-E. stain*).

Indications:

1. Glomerulus.
2. Hemosiderin granules in the cytoplasm of nephrocytes.
3. Hemosiderin granules in the lumen of the tubule.
4. Unchanged tubule.

In the epithelial cells of the convoluted renal tubules, brown hemosiderin granules are observed, which can be found in some places in the lumen of the tubules.

Renal hemosiderosis is a manifestation of generalized hemosiderosis, characterized by an increased content of hemosiderin in the body. It is due to massive and prolonged intravascular hemolysis of erythrocytes and is found in hemolytic anemias, intoxications with hemolytic toxins (eg, snake venom), infectious diseases (eg, in sepsis), incompatible blood transfusions. From the products of destruction of hemoglobin in the elements of the reticuloendothelial system (spleen, bone marrow, lymph nodes) and in some parenchymal organs (liver, kidneys) are formed and stored excessive amounts of hemosiderin, these organs acquiring a rusted nuance. At the same time, there is an increase in the synthesis of ferritin and bilirubin. Generalized hemosiderosis is also observed in hemochromatosis.



№ 180. Renal hemosiderosis. (*H-E. stain*).

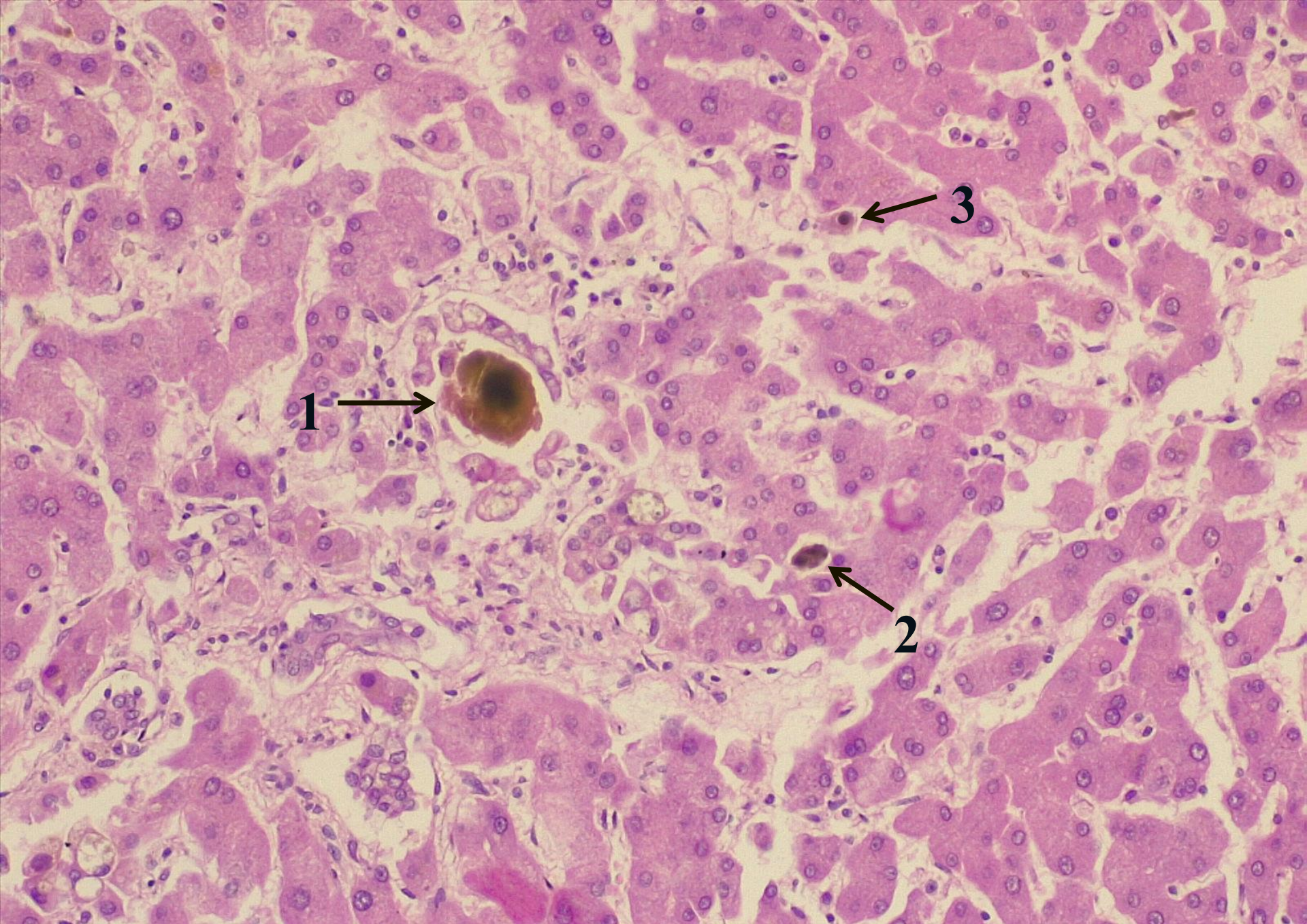
№ 135. Obstructive jaundice of the liver. (H-E. stain).

Indications:

1. Dilated bile ducts filled with bile pigments.
2. Accumulation of bile into the lumen of the intralobular bile capillaries.
3. Granules of bile pigment in the cytoplasm of hepatocytes.

The bile ducts and some interlobular ducts are dilated, in their lumen are observed brown bile coagulates (biliary “thrombi”), and in the cytoplasm of some hepatocytes - bile pigment granules; in some places in the center of the hepatic lobes there are foci of necrosis of hepatocytes, imbued with bile.

Bile stasis (mechanical jaundice) can be caused by gallstones, intra- and extrahepatic bile duct tumors, bile duct malformations or their external compression in pancreatic head cancer, duodenal papilla tumors, cancer metastases in the lymph nodes in hepatic hilum, adhesions. Excess of direct (conjugated) bilirubin in the blood, causes yellow-green pigmentation of organs and tissues, including skin and sclera. Apart from the intense coloration of the skin, in general obstructive jaundice there is general intoxication due to bile acids, hemorrhagic syndrome, dystrophic kidney damage, hepato-renal failure. Biliary stasis can be complicated by inflammation of the bile ducts (cholangitis), and if the process acquires a chronic evolution, cholestatic biliary cirrhosis can develop.



№ 135. Obstructive jaundice of the liver. (H-E. stain).

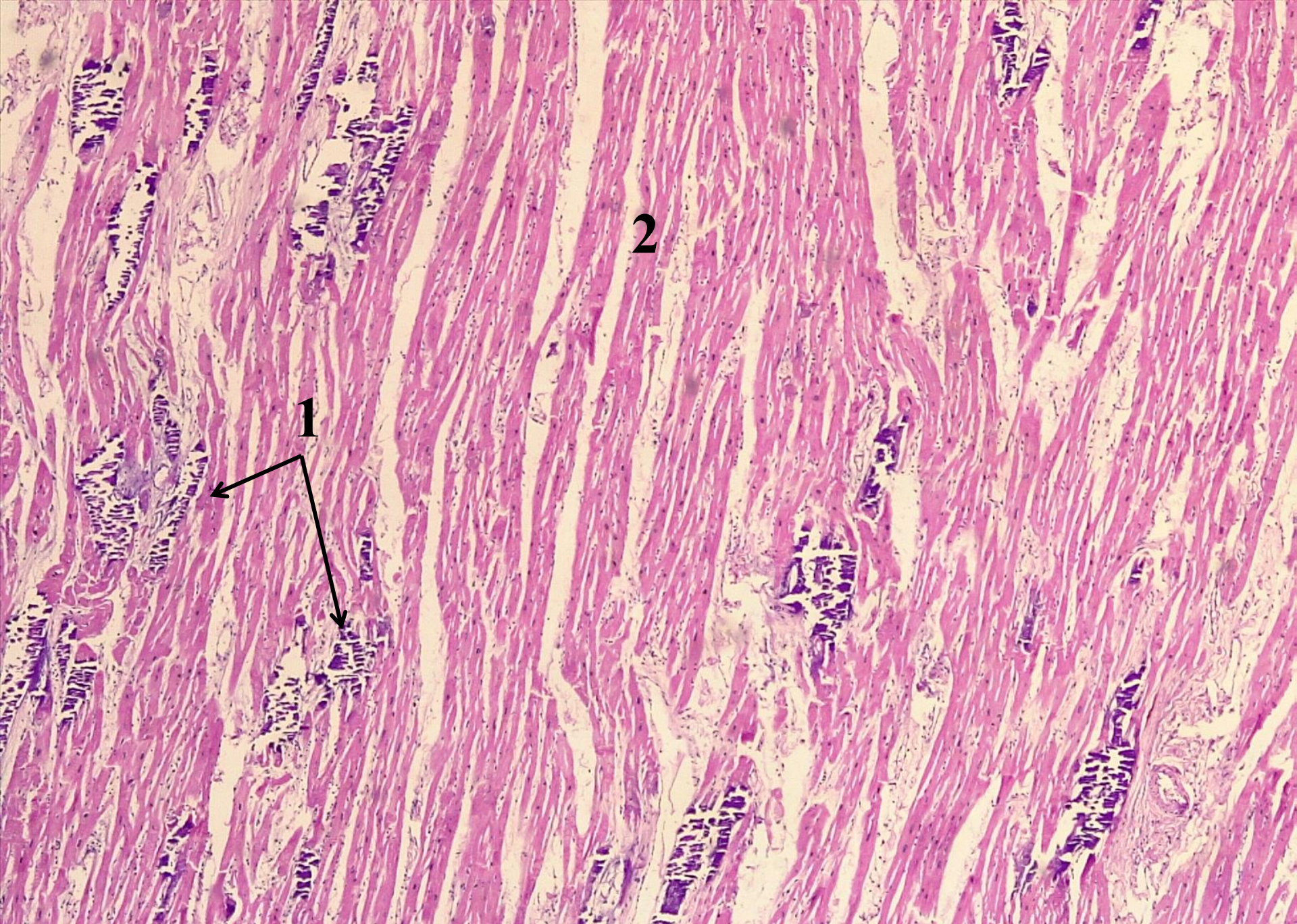
№ 197a. Metastatic calcinosis of the myocardium. (*H-E. stain*).

Indications:

1. Focal deposits of calcium salts.
2. Adjacent myocardium.

In the microspecimen are observed multiple small foci of powdered granular deposits of calcium salts, stained with hematoxylin in blue-purple. Calcium salts are stored in both the cardiomyocyte sarcoplasm and the myocardial stroma.

Metastatic calcinosis is caused by excess of calcium in the blood plasma (hypercalcemia) which is caused by the mobilization of calcium from the bones or by disturbing the processes of calcium elimination from the body. It is observed in primary hyperparathyroidism (parathyroid adenoma), bone tumors (multiple myeloma, bone metastases), multiple bone fractures, hypervitaminosis D, osteoporosis, chronic nephritis. Calcium deposits occur in healthy, unaltered tissues: lungs, gastric mucosa, kidneys, myocardium, arterial walls (on average) - organs and tissues, where there is a local alkalosis due to the fact that they eliminate acidic products, which promotes precipitation calcium salts (stomach - hydrochloric acid, kidneys - uric acid, lungs - carbon dioxide, and myocardium and arteries are in constant contact with arterial blood and have low carbon dioxide content). Macroscopically, the calcareous deposits are white, chalky in appearance.



№ 197a. Metastatic calcinosis of the myocardium. (*H-E. stain*).

№ 19. Renal amyloidosis. (*Congo-red and hematoxylin stain.*)

Indications:

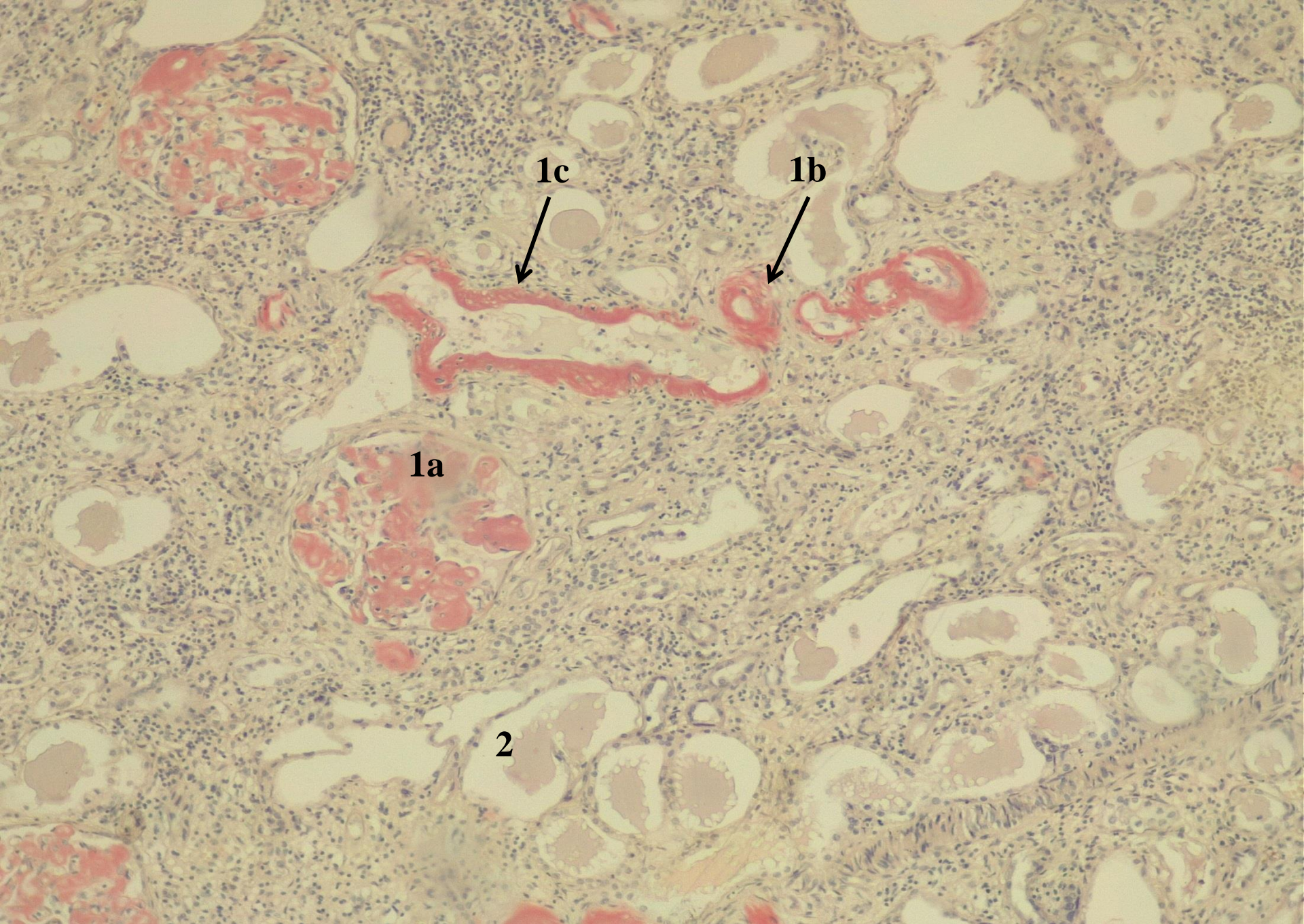
1. Amyloid deposits:
 - a. in glomerular capillaries;
 - b. in the artery wall;
 - c. on the basement membrane of the renal tubules.
2. Protein cylinders in tubule lumen.

In the kidneys it is observed the selective deposition of a homogeneous mass, colored in red, in the glomerular capillaries, under the endothelium, as well as in the walls of the arterioles and small arteries, in tubes containing the basement membrane, under the epithelium and on the path of the reticulum fibers of the stroma. In the epithelial cells of the tubes they contain granular dystrophy, in the lumen of some tubes - hyaline cylinders.

Kidney amyloidosis is a manifestation of generalized amyloidosis. *The macroscopic picture—macrospecimen № 82. Regardless of the organ, the amyloid deposits are detected histologically in: a) the walls of the blood and lymphatic vessels (in the intima or adventitia), b) in the glandular structures (tubes, collecting ducts) and c) in the stroma, along the reticular fibers and collagenic (perireticular and pericolagenic amyloidosis).*

The main methods of identification of the amyloid substance in the histological slides are Congo red (it is colored in red) and polarizing microscopy (it is colored in yellow-green). Macroscopically the amyloid can be identified with the help of the specific Virchow reaction: amyloid deposits are colored with iodine (Lugol solution) in red-brown, which turns after treating the section with a 10% solution of sulfuric acid from blue-violet to dark green.

Amyloidosis is an irreversible process, in the kidneys progressively evolving towards complete replacement of glomeruli and pyramids with amyloid masses, and subsequently diffuse proliferation of connective tissue and amyloid shrunken of the kidneys with the development of renal failure and azotemic uremia.



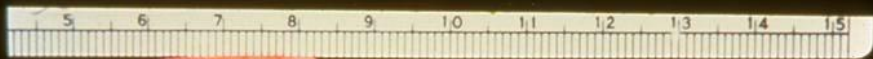
№ 19. Renal amyloidosis. (Congo-red and hematoxylin stain.)

II. Macrospecimens:

№ 76. Biliary calculi.

In the gallbladder there are multiple stones of different sizes from a few mm to a few cm, with a smooth, polished (faceted stones) or rough surface, yellow, olive or black, the bladder wall is thickened, sclerosed.

Risk factors in the development of gallstones are multiple, the most important: old age, female sex (in women it is 2 times more common than in men), obesity, oral contraceptives, hereditary predisposition and others. Among the local factors have an important role biliary stasis (gallbladder hypomobility) and mucus hypersecretion. According to the chemical composition there are 2 main types of stones: cholesterol (~80% of the total number), which contain cholesterol, are yellow and pigmented, which contain calcium salts of bilirubin, are brown or black. Possible complications: obstruction of the cystic duct, bile retention and development of gallbladder hydrops, mucocele, acute or chronic cholecystitis, gallbladder empyema, it is possible to perforate the bladder wall with bile flow into the peritoneal cavity and biliary peritonitis. The larger the stones, the lower the risk of obstruction of the cystic duct, and the smaller the stones ("sand") are more dangerous.



№ 76. Biliary calculi.

№ 87. Renal calculi.

The renal pelvis and calyces are dilated, contain multiple stones, some are free, others - overgrown with the pelvic / calyx wall, dimensions from 2-3 mm to 1-2 cm, smooth, polished surface (faceted stones) or irregular, rough, sometimes with branches, which take the shape of calyces - coral-shaped stones, white, yellow or brown depending on the chemical composition.

