Cell Adaptation, Cell Injury and Cell Death

pathology

LEC 4

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Intracellular Accumulations:

- Under some circumstances, cells may *accumulate abnormal amounts of various substances.*
- These *substances* may be *harmless* or cause varied degrees of *cell injury*.
- The *locations of these substances* either in the *cytoplasm*, *within organelles*, or *in the nucleus.*
- These substances may be *synthesized by the affected cells or may be produced elsewhere.*

Accumulation of these substances is occurred by three general pathways:

- Accumulation of normal substances, either due to increase their production or due to failure to remove these substances by metabolism, like **Fatty change** in the liver.
- A normal or abnormal endogenous substance accumulates because of genetic or acquired defects in its metabolism, like storage diseases or alph-1 antitrypsin deficiency (mutations cause defective folding and transport of this protein).
- An abnormal exogenous substance is accumulated within the cells without defects that are seen in previous two points. Like accumulation of **carbon or silica.**

Fatty changes or fatty degeneration (steatosis):

- abnormal accumulations of triglycerides within the hepatocytes, (can also involved heart, skeletal muscles, & kidney)

Why it is common in the liver?

- Because the liver play central role in fat metabolism.
- The fatty change may be mild reversible or producing severe irreversible cell injury &death.
- This depends on the cause &amount of fat accumulation.

Etiology(causes):

- **Alcoholism**
- **Starvation: increases FA mobilization from peripheral store.**
- **Protein malnutrition: decrease synthesis of apoprotein.**
- **Obesity**
- **Diabetes mellitus**
- **Hypoxia**
- **Liver toxin like CCL4**
- **Drugs like estrogen, steroid, tetracycline**

- When the fatty change is mild, it may have no effect on cellular function.
- More severe fatty change may impair cellular function (e.g., in CCl_4 poisoning).
- Recently proved, that **severe form** of fatty change may lead to liver cirrhosis & hepatocellular carcinoma.

Mechanisms of Fatty changes (steatosis):

- Excess accumulation of triglycerides within the liver may result from defects in any one of the events in the sequence from fatty acid entry to lipoprotein exit from hepotocytes.

Morphology of Fatty Changes:

- In any site, Fat accumulation appears as ***clear vacuoles*** within parenchymal cells.
- Accumulation of glycogen & water also produce clear vacuoles.
- special techniques are needed to distinguish these three types of clear vacuoles:

1. The identification of clear vacuoles of lipids require preparation of frozen tissue sections (avoid formalin), and then the sections are stained with Sudan black or Oil red-O.
2. The identification of glycogen clear vacuoles requires staining with periodic acid-Schiff (PAS) reaction .
3. Clear vacuoles of water are negative staining for Sudan IV or Oil red- O, & (PAS).

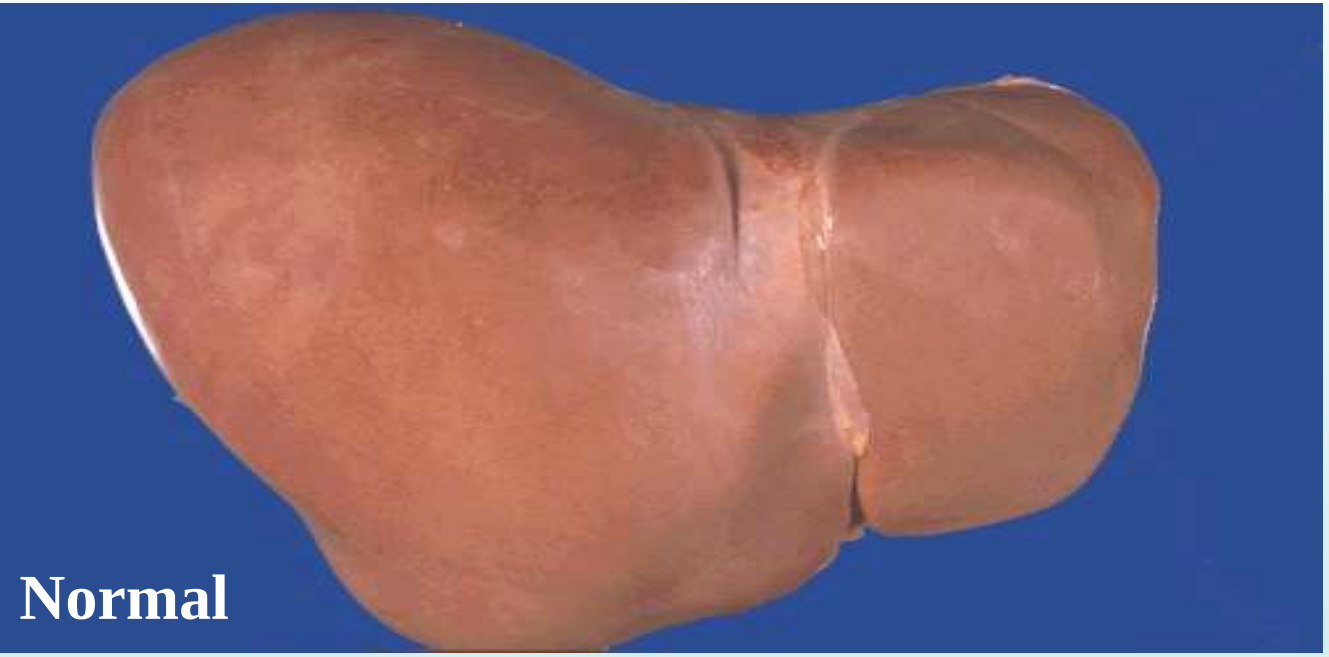
Gross

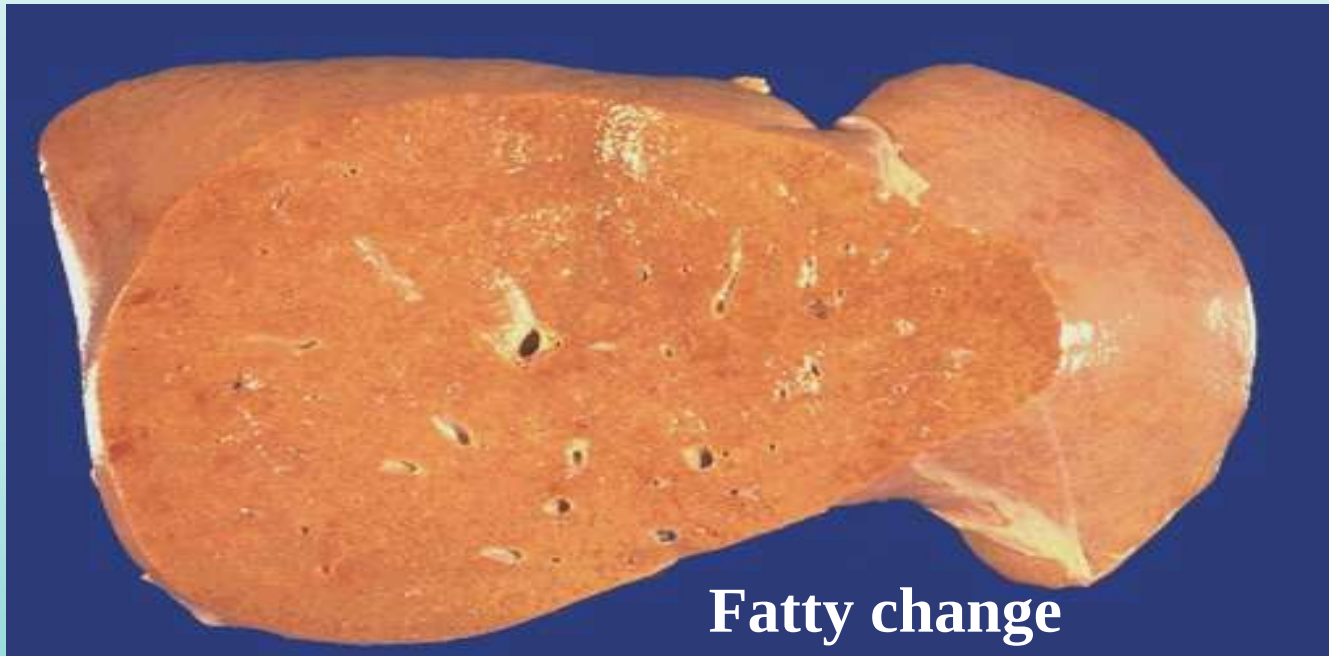
- In the liver, mild fatty change …….not affect the gross appearance.
- In progressive fatty changes …… the organ enlarges & more yellowish,
- In extreme instances……. bright yellow, soft, greasy liver.

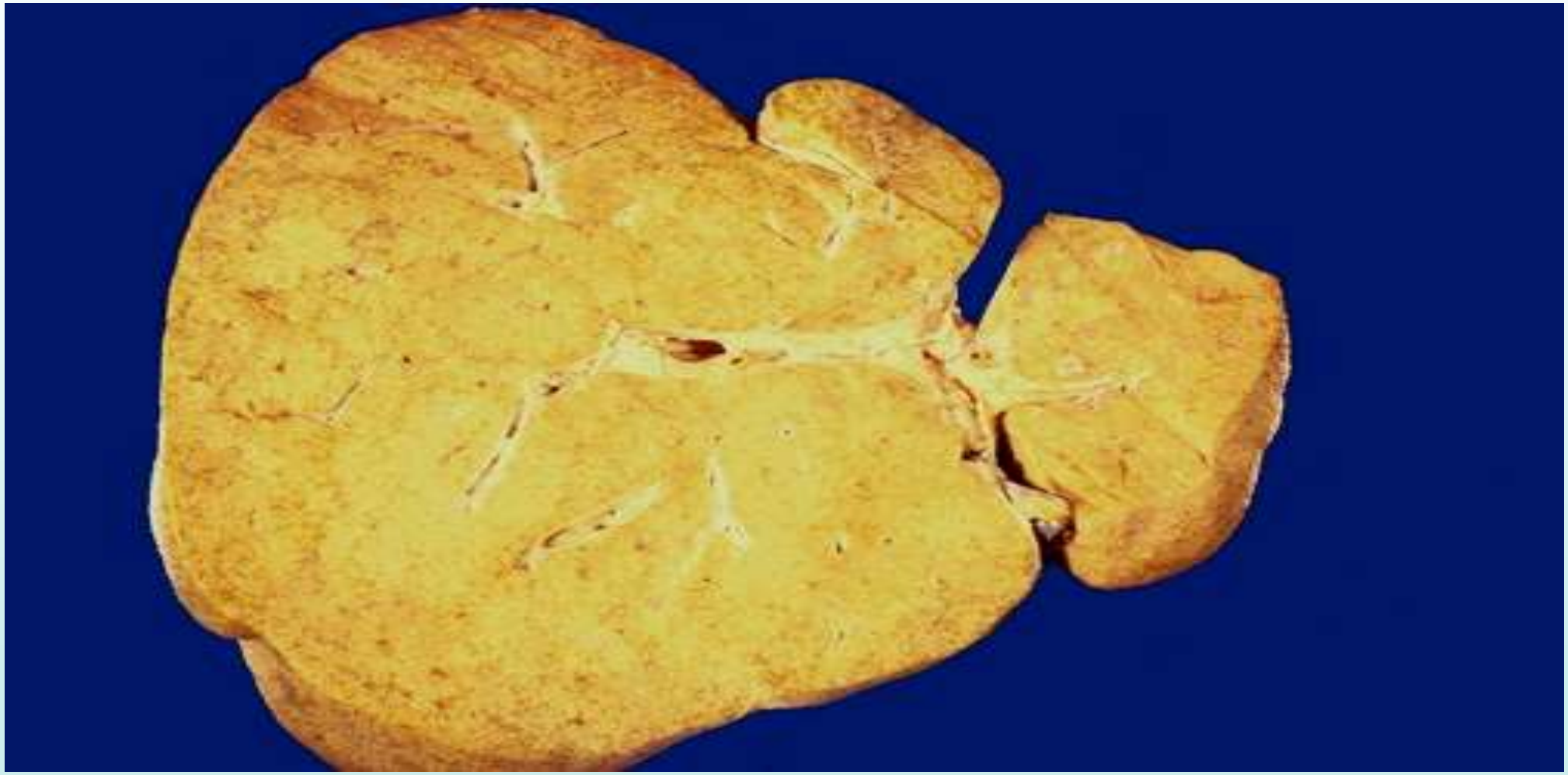
Mic.

- Early fatty change, there are **minute vacuoles** in the cytoplasm & around the nucleus of fat cells.
- As the process progresses, the vacuoles coalesce, creating cleared spaces that **displace the nucleus** to the periphery of the fat cells.

Fatty change liver





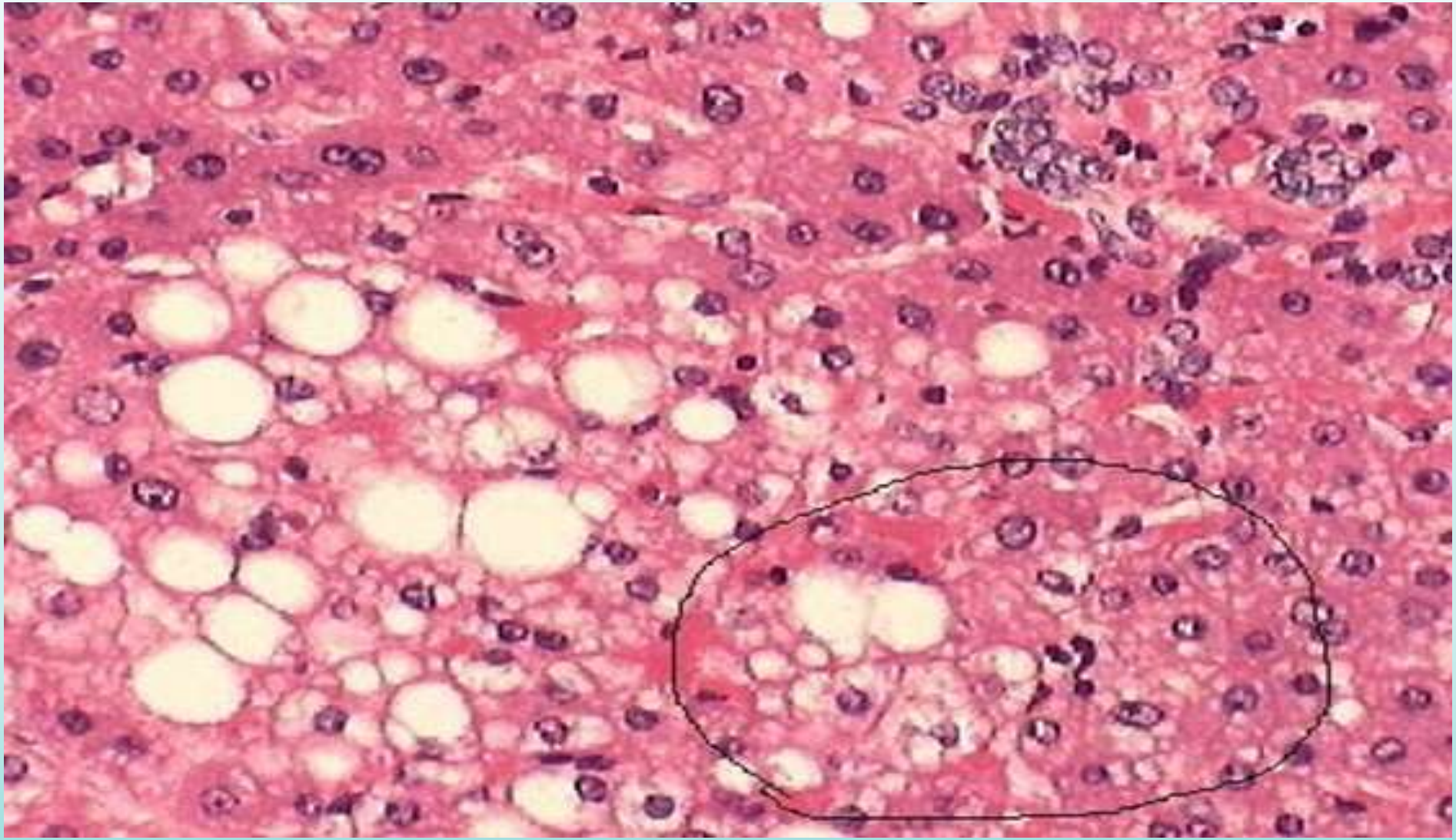


Severe fatty change liver

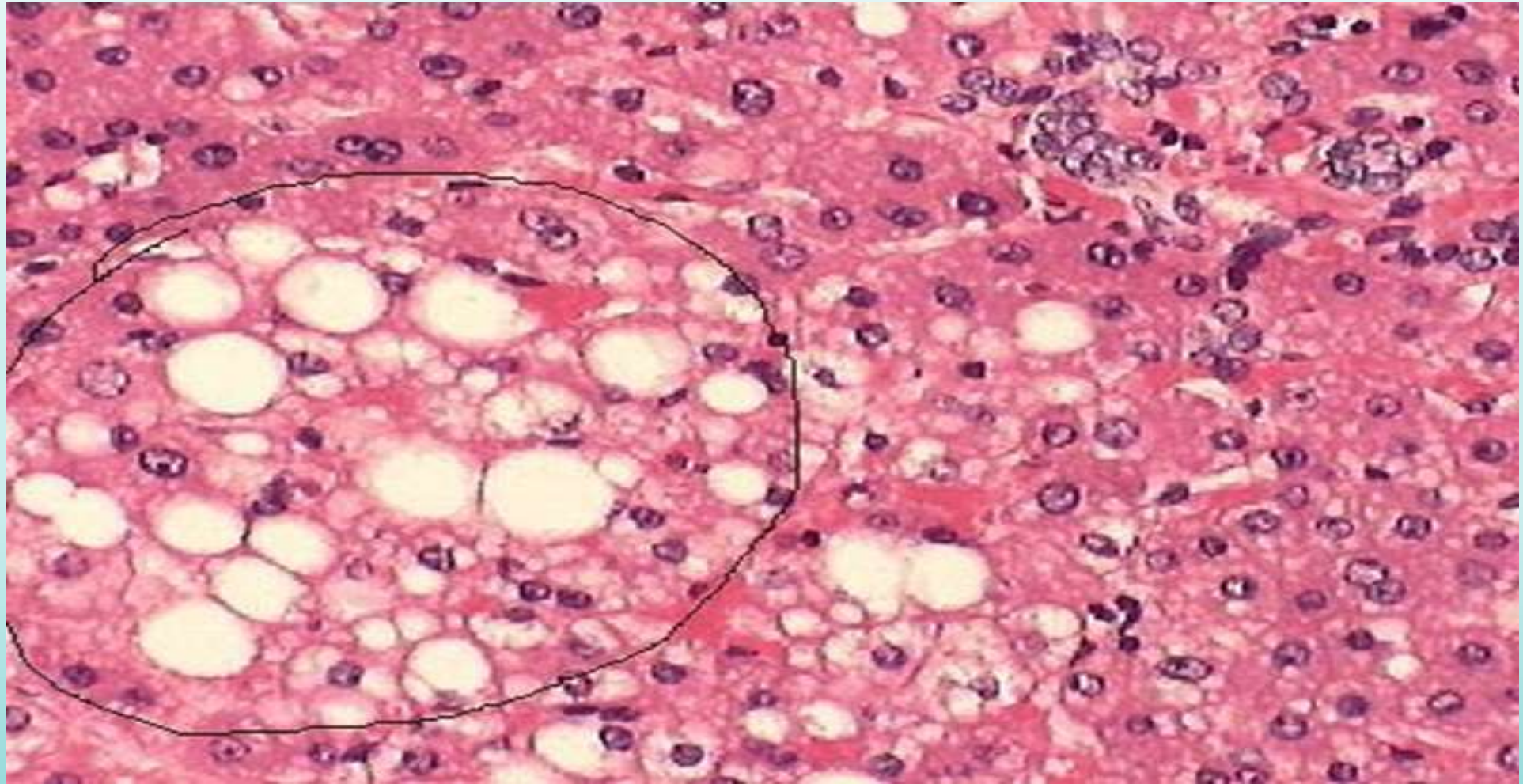
In the liver mild fatty change shows no gross changes, but with progressive accumulation, the organ enlarges and become increasingly yellow, soft and greasy to touch.

