Cellular Pathology

Intracellular Accumulations and Pigments

Overview

- In this lecture you will learn about:
  - The types and significance of intracellular inclusions.
  - Mechanisms of accumulation

Intracellular Inclusions

- **Normal cellular** constituents in excess:
  - Water
  - Fat
  - Protein
  - Carbohydrate
- **Abnormal substance**
  - Product of abnormal metabolism
  - Pigment
  - Infectious particles

Cells may be

- Producing the abnormal substance

  or

- Storing products of pathologic processes occurring elsewhere in the body

3 Types Of Processes Result In Intracellular Accumulations

1) Normal endogenous substance produced at normal or increased rate, with inadequate rate of metabolism:
   - Hepatic fatty change
   - Plasma cell Russell bodies

2) Normal or abnormal endogenous substance accumulates because it cannot be metabolized or excreted:

(a) Storage diseases

Definition: Excess accumulation of complex substrates within lyzosomes as a result of a genetic enzymatic defect in a specific metabolic pathway

1. Glycogen
2. Mucopolysaccharide
3. Sphingolipid

(b) Disorders in protein folding (α-AT def/CF/Alzheimers)

(c) Cholesterol

3) Abnormal exogenous substance accumulates due to inability of cell to metabolize the substance or to transport it to other sites

(a) Inorganic particulate material:

- Carbon,
- silica,
- metals

(b) Infectious inclusions:

- Obligate intracellular bacteria
- Viruses
- Prions

Significance Of Intracellular Inclusions

- Is the process reversible?
- Is the substance toxic?
- Does the substance result in cellular swelling, occupying a substantial amount of space?
- Should the substance be somewhere else?

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Intracellular Inclusions

- Normal cellular constituents in excess:
  - Water
  - Fat
    - Triglyceride
    - Cholesterol
  - Protein
  - Carbohydrate
- Abnormal substance
  - Mineral
  - Product of abnormal metabolism
- Pigment
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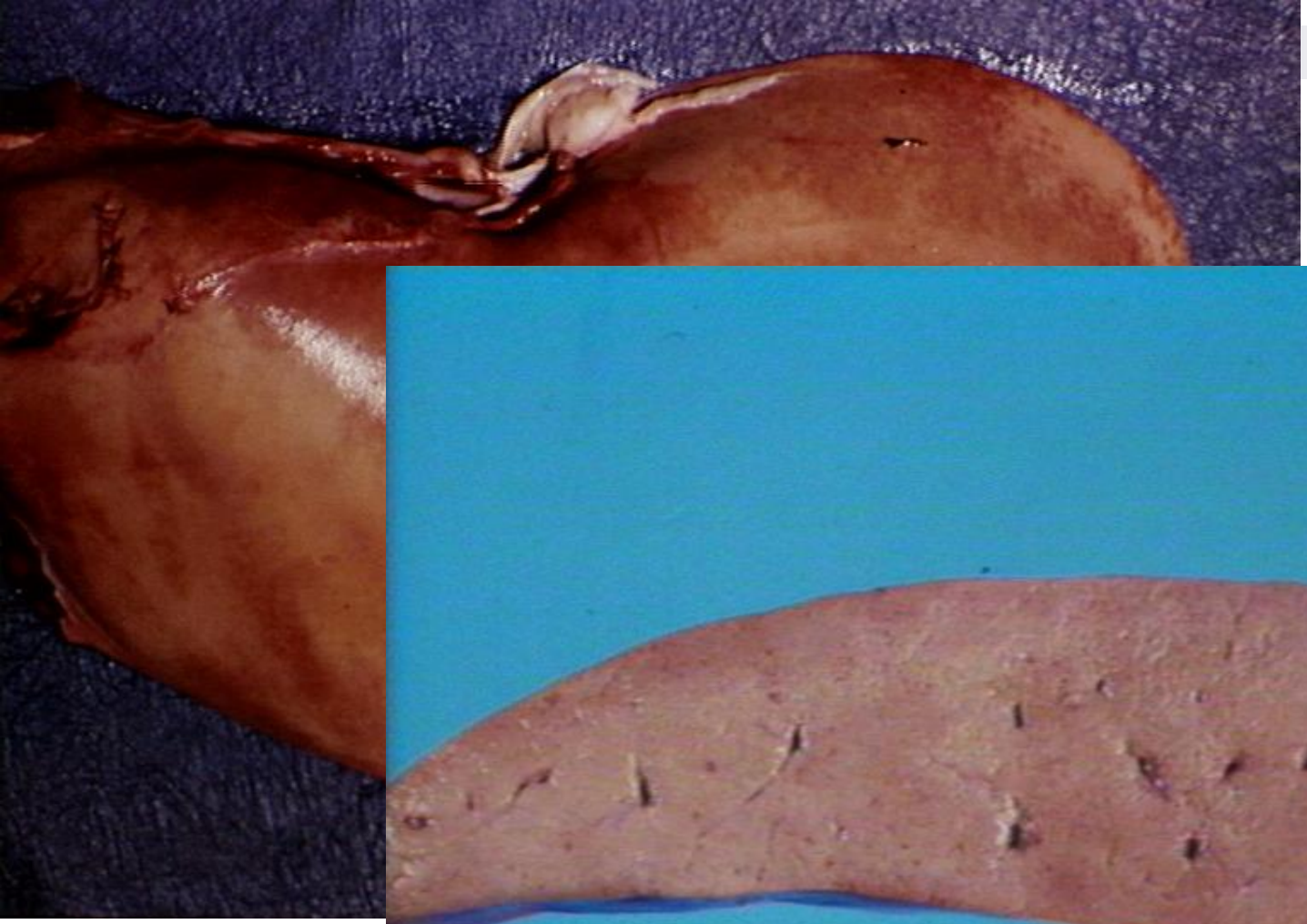
Triglyceride

- Intracellular and extracellular vacuoles
- Liver
  - Alcohol, malnutrition, diabetes, obesity, drugs
- Heart
- Muscle
- Renal cortex



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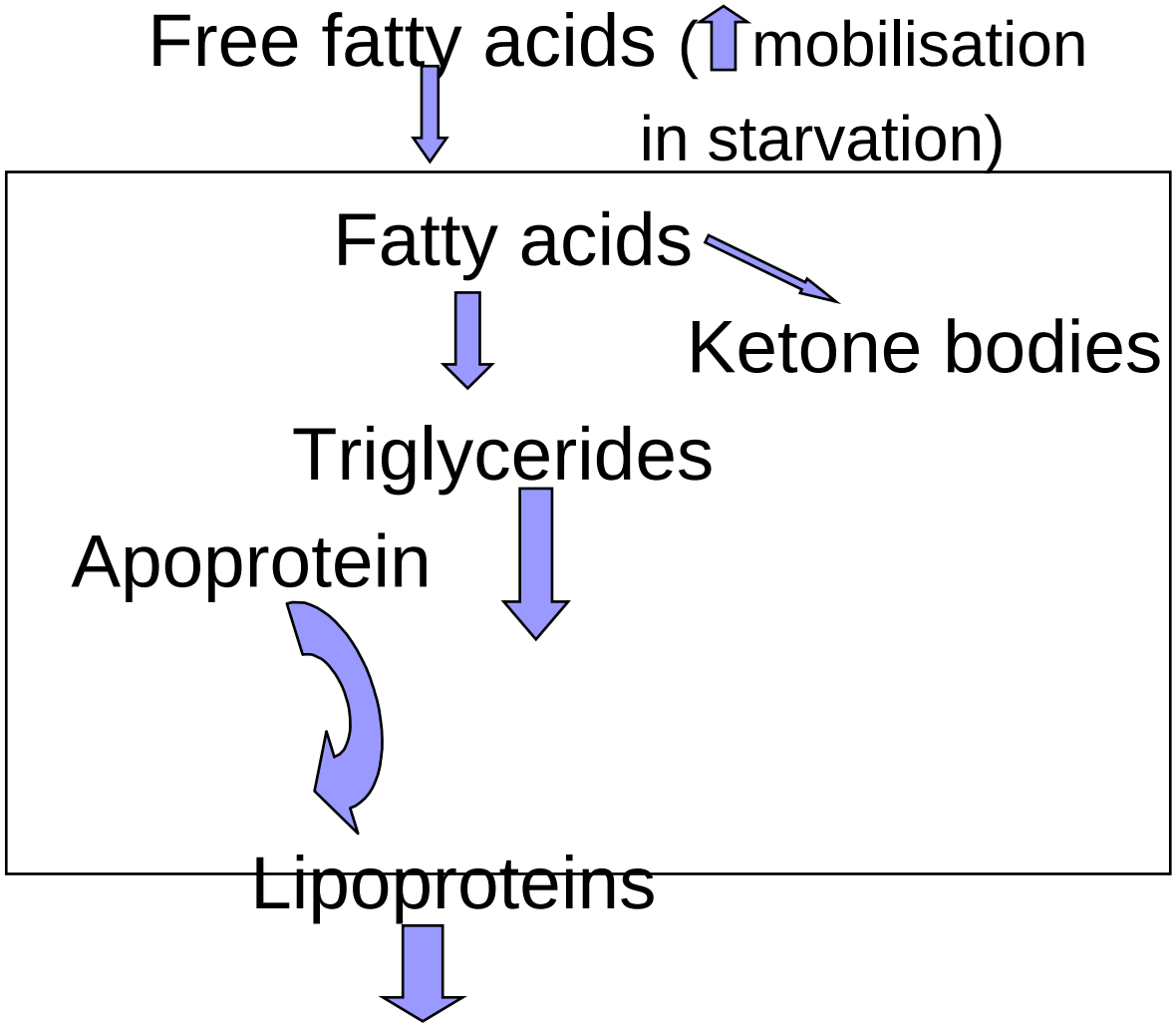
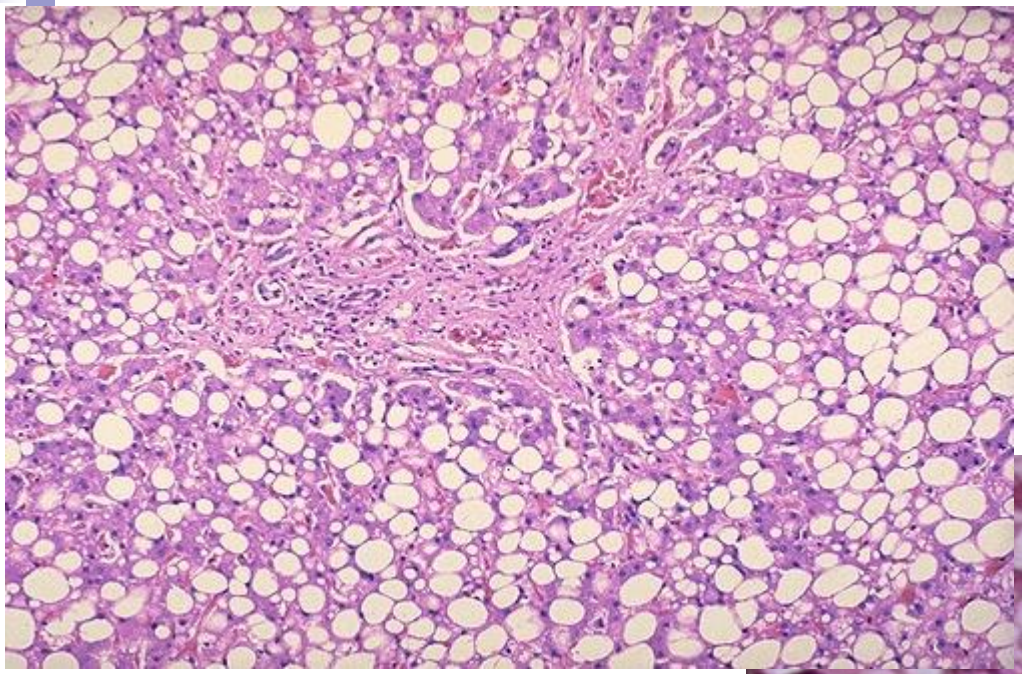
Mechanism of hepatic lipid accumulation