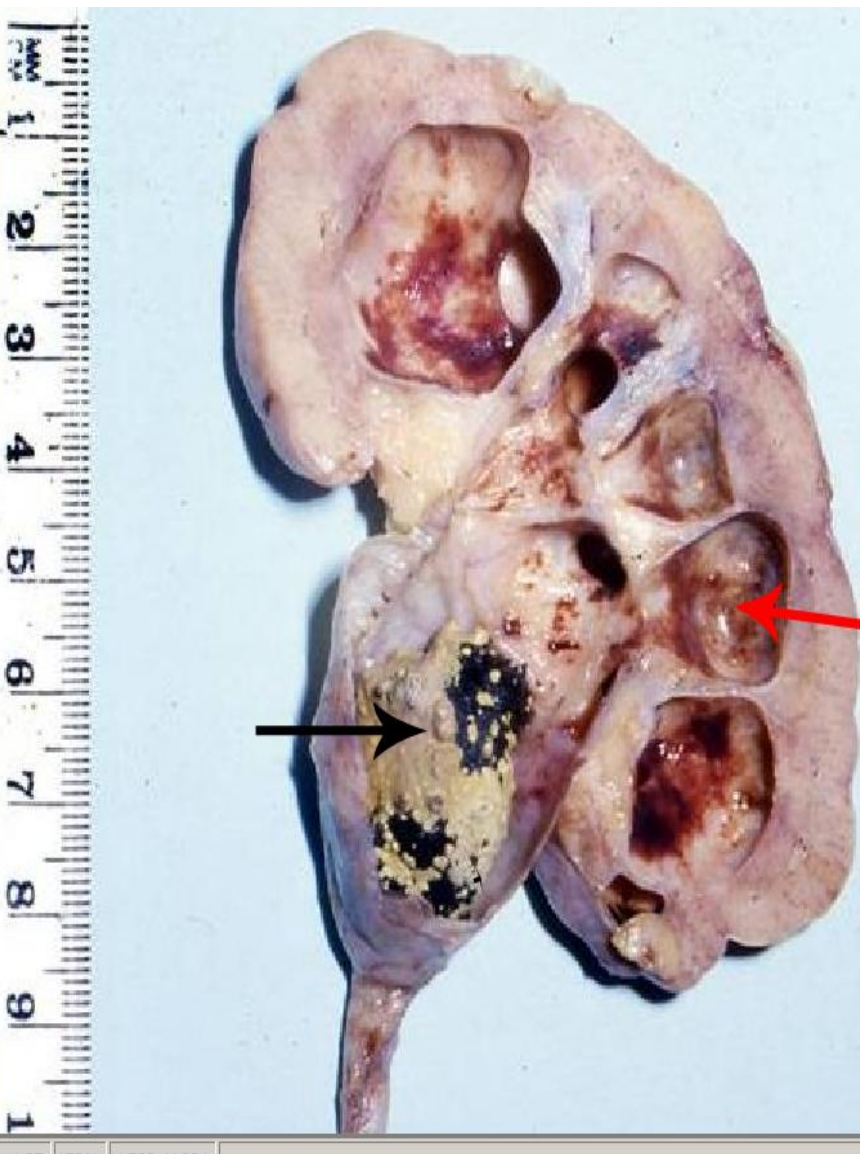
There are 3 main types of urinary stones:

a) calciform stones (calcium oxalates and phosphates), which are observed in ~ 75% of cases, have a granular-rough surface, brown color due to hemosiderin, which occurs after mucosal trauma and repeated hemorrhages;

b) mixed stones, so-called "crushed stones" or "triple phosphates", consisting of ammonium-magnesium phosphate; are found in ~ 15% of cases, especially in patients with urinary tract infections (Proteus vulgaris, Klebsiella, Staphylococcus); bacteria produce proteases, which cleave urea (infection-induced stones); they are white-yellow;

c) stones with uric acid (urates) - occur after hyperuricemia and hyperuricuria, which is observed in cases of primary or secondary gout in myeloproliferative diseases (eg, in leukosis), have yellow-gray color.

Complications: pyelonephritis, nephrosclerosis and macronodular shedding of the kidney, if the process is bilateral - progressive chronic renal failure.



№ 87. Renal calculi.

№ 82. Renal amyloidosis.

The kidney is enlarged in size of dense consistency, gray yellowish color and lardy or waxy appearance, the surface is slightly wavy, on section layers are poorly delimited - "big white amyloidic kidney".

Renal amyloidosis (amyloid nephropathy) is found in both primary amyloidosis, e.g., multiple myeloma (AL amyloidosis) and secondary amyloidosis, eg, purulent osteomyelitis, tuberculosis, bronchiectasis, rheumatoid arthritis (AA amyloidosis).

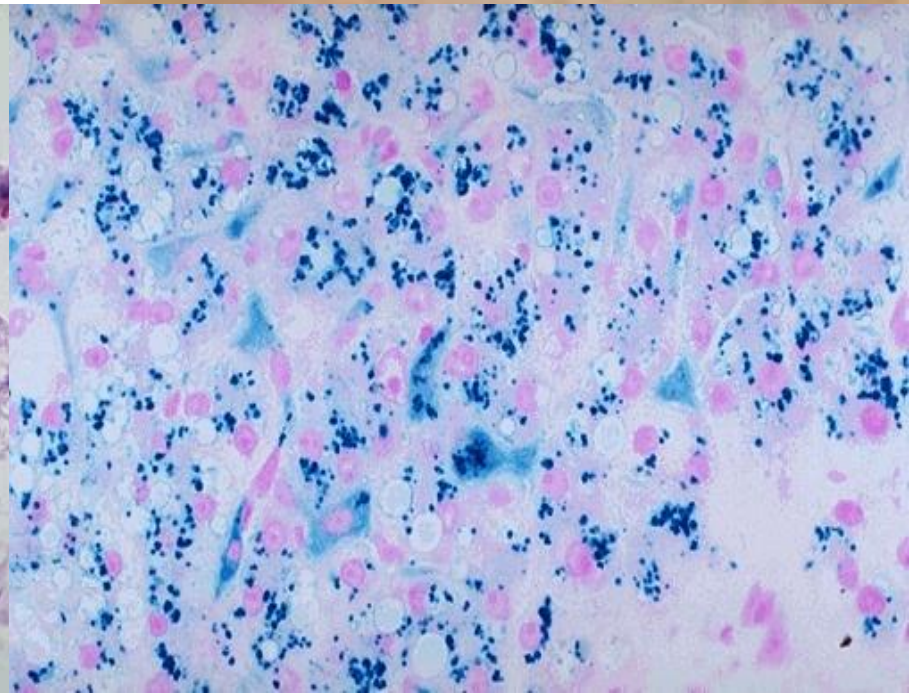
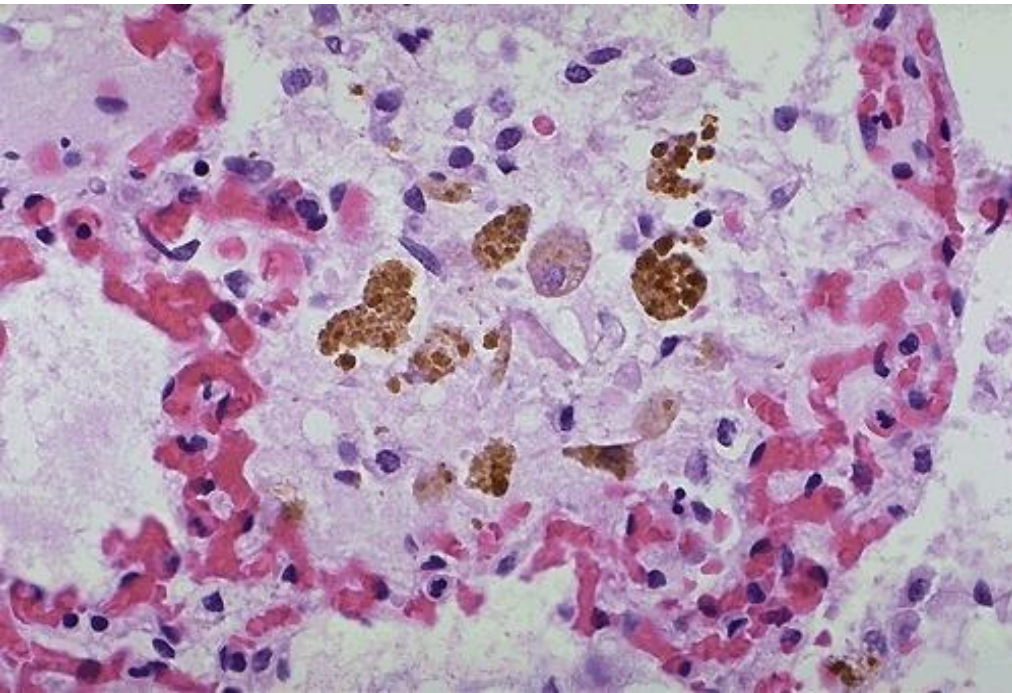
Clinically manifested by nephrotic syndrome: massive proteinuria (more than 3.5 g in 24 hours, hypoalbuminemia, generalized edema, hyperlipidemia and lipiduria, azotemia, hypertension (in 50% of cases).

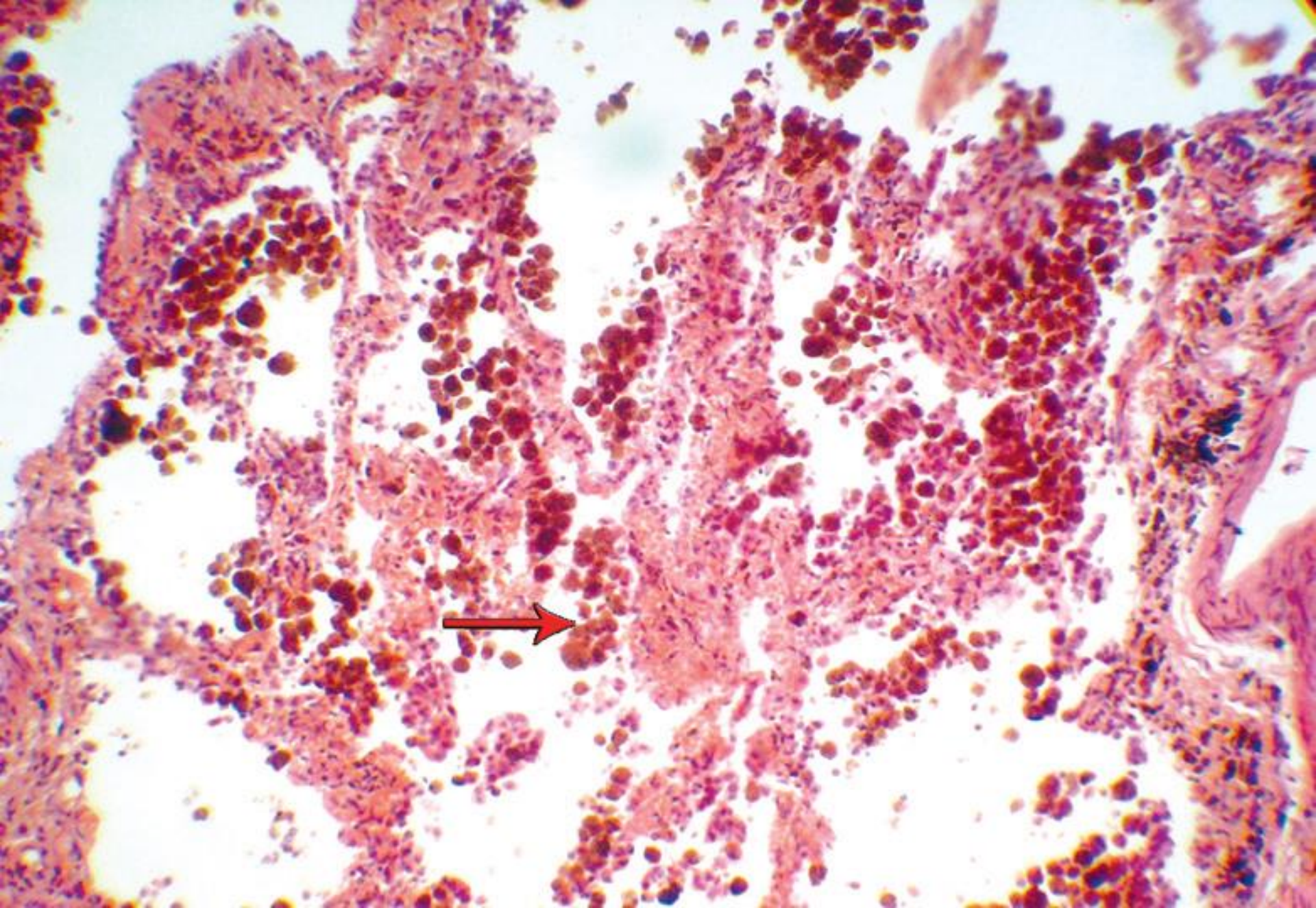
Complications: renal failure, association of infections due to decreased immunity, cardiovascular insufficiency, predisposition to thrombosis of vessels due to loss with urine of immunoglobulins and anticoagulant system proteins.



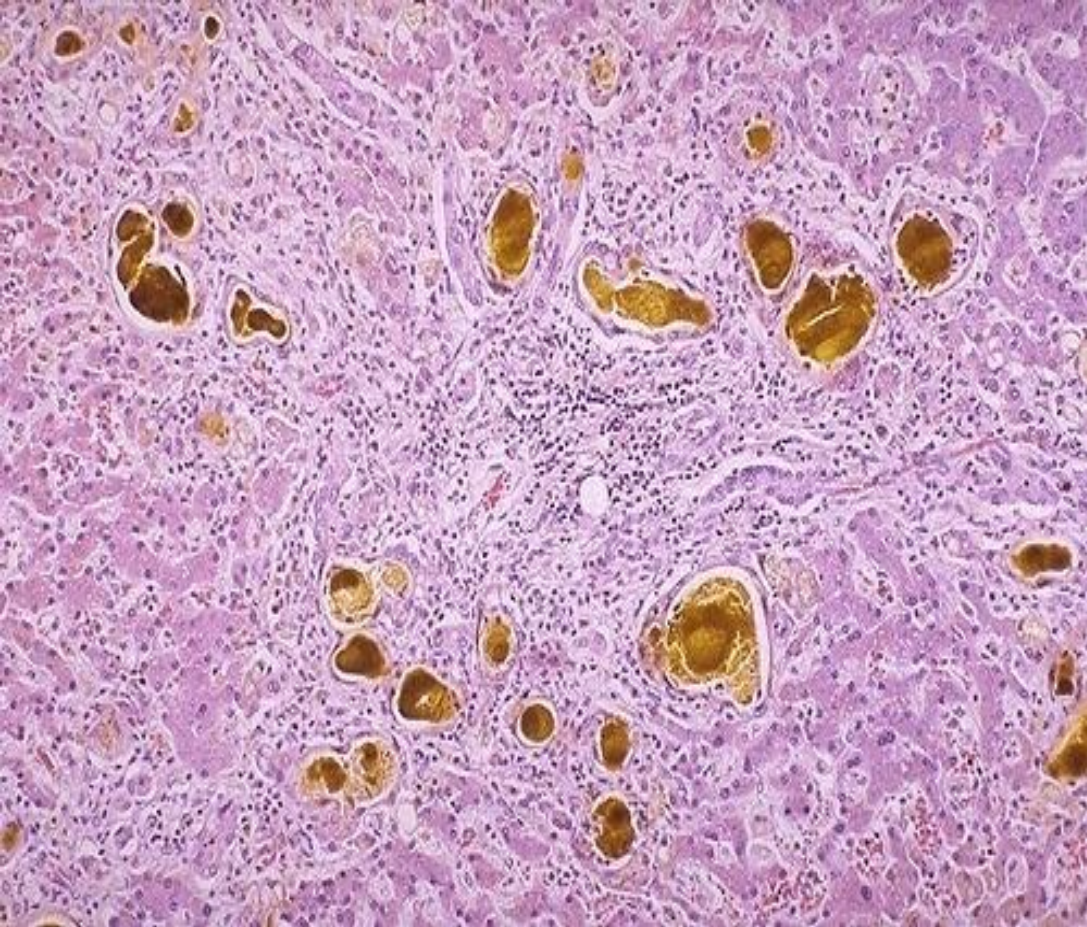
№ 82. Renal amyloidosis.

Hemosiderin.

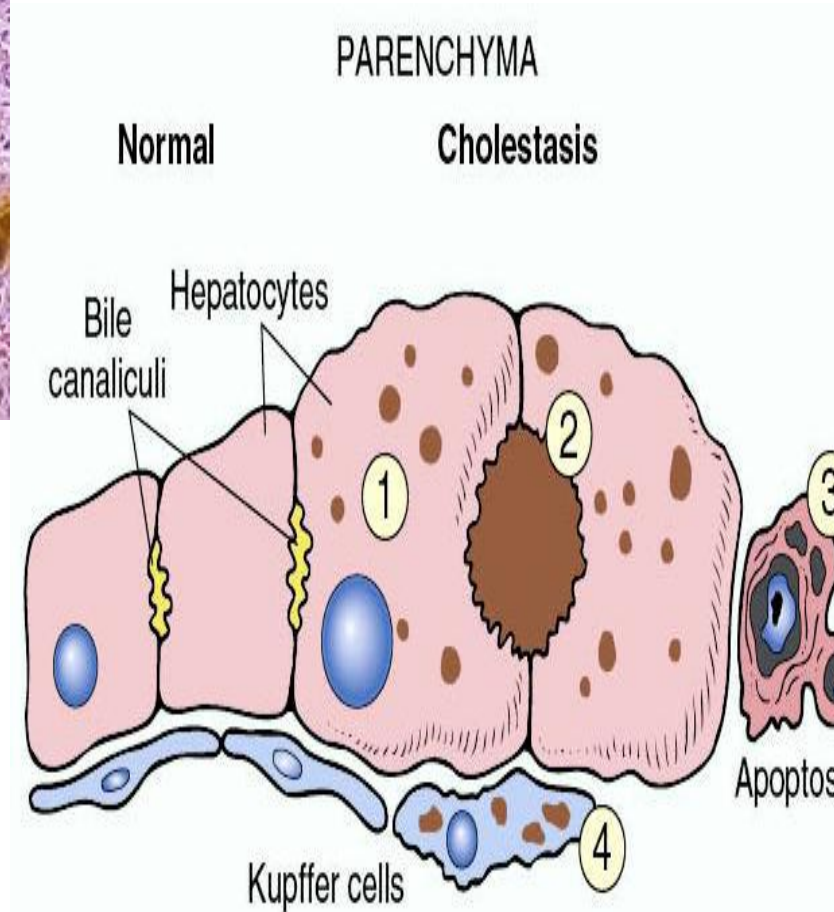




Pulmonary hemosiderosis.