Microscopy:
In parenchymal cells

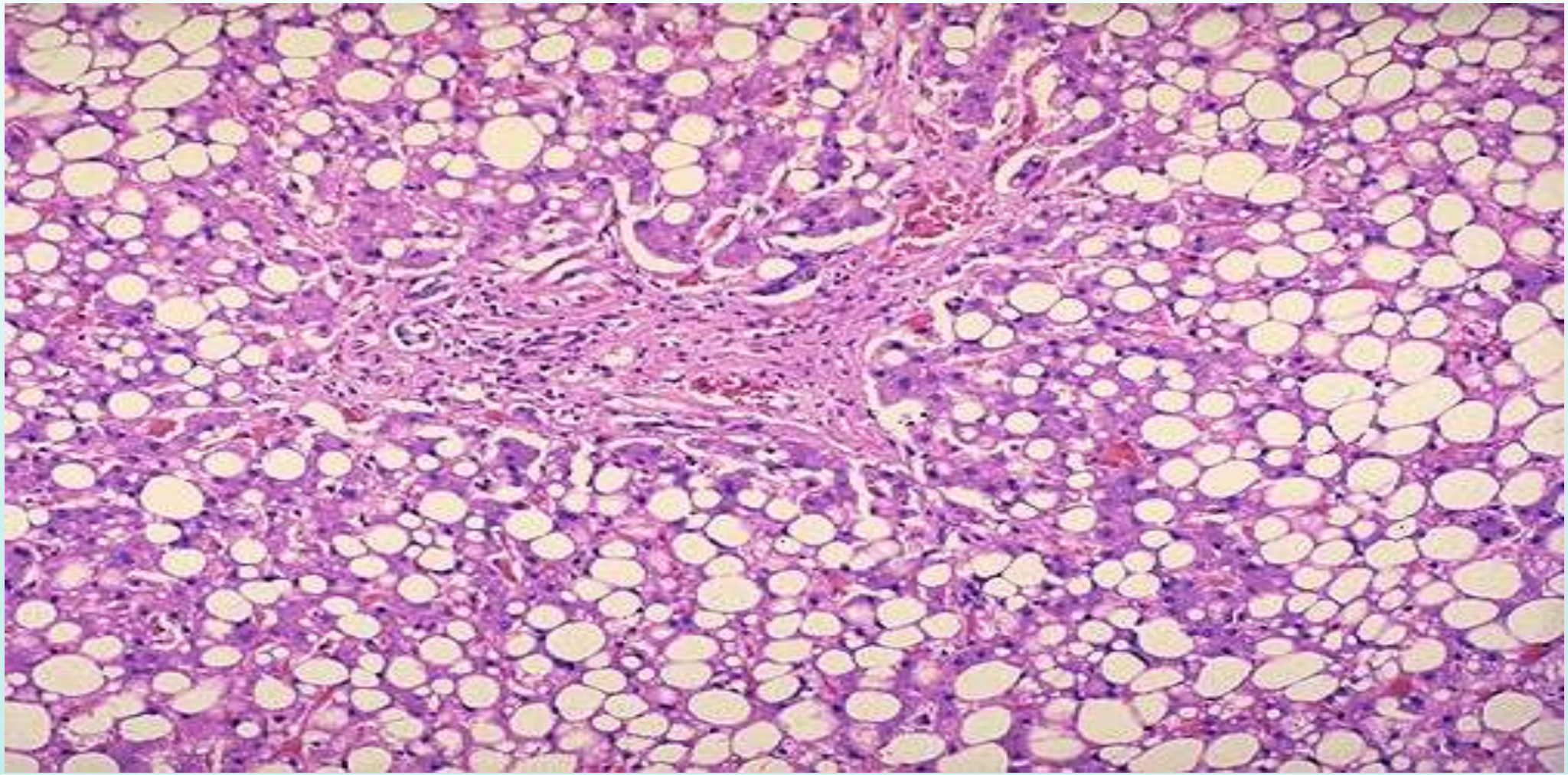
Early – small vacuoles in cytoplasm around the nucleus



Late – Vacuoles coalesce and create clear spaces that displace nucleus to periphery of cell Circled area shows late fatty change – fat displacing nucleus to periphery

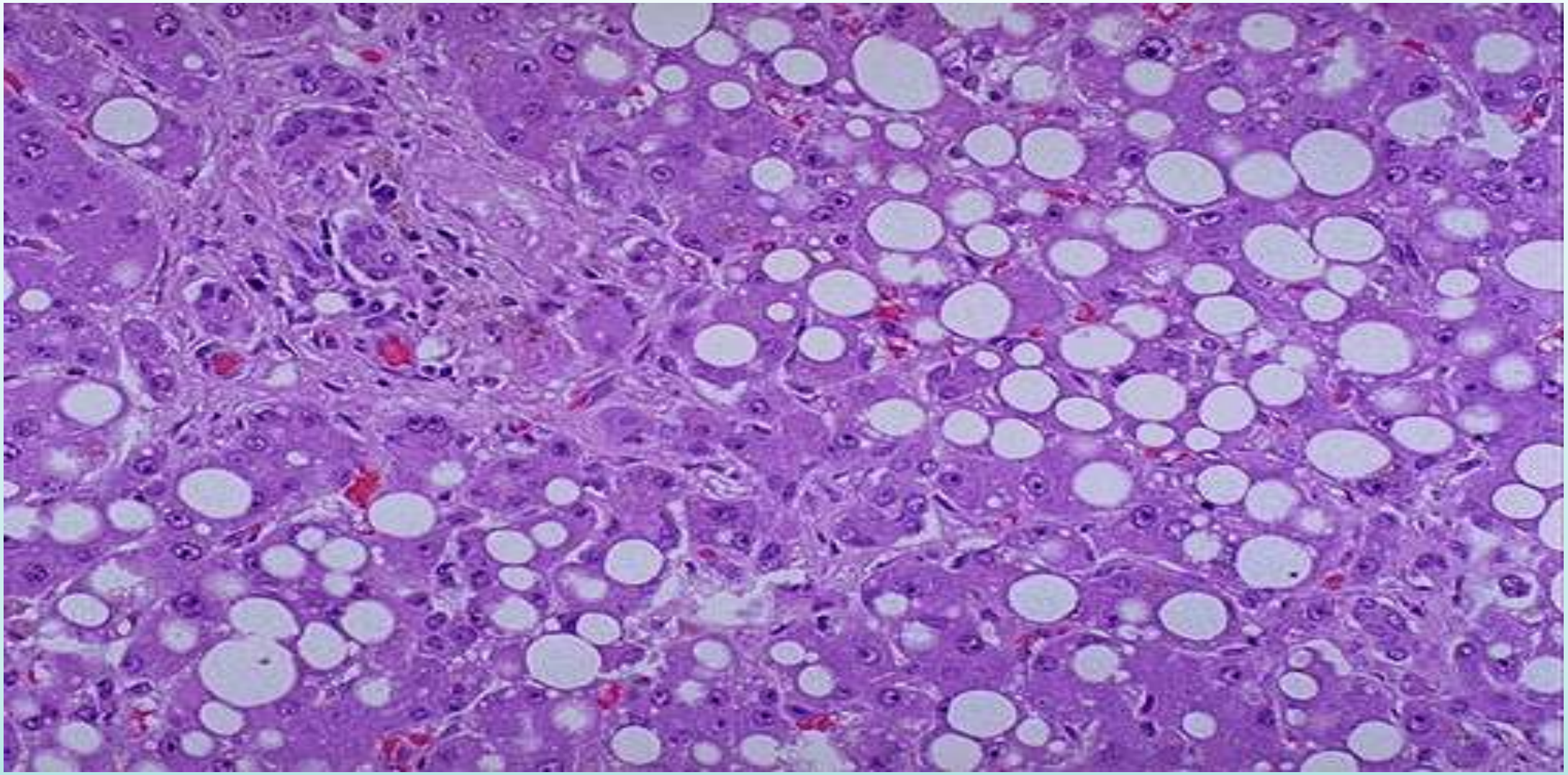


Fatty change liver



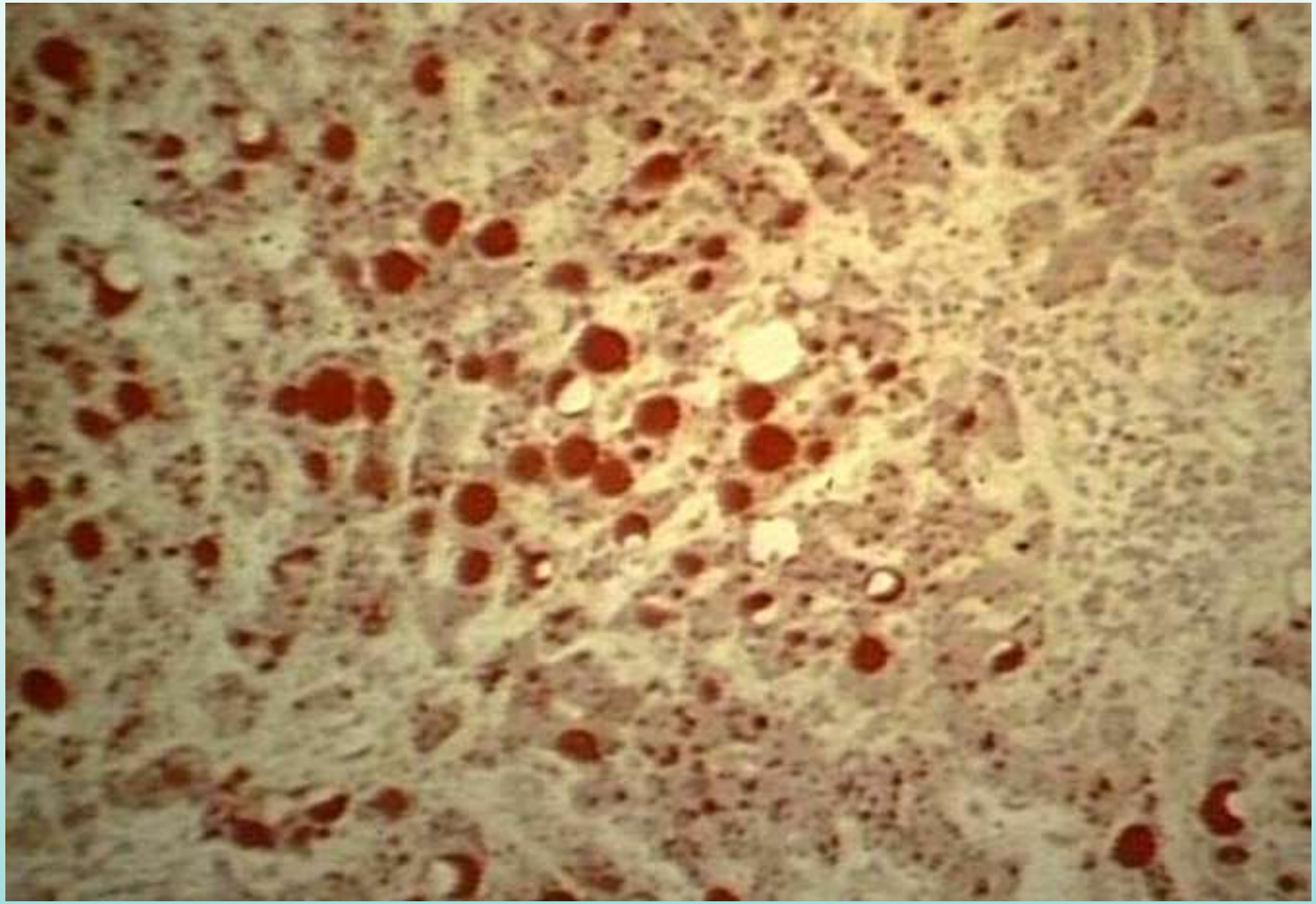
In the early stages: small fat vacuoles around the nucleus but with progression these coalesce into a large clear space that displaces the nucleus to the periphery (macrovesicular steatosis).

Fatty change liver

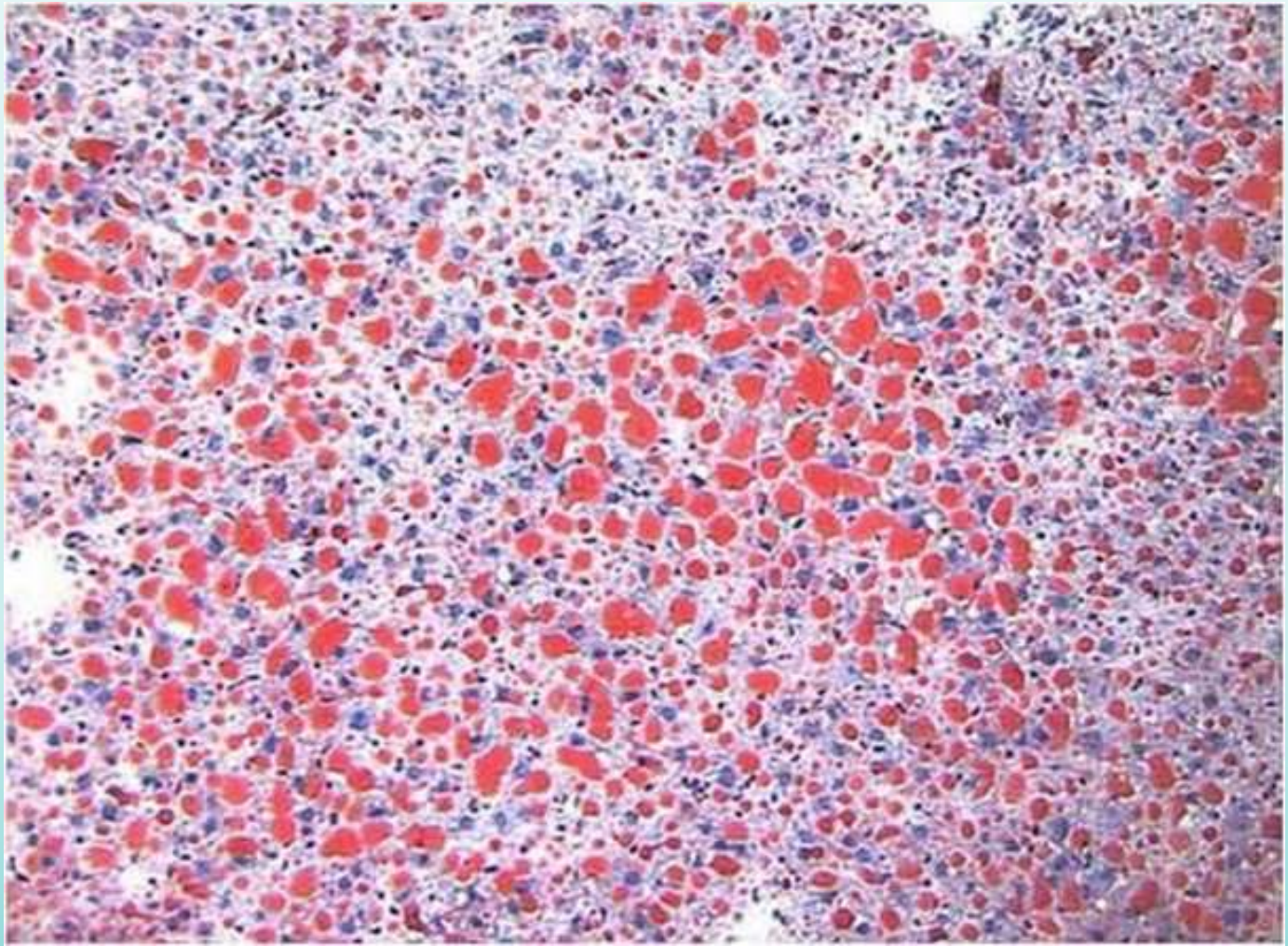


Macrovesicular steatosis a higher power of previous figure.