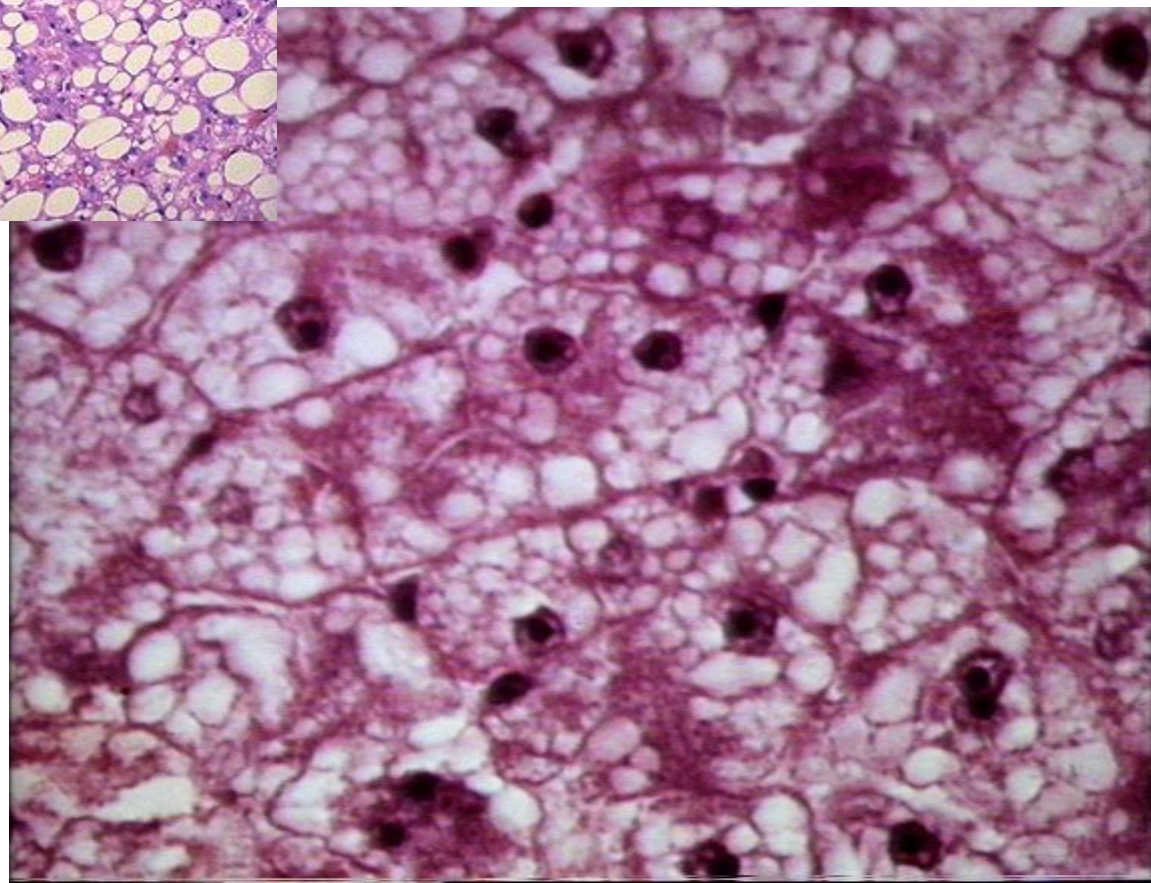


1. Excess entry
2. Decreased oxidation
3. Increased synthesis
4. Increased esterification to TG's
5. Decreased apoprotein synthesis
6. Impaired lipoprotein secretion

Mechanism of fat accumulation

- Ethanol:
  - Impaired assembly and secretion of lipoproteins
  - Increased peripheral fat catabolism
- Starvation: Mobilisation of free fatty acids
- Anoxia: Inhibition of fatty acid oxidation
- Carbon tetrachloride poisoning and protein malnutrition: Decrease synthesis of apoproteins
- Acute fatty liver of pregnancy, Reye's syndrome - rare fatal conditions (Defect in mitochondrial oxidation suspected)

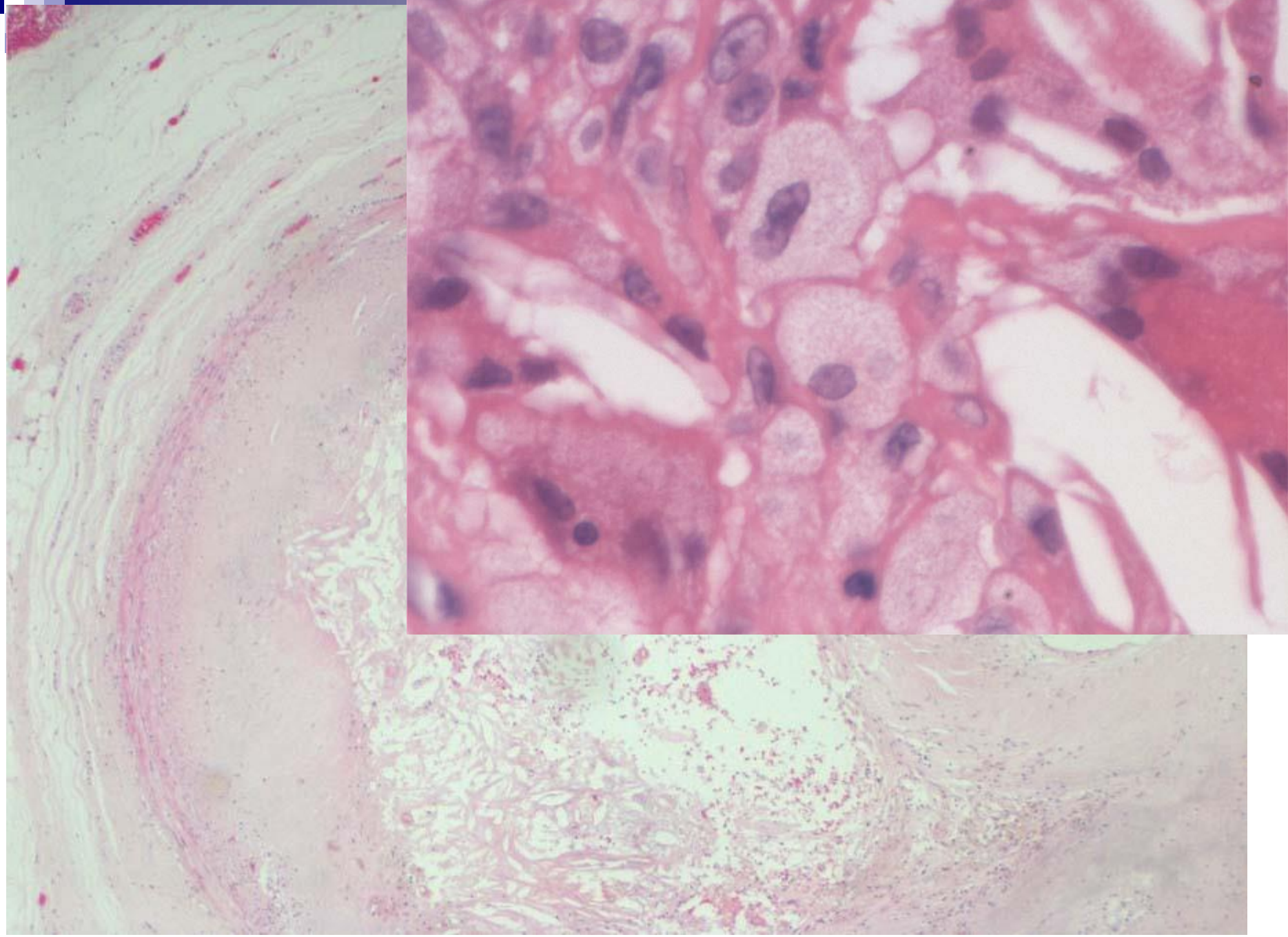




Intracellular accumulations of a variety of materials can occur in response to cellular injury. Here is fatty metamorphosis (fatty change) of the liver in which deranged lipoprotein transport from injury (most often alcoholism) leads to accumulation of lipid in the cytoplasm of hepatocytes.