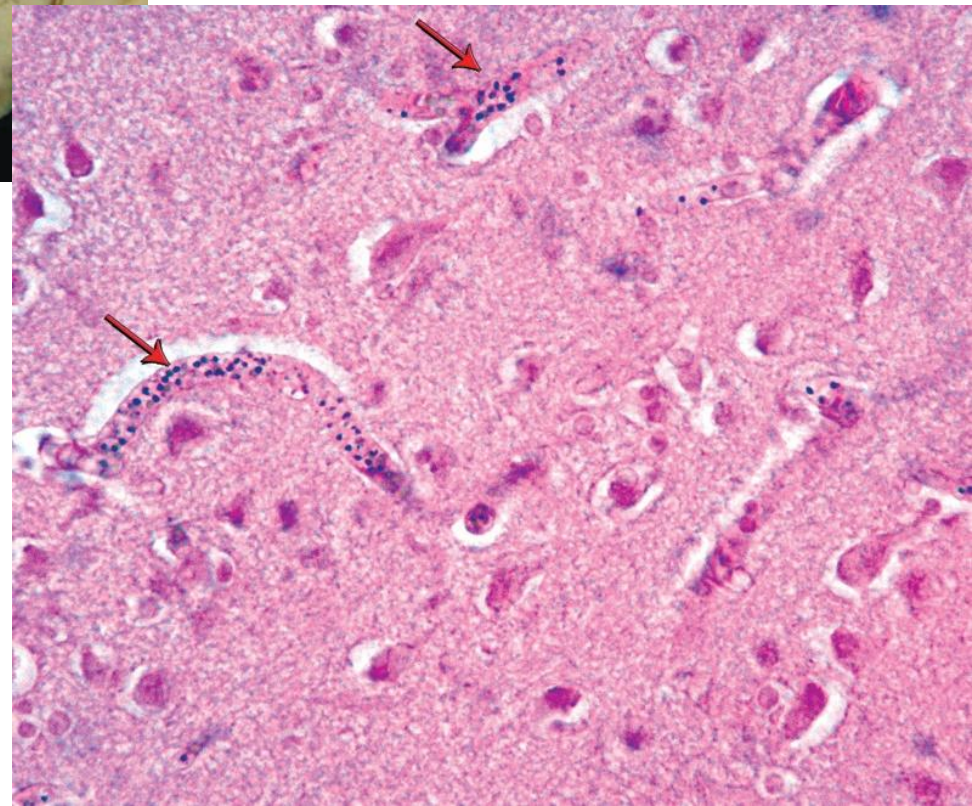
Bilirubin

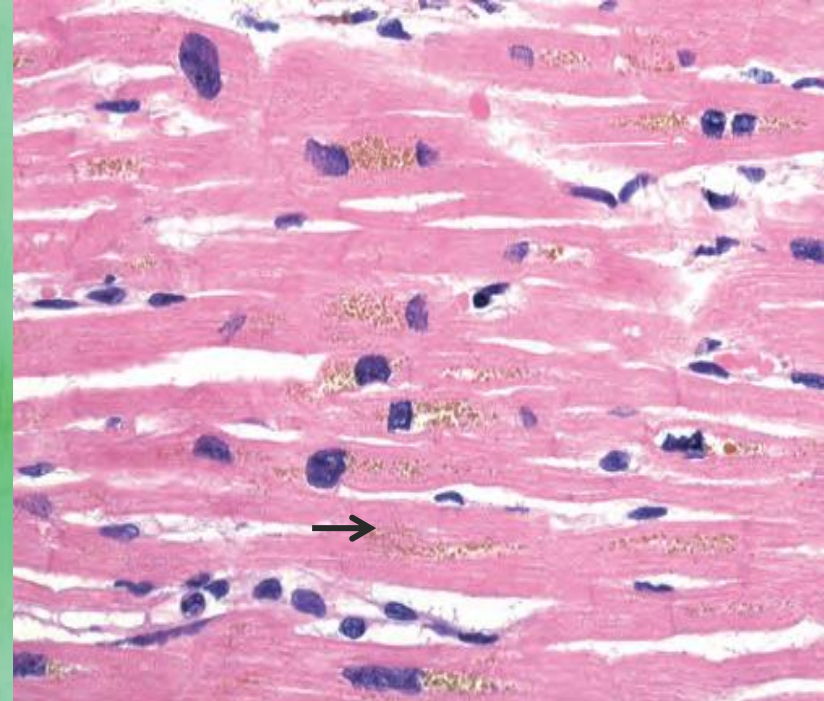
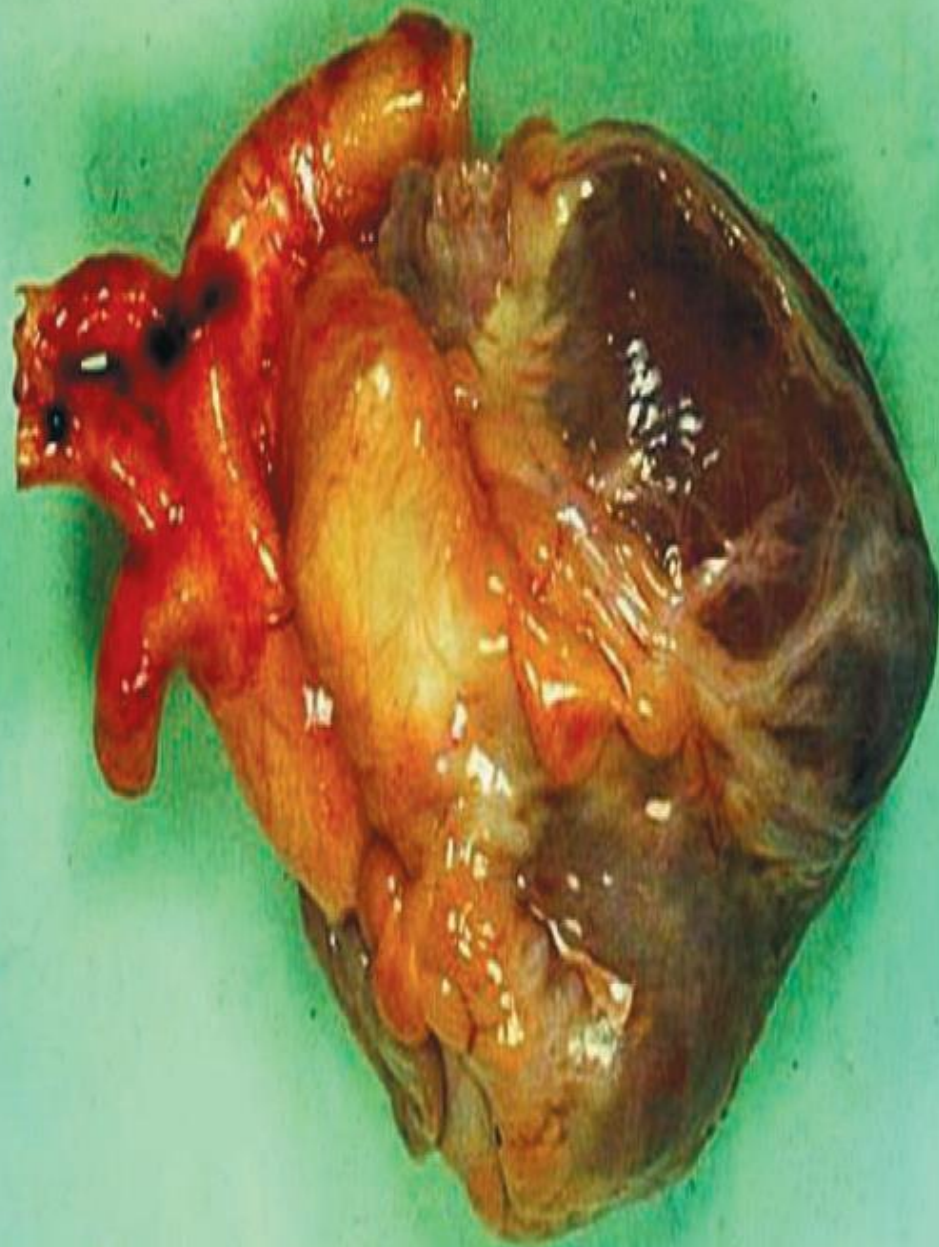




**Brain
hemomelanosis
in malaria.**

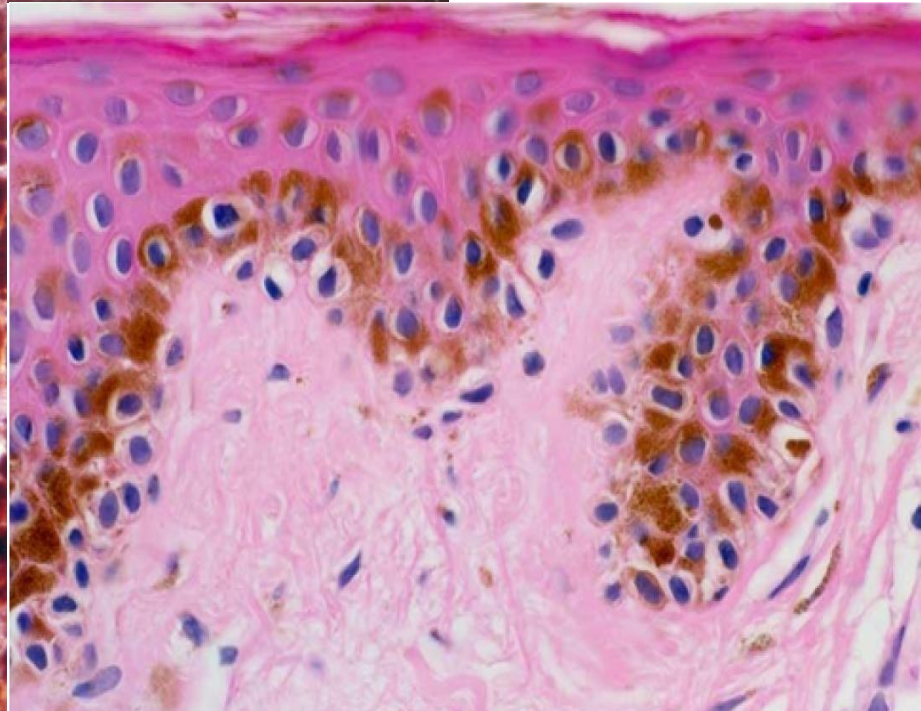
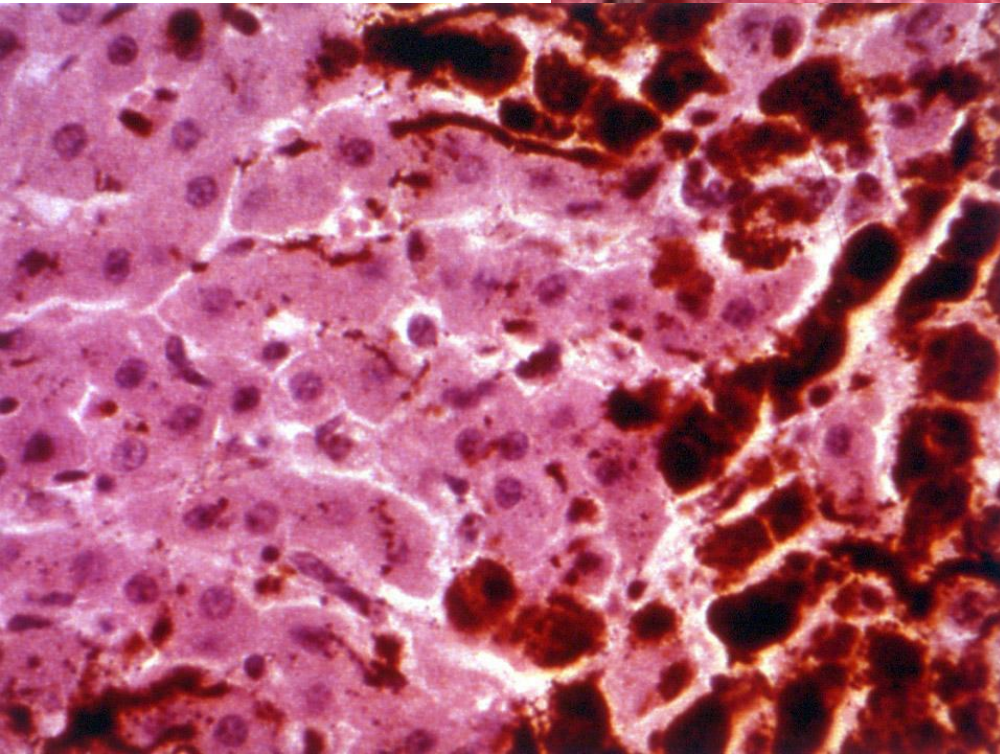
**Hydrochloric hematin
on the bottom of gastric
mucosal erosions.**

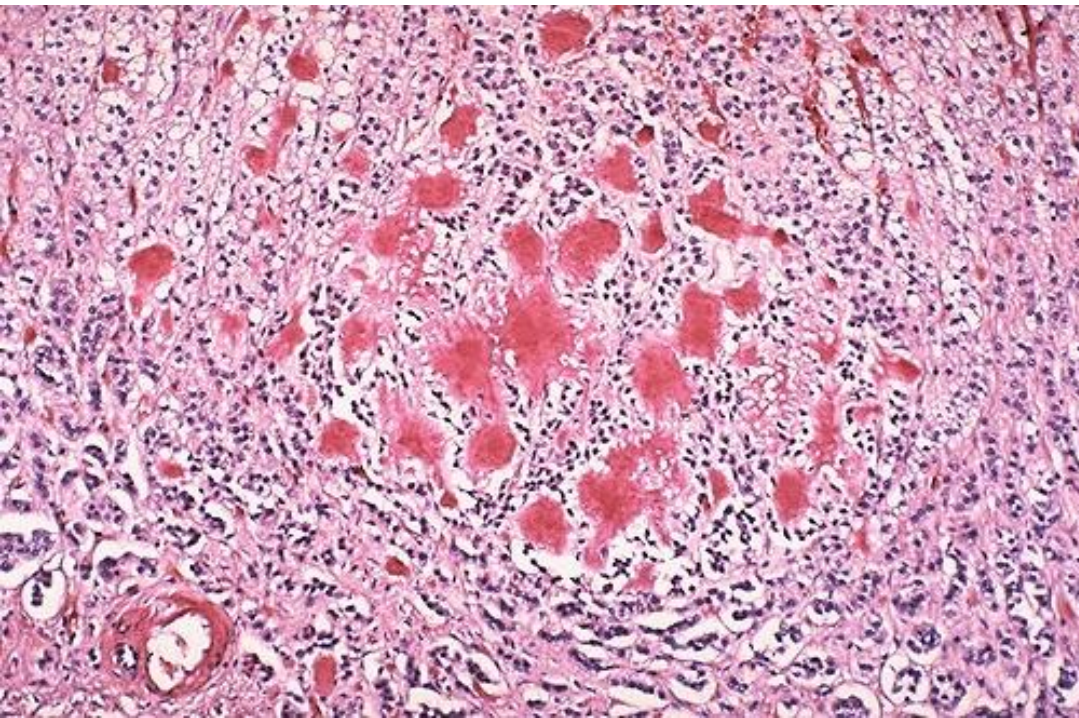
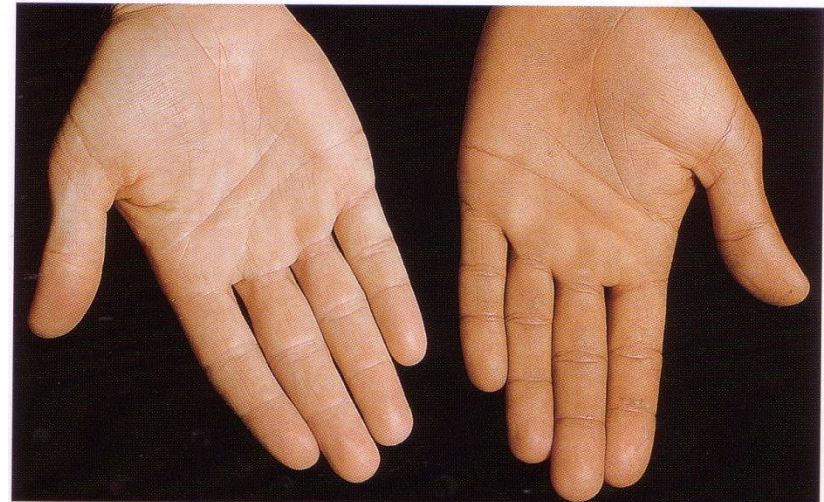
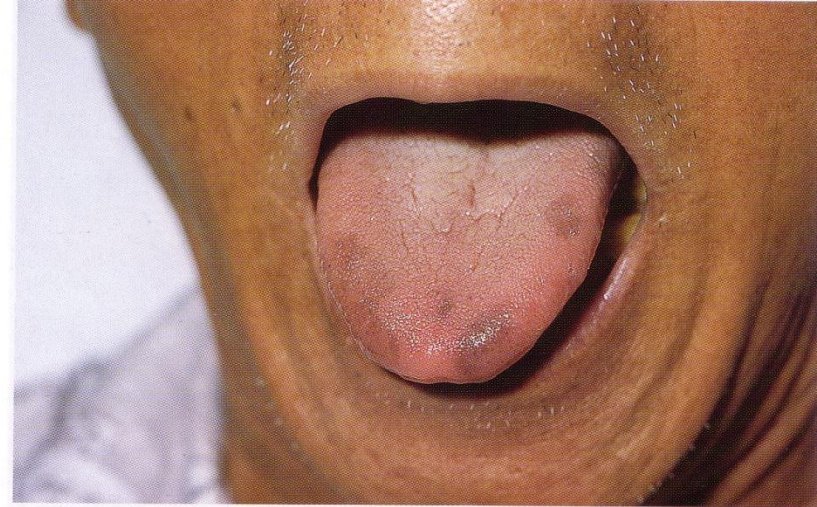




**Brown atrophy of
the heart.**

Melanin / Melanosis





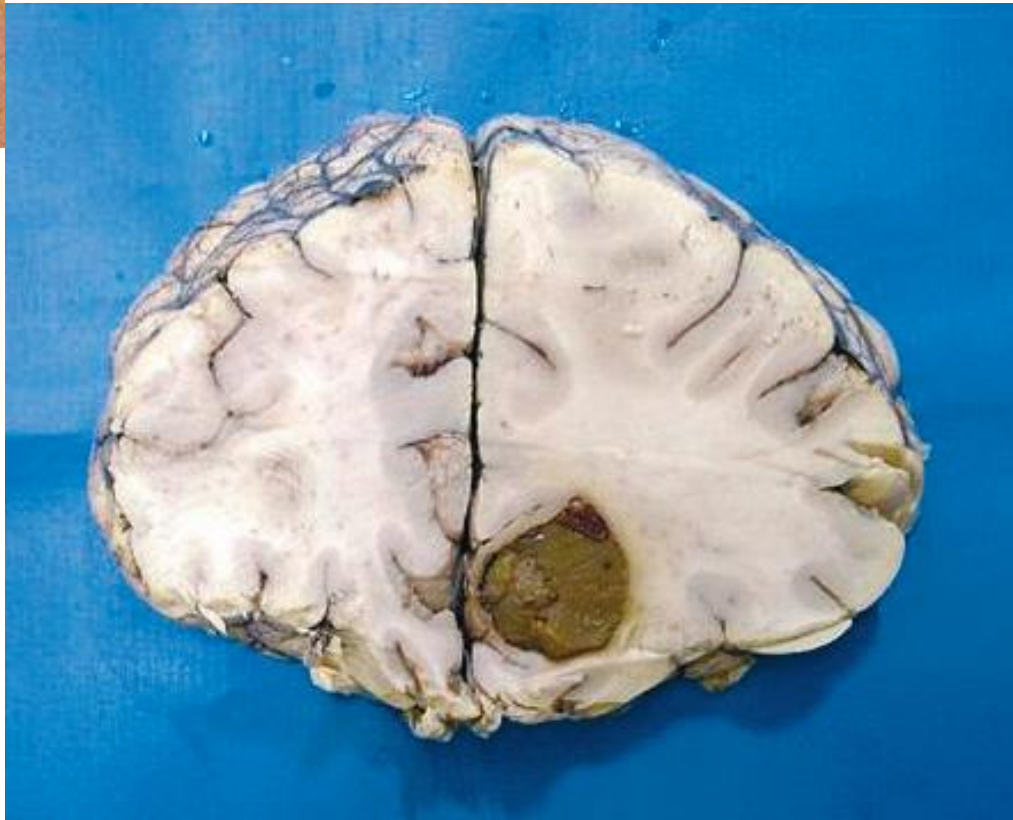
**Tuberculosis (caseous necrosis)
and amyloidosis (Congo red) of
the adrenal glands.**

Clinic - Addison's disease.