1. Sudan black

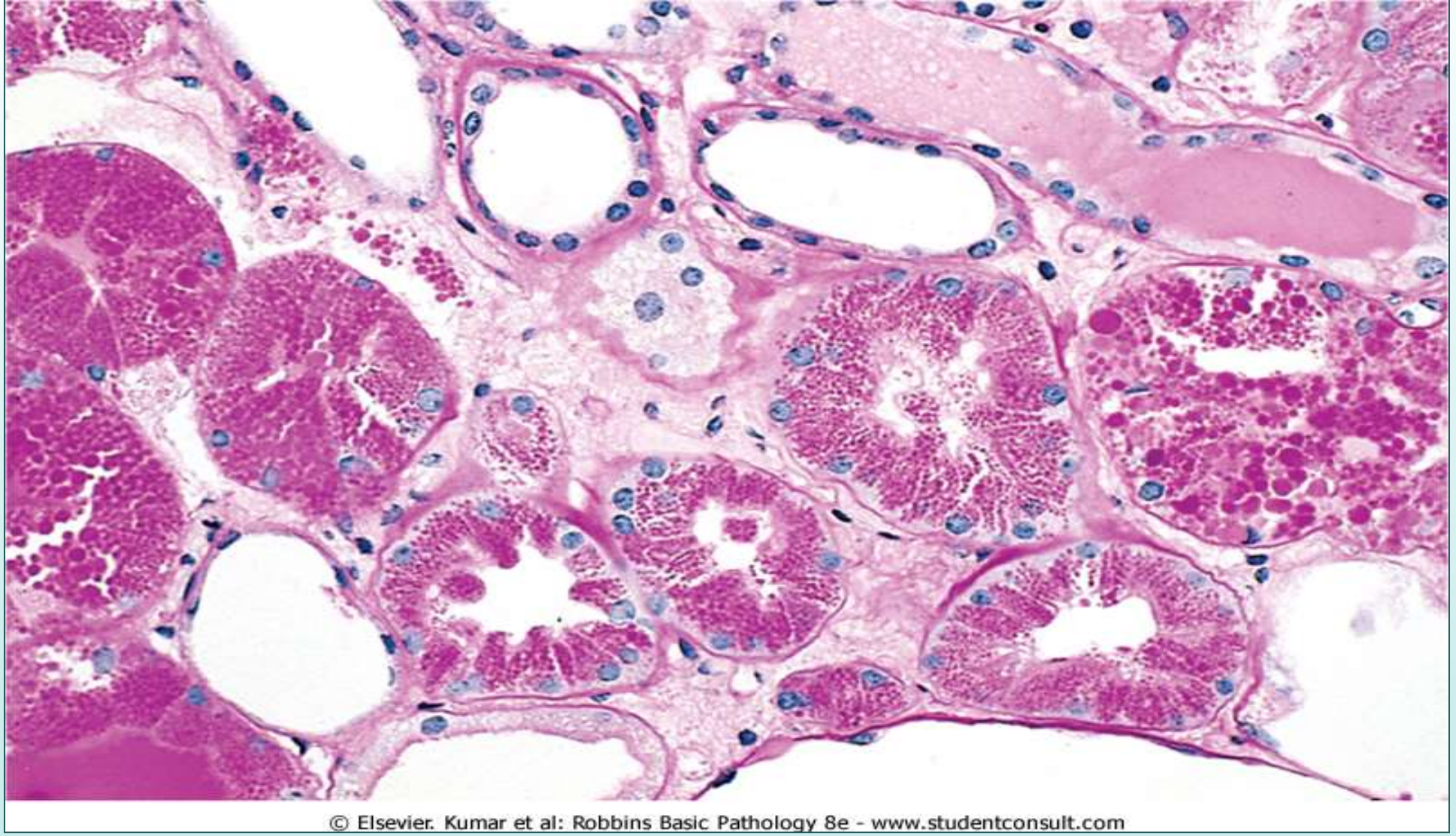


2. oil red O



Protein Accumulation:

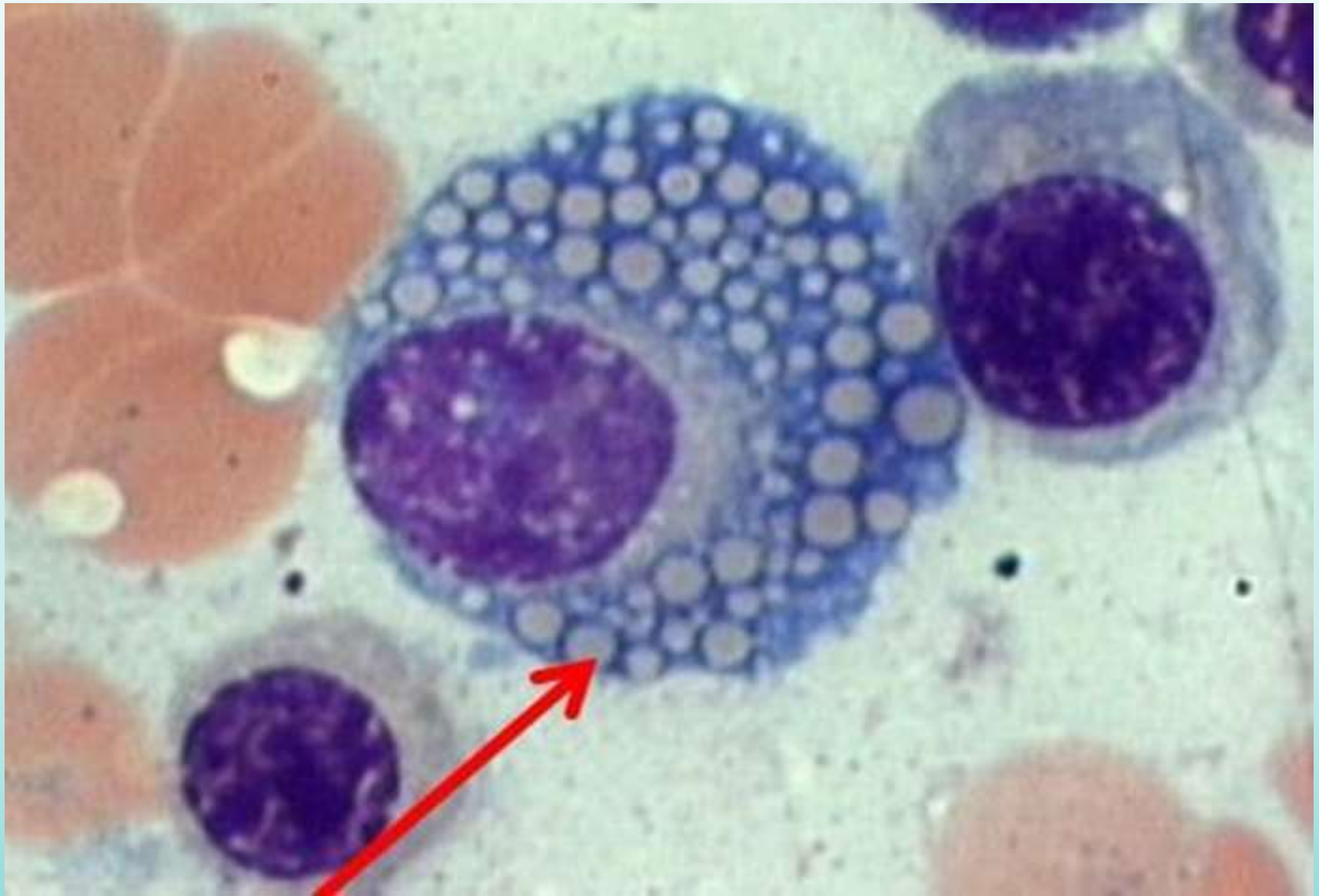
- Protein accumulation is less common than lipid accumulation.
- Intracellular accumulations of proteins usually appear as rounded, eosinophilic droplets, vacuoles, or aggregates in the cytoplasm.
- Examples of protein accumulation:
- In the kidney, there is accumulation of albumin in the cytoplasm of tubular cells of proximal tubules, which occur in diseases associated with increased protein filtration through the glomeruli (like nephrotic syndrome) & increase reabsorption of albumin by the tubular cells, accumulated protein appear as **pink, hyaline cytoplasmic droplets, this is reversible process.**



Protein reabsorption droplets in the renal tubular epithelium.

- There is marked accumulation of newly synthesized immunoglobulins that may occur in the RER of some plasma cells resulting in rounded, eosinophilic Russell bodies.
- In alcoholic liver diseases, there is accumulation of intracellular proteins (keratin intermediate filaments) (Mallory body), which appear as an eosinophilic inclusion in the liver cells.
- Neurofibrillary tangle which is aggregation of proteins that are present in the brain of Alzheimer disease.

Russel bodies on MGG



Russell bodies

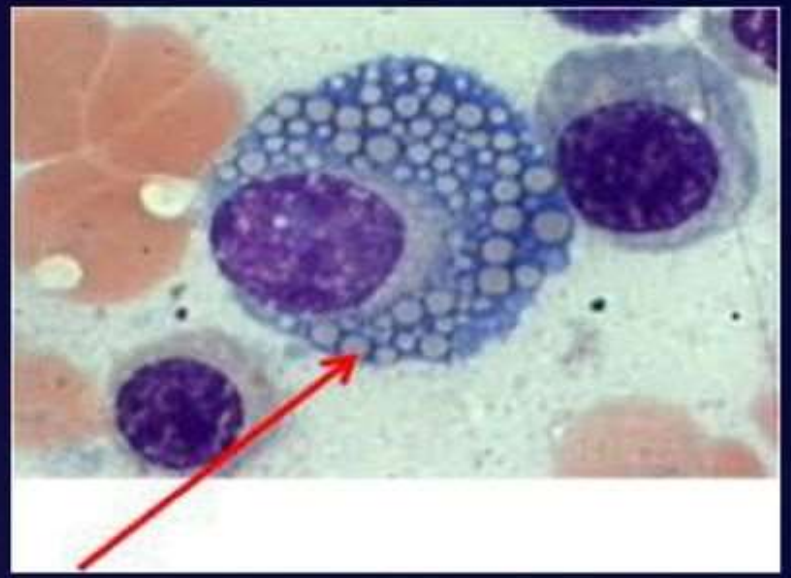
Morphology

are eosinophilic, large, homogenous immunoglobulin-containing inclusions usually.

Found in

a plasma cell undergoing excessive synthesis of immunoglobulin; the Russell body is characteristic of the distended endoplasmic reticulum

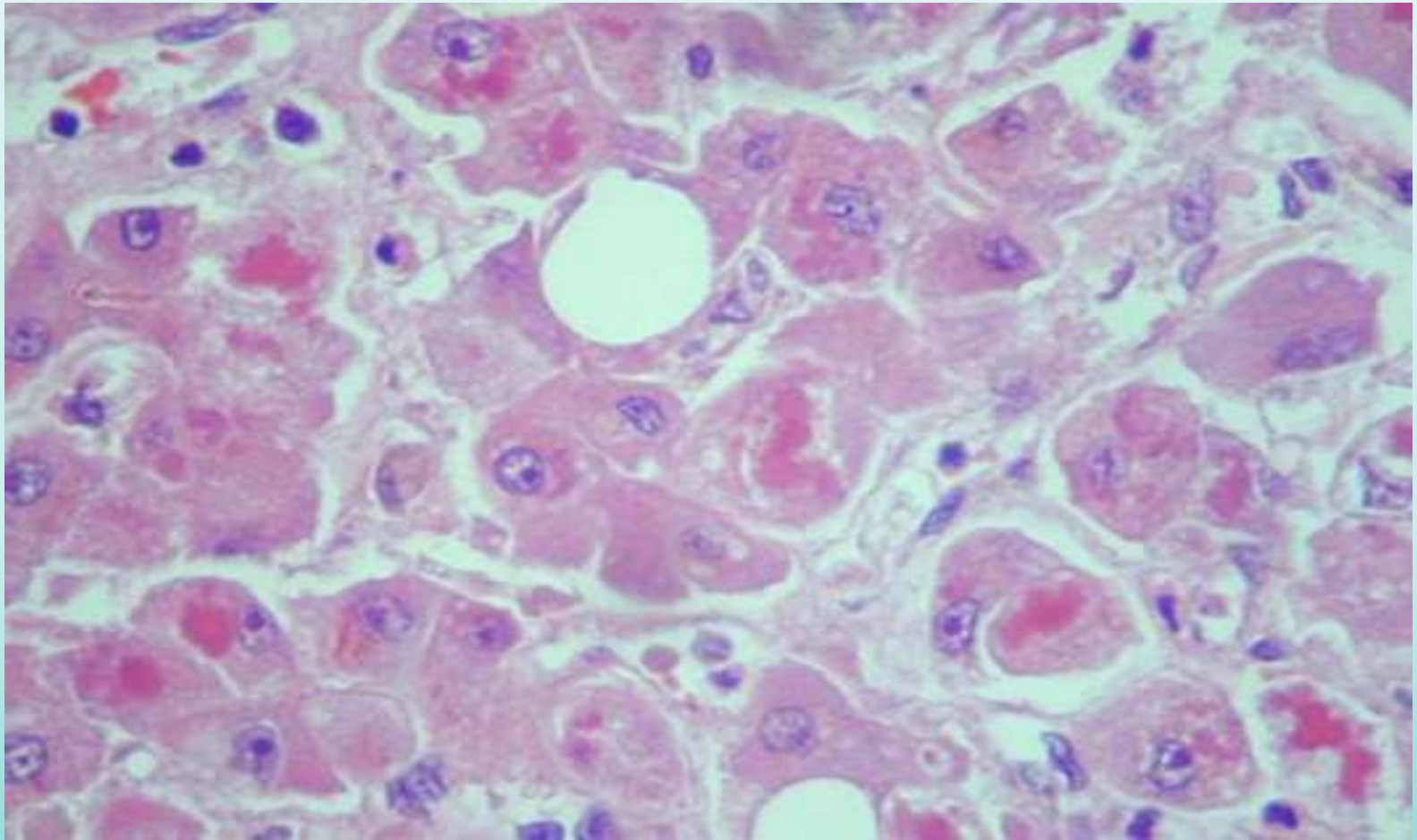
This is one cell variation found in multiple myeloma.



. Accumulation of cytoskeletal proteins

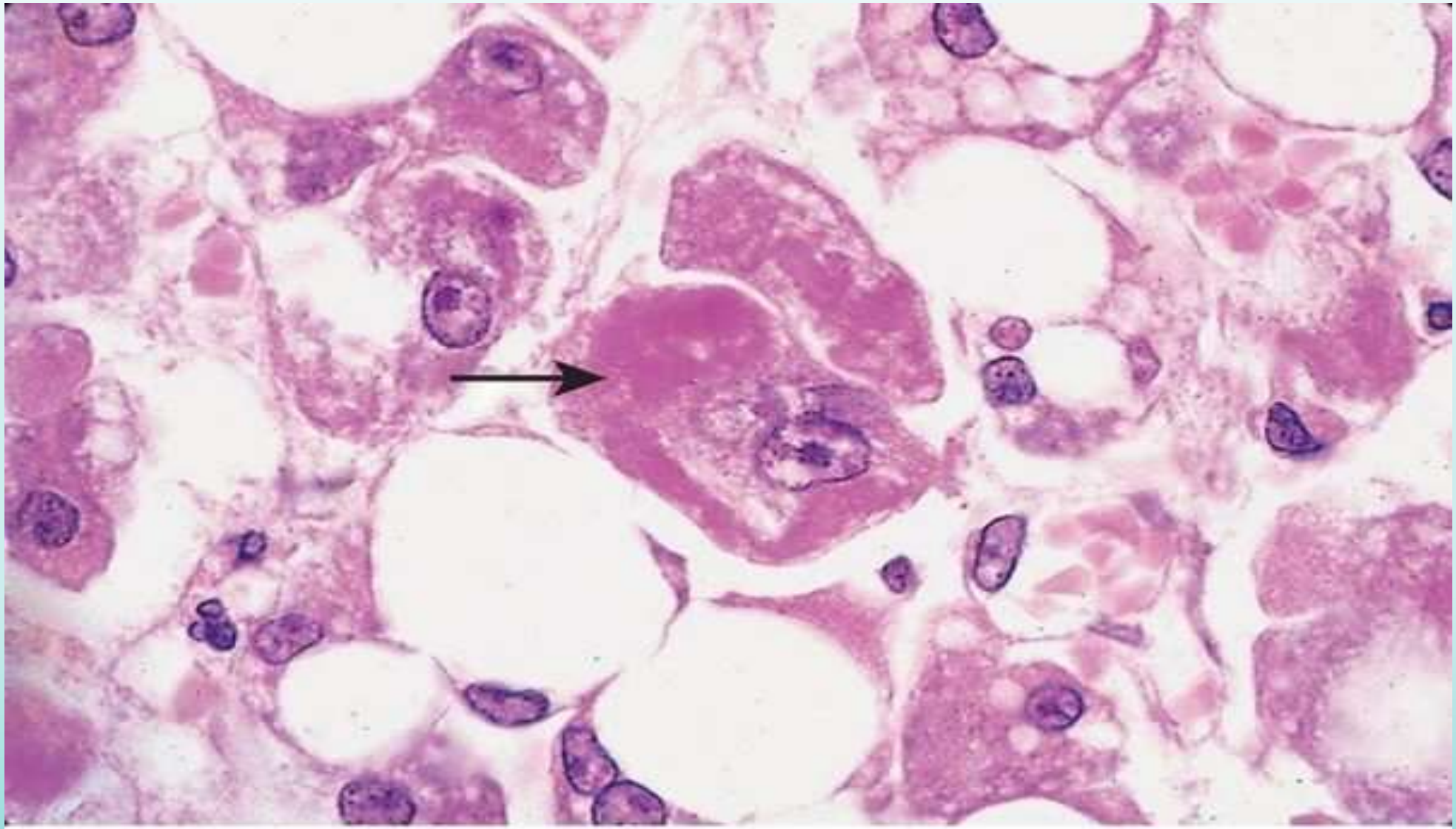
ALCOHOLIC HYALINE (MALLORY HYALINE)