Cholesterol and cholesterol esters

- Lipid-laden macrophages – ‘Foam cells’
- Also extracellular cholesterol clefts
- Atherosclerosis: Intimal layer of aorta & large arteries
- Hyperlipidaemia: Xanthomas in subcutaneous connective tissue
- Inflammation & necrosis
- Cholesterolosis: Gallbladder



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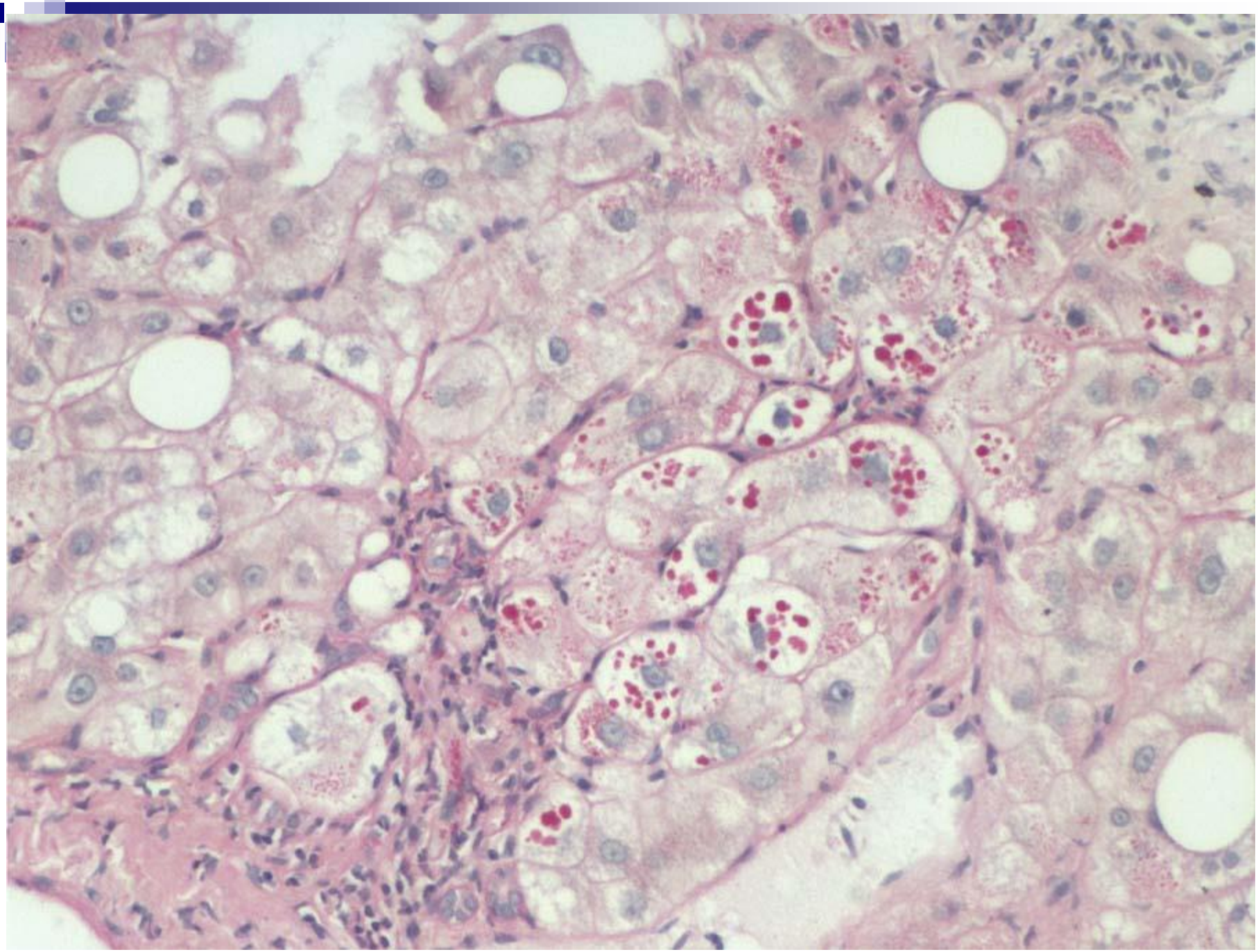
Proteins

- Cytoplasmic eosinophilic droplets
- Reabsorption droplets in proximal renal tubules - proteinuria
- Immunoglobulin in plasma cells (Russell bodies)
- Defective protein folding
  - Alpha-1 Antitrypsin deficiency
  - Neurodegenerative diseases



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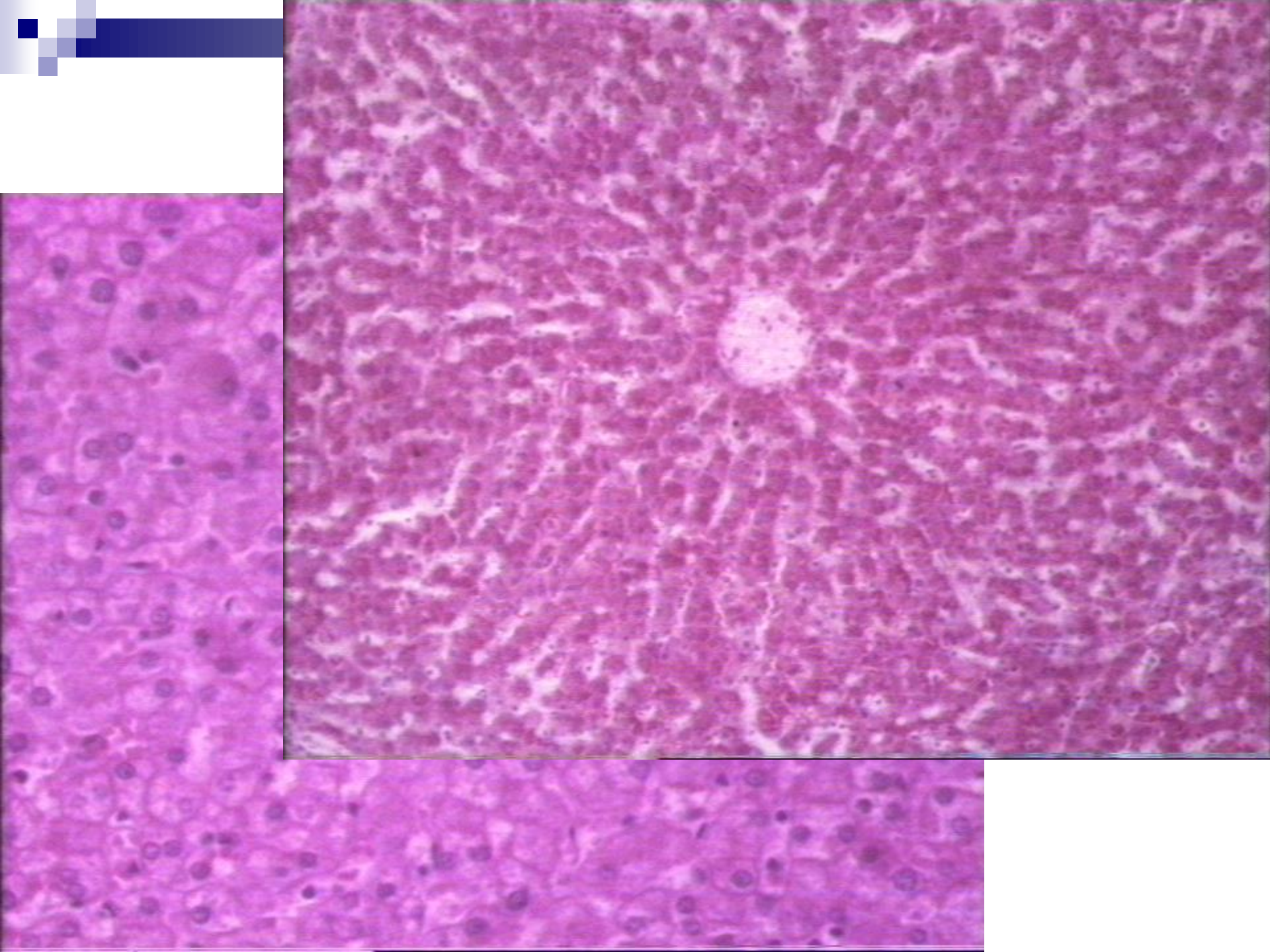
Glycogen

- Clear vacuoles in cytoplasm, PAS positive
- Diabetes mellitus
  - Distal portions of the proximal convoluted tubules
  - Descending loop of Henle
  - Hepatocytes
  - Beta cells of islets of Langerhans
  - Cardiac muscle cells
- Glycogen storage diseases
  - Liver, skeletal muscle, heart, brain

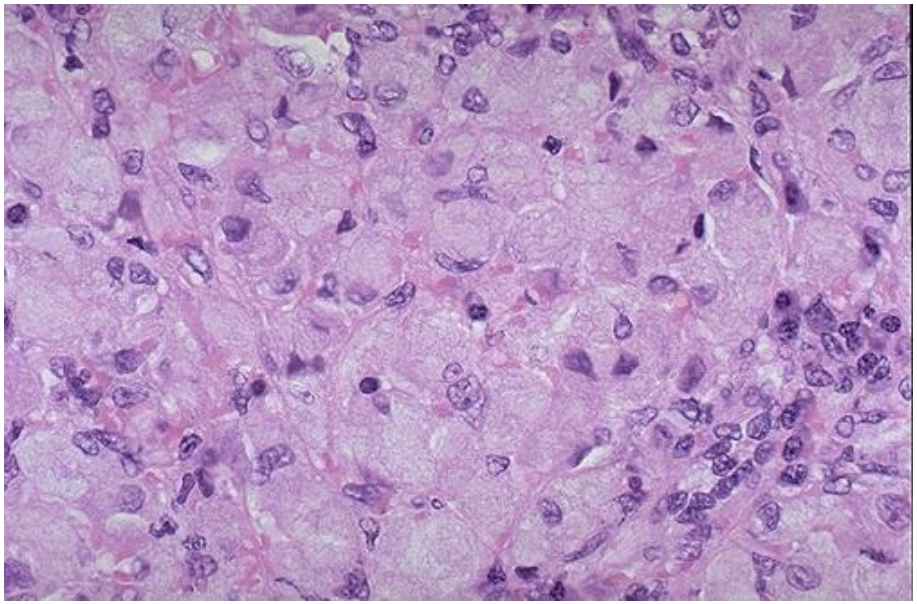


Complex lipids & polysaccharides

- Lysosomal storage diseases
  - Liver, nervous system (brain and retina), reticuloendothelial system (spleen, lymph nodes, bone marrow)
  - Sphingolipidoses
    - sphingomyelins, gangliosides
    - e.g. Tay-sachs, Gaucher, Niemann-Pick
  - Mucopolysaccharidoses
    - e.g. Hurlers, Hunters

Gaucher disease

- Many inherited disorders of metabolism involving enzymes in degradation pathways can lead to accumulation of storage products in cells, as seen here with **Gaucher disease** involving spleen.
- The large pale cells contain an accumulated storage product from lack of the glucocerebrosidase enzyme.