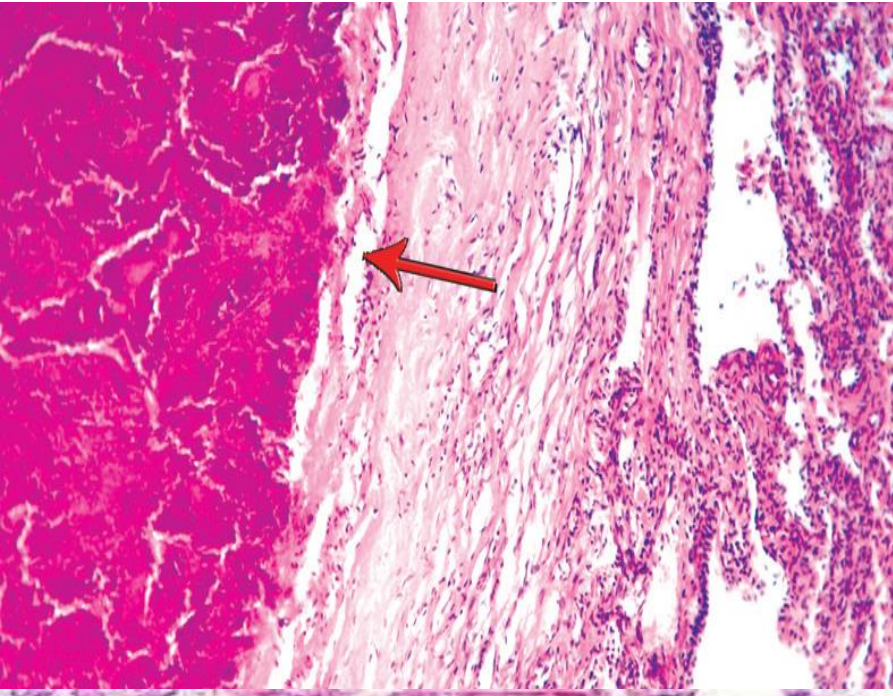


Pigmented nevus

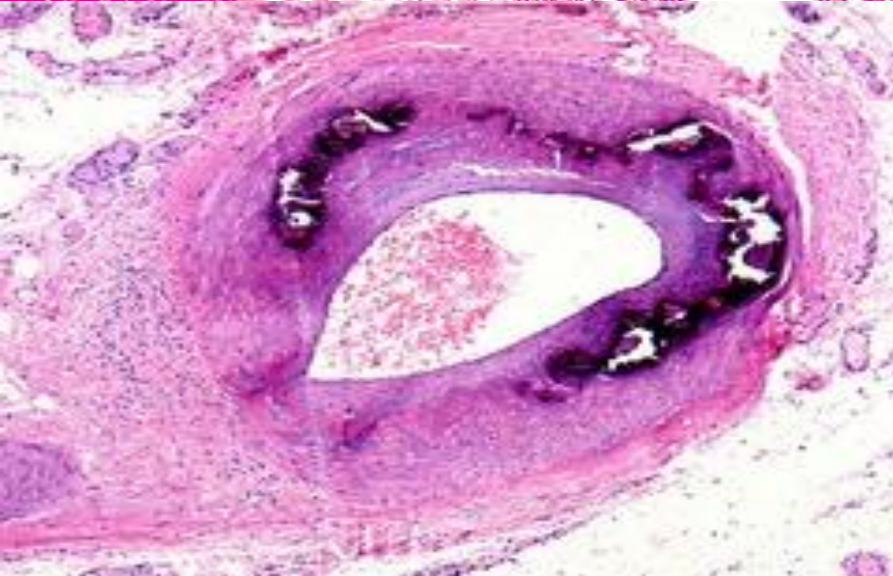
Melanoma metastases in the brain.



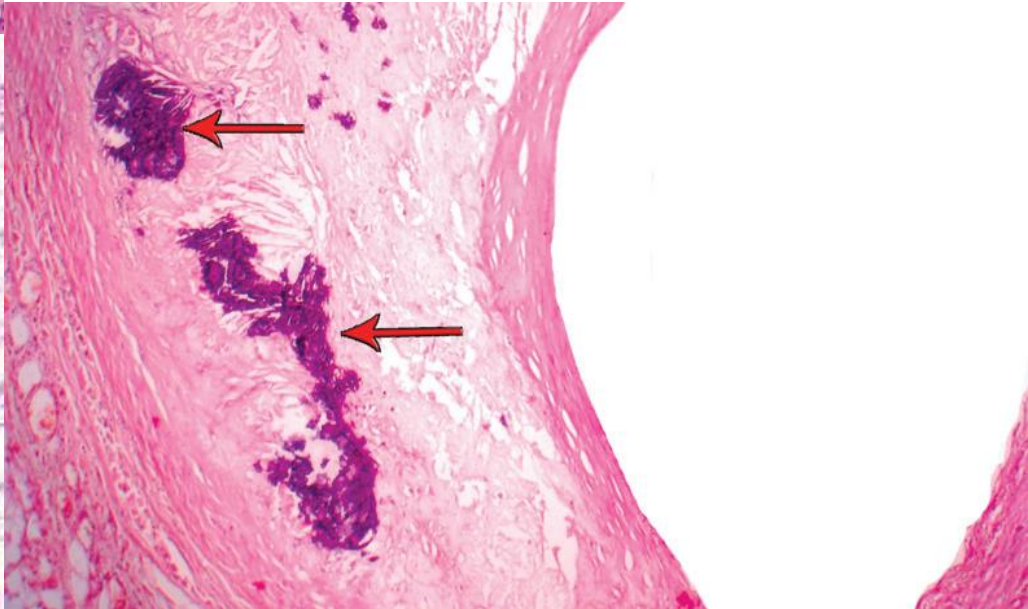
Dystrophic calcinosis



Lung tissue.



**Coronary artery in
atherosclerosis.**



Dystrophic calcinosis

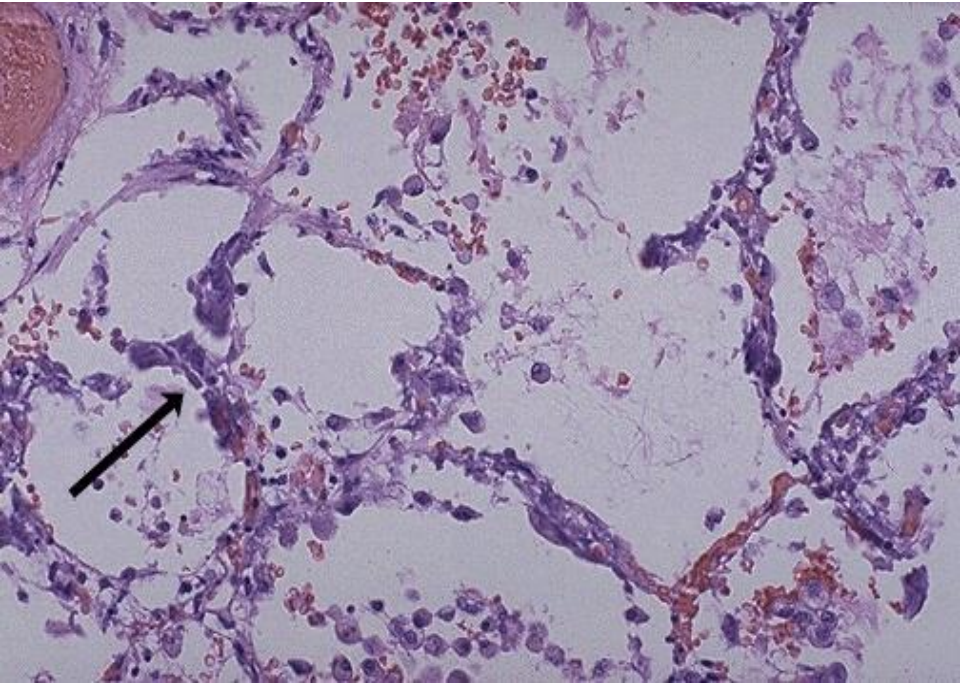


LITHOPEDION - in which the calcification of a dead fetus is almost complete.

Aortic valve calcinosis.

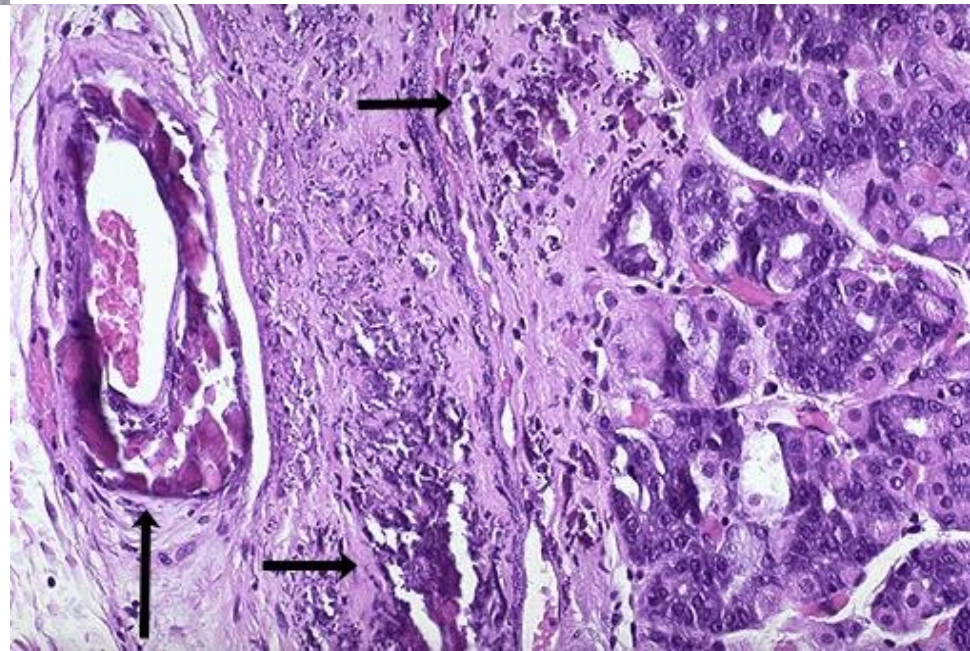


Metastatic calcinosis



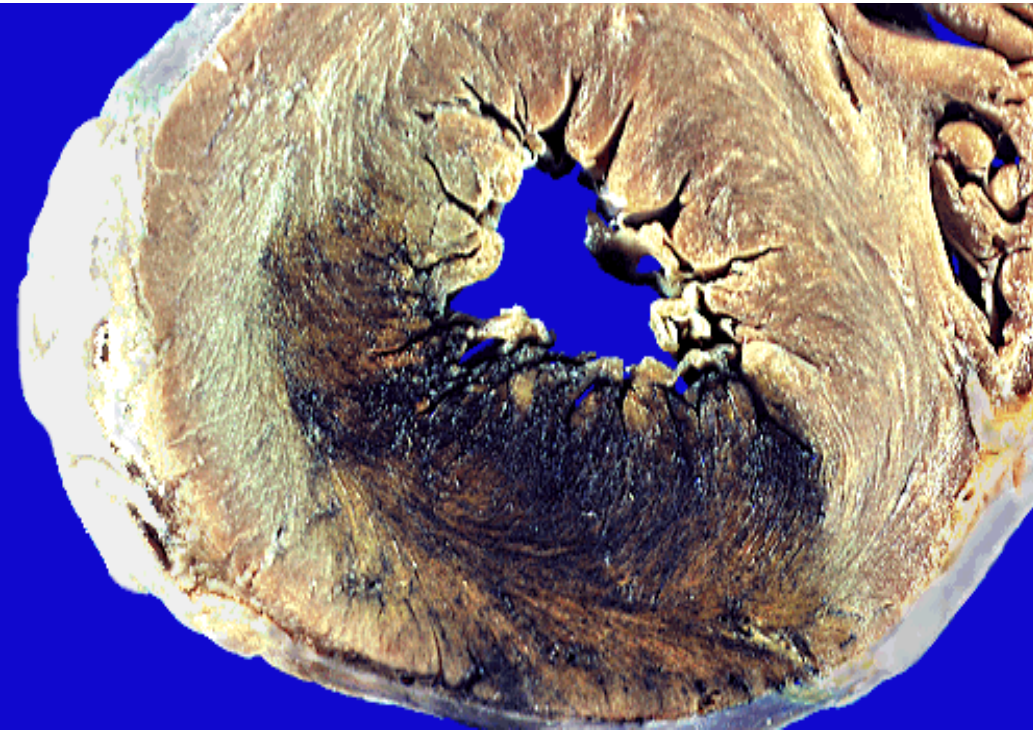
Stomach.

Lung tissue.

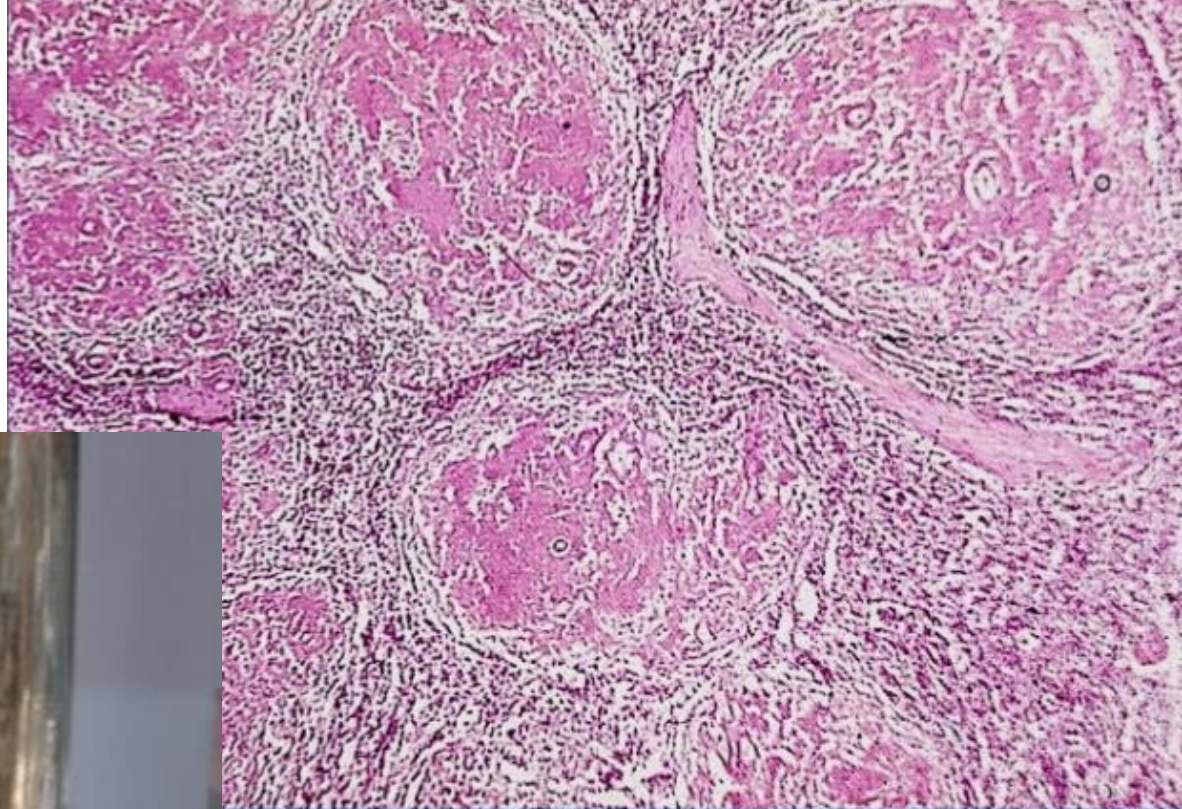


Myocardial amyloidosis

Macroscopic identification.



Virchow macroscopic reaction: on successive application to the section surface of iodine or Lugol's solution and sulfuric acid (10%) the amyloid stains in blue-violet or dark green.



Focal spleen amyloidosis (*sago spleen*).



Diffuse spleen amyloidosis.
Image beneath - norm.

PIGMENTS AND OTHER TISSUE DEPOSITS

many pathologic processes are accompanied by accumulations of material either within the cell (intracellular) or within the extracellular space.

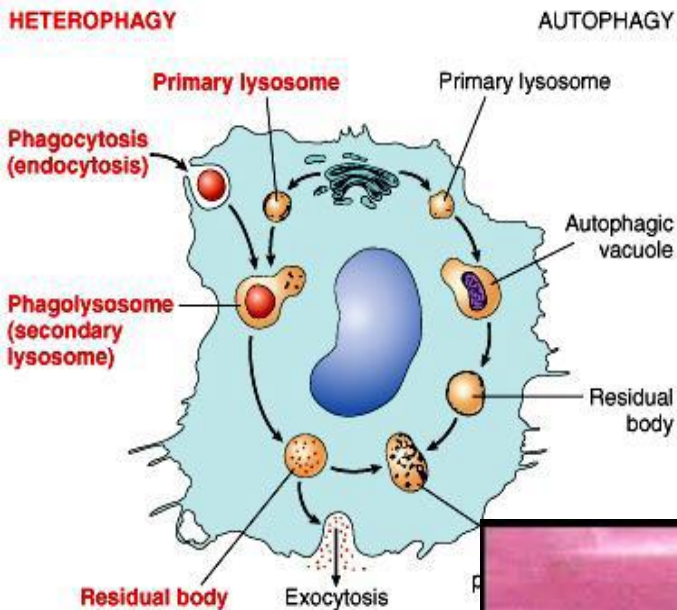
Pigments

Pigments are colored substances, some of which are normal constituents of cells whereas others are abnormal and collect in cells only under special circumstances

Pigments can be either exogenous or endogenous

Lipofuscin

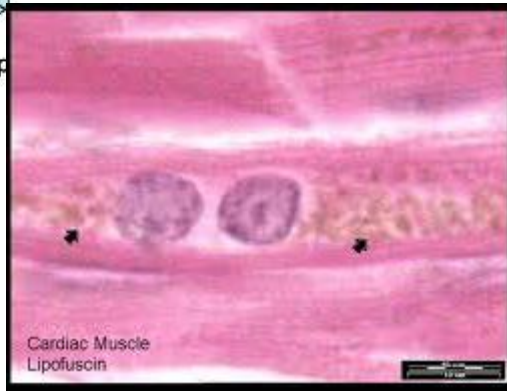
Also known as lipochrome and “wear-and-tear” or aging pigment



- origin: lysosomal breakdown products of lipids.