Eosinophilic globules seen in liver cells, consists predominantly of keratin intermediate filaments Seen to be accumulated in alcoholic liver disease

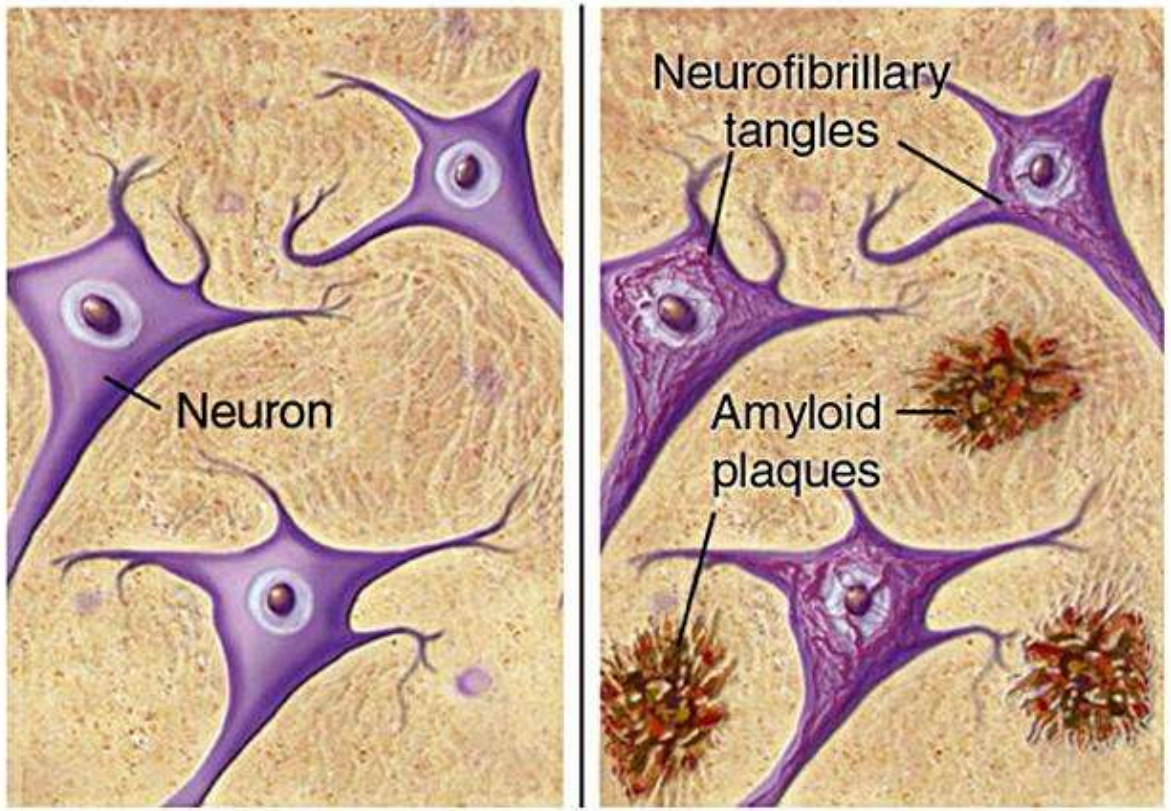


Mallory bodies (the red globular material) composed of intermediate keratin filaments in liver cells

At high magnification can be seen globular red hyaline material within hepatocytes.



Normal vs. Alzheimer's Diseased Brain



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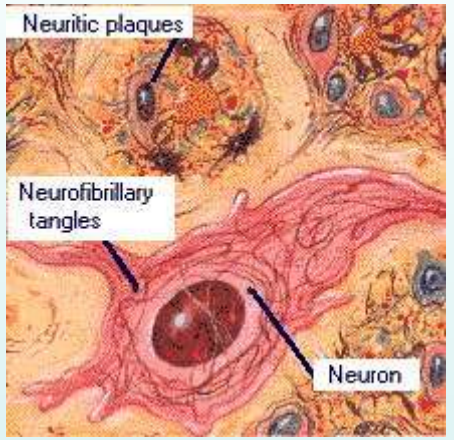
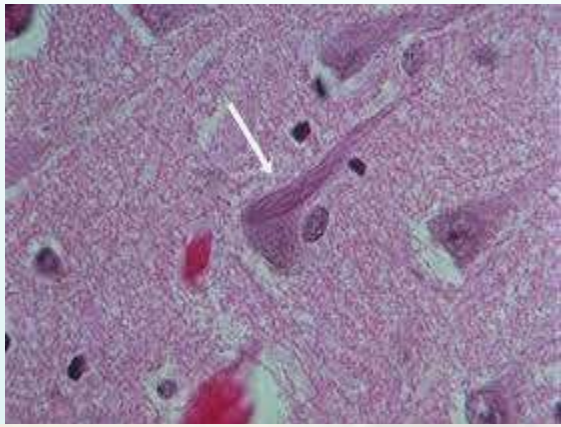
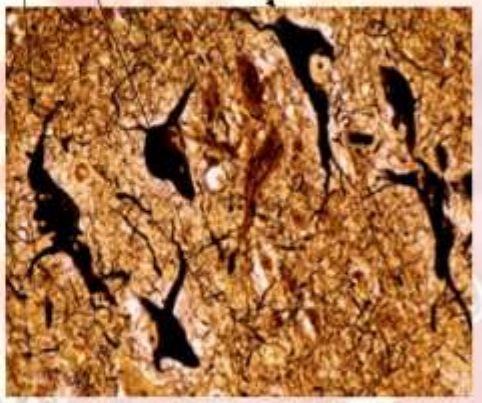


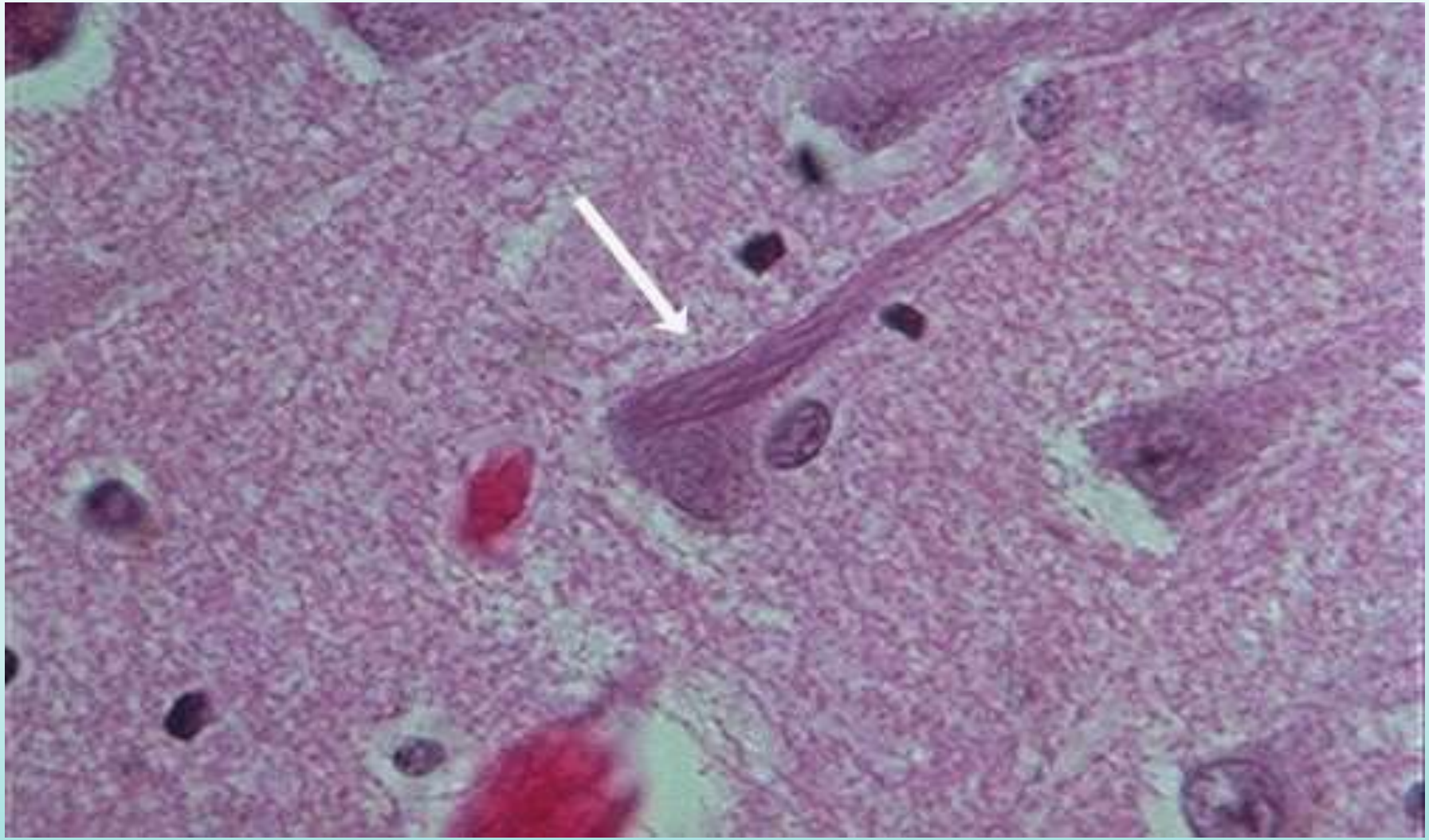


Neurofibrillary Tangles

- Tangles develop inside nerve cells
- Abnormal collections of twisted protein fibers
- Protein threads are composed of the hyperphosphorylated *tau* protein



Neurofibrilary Tangles-Alzheimers disease

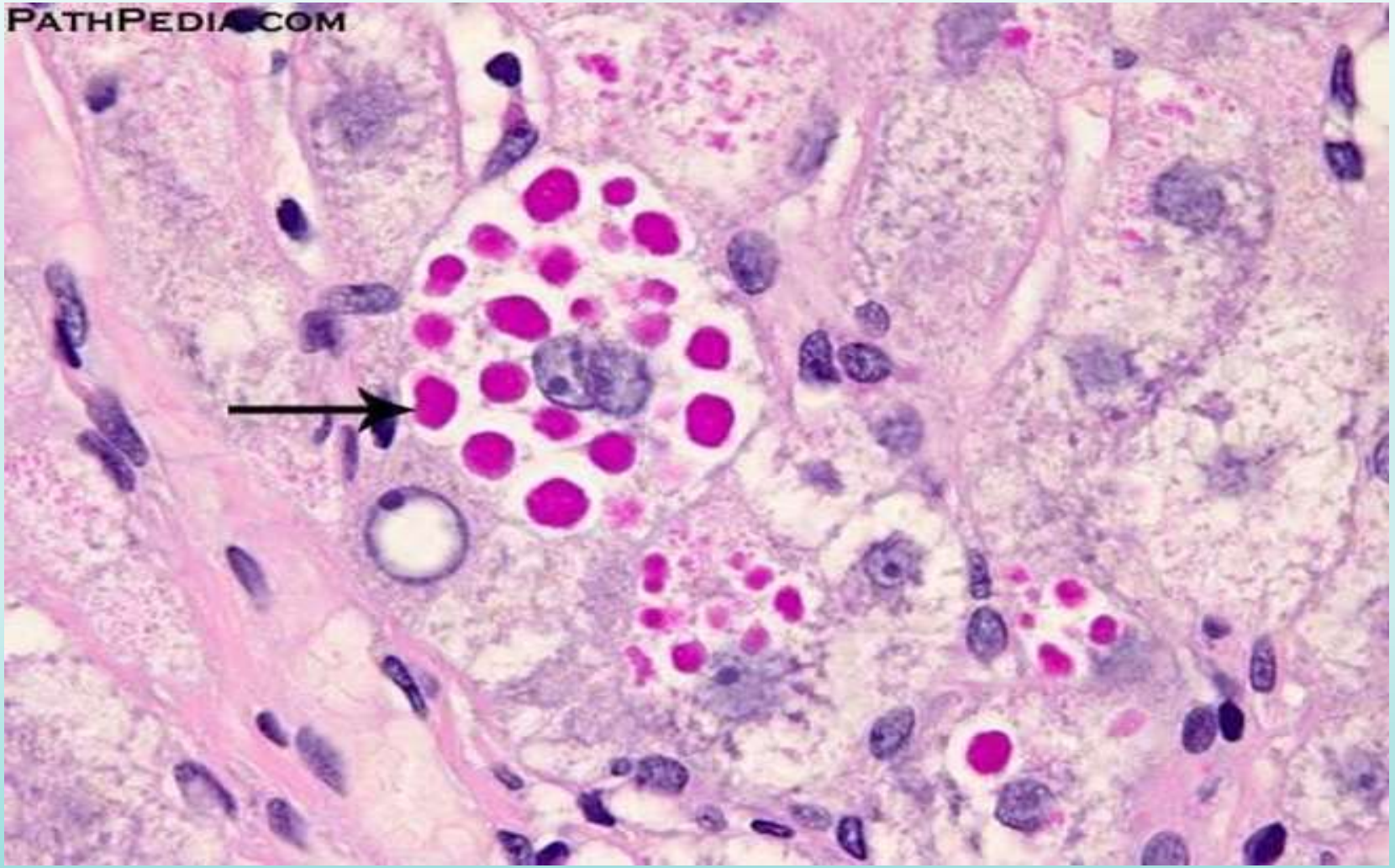


α1 antitrypsin deficiency

- Protein folding defect →
- Build up of partially folded proteins →
- Aggregate in ER of liver

α1 antitrypsin deficiency

the synthesized protein lacks the ability to migrate from endoplasmic reticulum (ER) to Golgi zone and thus accumulates inside ER as hyaline globules



Glycogen Accumulation:

- Excess accumulation of glycogen can be seen in the followings:
- In poorly controlled Diabetes Mellitus, glycogen will accumulate in renal tubular epithelium, cardiac muscles, & beta cells of Islet cells of pancreas.
- In glycogen storage diseases, there is **enzymatic defect** that result in accumulation of glycogen in various cells of body.

Pathologic Calcification

- is the abnormal tissue deposition of calcium salts, together with smaller amounts of iron, magnesium, and other mineral salts
- **There are two forms of pathologic calcification.**

1.Dystrophic CALCIFICATION:

2. **Metastatic CALCIFICATION**:

1.Dystrophic Calcification:

The cause is NOT hypercalcemia; typically, the serum calcium concentration is normal

- occurs locally in **Dying tissue (areas of necrosis**, whether they are of coagulative, caseous, or liquefactive type, and in foci of enzymatic necrosis of fat,
- **or previously Damaged tissue,** such as:
- areas of old trauma
- **in the atheromas of advanced atherosclerosis**,
- **develops in aging or damaged scarred heart valves ,**
- **tuberculous lymph node**.
- **Gross:** fine, white granules, often felt as gritty deposits
- **Mic:** By H&E the calcium salts have a **basophilic, amorphous granular, sometimes clumped appearance.**

(intracellular, extracellular, or in both locations)

2. Metastatic calcification:

- Deposition of calcium salts in otherwise **normal tissues**
- it almost always **results from hypercalcemia** secondary to some disturbance in calcium metabolism.
- There are four principal causes of hypercalcemia:
- 1**. hypercalcemia**: Excess calcium intake, such as in the milk-alkali syndrome (nephrocalcinosis and renal stones caused by milk and antacid self-therapy)

1) **hyperparathyroidism** due to primary hyperthyroidism or produced by other tumors .

2) destruction of bone tissue, occurring with primary tumors of bone marrow (e.g., multiple myeloma)

3) **vitamin D–related disorders**, including vitamin D intoxication, sarcoidosis(MQ activate a vit D precursor).

4) **renal failure**, which causes retention of phosphate, leading to secondary hyperparathyroidism

- Metastatic calcification may occur widely throughout the body but principally affects the interstitial tissues of the gastric mucosa, kidneys, lungs, systemic arteries, and pulmonary veins.

Pigments:

- They are colored substances,.

Exogenous Pigments (coming from outside).

- Anthracosis (Carbon accumulation) .
- Tattooing.