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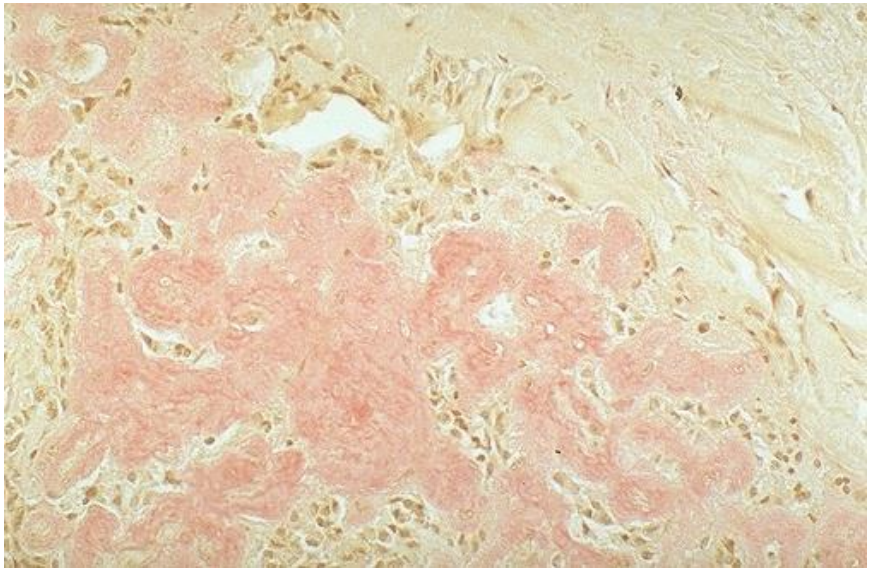
Defective Protein Folding

- Defective transport and secretion
  - Alpha-1 Antitrypsin deficiency
  - Cystic Fibrosis
- Toxicity of abnormal proteins
  - Neurodegenerative diseases (proteinopathies)
    - Alzheimers, Huntingtons, Parkinsons
  - Amyloidosis

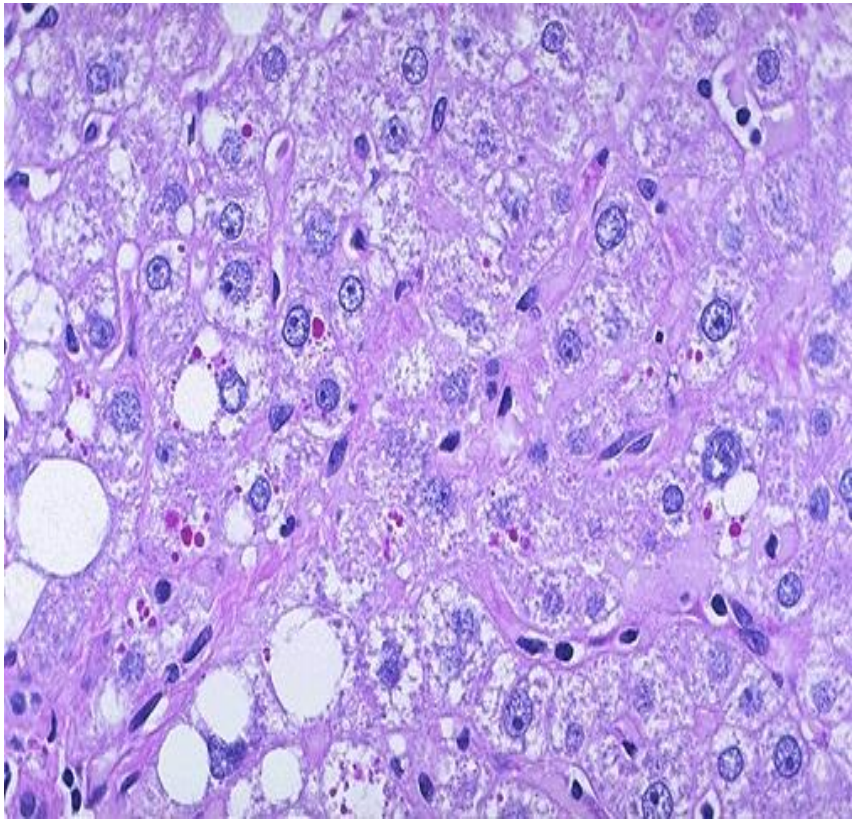
Amyloidosis

- This Congo red stain reveals orange-red deposits of amyloid, which is an abnormal accumulation of breakdown products of proteinaceous material that can collect within cells and tissues.



Alpha 1 anti-trypsin deficiency

- Sometimes cellular injury can lead to accumulation of a specific product.
- Here, the red globules seen in this PAS stained section of liver are accumulations of alpha-1-antitrypsin in a patient with a congenital defect involving cellular metabolism and release of this substance.



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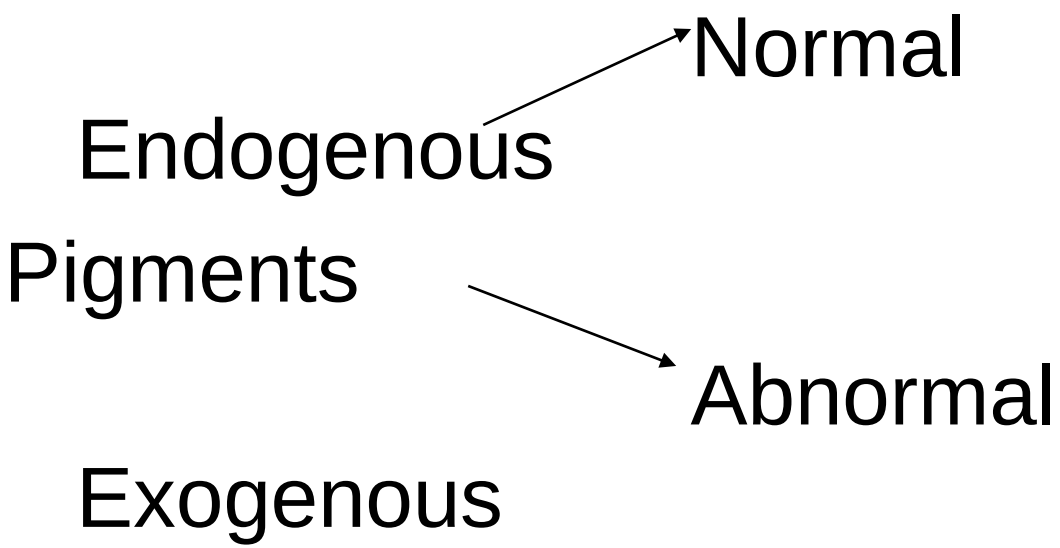
Pigments