- sites: aged or chronically injured cells.

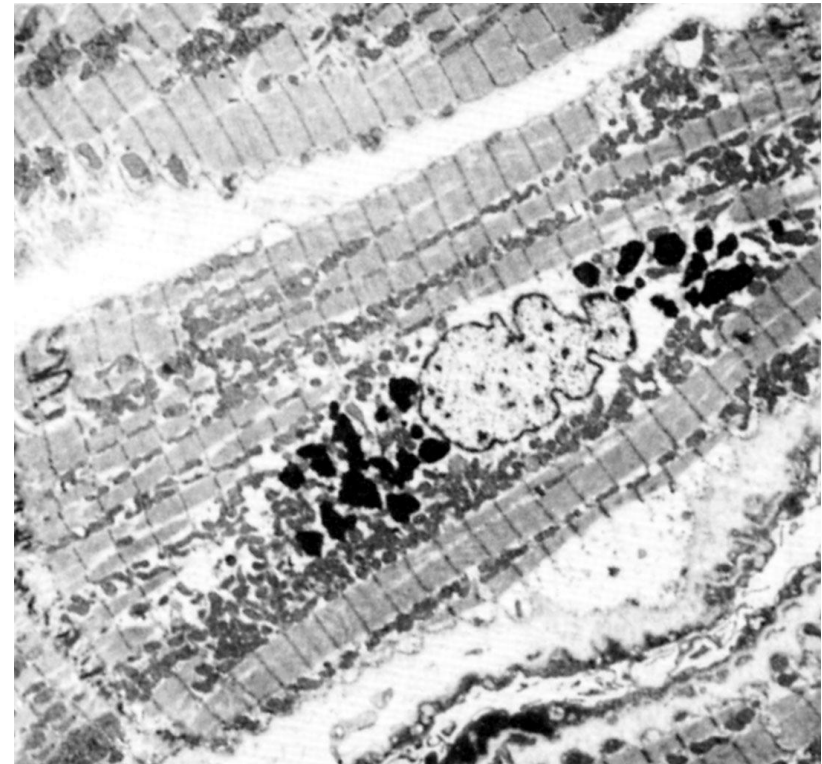
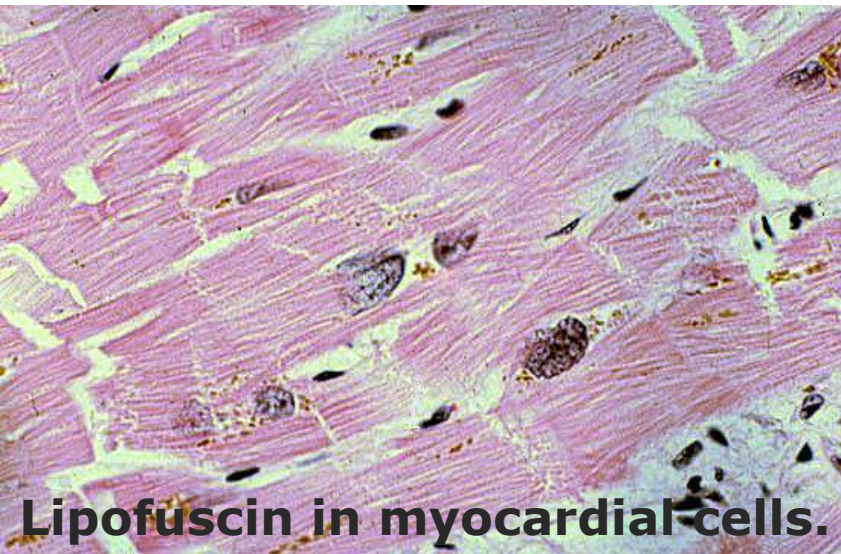
- significance: doesn't injure cell, but a sign of aging or excess free radical damage.



Lipofuscin



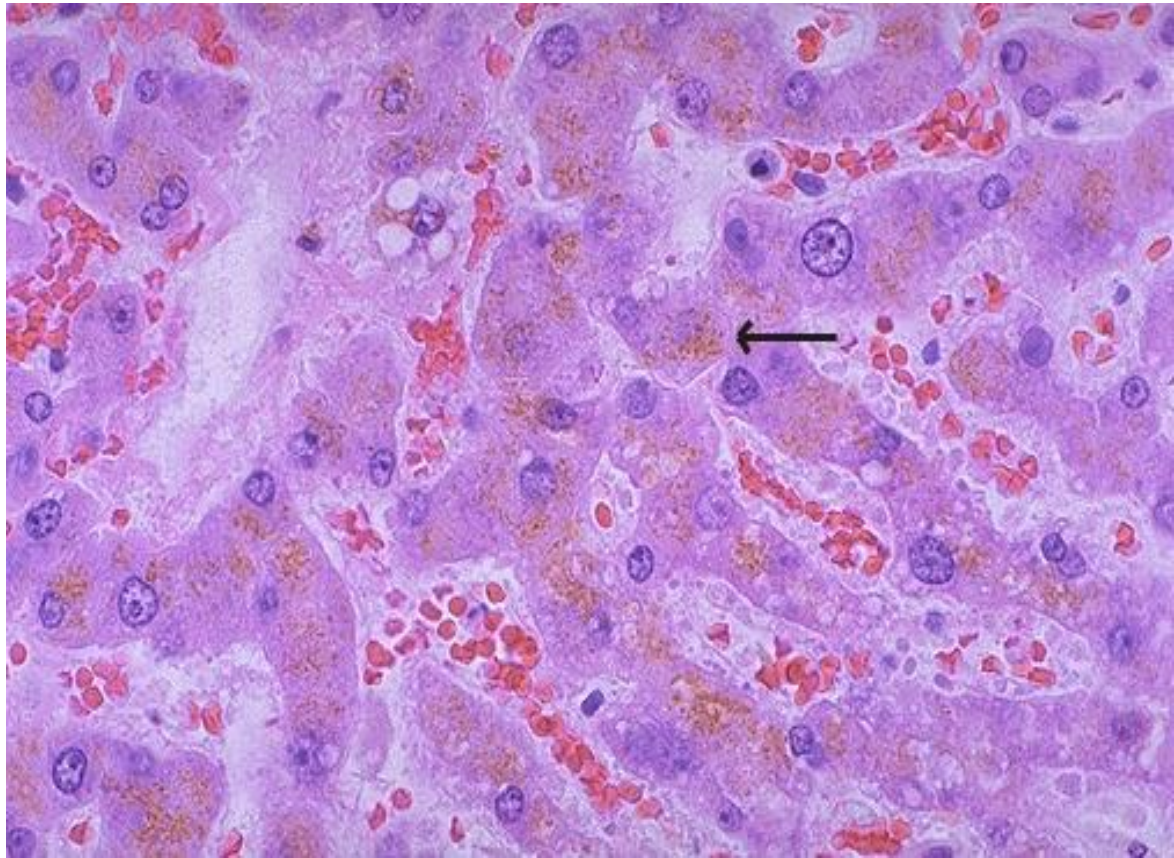
Electron micrograph showing electron dense pigment (lipofuscin) in myocardial cells.



Lipofuscin

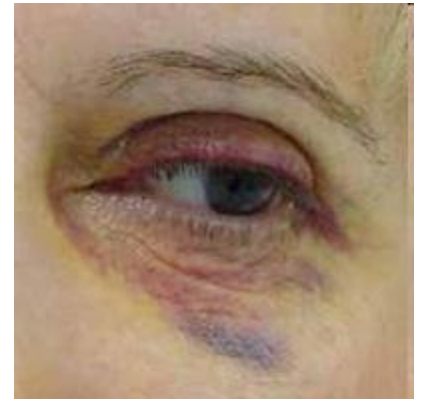
It is particularly prominent in the liver and heart of aging patients or patients with severe malnutrition and cancer cachexia.

It is usually accompanied by organ shrinkage (brown atrophy).



Hemosiderin

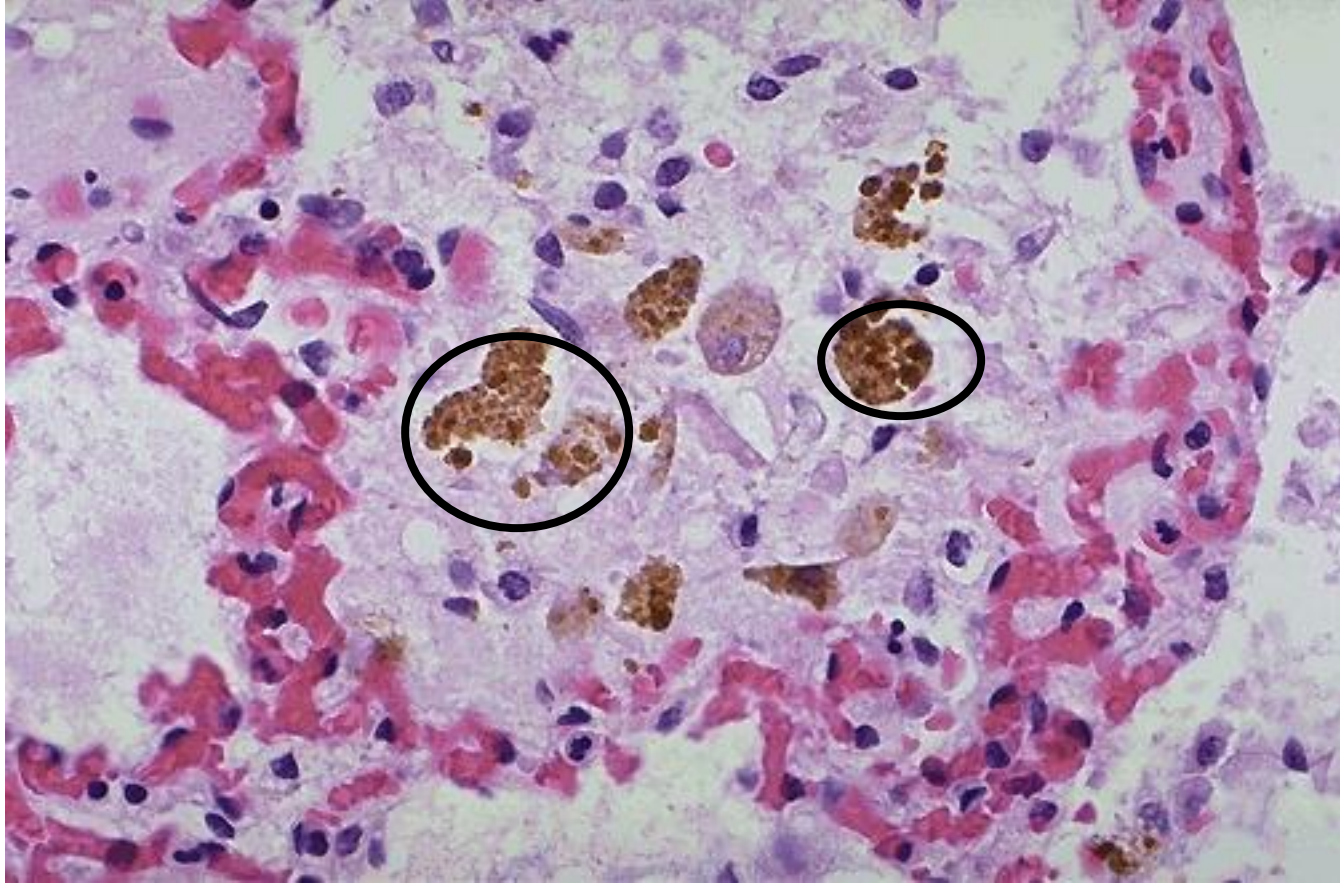
A hemoglobin-derived, golden-yellow to brown, pigment in which form iron is stored in cells Excesses of iron cause hemosiderin to accumulate within cells



Hemosiderin

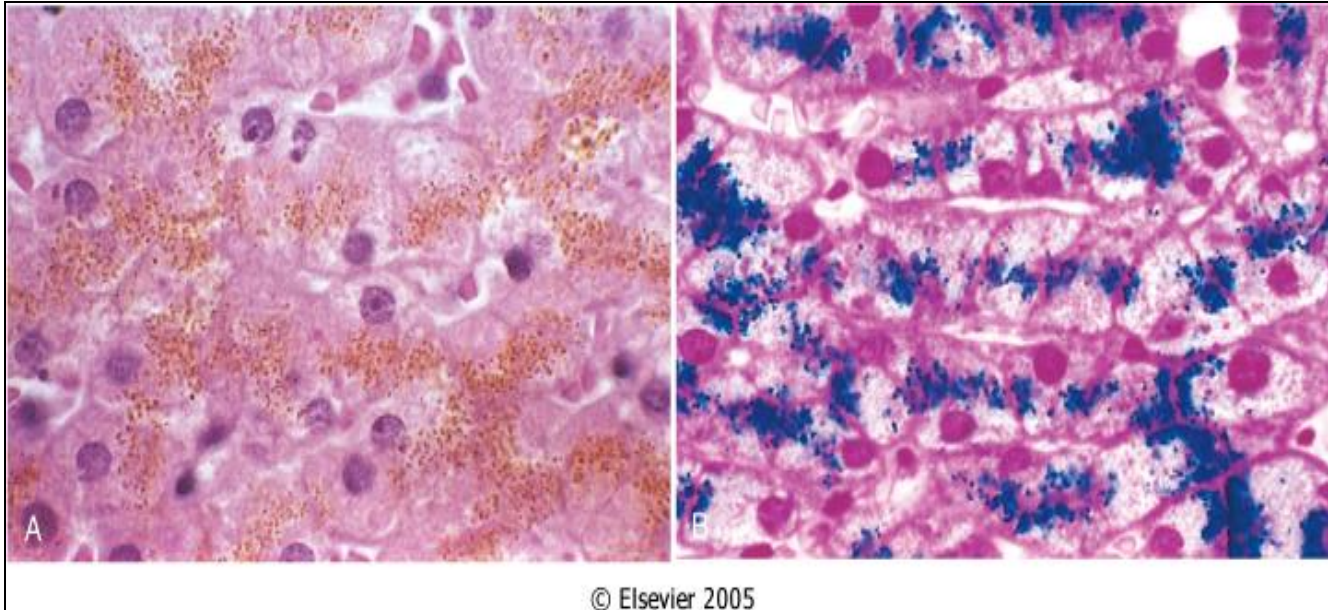
- **• origin:**
 - represents stored iron (esp from recycled Hb).
- **• sites:-normal in MΦ's of spleen, bone marrow.**
 - anywhere – increased breakdown of erythrocytes or increased accumulations of iron.
 1. areas of congestion or hemorrhage (eg bruise)
 2. Kupffer cells in hemolytic anemia
 3. alveolar macrophages in congestive heart failure (heart failure cells)

Hemosiderin

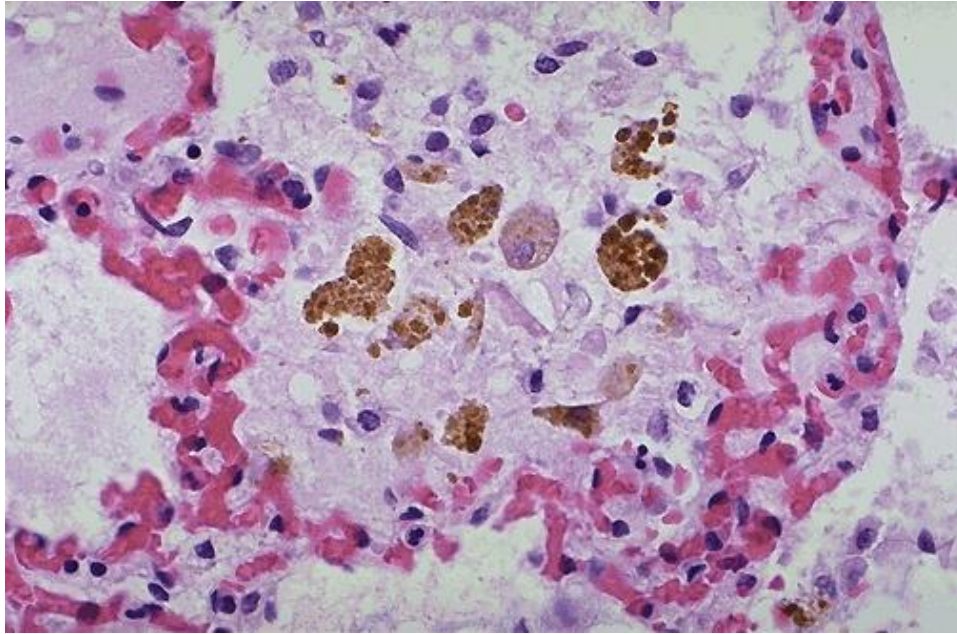


Hemosiderin
Deposition
In renal tubules

Hemosiderin

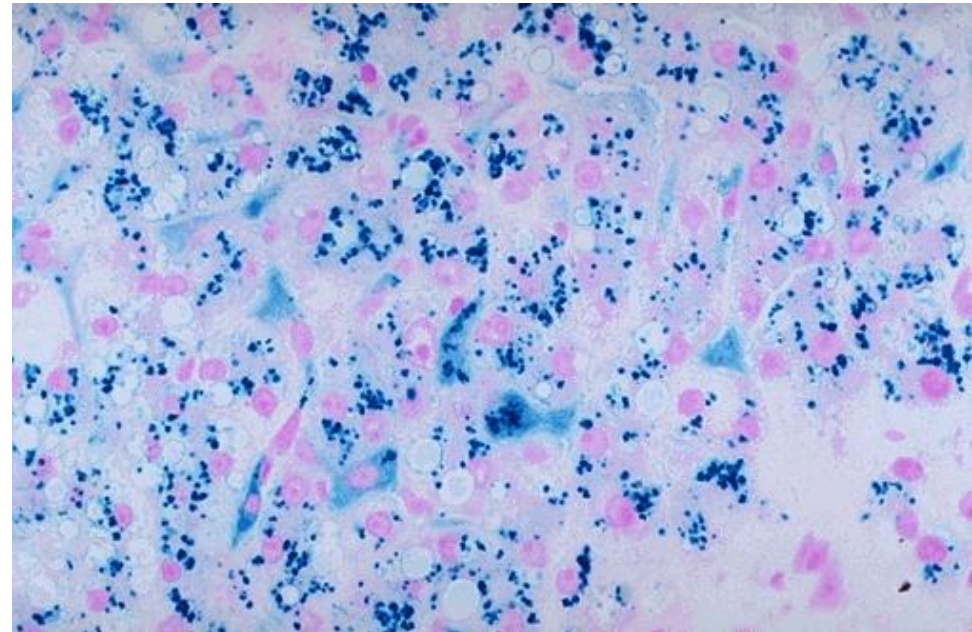


Hemosiderin granules in liver cells. A, H&E section showing golden-brown, finely granular pigment. B, Prussian blue reaction, specific for iron.