Endogenous Pigments. (synthesized within the body itself)

Lipofuscin

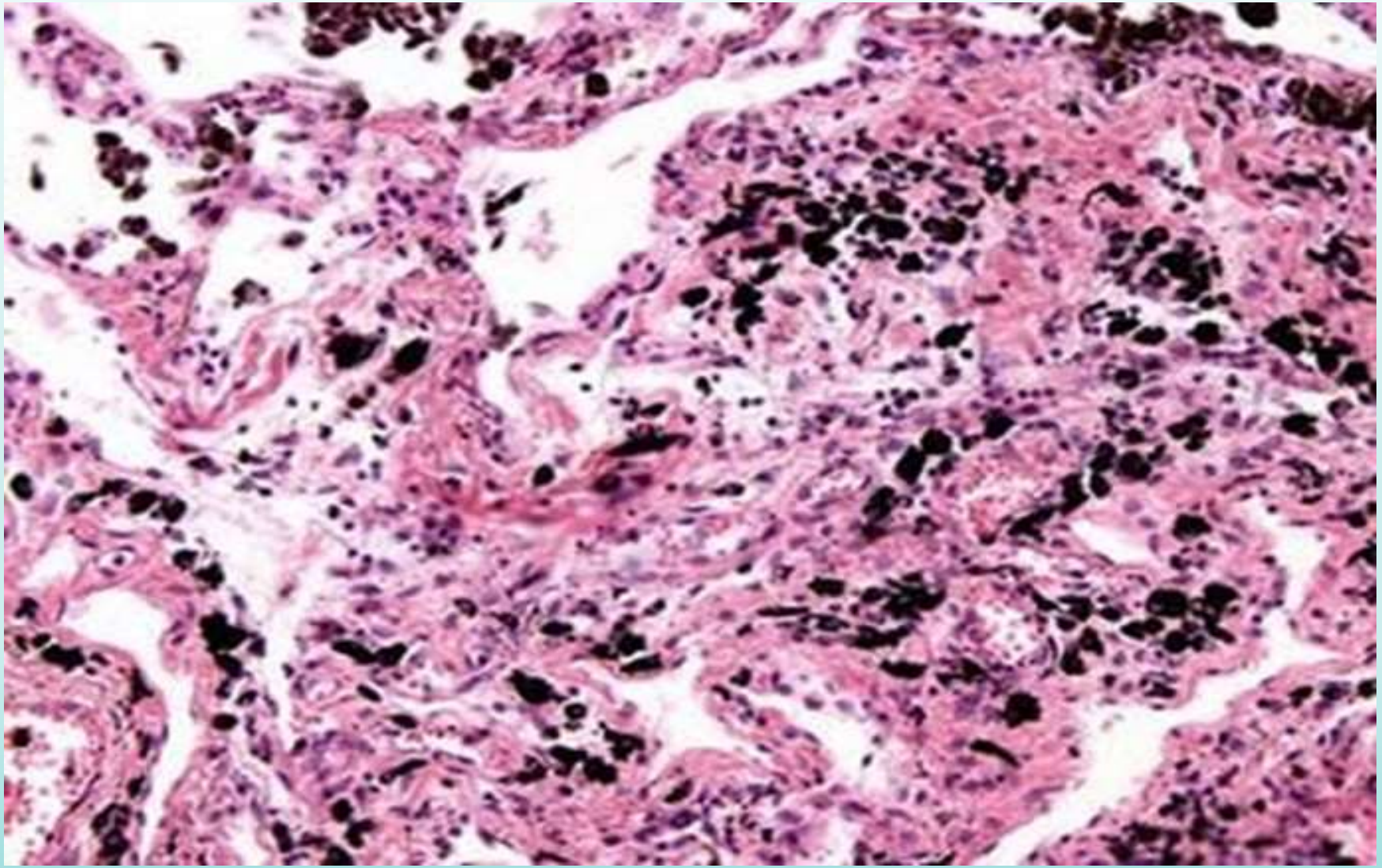
Melanin

hemosiderin

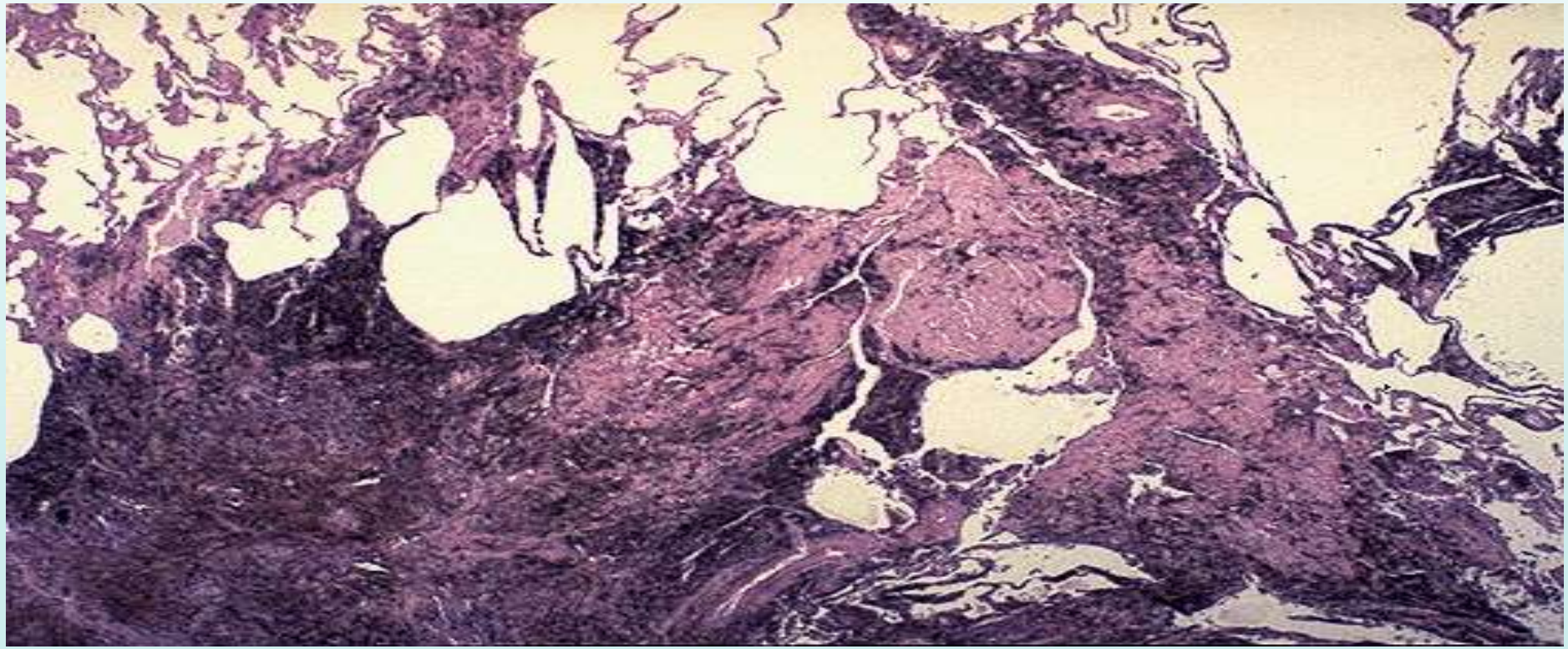
Exogenous Pigments.

- **Anthracosis (Carbon Accumulation)** : accumulation of carbon particles within the alveolar macrophages & transported to the lymph nodes of the tracheobronchial tree. (appear as **black** discoloration).
- **Tattooing:** is a form of localized, exogenous pigmentation of the skin. The pigments inoculated are phagocytosed by dermal macrophages.

Coal workers pneumoconiosis

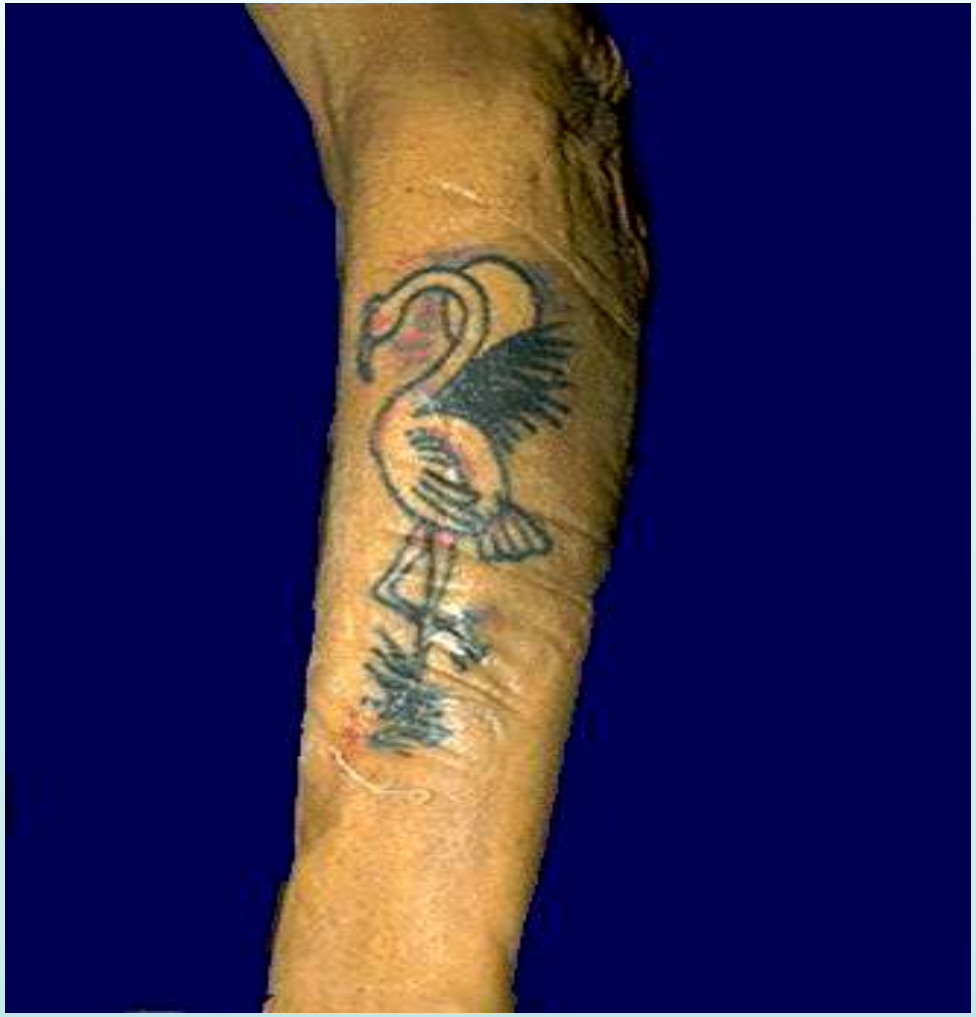


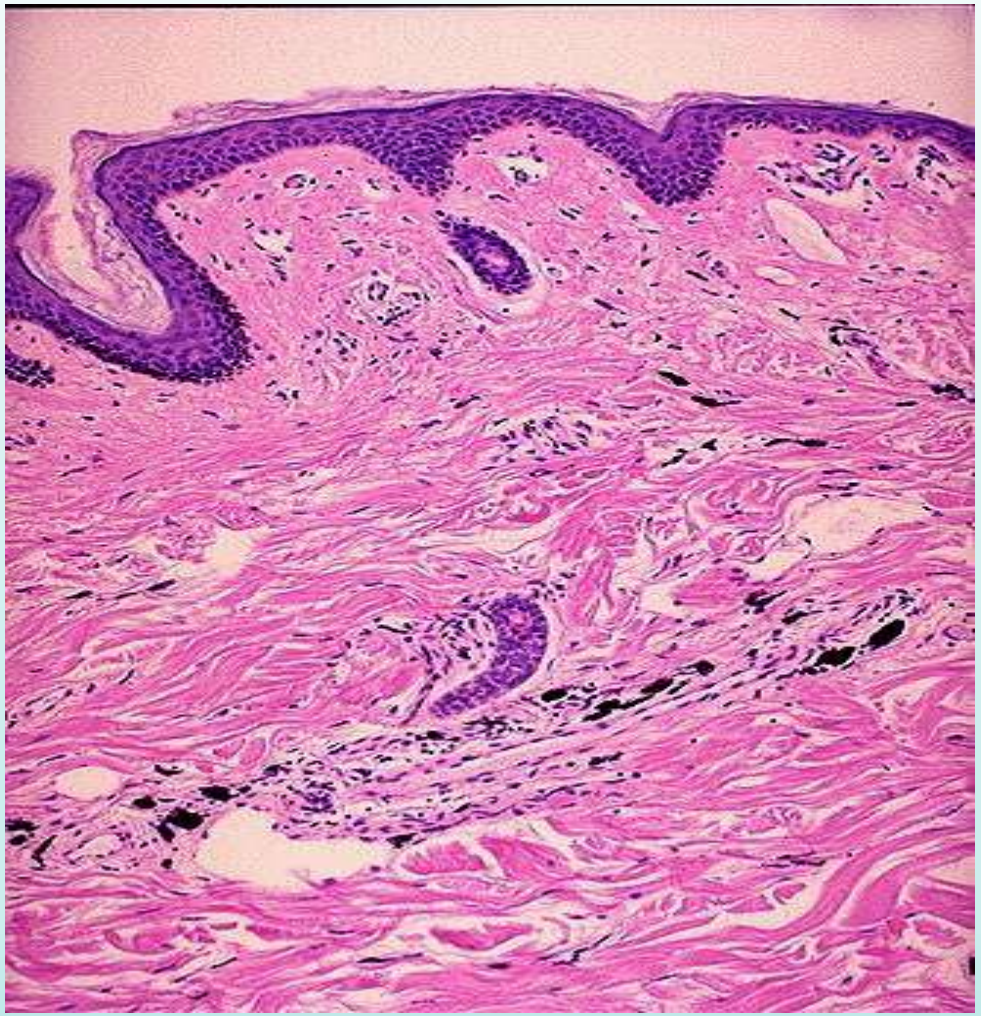
Lung: coal worker’s pneumoconiosis



Anthracotic pigment ordinarily is not fibrogenic, but in massive amounts (as in "black lung disease" in coal miners) a fibrogenic response can be elicited to produce excessive collagenous fibrosis impregnated with the black pigment.

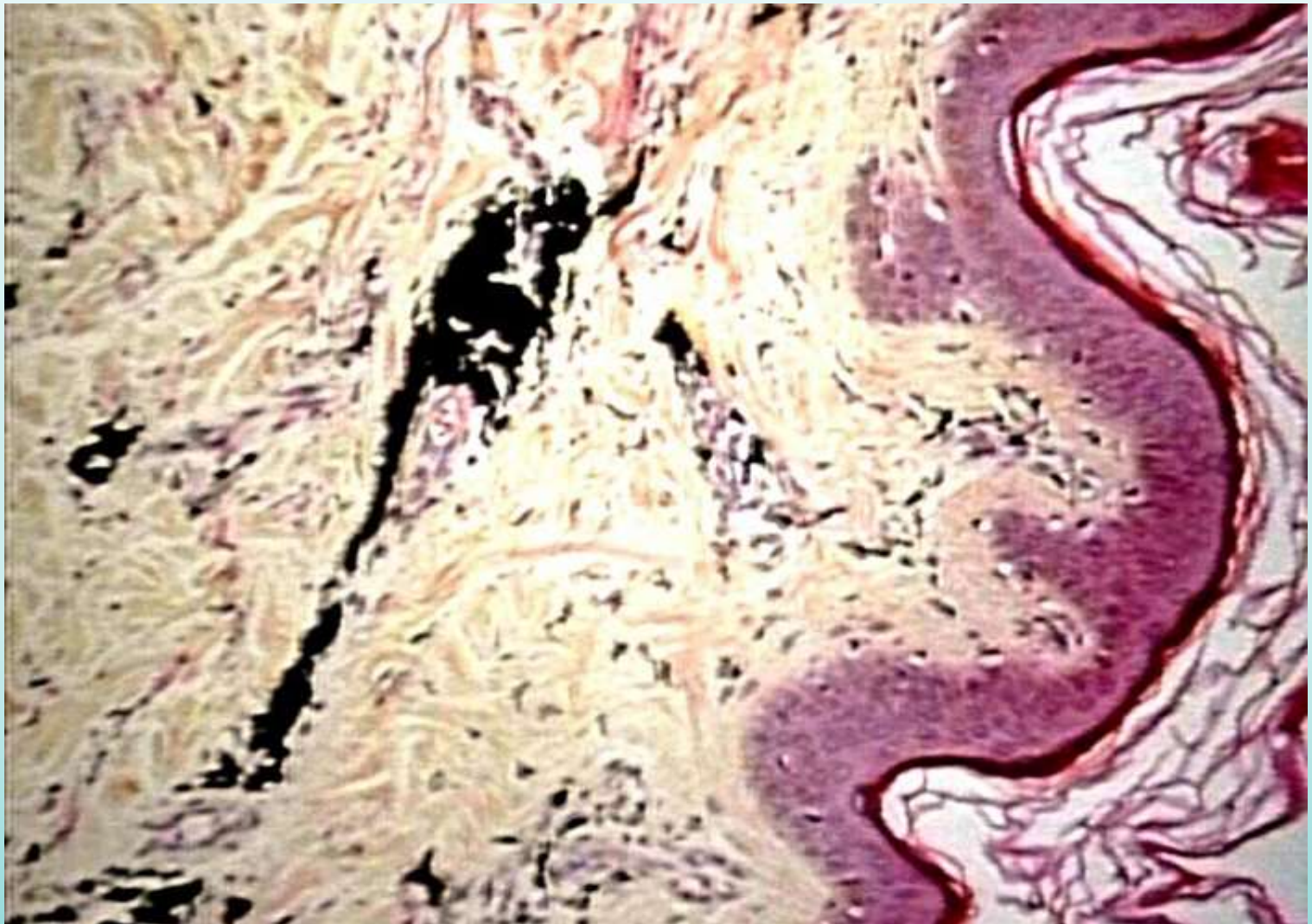
Skin tattoo





Lt. Here is a tattoo. The pigment in tattoos is transferred to the dermis with a needle. Rt. This is the microscopic appearance of tattoo pigment (black) in the dermis.