Exogenous pigments

- Carbon or coal dust

  inhaled → macrophages in alveoli

  ↓

  lymphatic channels

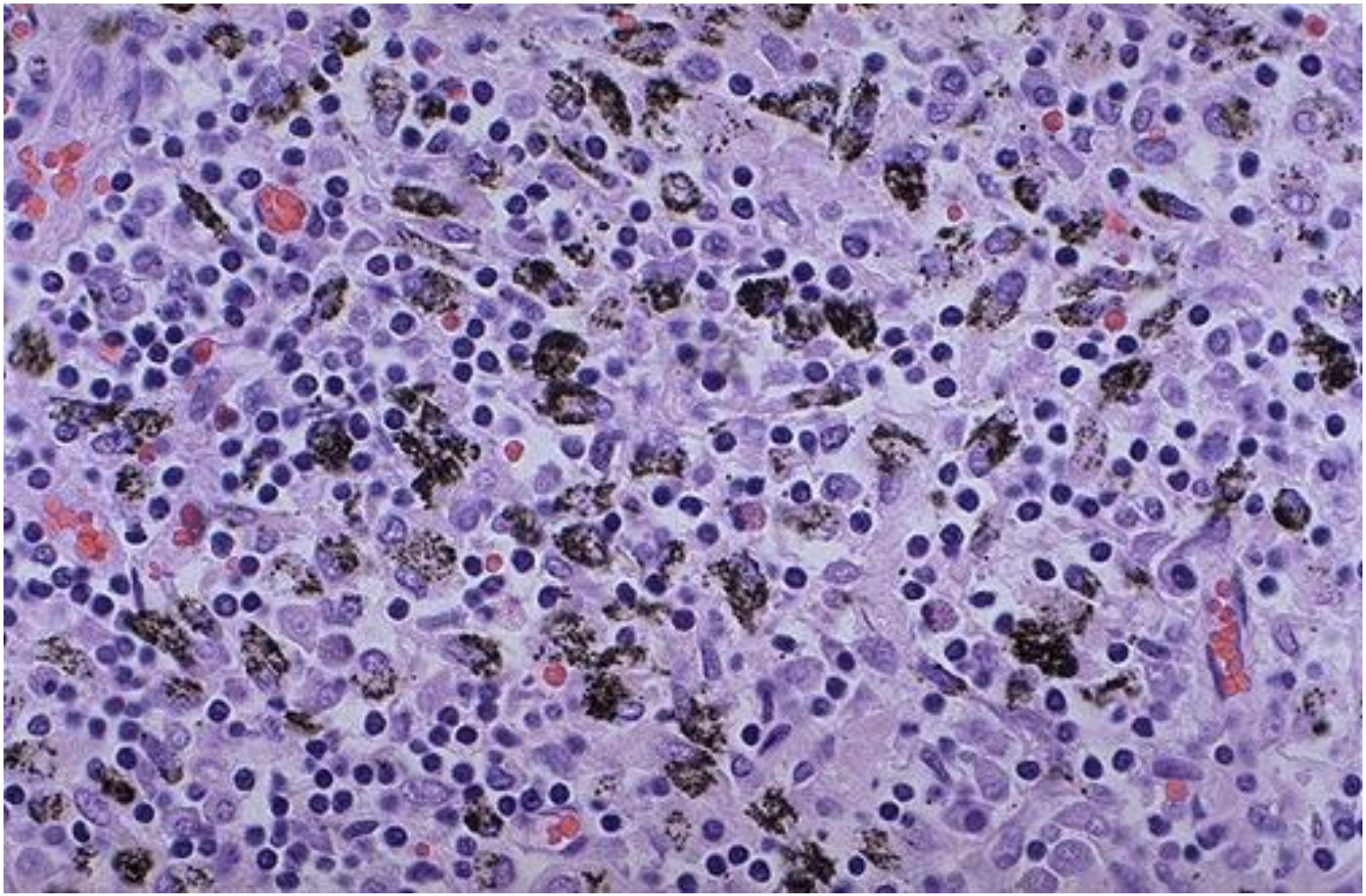
  ↓

  regional lymph nodes

  ↓

  anthracosis (blackening of lung)

  Heavy pollution → fibroblastic reaction, emphysema, coal workers' pneumoconiosis



-Anthracotic pigment in macrophages in a hilar lymph node.
-Anthracosis is an accumulation of carbon pigment from breathing dirty air.
-Smokers have the most pronounced anthracosis.

Exogenous pigments cont'd

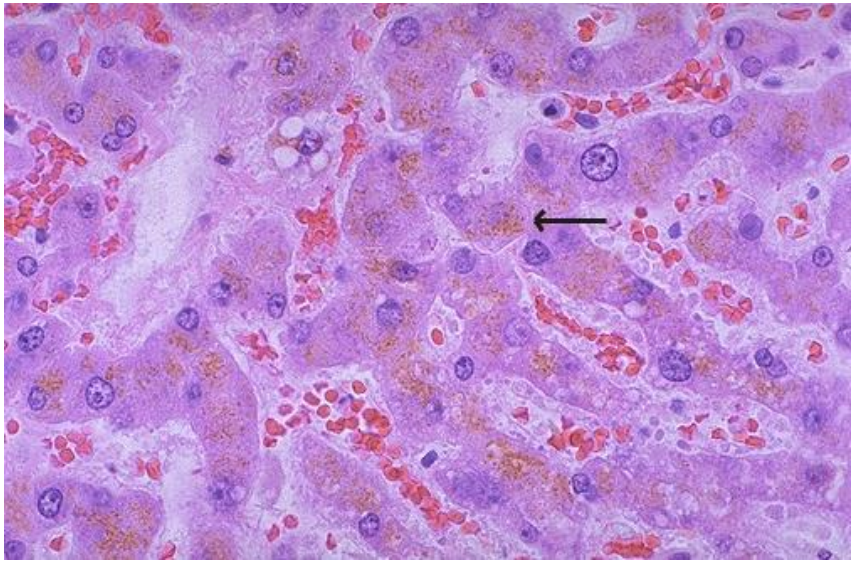
2) Tattooing

Pigments inoculated → phagocytosed by dermal macrophages

Endogenous Pigments

- Lipofuscin (“wear and tear” pigment)
- Lipids and phospholipids complexed with protein
- Derived from lipid peroxidation of subcellular membranes - indicative of free radical injury
- Tissue sections: yellow brown finely granular intracytoplasmic peri-nuclear pigment
- Liver, heart and neurons of elderly

Lipofuscin



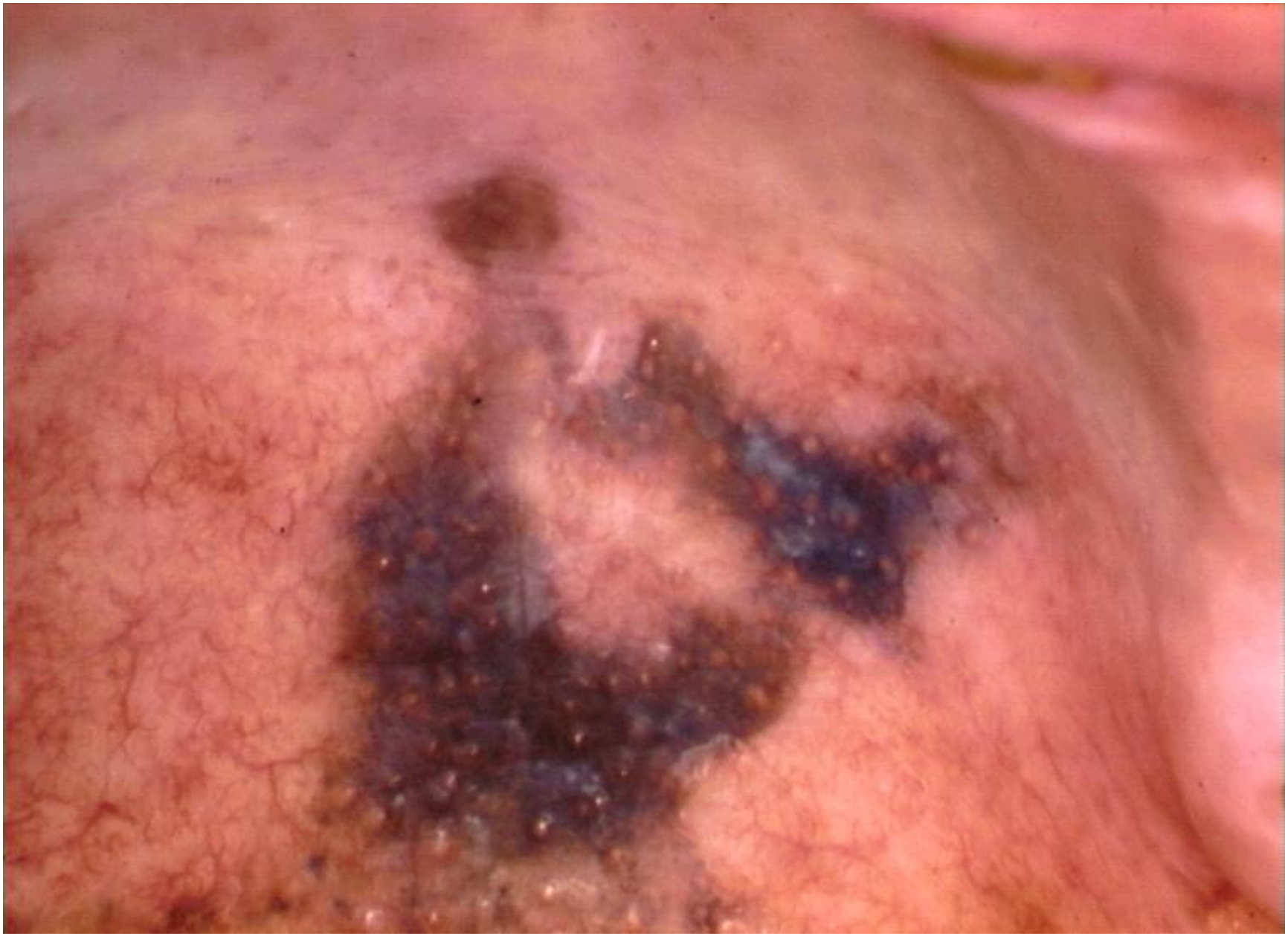
- The yellow-brown granular pigment seen in the hepatocytes here is lipochrome (lipofuscin) which accumulates over time in cells (particularly liver and heart) as a result of "wear and tear" with aging.
- It is of no major consequence, but illustrates the end result of the process of autophagocytosis in which intracellular debris is sequestered and turned into these residual bodies of lipochrome within the cell cytoplasm.