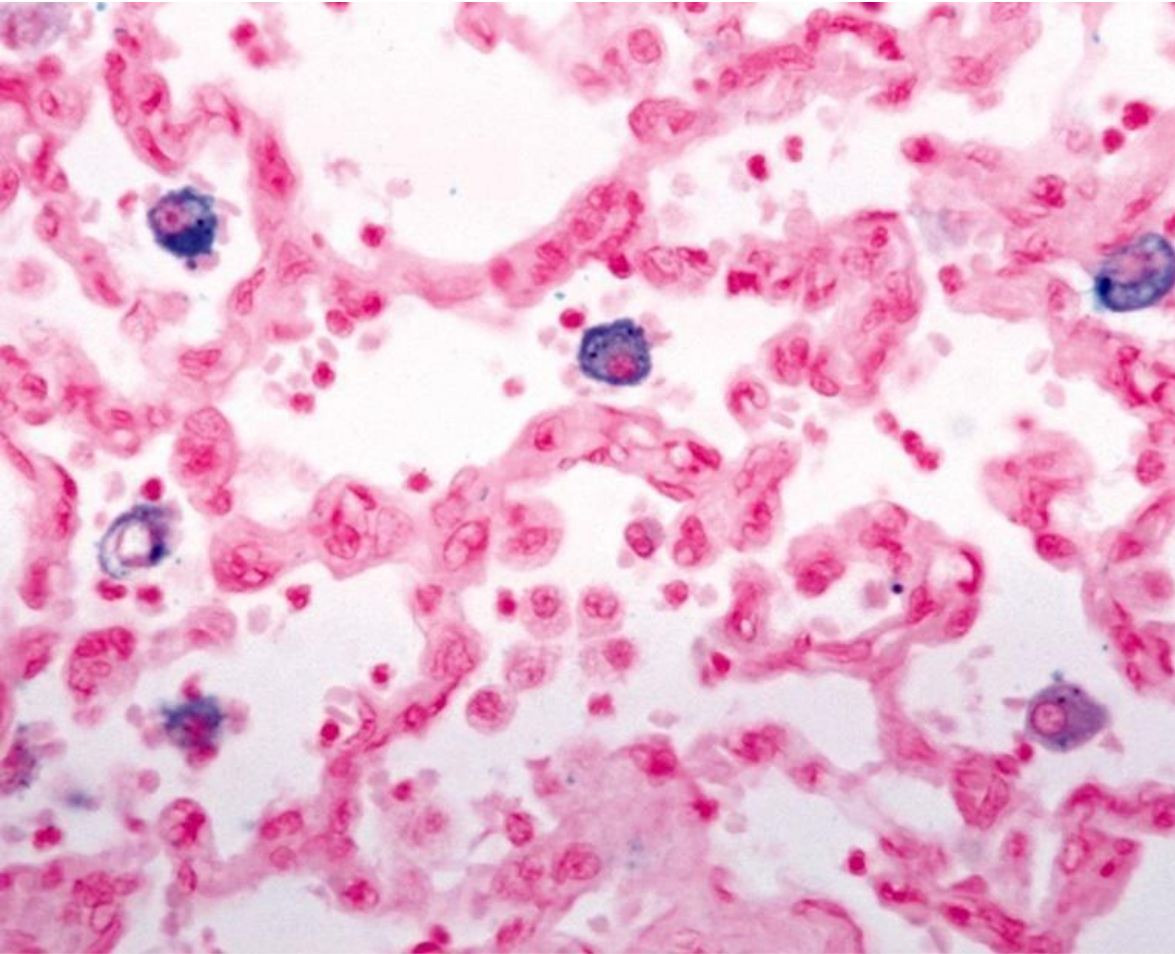


**Hemosiderin in
lung**

**Hemosiderin in
liver**



Hemosiderin in lung

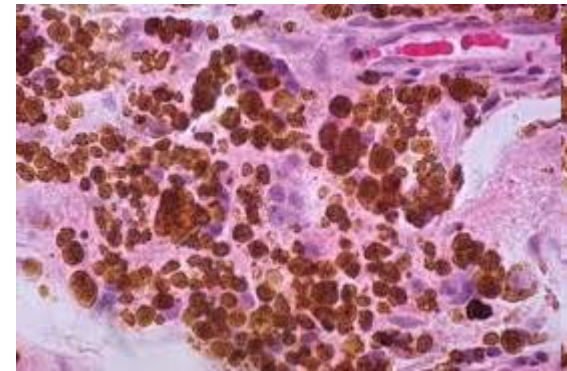


**Chronic passive
congestion, lung.
Prussian blue
reaction.**

Hemosiderosis

An example of localized hemosiderosis is the common bruise

Following local hemorrhage, the area is at first red-blue. With lysis of the erythrocytes, the hemoglobin eventually undergoes transformation to hemosiderin



Hemosiderosis

The original red-blue color of hemoglobin is transformed to varying shades of green-blue, comprising the local formation of biliverdin, then bilirubin and thereafter the iron moiety of hemoglobin is deposited as golden-yellow hemosiderin

Hemochromatosis

The more extreme accumulation of iron, however, in a disease called hemochromatosis is associated with liver and pancreatic damage, resulting in liver fibrosis, heart failure, and diabetes mellitus

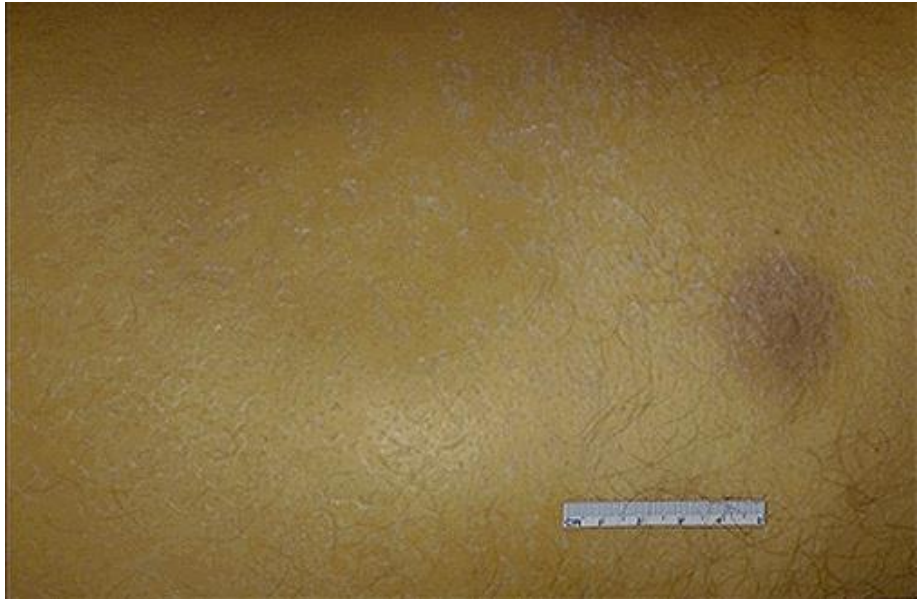
Bilirubin

The normal major pigment found in bile.

It is derived from hemoglobin but contains no iron.

Jaundice is a common clinical disorder due to excesses of this pigment within cells and tissues

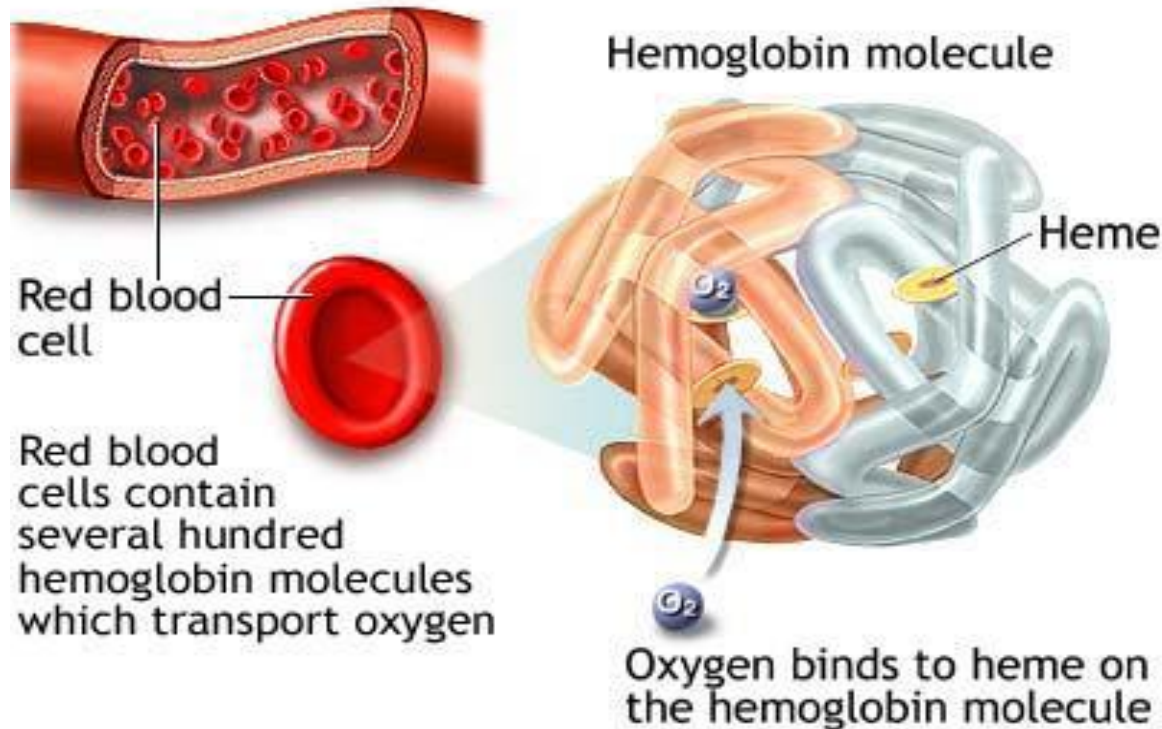
Jaundice

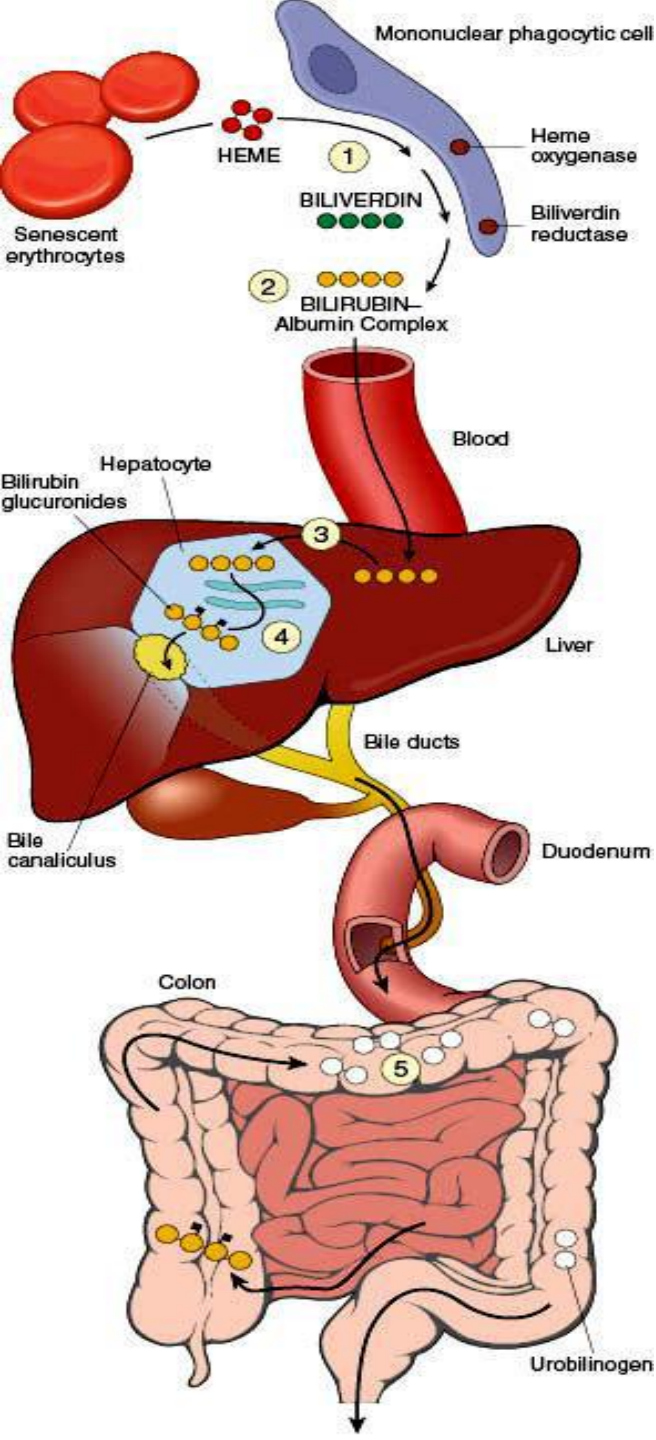


Bilirubin

- bilirubin is end product of heme degradation (after removal of iron).
- mostly from senescent rbc's via MΦ's.

Each hemoglobin molecule is an assembly of four globular protein subunits. Each subunit is composed of a protein chain tightly associated with a non-protein hemegroup.

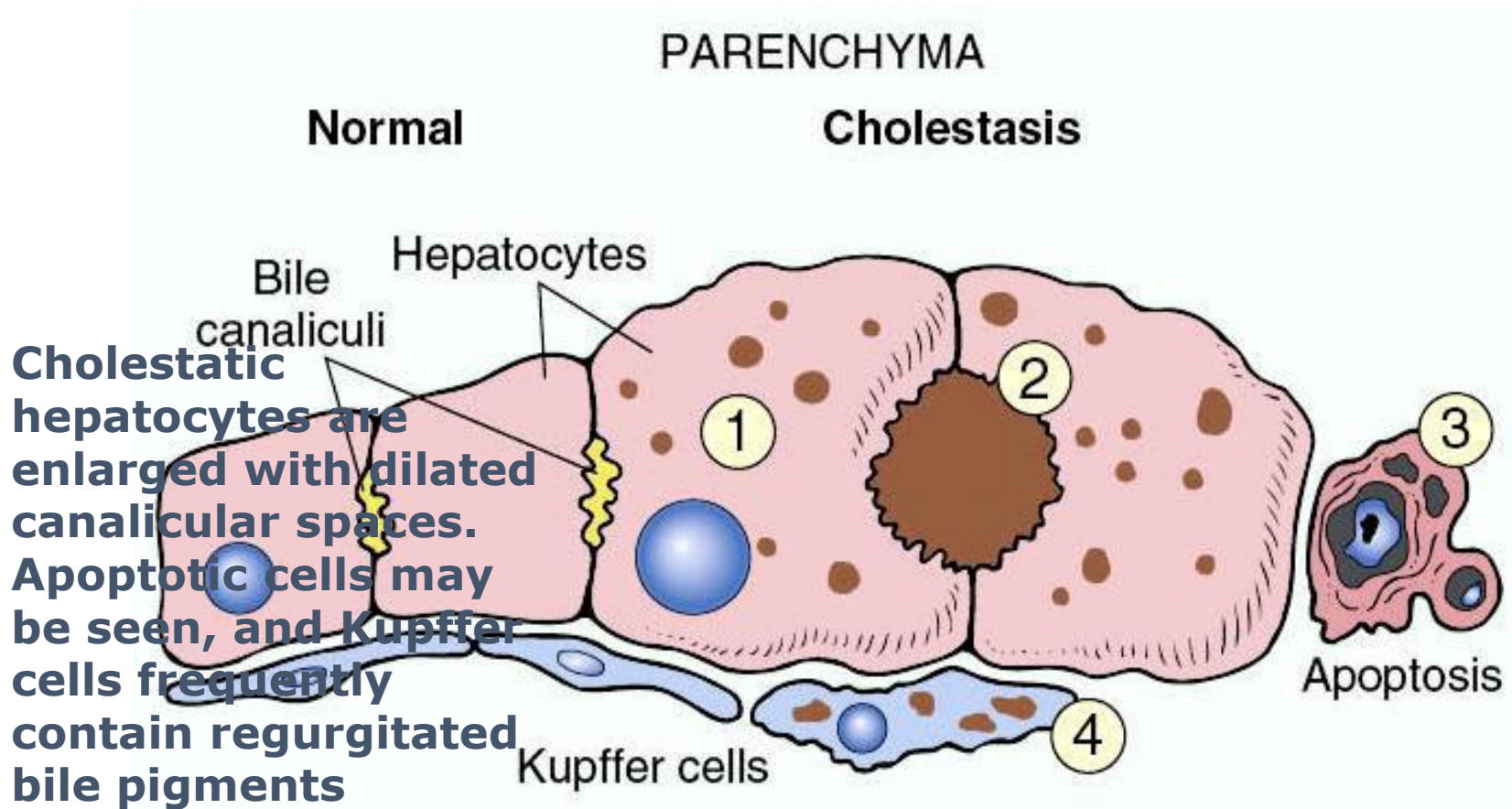




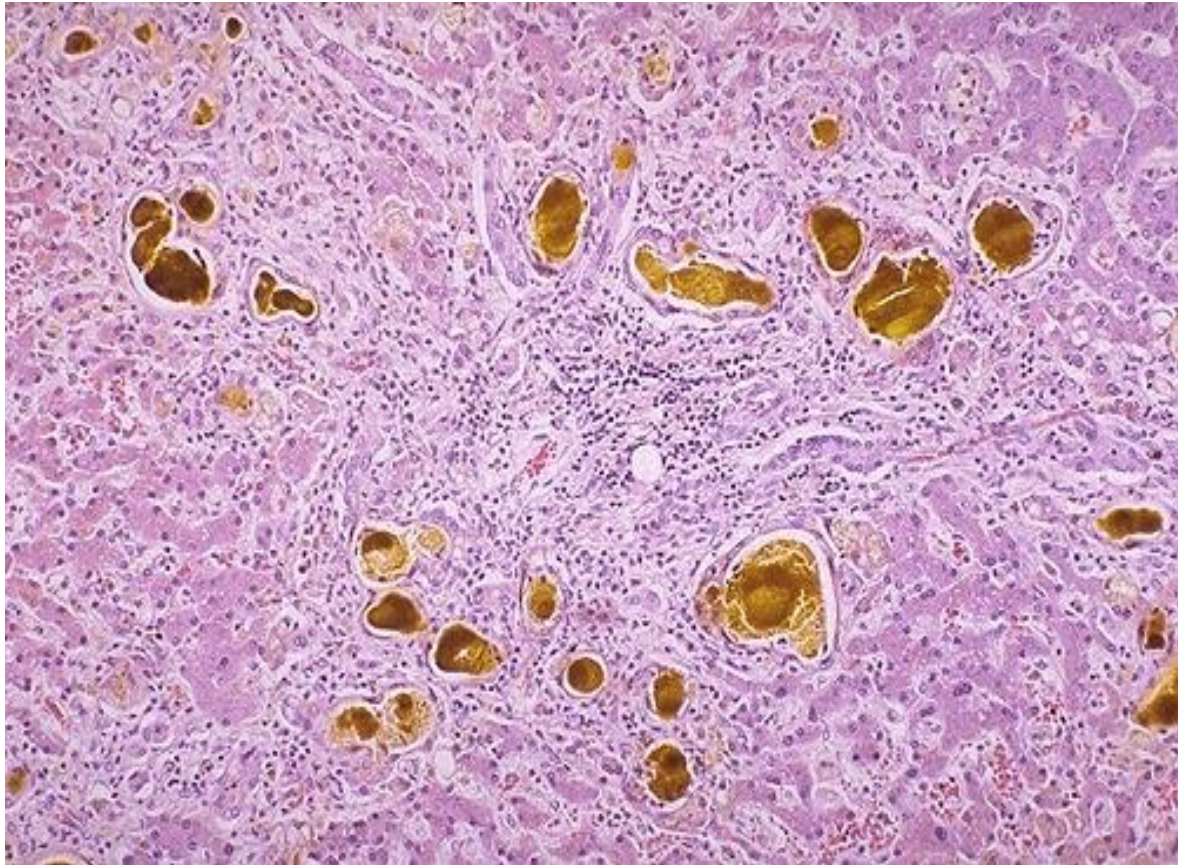
Bilirubin metabolism and elimination.