Tattooing:
Pigments reside in dermal macrophages

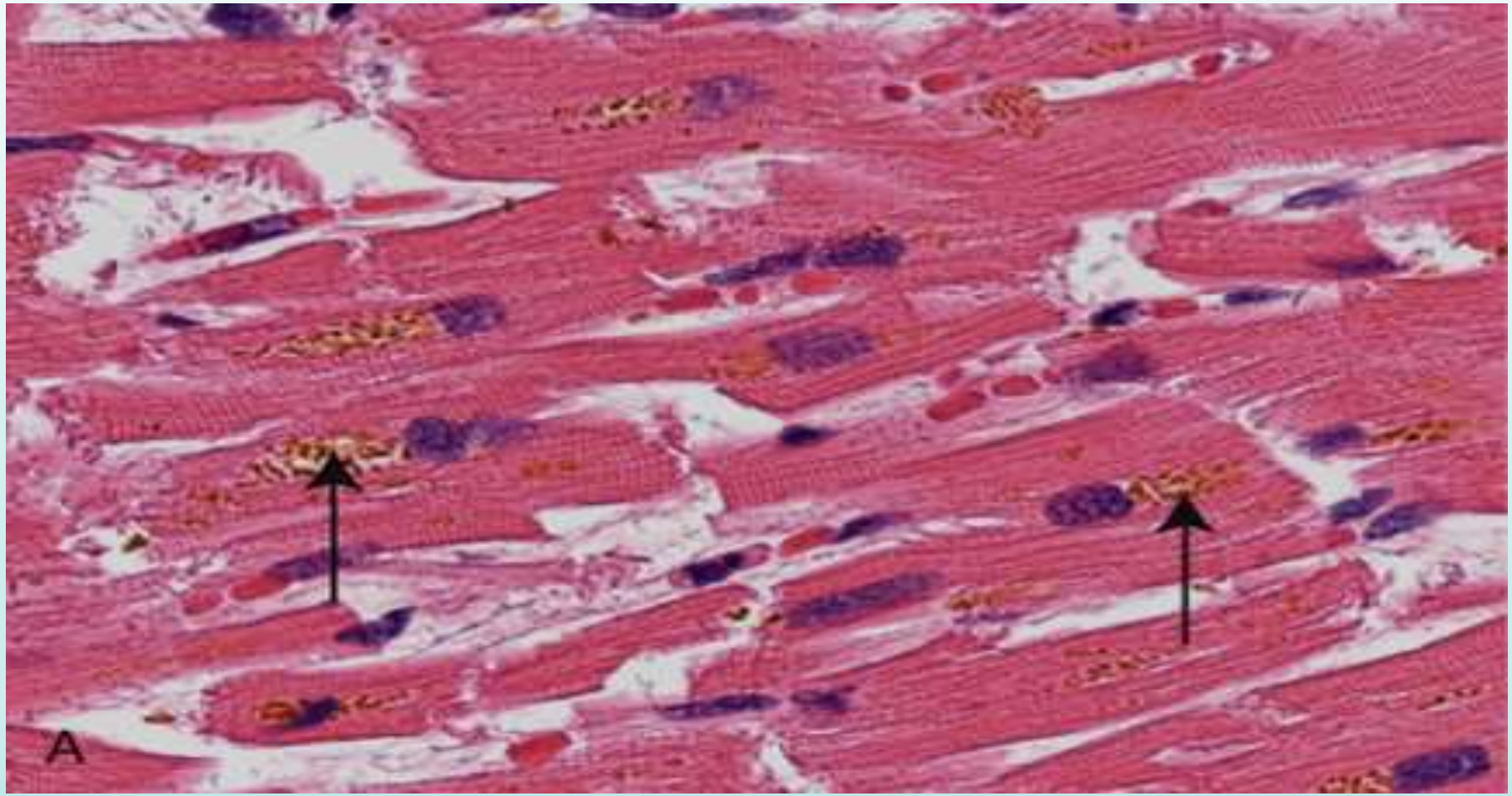


Endogenous Pigments.

Lipofuscin:

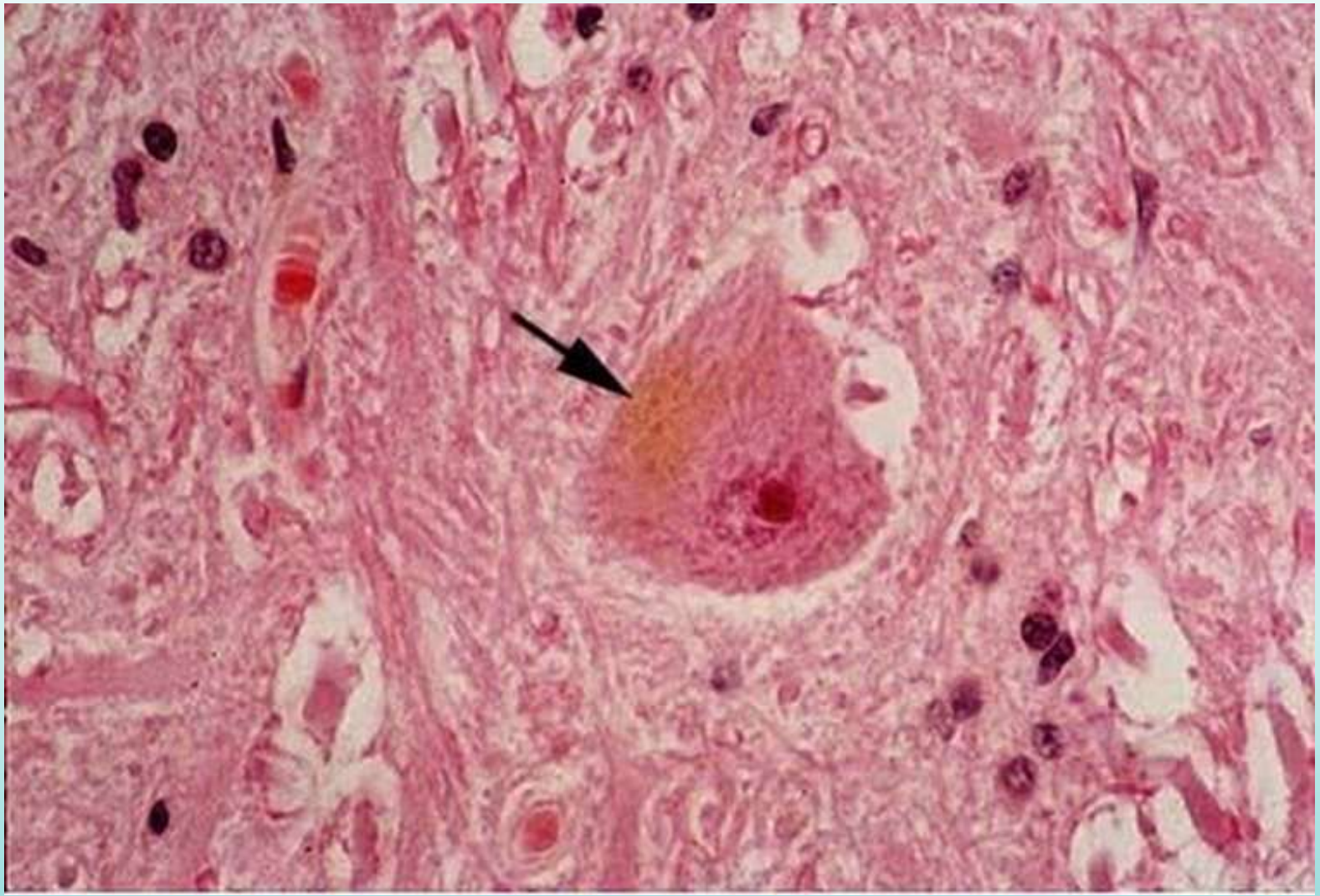
- composed of polymers of lipids and phospholipids complexed with protein,
- Lipofuscin is NOT injurious to the cell or its functions.
- Its important sign of free radical injury and lipid peroxidation.
- **MIC.** it appears as a yellow-brown, finely granular intracytoplasmic, often perinuclear pigment.
- Typically seen in the liver and heart of **aging patients** or patients with severe malnutrition and cancer cachexia.
- Combination of lipofuscin accumulation and atrophy of organ is called brown atrophy.
-

Lipofuscin granules in a cardiac myocytes



Brownish-yellow granular intracellular material (deposits indicated by arrows).

Neuronal lipofuscin



Melanin:

- is an endogenous, non-hemoglobin-derived, brown-black pigment.
- formed when the enzyme tyrosinase catalyzes the oxidation of tyrosine to dihydroxyphenylalanine in melanocytes in skin and various organs.
- melanocyte that found in the epidermis act as endogenous screen against harmful UV radiation.
- Excess of melanin can be seen in **malignant melanoma.**

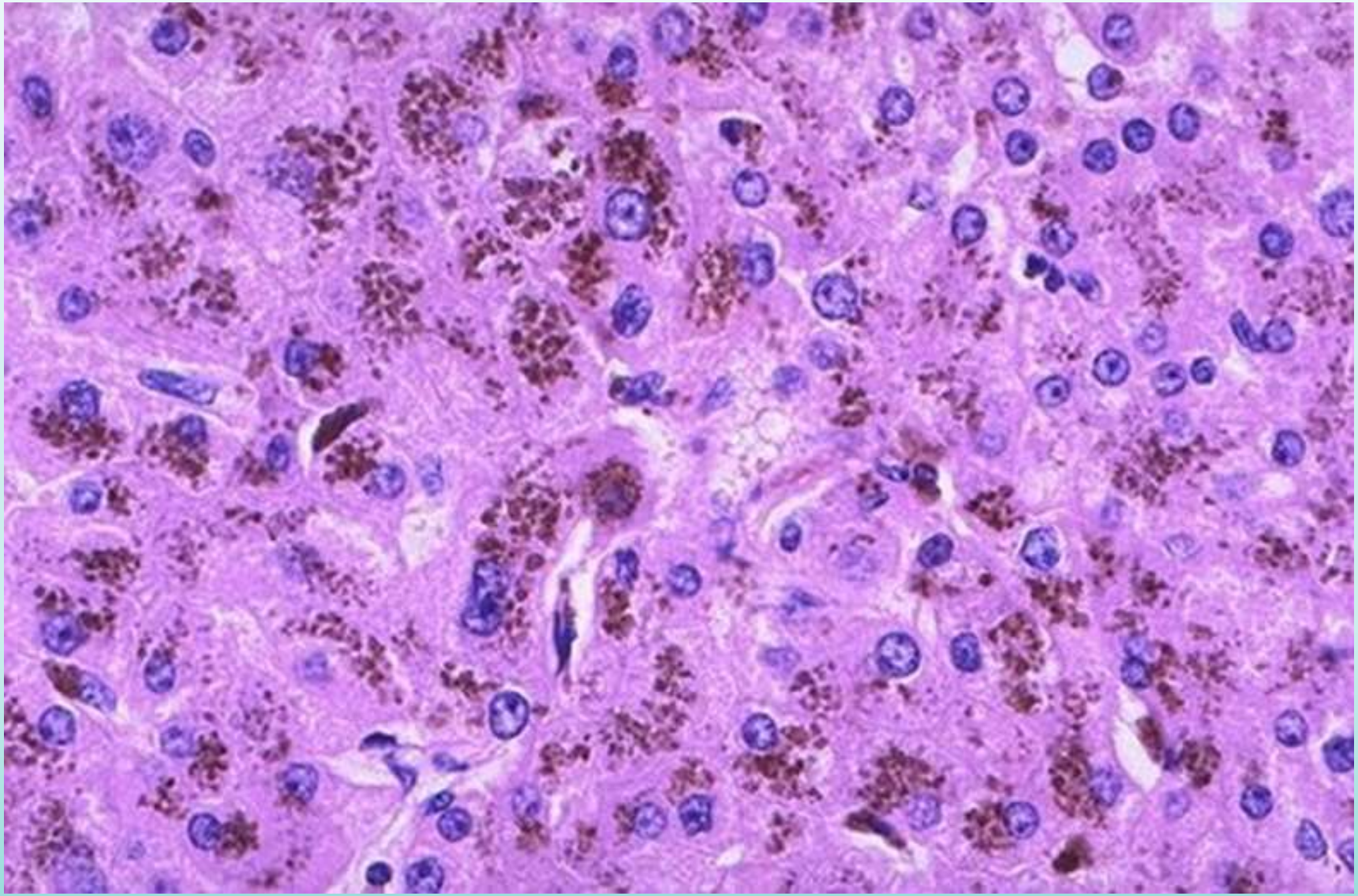
Hemosiderin:

- is a hemoglobin-derived, golden yellow-to brown, granular pigment(iron containing pigment)
- Hemosidrin is representing **aggregation of ferritin**
- Iron can be identified in the tissue by Prussian blue reaction,
- Excesses of iron cause hemosiderin to accumulate within cells, either as a **localized** process or as a **systemic** iron overload.

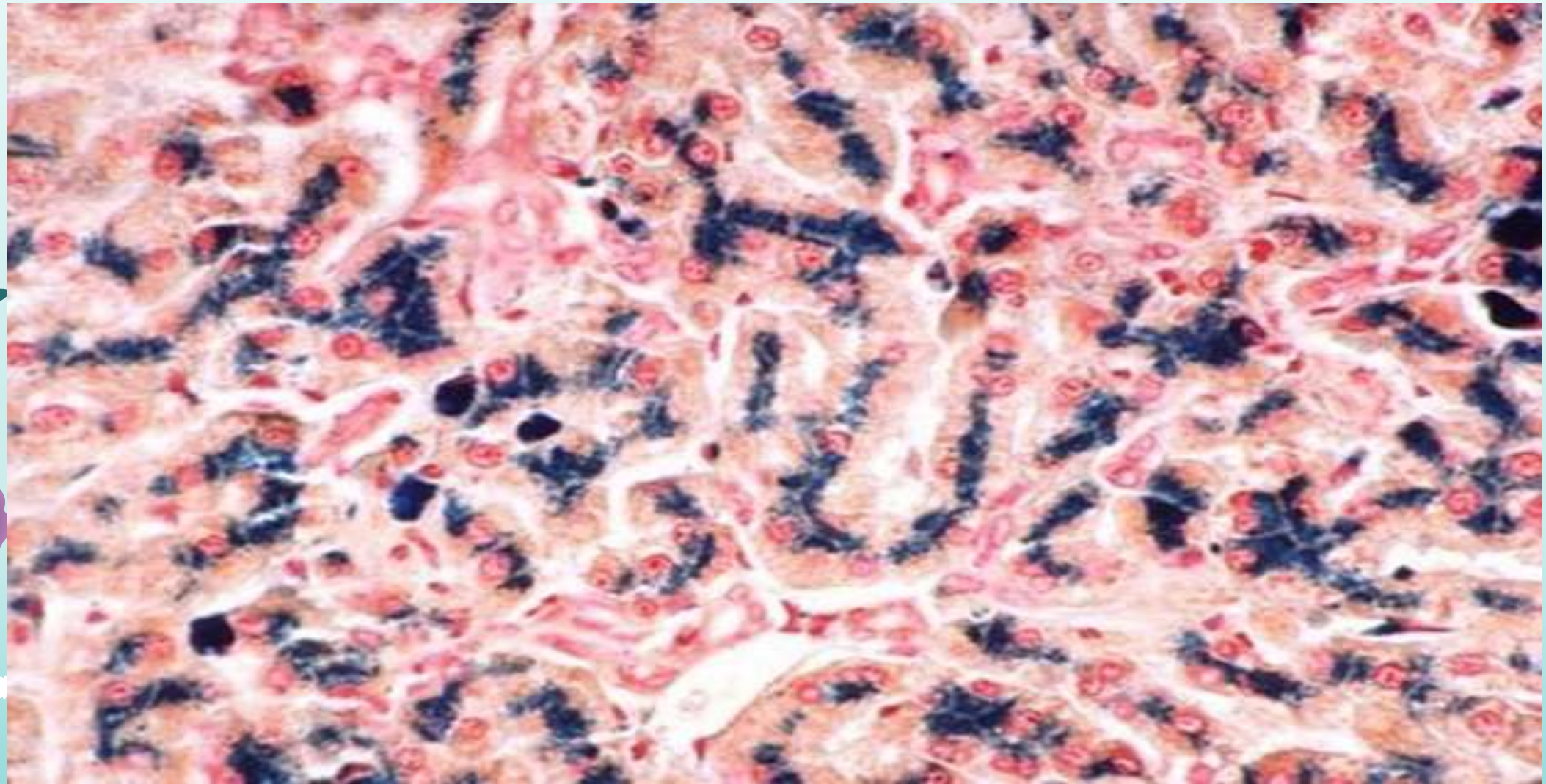
Local excesses of iron:

- The best example of localized hemosiderosis is the common bruise, (color changes in the bruises are due to deposition of hemosidrin in the macrophages)
- .

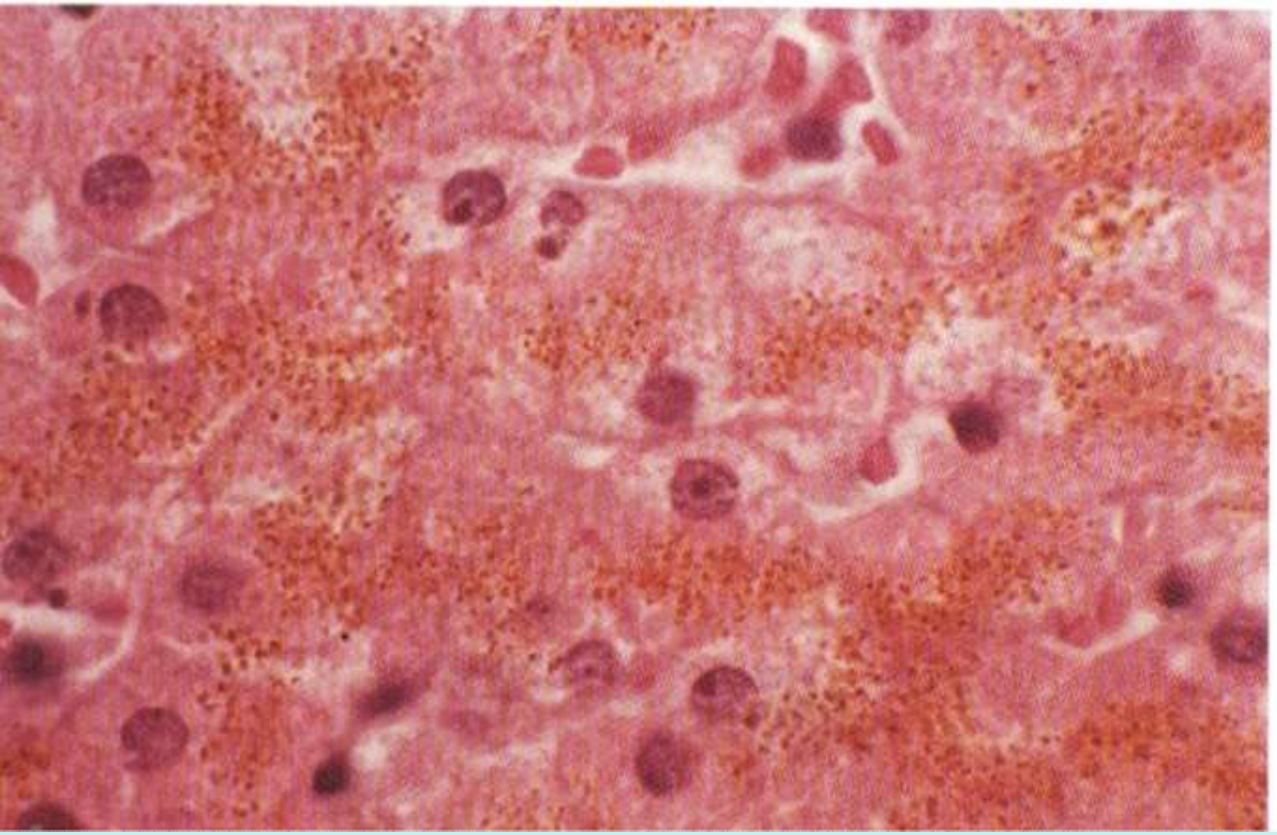
The hepatocytes and Kupffer cells here are full of granular brown deposits of hemosiderin from accumulation of excess iron in the liver.