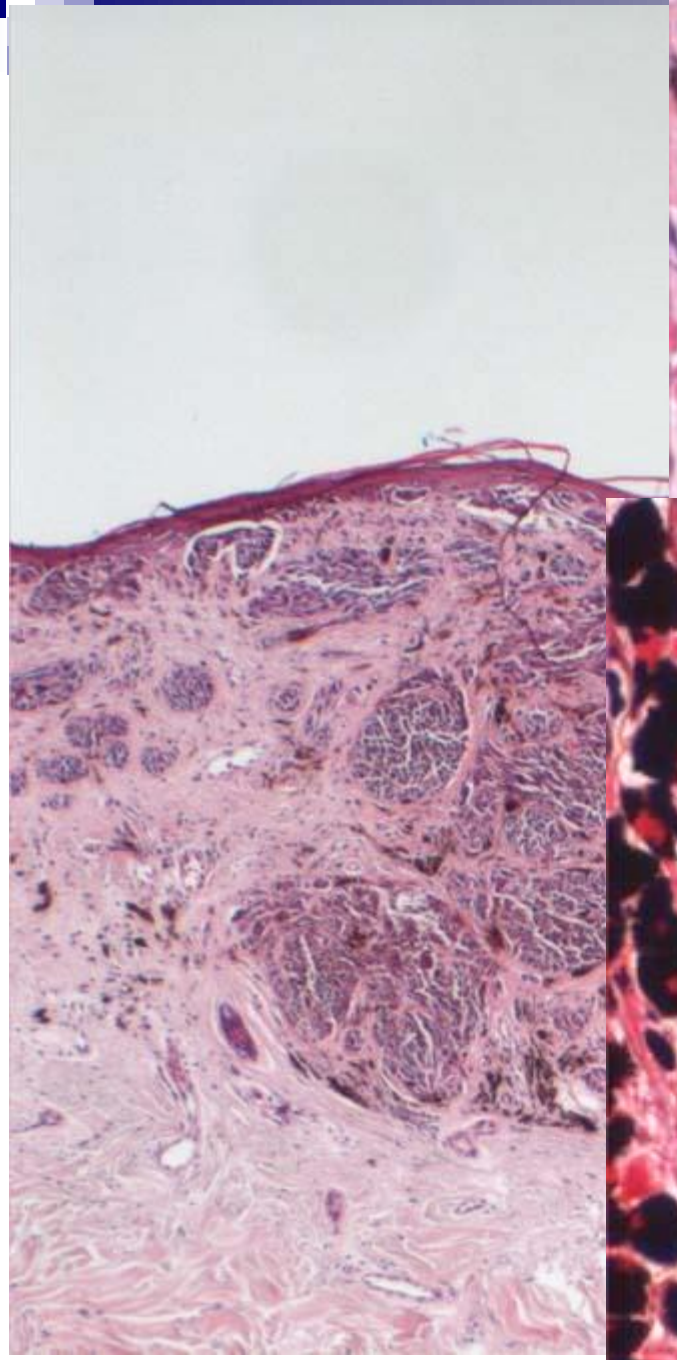
Endogenous pigments cont'd

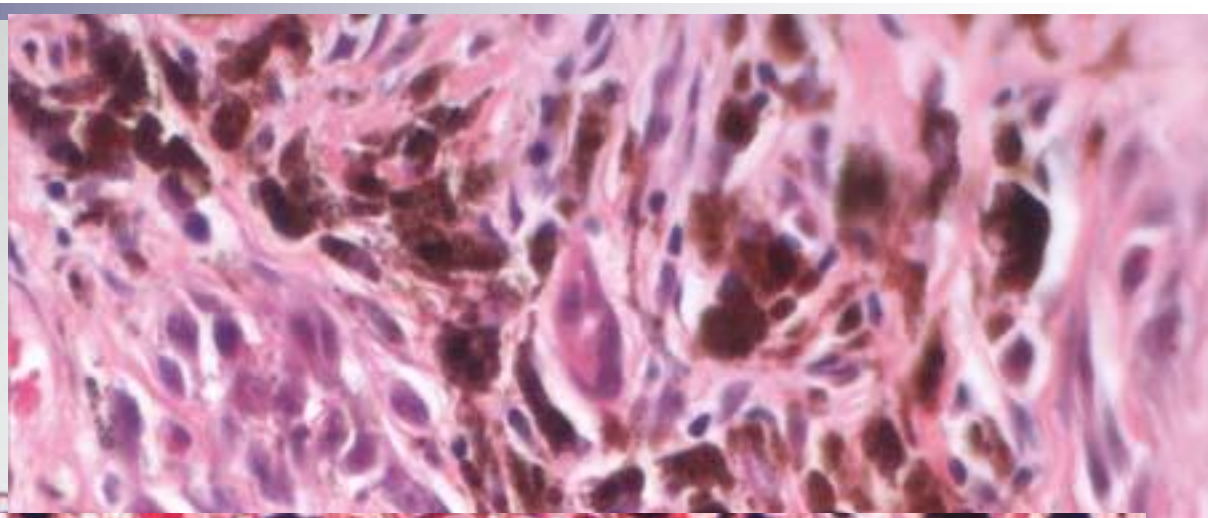
- Melanin: Brown black pigment found in melanocytes, Masson Fontana positive
- Endogenous screen against ultraviolet rays
- Tyrosine $\xrightarrow{\text{tyrosinase}}$ Dihydroxyphenylalanine

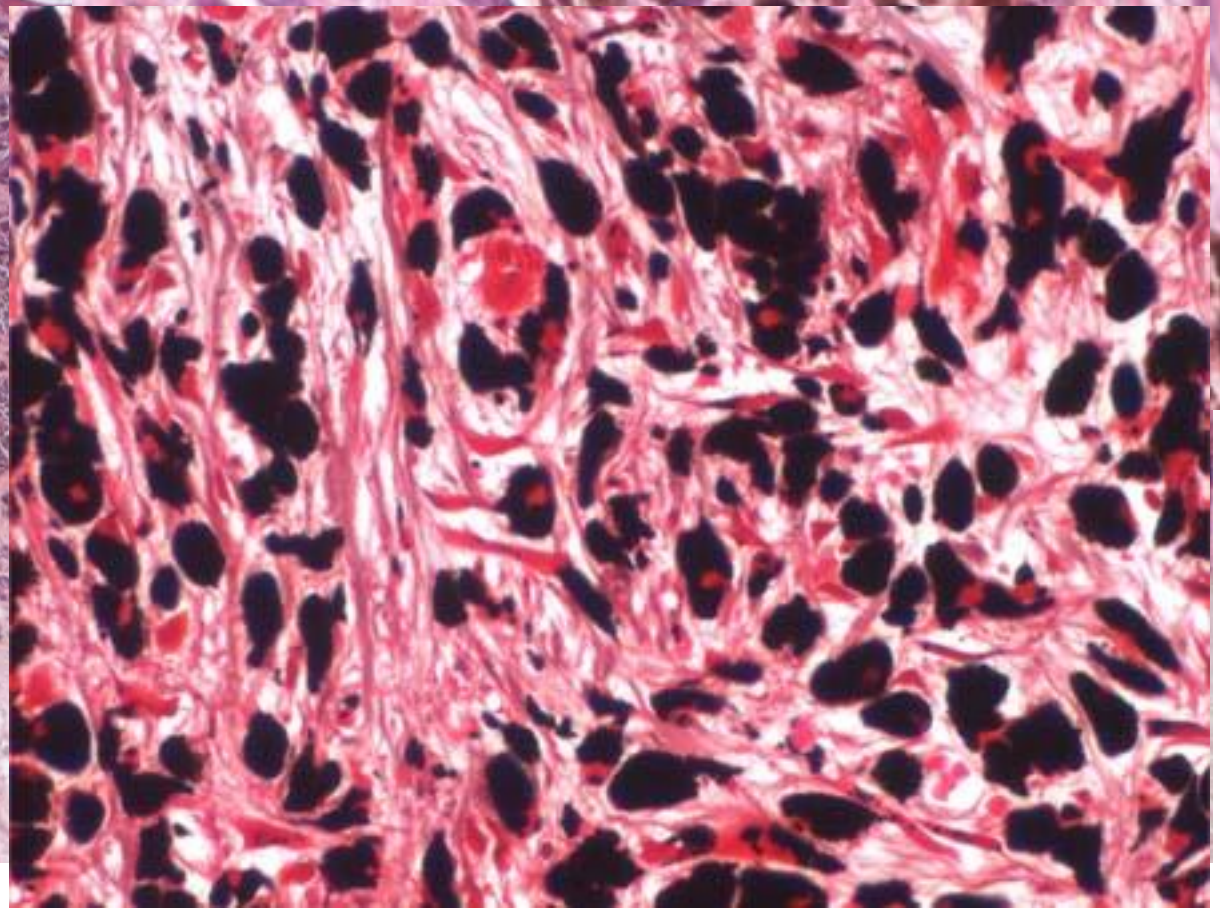
  ↓

  Melanin
- Vitiligo – loss of pigment producing melanocytes within the epidermis
- Albinism – melanocytes are present but no melanin is produced because of a lack or defect in tyrosinase enzyme