1, Normal bilirubin production from heme (~ 0.2 to 0.3 gm/day in humans) is derived primarily from the breakdown of senescent circulating erythrocytes, with a minor contribution from degradation of tissue heme-containing proteins. **2,** Extrahepatic (unconjugated) bilirubin is bound to serum albumin and delivered to the liver. **3,** Hepatocellular uptake and **4,** Glucuronidation in the endoplasmic reticulum generate conjugated bilirubin (monoglucuronides and diglucuronides), which are water soluble and readily excreted into bile. **5,** Gut bacteria deconjugate the bilirubin and degrade it to colorless urobilinogens. The urobilinogens and the residue of intact pigments are excreted in the feces, with some reabsorption and excretion into urine.

Illustration of the morphologic features of cholestasis in the liver parenchyma,



Bilirubin pigment



prehepatic jaundice
hepatic jaundice
post hepatic jaundice

Melanin / Melanosis

- **intracellular, brown-black pigment.**
 - **origin: normal pigment found in the epidermis and eye.**
- **sites: melanin can also occur in other sites & when in excess called melanosis,**
- **eg leptomeninges (esp ruminants), intestine, kidney, lung, base of aorta, etc.**

Melanin / Melanosis

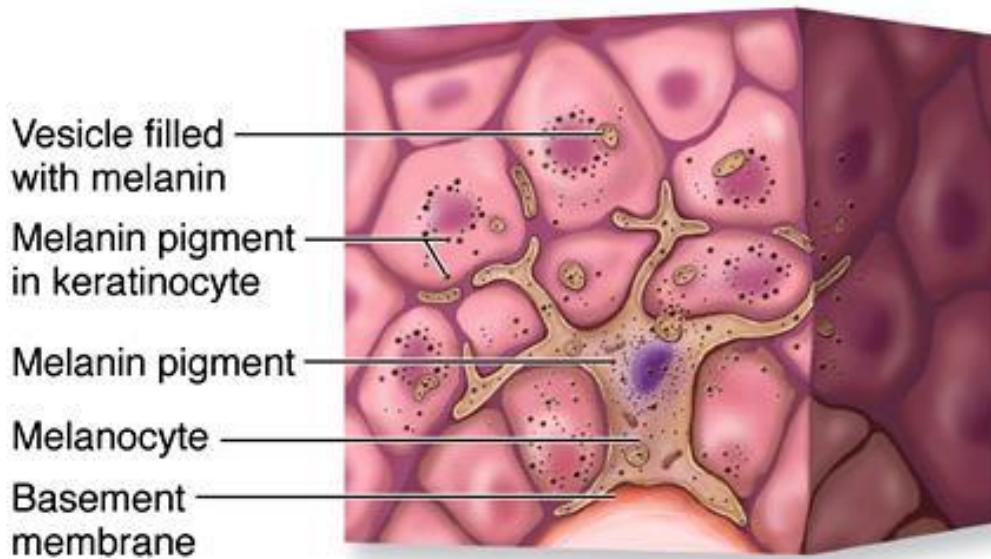
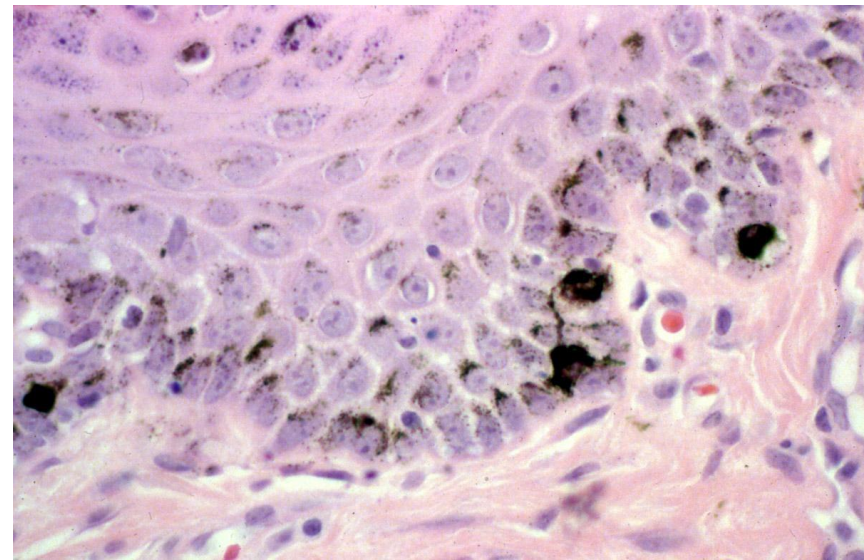


Diagram of a melanocyte. It sends irregular dendritic processes between neighboring keratinocytes for transfer of melanin to those cells.

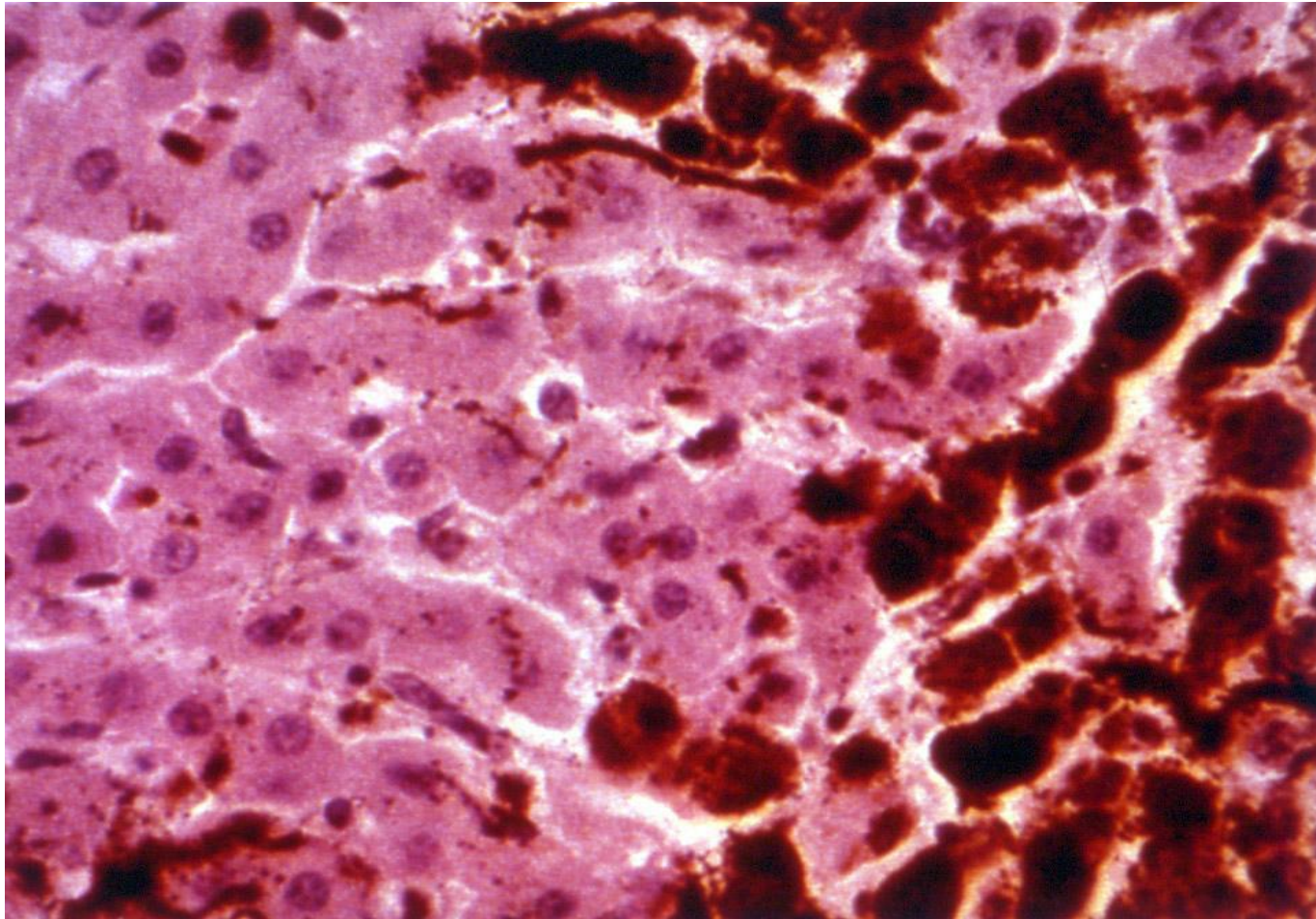
melanocytes and keratinocytes containing melanin granules.



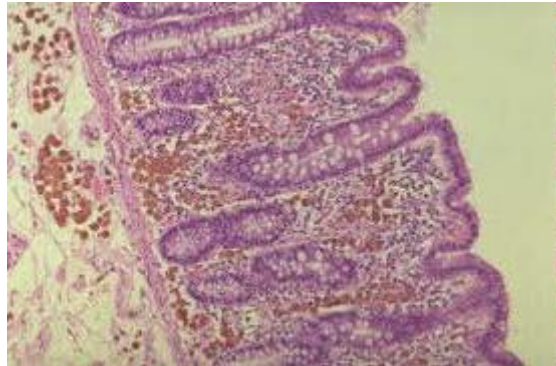
Melanin / Melanosis



Melanin / Melanosis



Melanin / Melanosis



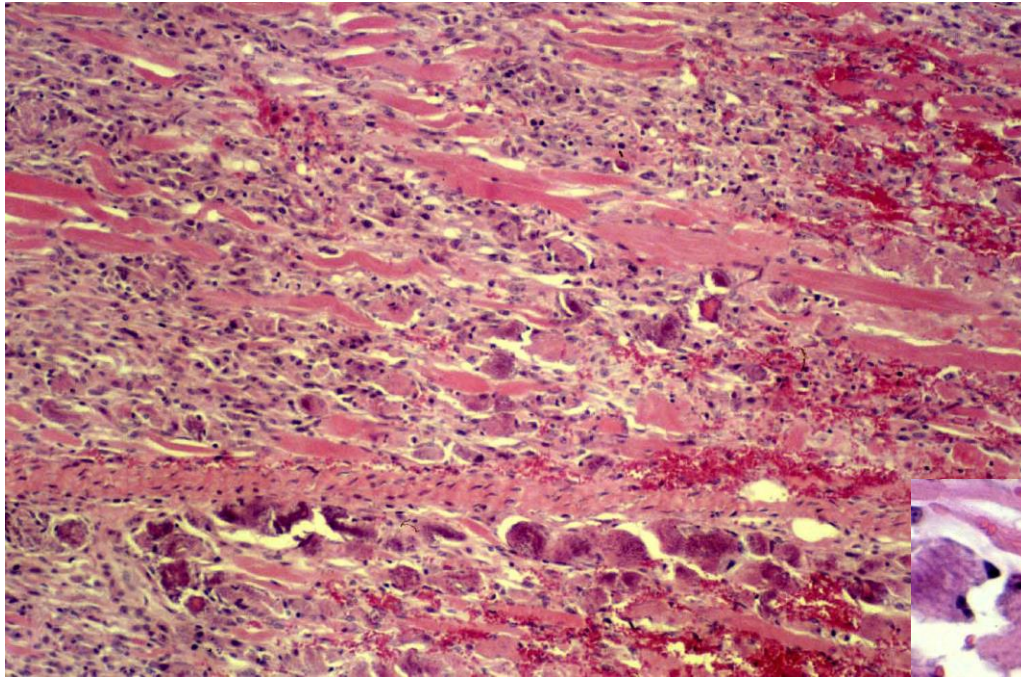
Calcification

**Pathologic calcification
implies the abnormal
deposition of calcium salts,
together with smaller
amounts of iron, magnesium,
and other mineral salts**

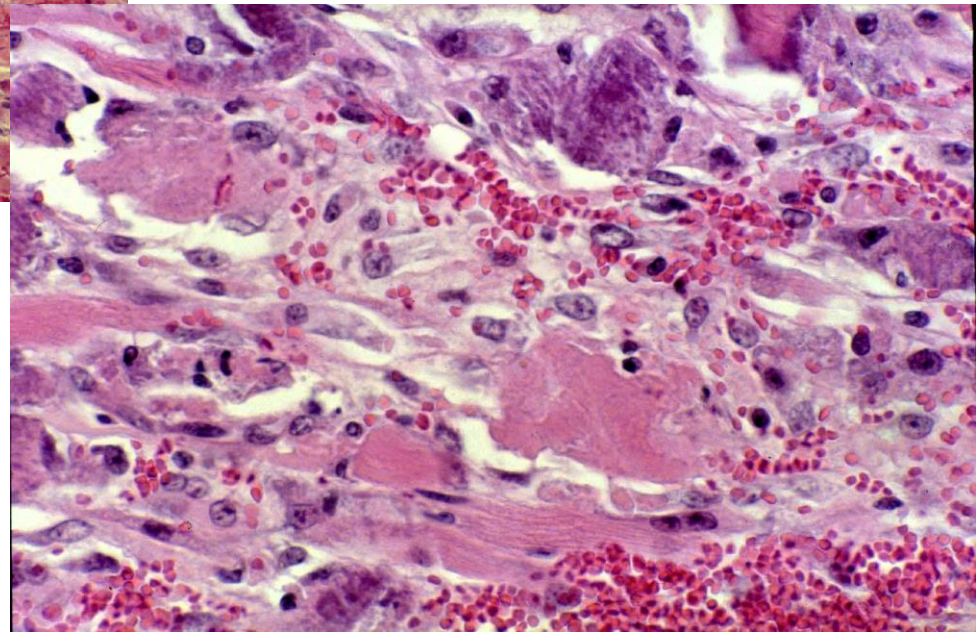
Dystrophic calcification

Occurs in nonviable or dying tissues. It occurs despite normal serum levels of calcium and in the absence of derangements in calcium metabolism

Dystrophic calcification



note degeneration / necrosis and mineralization of myofibers. On H&E staining mineral is seen as basophilic granules and/or clumps.



Metastatic Calcification

Metastatic Calcification • when apparently normal tissue undergoes calcification (with hypercalcemia / altered Ca^{++} metabolism).

- pathogenesis:

- primary hyperparathyroidism

- renal failure / secondary hyperparathyroidism

- hypervitaminosis D

- paraneoplastic syndromes

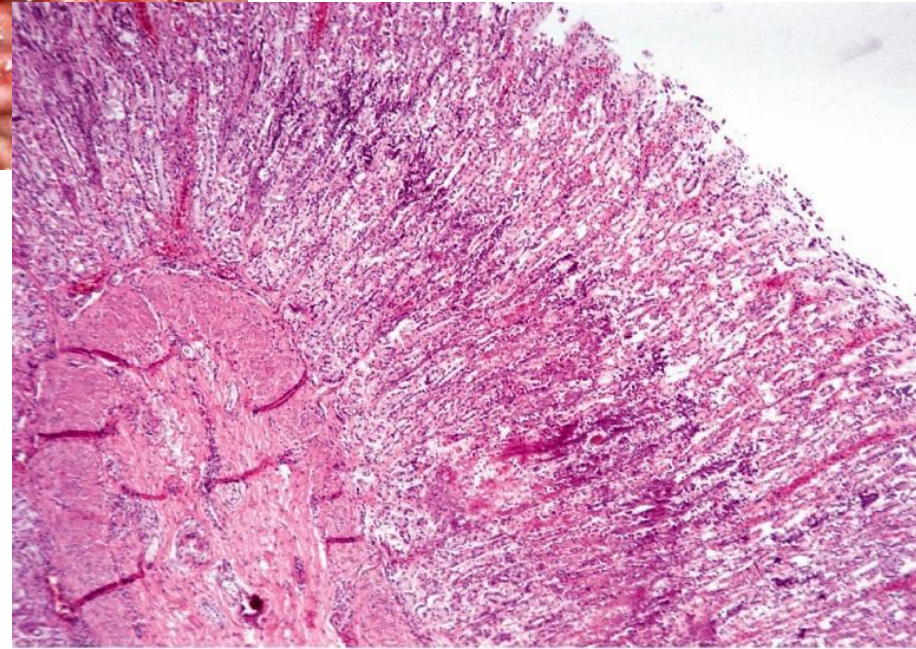
• sites: many sites can be affected, especially gastric and intestinal mucosa, blood vessel walls, BMZ of lung, kidney, etc.

Hypercalcemia >11.0mg/dl

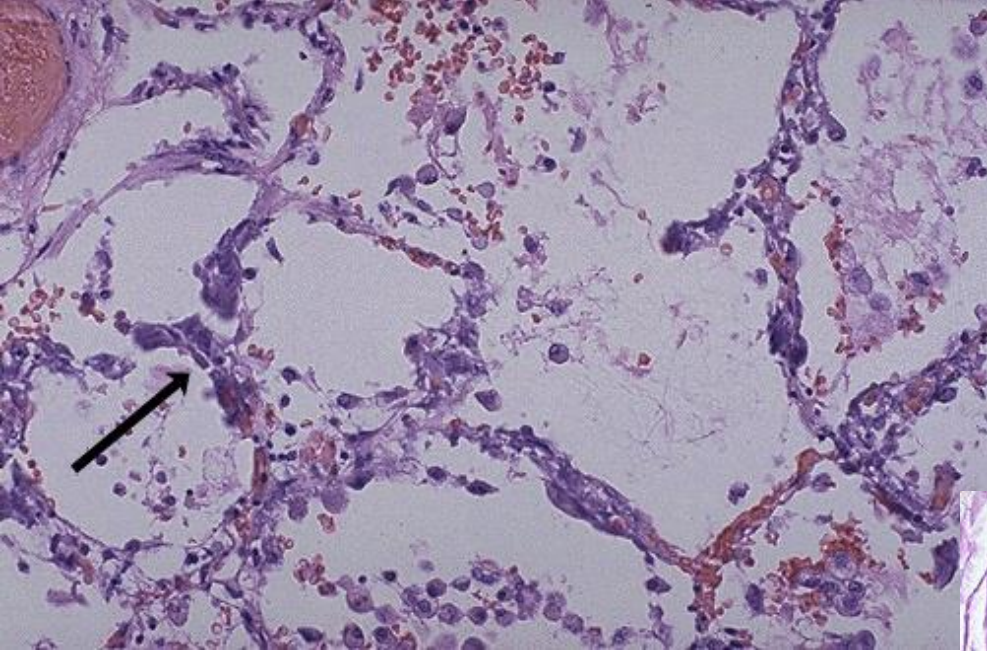
Metastatic Calcification



A band of calcium has been laid down the middle of the gastric mucosa.