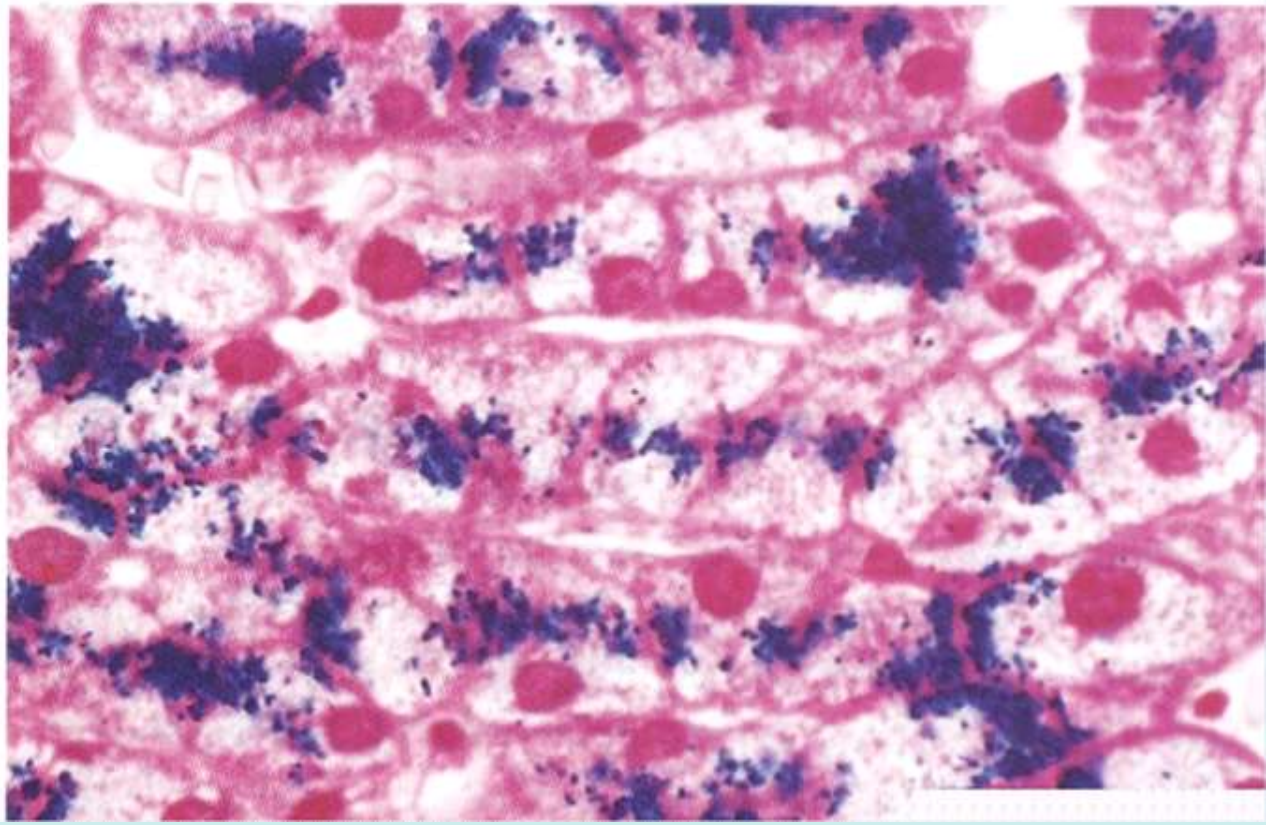


A **Prussian blue iron stain** demonstrates the blue granules of hemosiderin in hepatocytes and Kupffer cells.



Hemosiderin granules liver cells





Rt: H&E stained section showing hemosiderin as yellow-brown finely granular pigment within hepatocytes.

Lt.: same section stained with an iron stain (Prussian blue); the hemosiderin granules are deep blue.

systemic overload of iron:

hemosiderin is deposited in many organs and tissues, a condition called hemosiderosis:

(1) increased absorption of dietary iron,

(2) impaired use of iron,

(3 hemolytic anemias,

(4) transfusions because the transfused red cells constitute an exogenous load of iron.

- Hemosidrin is found at first in the mononuclear phagocytes of the liver, bone marrow, spleen, & lymph nodes.
- With progressive accumulation of hemosidrin, parenchymal cells throughout the body (mainly liver, pancreas, heart & endocrine organs) become bronzed in color.
-

- At the stage of hemosiderosis, iron pigment does not damage the parenchymal cells or impair the function of the organs.
- While at the stage of **hemochromatosis** (more extensive accumulation of iron), associated with tissue injury , scarring and organ dysfunction . e.g. liver fibrosis, heart failure, & diabetes mellitus.
- Bronze color of skin with diabetes mellitus is called **Bronze Diabetes Mellitus**

- **Hemosiderosis** is defined by accumulation of hemosiderin, primarily within tissue **macrophage**s, **without** associated tissue or **organ damage.**
- **Hemochromatosis** is **more extensive** accumulation of hemosiderin, often within **parenchymal cells**, with accompanying tissue damage, scarring, and organ dysfunction.
- This condition occurs in both hereditary (primary) and secondary forms.

•Amyloidosis

- is a disorder characterized by the extracellular deposits of abnormal proteinaceous material (misfolded proteins) that aggregate to form insoluble fibrils (which are soluble in their normal folded configuration).
- is a condition associated with a number of inherited and inflammatory disorders

pathogenesis

- Amyloidosis results from abnormal folding of proteins,
- which become insoluble, aggregate, and deposit as fibrils in extracellular tissues

Amyloidosis: physical nature

By EM :

- amyloid is composed mainly of continuous,
- nonbranching fibrils
- Insoluble , linear, rigid
- measuring 7.5 to 10 nanometers in width.

Chemical nature of Amyloidosis:

- Most common three forms of amyloid proteins are,
- AL (amyloid light chain), derived from plasma cell & contains immunoglobulin light chain.
- AA (amyloid associated) amyloid fibril, associated with chronic inflammatory diseases, not related to immunoglobulins, & synthesized in the liver.
- Aβ is found in the **cerebral lesion** of Alzheimer disease.

- **Transthyretin (TTR)** is a normal serum protein that binds and transports thyroxine. mutant forms of TTR are deposited in a group of genetically determined disorders referred to as **familial amyloid polyneuropathies**. Normal TTR is also deposited in the heart of aged individuals **(senile systemic amyloidosis).**
- **β2 microglobulin**, found in patients on long-term **hemodialysis**.

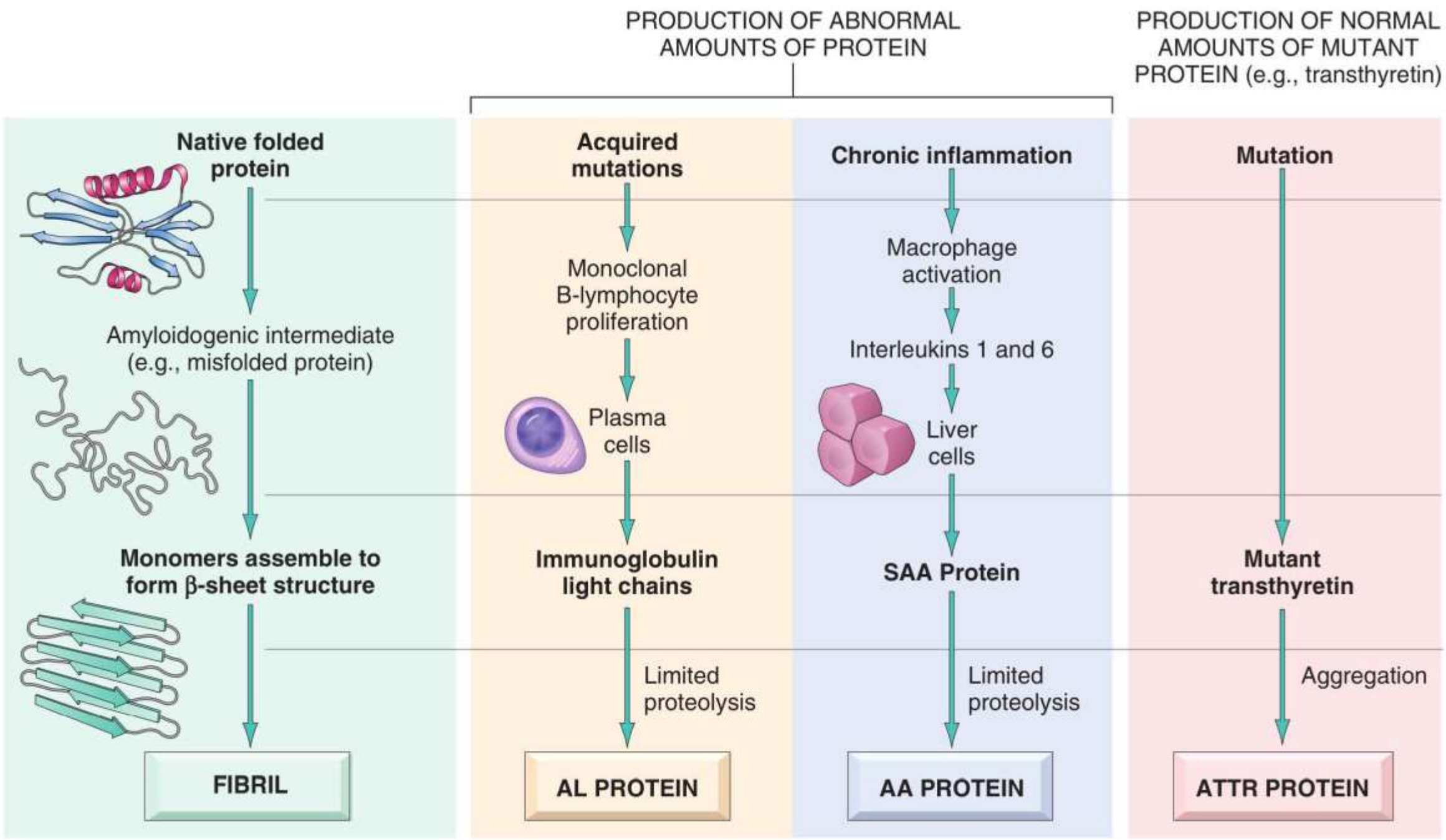
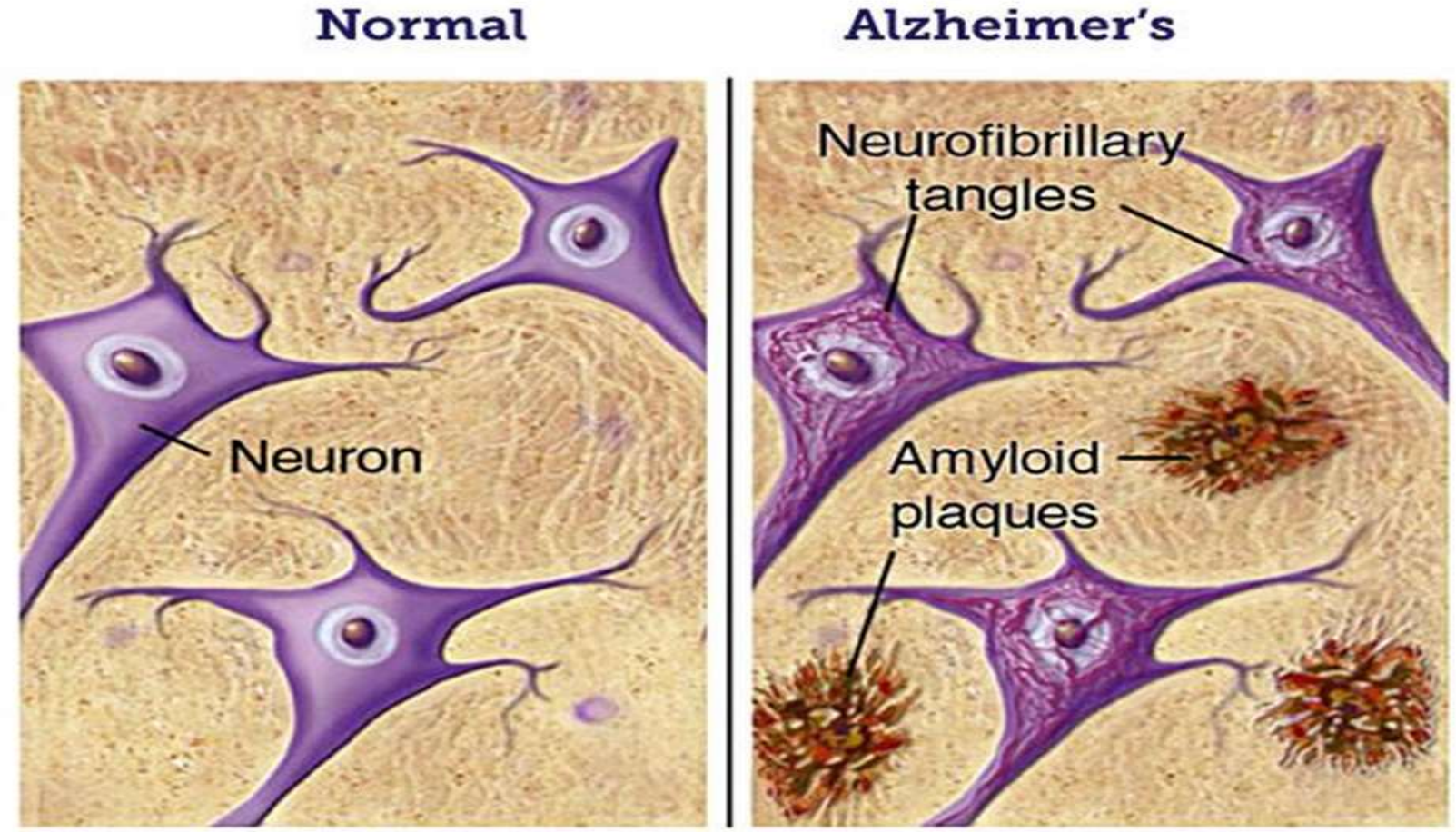


Figure 6-45 Pathogenesis of amyloidosis, showing the proposed mechanisms underlying deposition of the major forms of amyloid fibrils.

Classification of Amyloidosis

- Localized Amyloidosis. which include
- 1- **Senile Amyloidosis**. in the Alzheimer disease.
- 2- **Endocrine amyloid**. Localized deposits of amyloid in certain endocrine tumors (medullary carcinoma of the thyroid)
- 3- **Isolated atrial Amyloidosis.**

Normal vs. Alzheimer's Diseased Brain



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Cure in Mind. Cure in Sight.

Systemic (Generalized) amyloidosis , which include

Primary Amyloidosis (immunocyte associated Amyloidosis).

- This is the most common type.
- e.g.amyloidosis associated with multiple myeloma (malignant neoplasm of plasma cells).

Major amyloid protein in this type is **AL** protein

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- **Secondary Amyloidosis(Reactive Systemic Amyloidosis)**.
- 1-associated with many **Chronic Inflammatory Conditions** like,Tuberculosis, bronchiectasis, & chronic osteomyelitis are the common causes.
- **2-Autoimmune diseases** e.g. rheumatoid arthritis
- 3- associated with **tumors** like :Renal cell carcinoma, Hodgkin lymphoma
- Major amyloid protein in this type is AA.