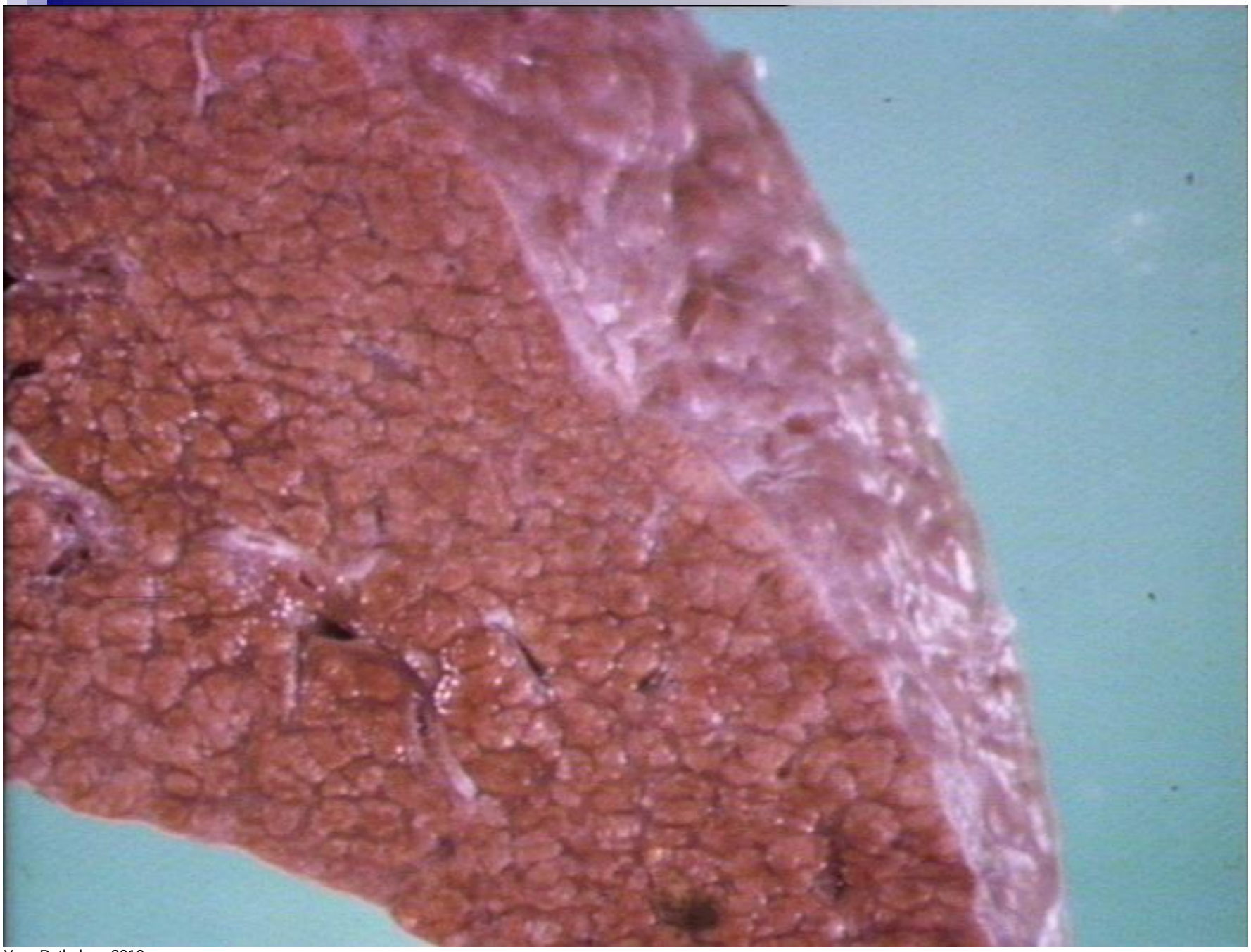




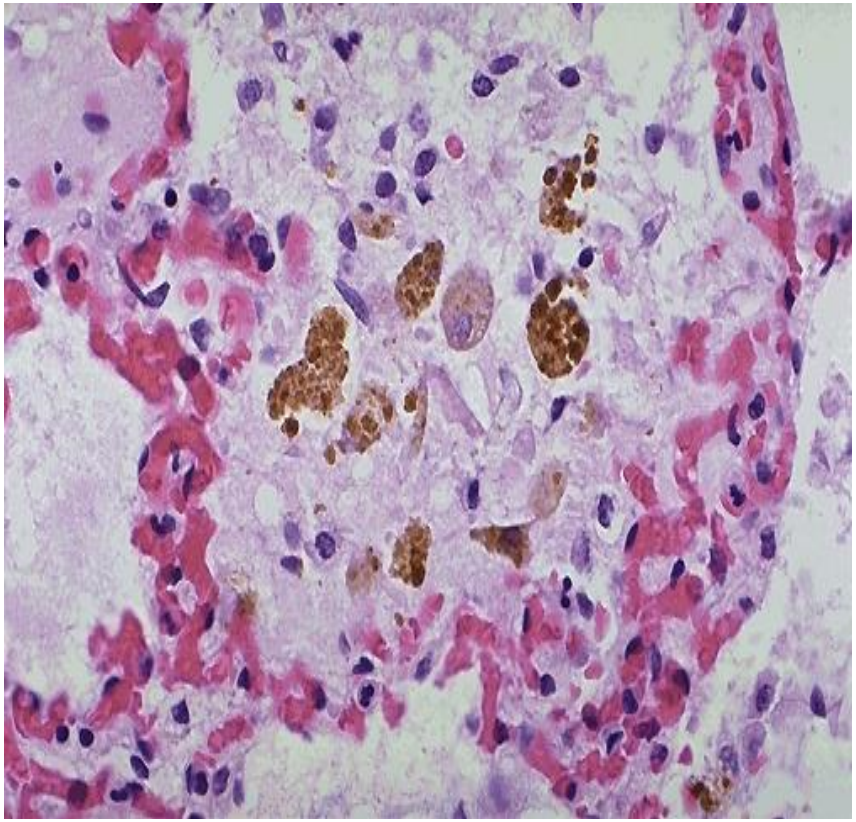


Endogenous pigments cont'd

- Haemosiderin
  - Haemoglobin derived
  - Golden yellow to brown granular pigment
  - Prussian blue positive
- In cells iron normally stored in association with a protein apoferritin → ferritin micelles
- Local or systemic excess of iron → aggregates of ferritin micelles = haemosiderin granules



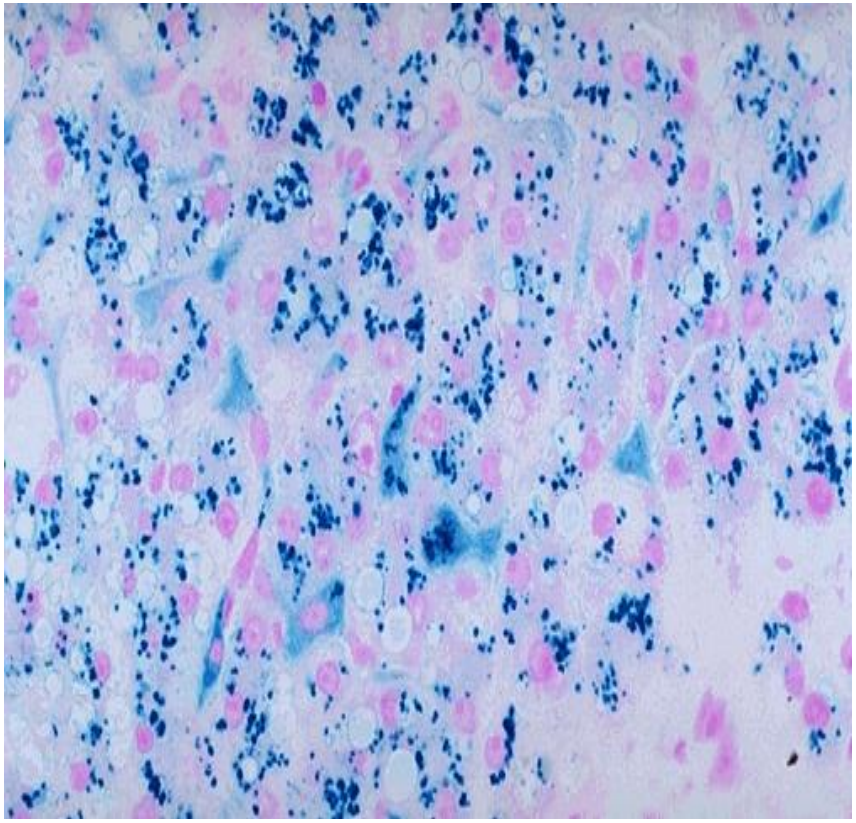
Haemosiderin

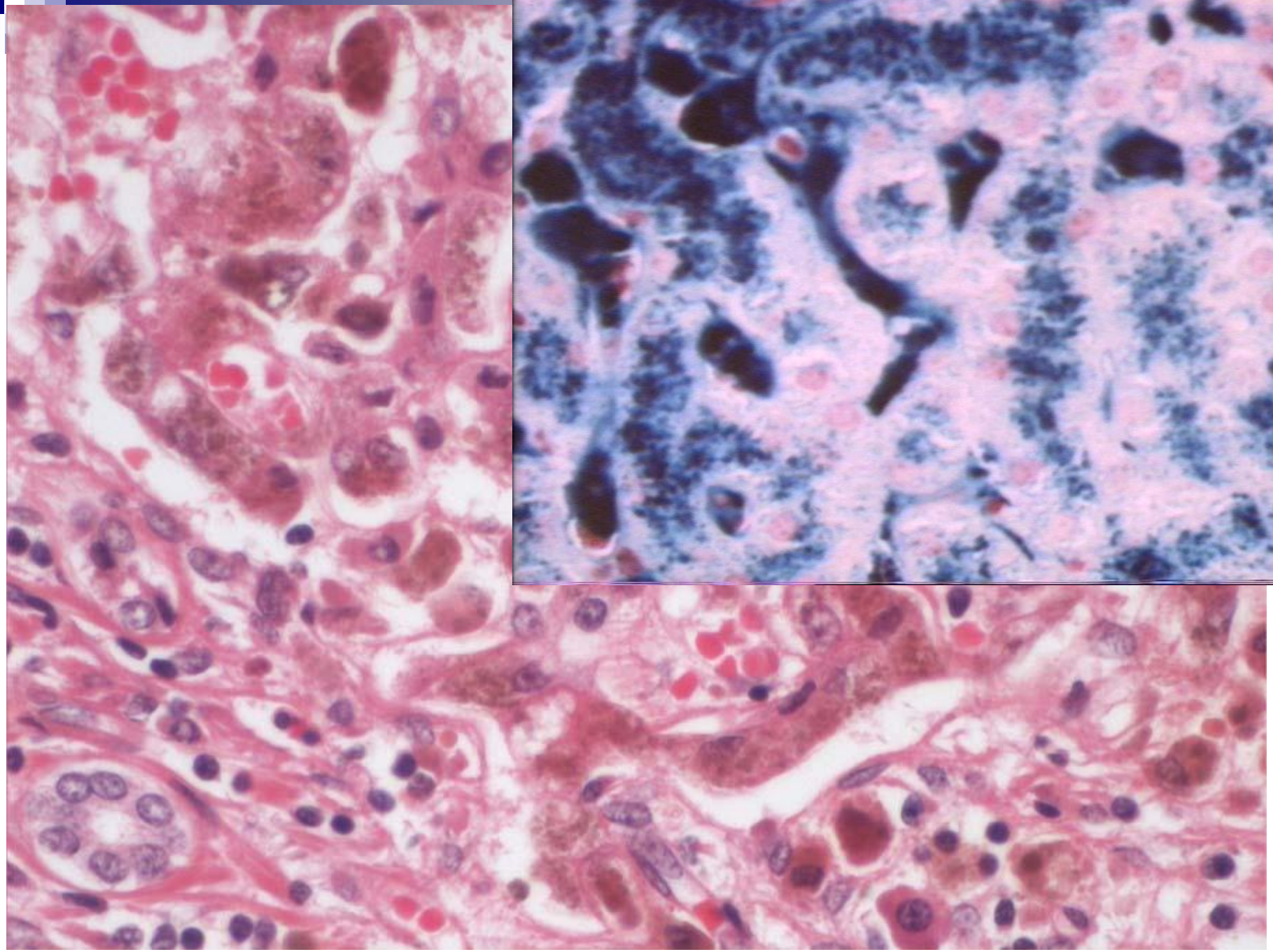


- The brown coarsely granular material in macrophages in this alveolus is hemosiderin that has accumulated as a result of the breakdown of RBC's and release of the iron in heme.
- The macrophages clear up this debris, which is eventually recycled.