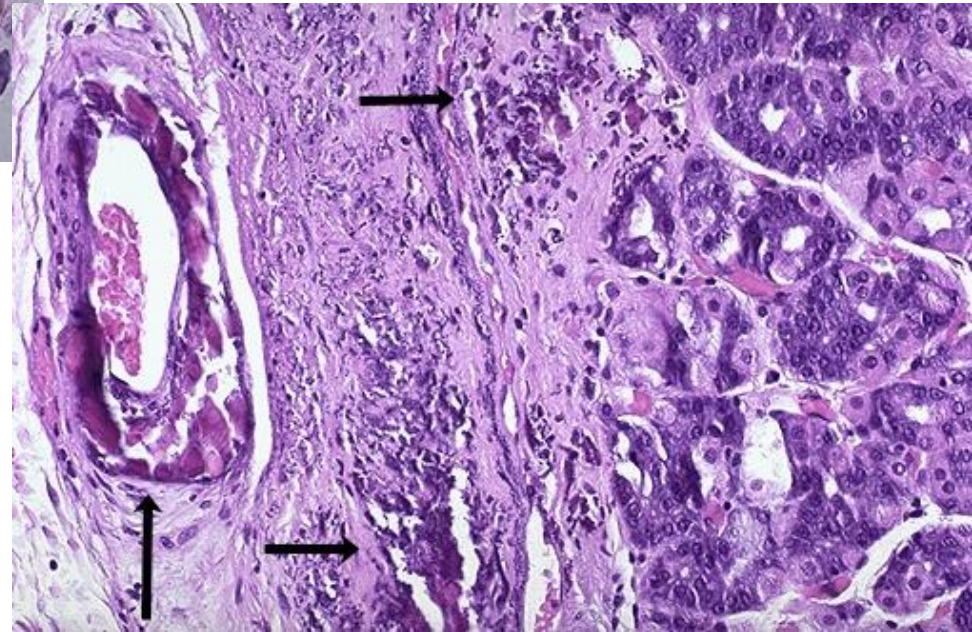


Calcification



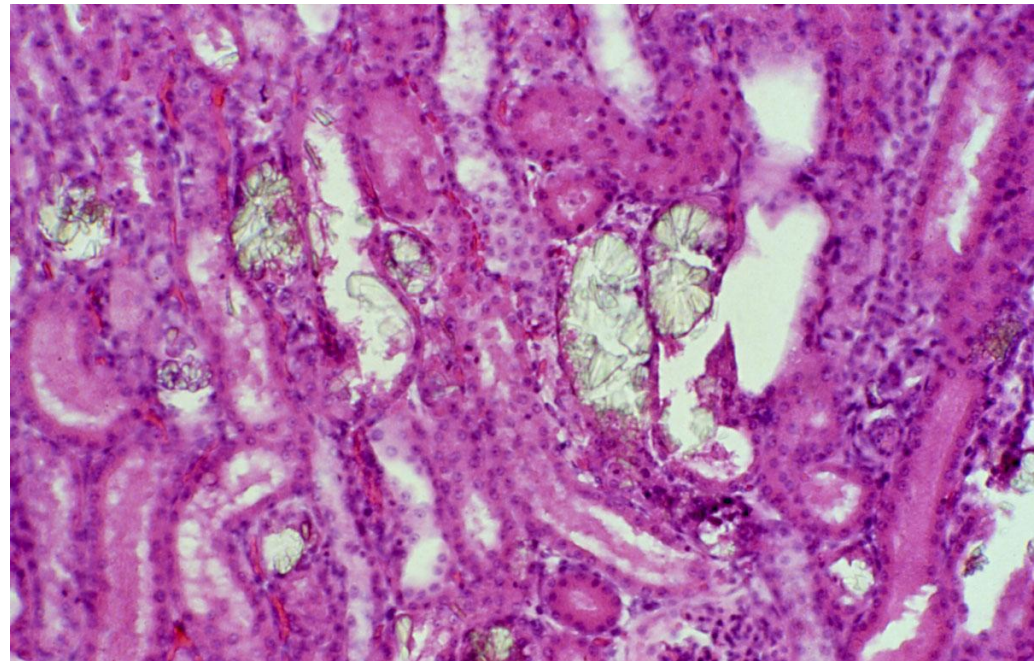
**Dystrophic calcification
Stomach**

**Metastatic calcification
Lung**

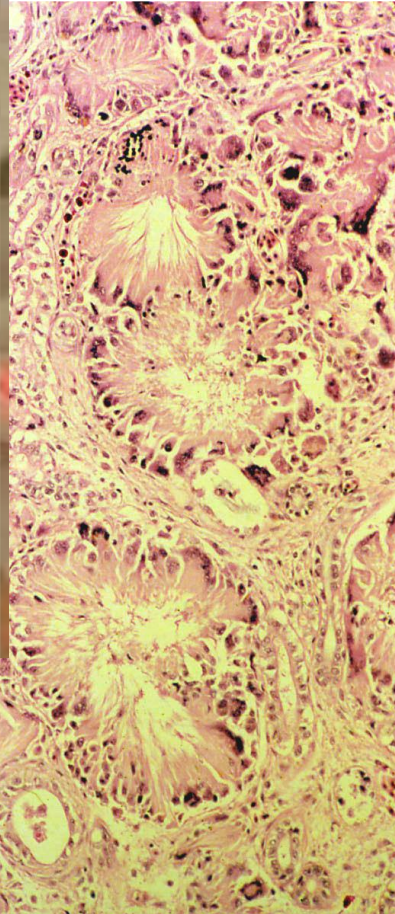


Crystals

- significance:
severe renal dysfunction
& electrolyte imbalances



Urates and Uric Acid

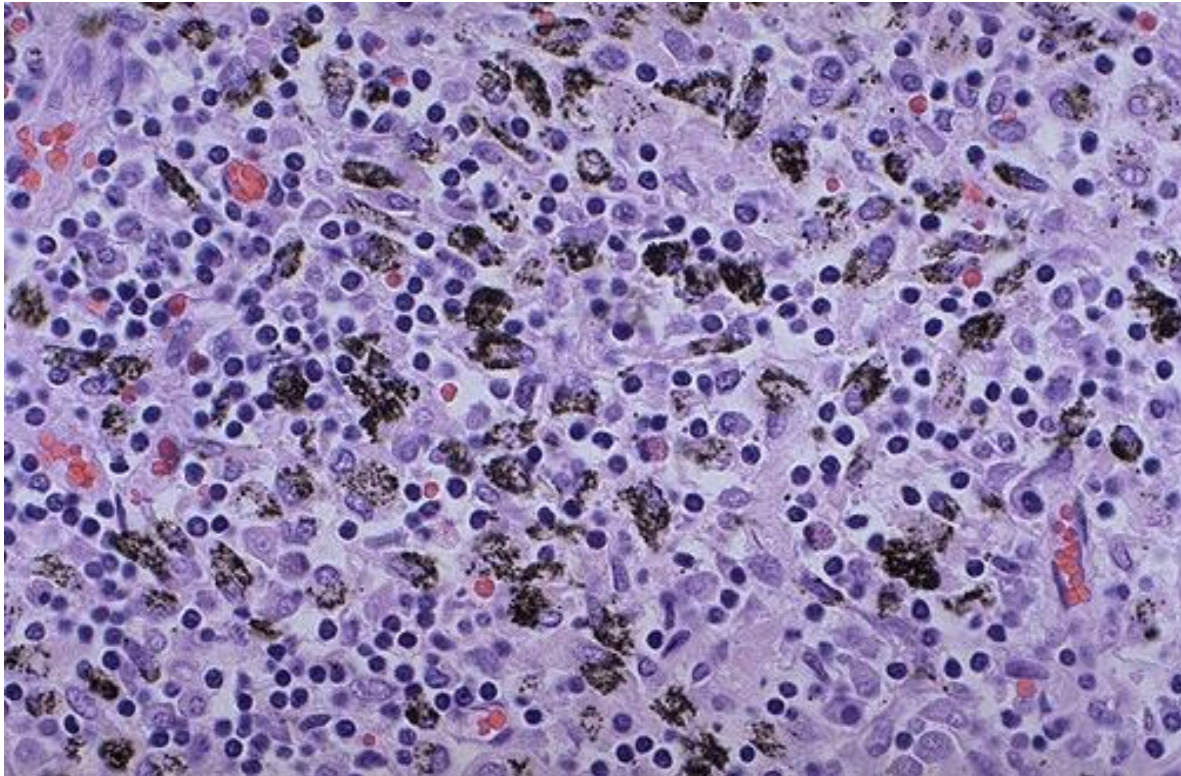


**note clear crystals
surrounded by
granulomatous
inflammation.**

Carbon

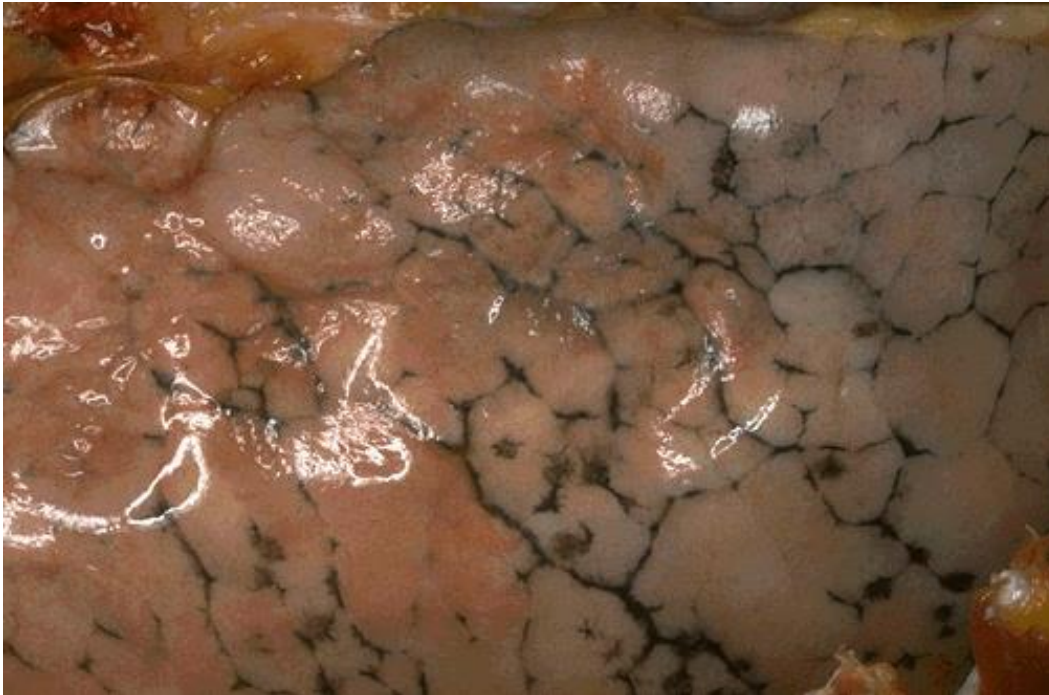
Accumulations of this pigment blacken the tissues of the lungs (anthracosis) and the involved lymph nodes.

Anthracosis



**Lymph node
of the lung
showing
carbon
deposition**

Anthracosis



**lung
showing
carbon
deposition**

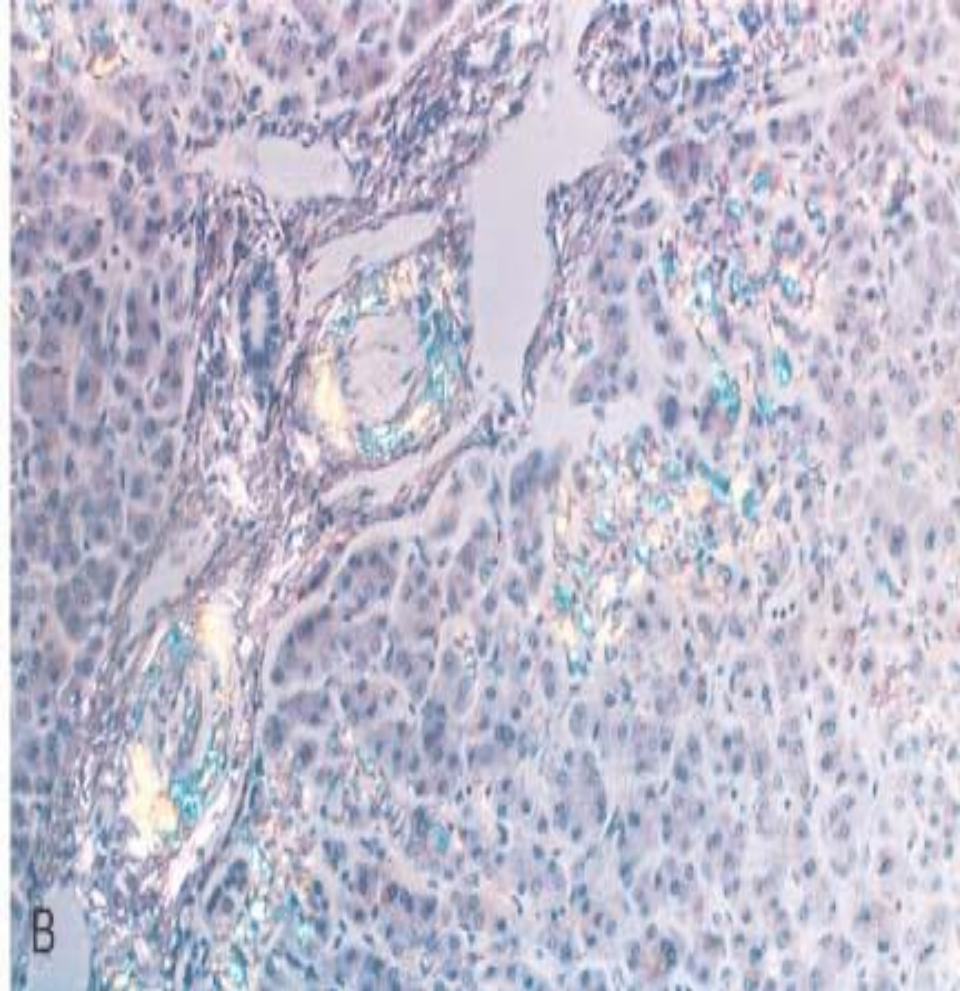
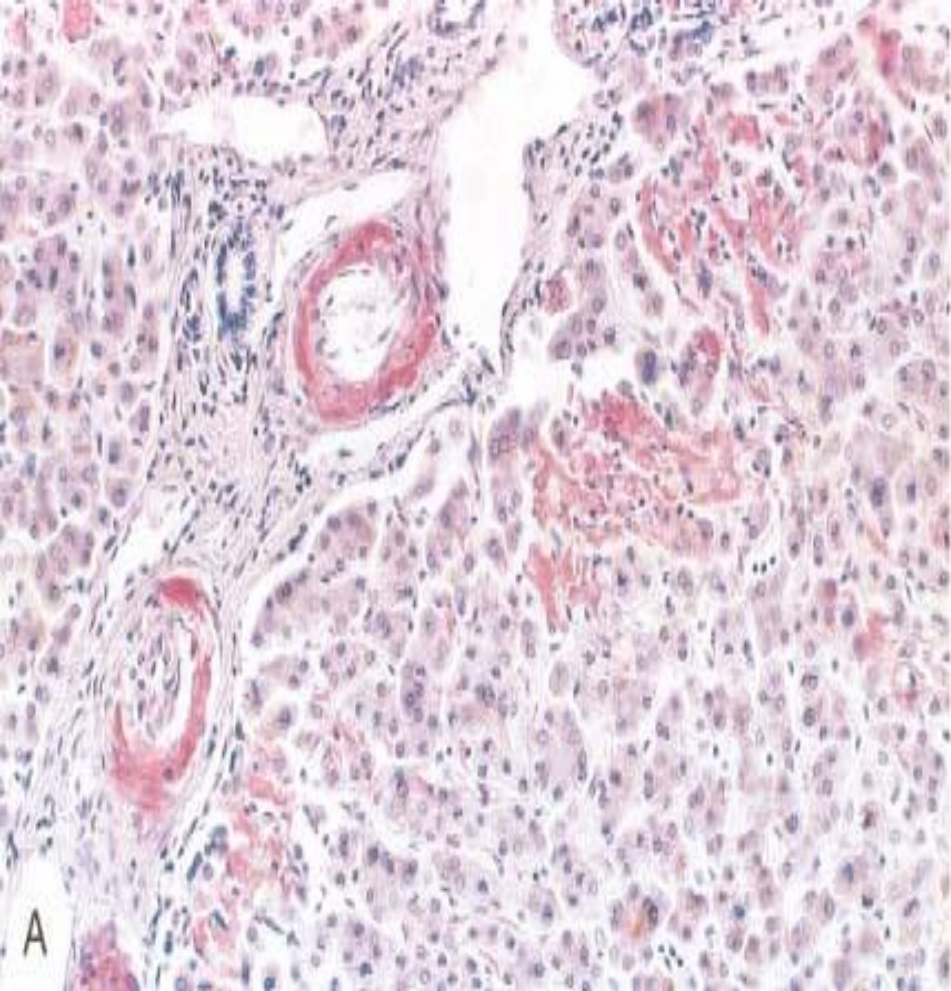
AMYLOIDOSIS

- **BUILDUP OF AMYLOID “PROTEIN”**
 - AL (**A**myloid **L**ight **C**hain)
 - AA (**N**ON-immunoglobulin protein)
 - A β (**A**lzheimer's)
- **WHERE? BLOOD VESSEL WALLS, at first**
 - **KIDNEY**
 - **SPLEEN**
 - **LIVER**
 - **HEART**

Why is amyloid called amyloid? Because in the early days, it took up STARCH stains applied to GROSS specimens, e.g., IODINE stains.

But of course now we know it's a PROTEIN, chiefly immunoglobulin protein chronic buildup.

It is therefore not surprising that diseases which have chronic immunoglobulin buildup over many years are associated with amyloidosis, i.e., multiple myeloma (also called plasma cell “dyscrasias”), granulomatous diseases, classically.



**CONGO RED STAIN, WITHOUT,
and WITH, POLARIZATION**

AMYLOID ASSOCIATIONS

- PLASMA CELL “DYSCRASIAS”, i.e., MULTIPLE MYELOMA
- CHRONIC GRANULOMATOUS DISEASE, e.g., TB
- HEMODIALYSIS
- HEREDOFAMILIAL
- LOCALIZED
- ENDOCRINE MEAs (Multiple Endocrine Adenomas)
- AGING

Diseases in which there is a cumulative buildup of immunoglobulin would be a setting for amyloidosis, so myelomas and chronic granulomatous diseases are at the top of the list.