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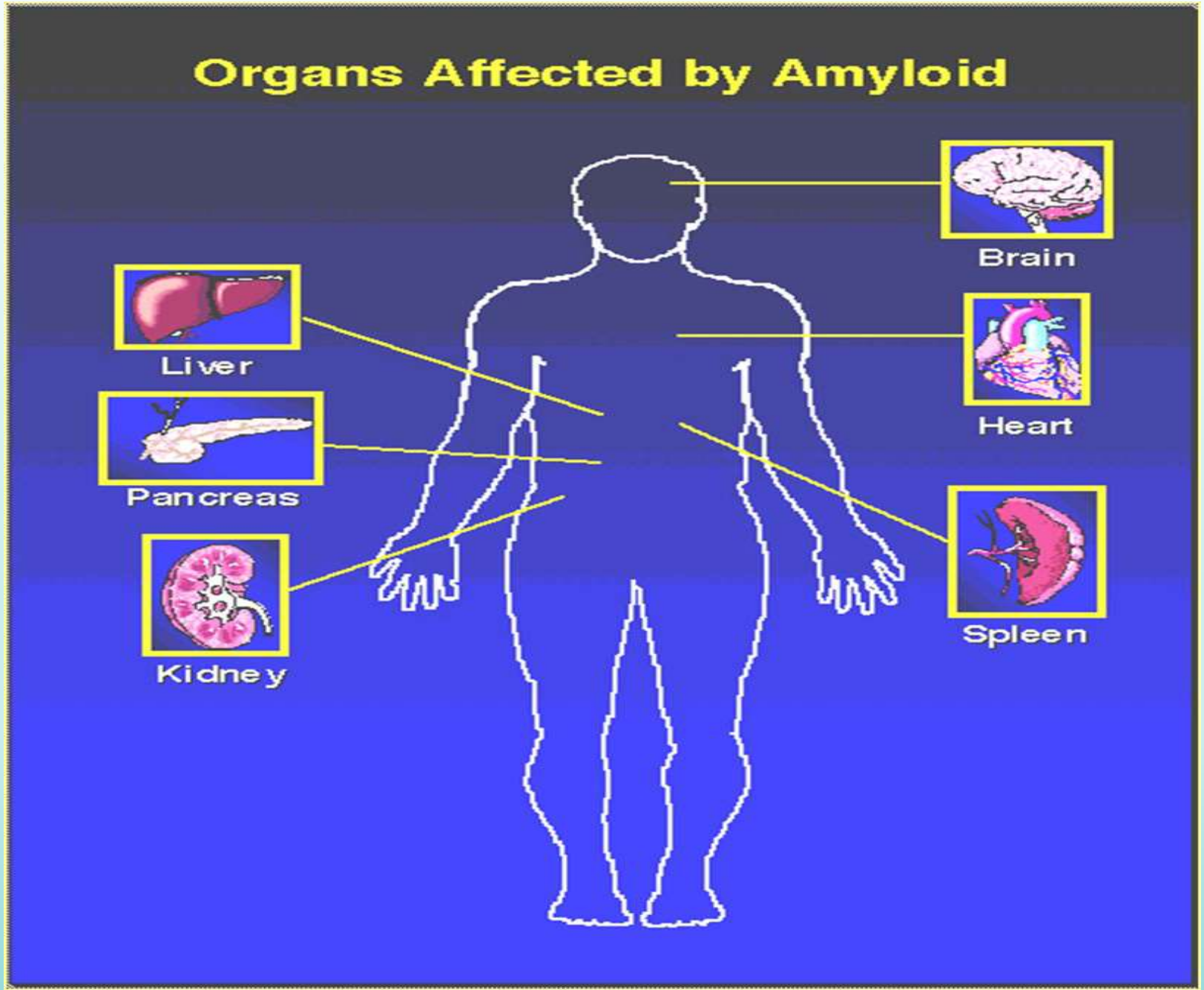
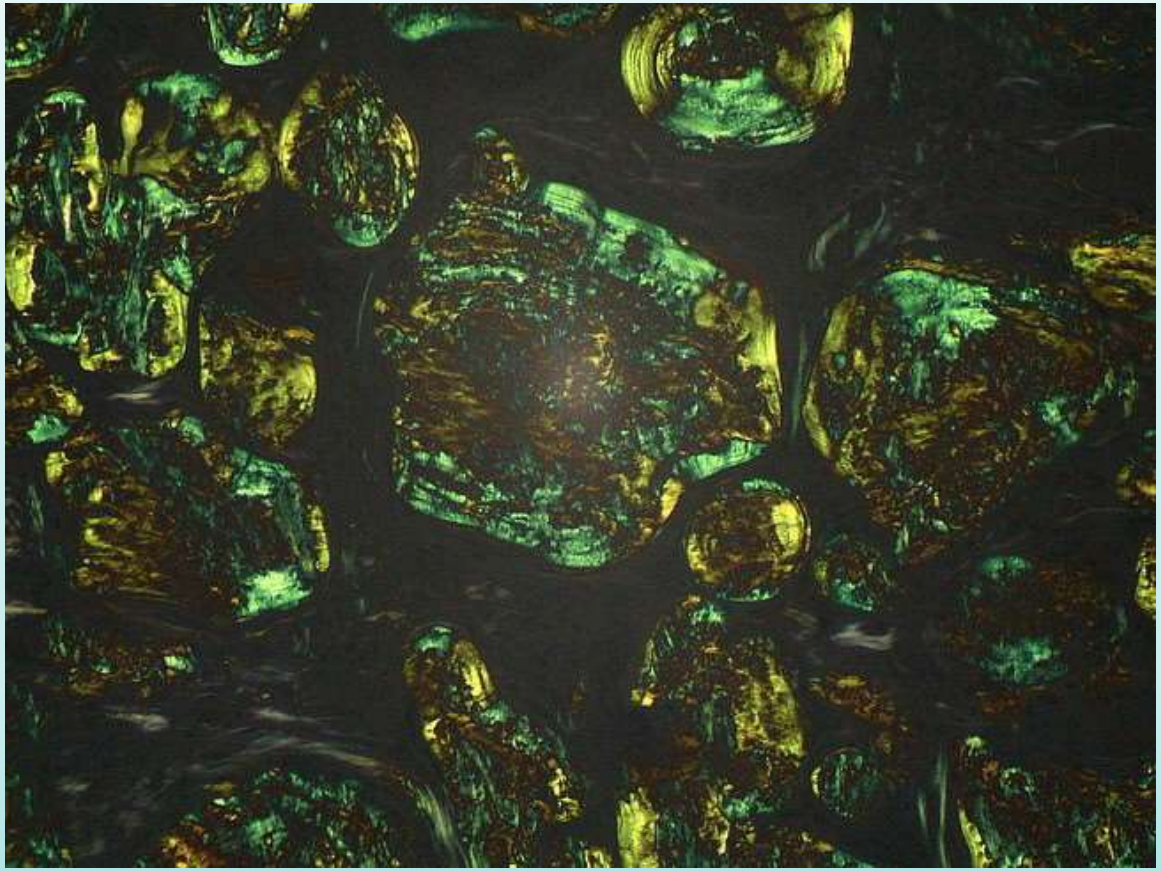
- Morphology of Amyloidosis:
- There are no distinctive patterns of organ distribution of amyloid deposits, e.g. in secondary amyloidosis: liver, spleen, LN, adrenal & thyroid are commonly affected,
- while in primary amyloidosis is commonly affect the: heart, GIT, respiratory tract, peripheral nerves & skin.


Organs Affected by Amyloid
Brain
Liver
Heart
Pancreas
Spleen
Kidney

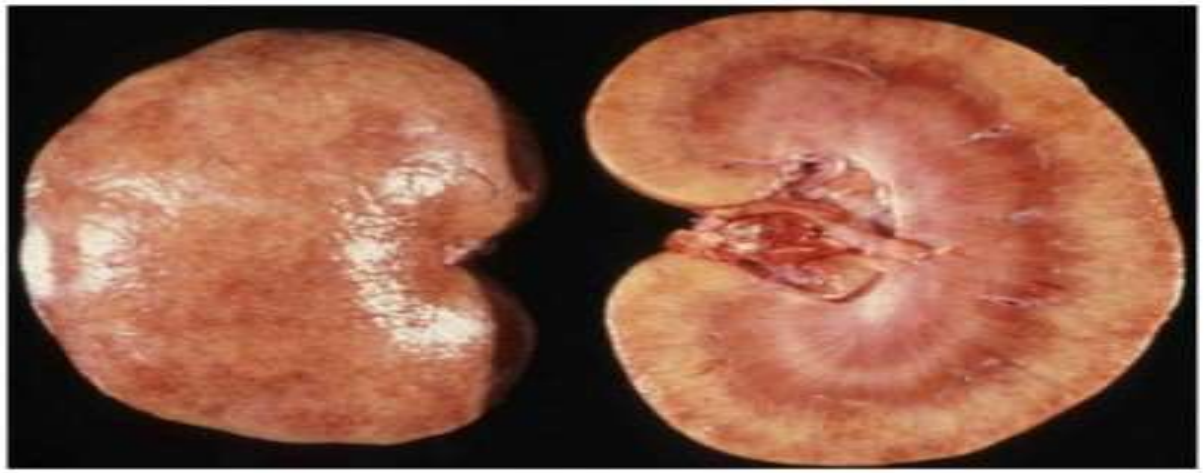
- Accumulation of larger amounts of amyloid will result in enlargement of organs, & waxy firm consistency.
- • **MIC.** , the deposition of amyloid is always begins between the cells, often closely adjacent to basement membranes & with more deposits will result in destruction of the cells.
- The histologic diagnosis of amyloid is based almost entirely on its staining characteristics, which include
- • Congo red: under light microscope show **pink or red color of amyloid** deposits, while under polarized microscope, it appears as apple green •
- **Immunohistochemistry staining**: can demonstrate the AA, AL,
- **Electron microscope**: reveals amorphous non oriented thin fibrils.
- • .



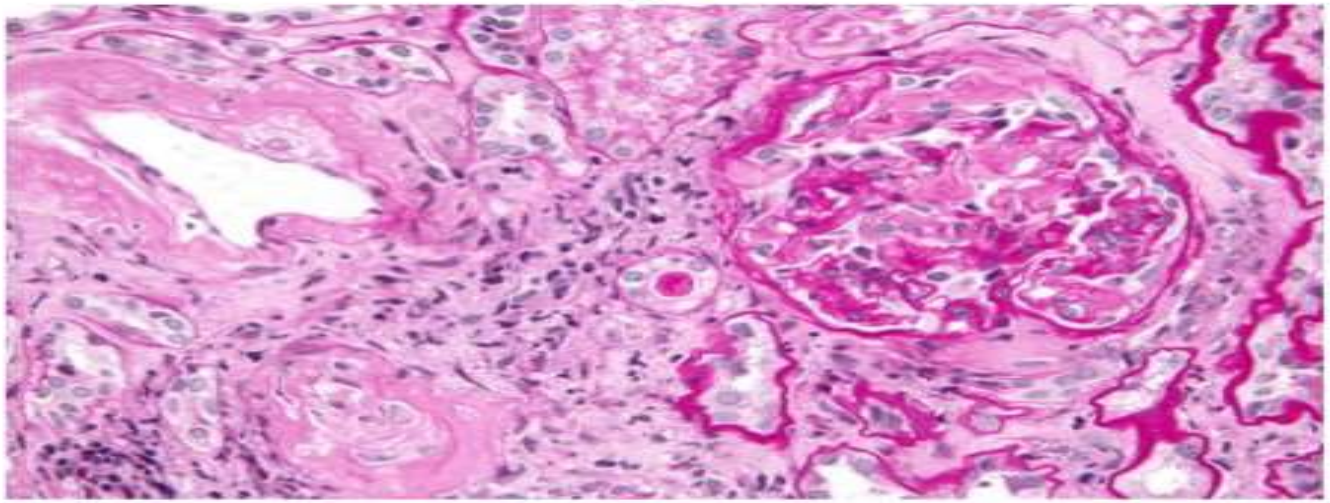
Kidney:

- Amyloidosis of the kidney is the most common & most serious involvement in the disease.
- **Gross**. Either unchanged in the size or abnormally become enlarged, pale, gray, firm; & in advanced cases, the kidney may be reduced in their size.
- **Mic**. Amyloid principally deposited in the glomeruli & peritubular tissue

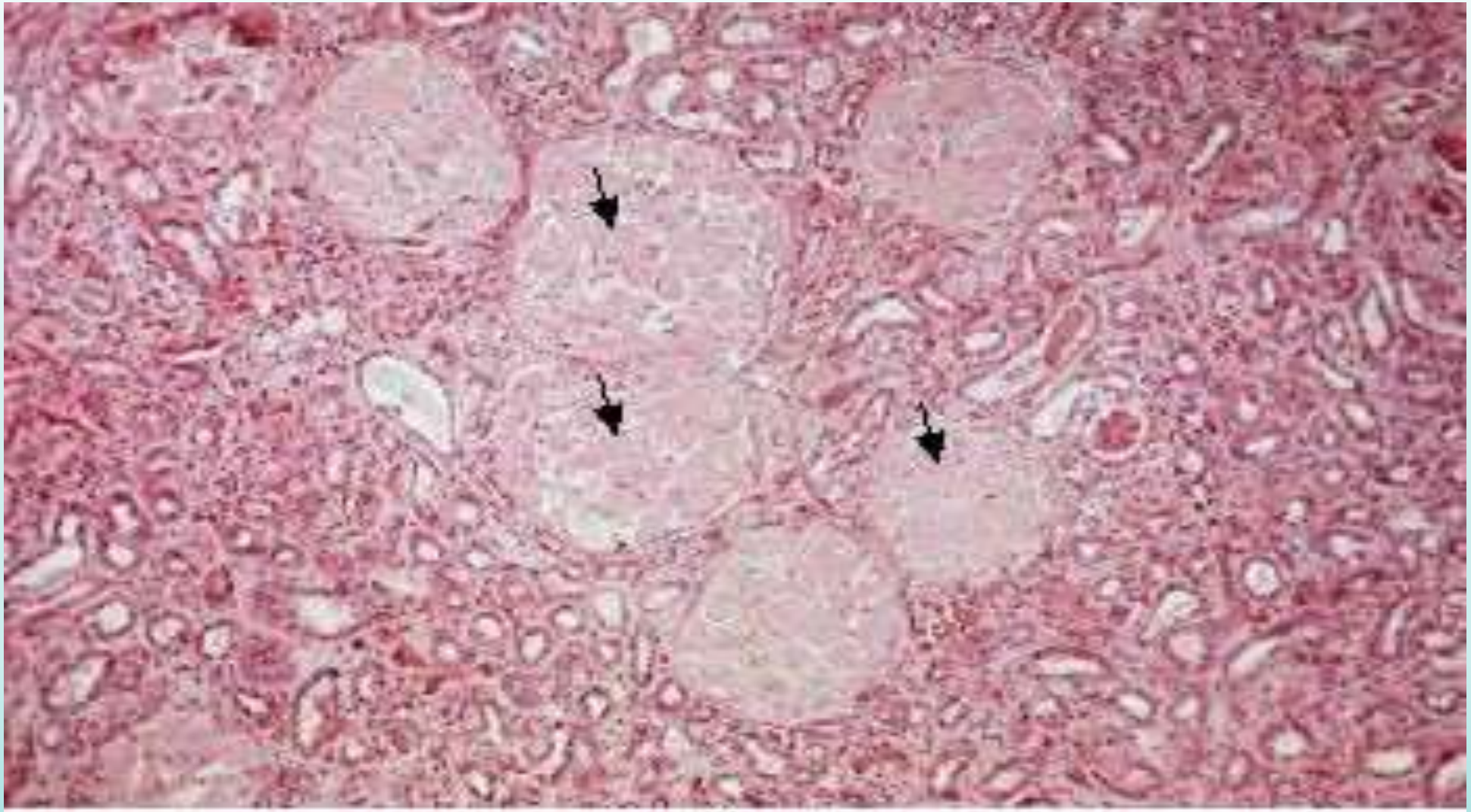
Macroscopic



Microscopic



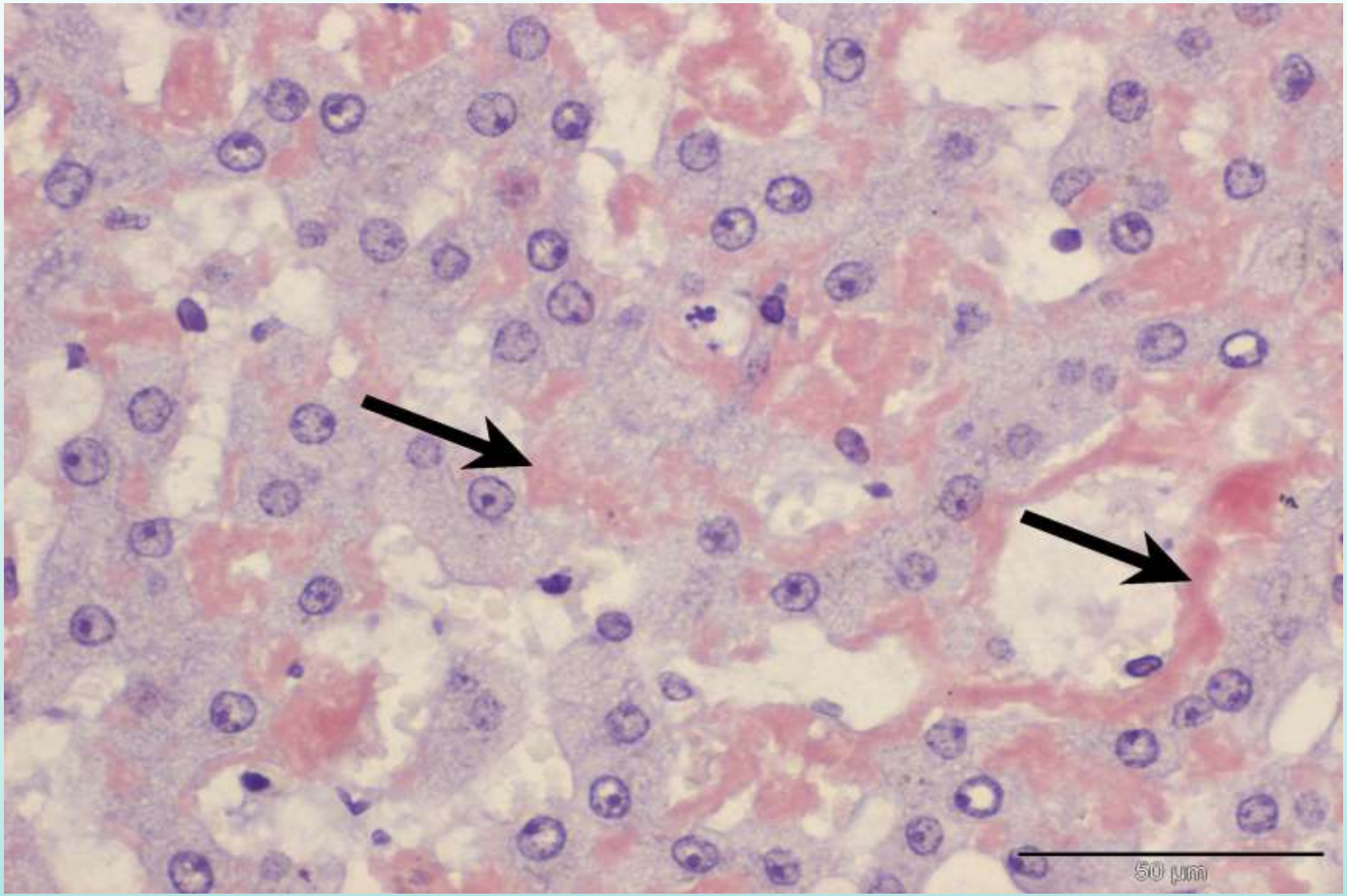
Glomeruli: -Begins in mesangium extending into capillary walls glomerulus is flooded by confluent masses or interlacing ribbons of amyloid. • Homogenous amorphous eosinophilic deposits: H&E



Histology of the kidney in amyloidosis. Deposits are present in the vessels of the renal glomeruli.

Liver:

- Gross. Massive enlargement of liver (up to 9000 grams), pale, gray, & waxy in consistency.
- Mic. Amyloids first appear in the space of Disse, and then extend to involve the hepatocytes & sinusoids


50 µm

•THANK YOU