Haemosiderin

- A Prussian blue reaction is seen in this iron stain of the liver to demonstrate large amounts of hemosiderin that are present within the cytoplasm of the hepatocytes and Kupffer cells.
- Ordinarily, only a small amount of hemosiderin would be present in the fixed macrophage-like cells in liver, the Kupffer cells, as part of iron recycling.





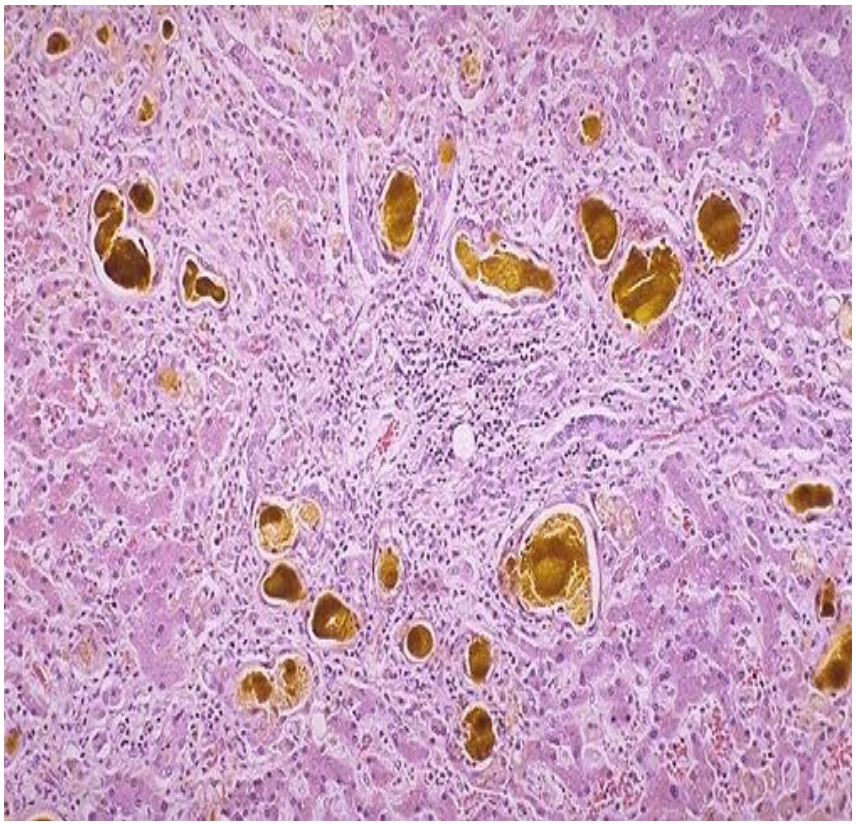
Endogenous pigments cont'd

- Normally small amounts of haemosiderin can be seen in mononuclear phagocytes of bone marrow, spleen and liver (all engaged in red cell breakdown)
- Common bruise → haemorrhage → lysis of erythrocytes → series of pigments → biliverdin → bilirubin → haemosiderin

Endogenous pigments cont'd

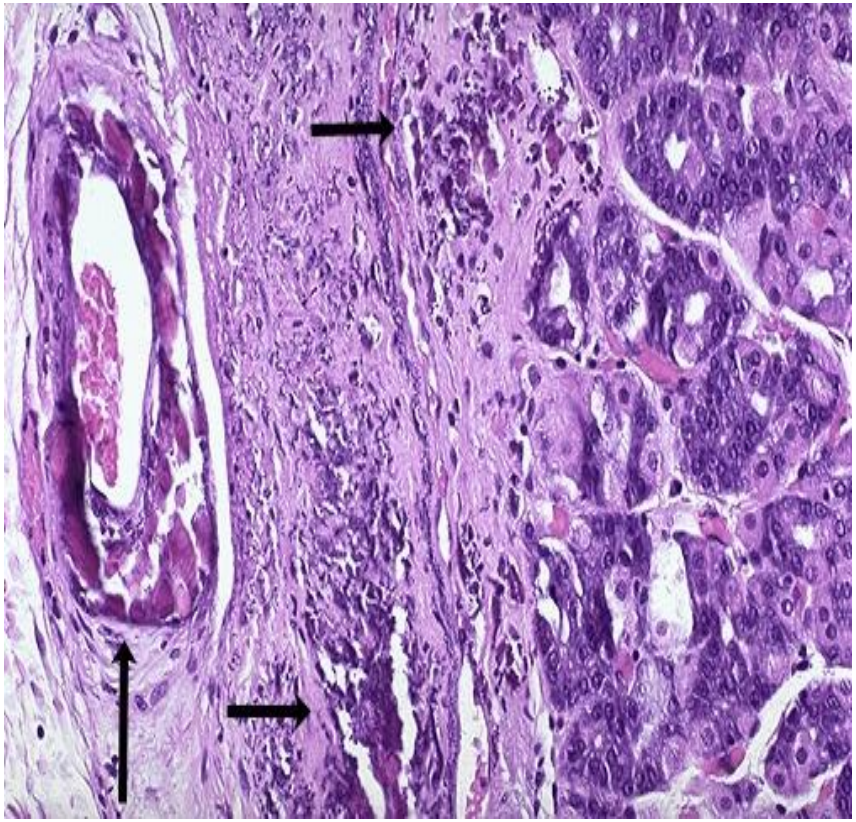
Systemic excess of iron

- Increased absorption of dietary iron
- Impaired utilization of iron
- Haemolytic anaemias
- Transfusions



- The yellow-green globular material seen in small bile ductules in the liver here is bilirubin pigment.
- This is hepatic cholestasis.

Calcification



- This is dystrophic calcification in the wall of the stomach.
- At the far left is an artery with calcification in its wall.
- There are also irregular bluish-purple deposits of calcium in the submucosa.
- Calcium is more likely to be deposited in tissues that are damaged.

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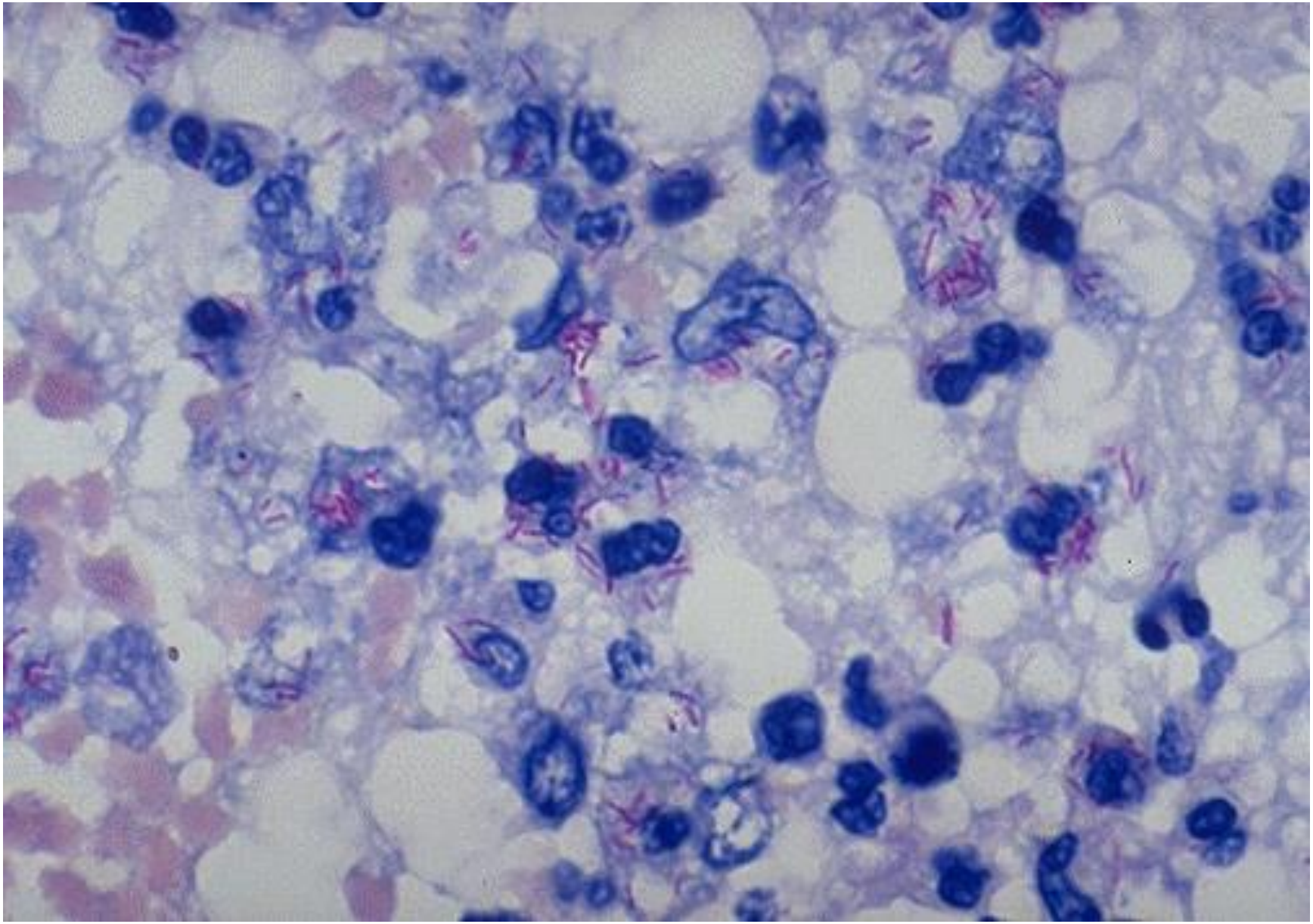
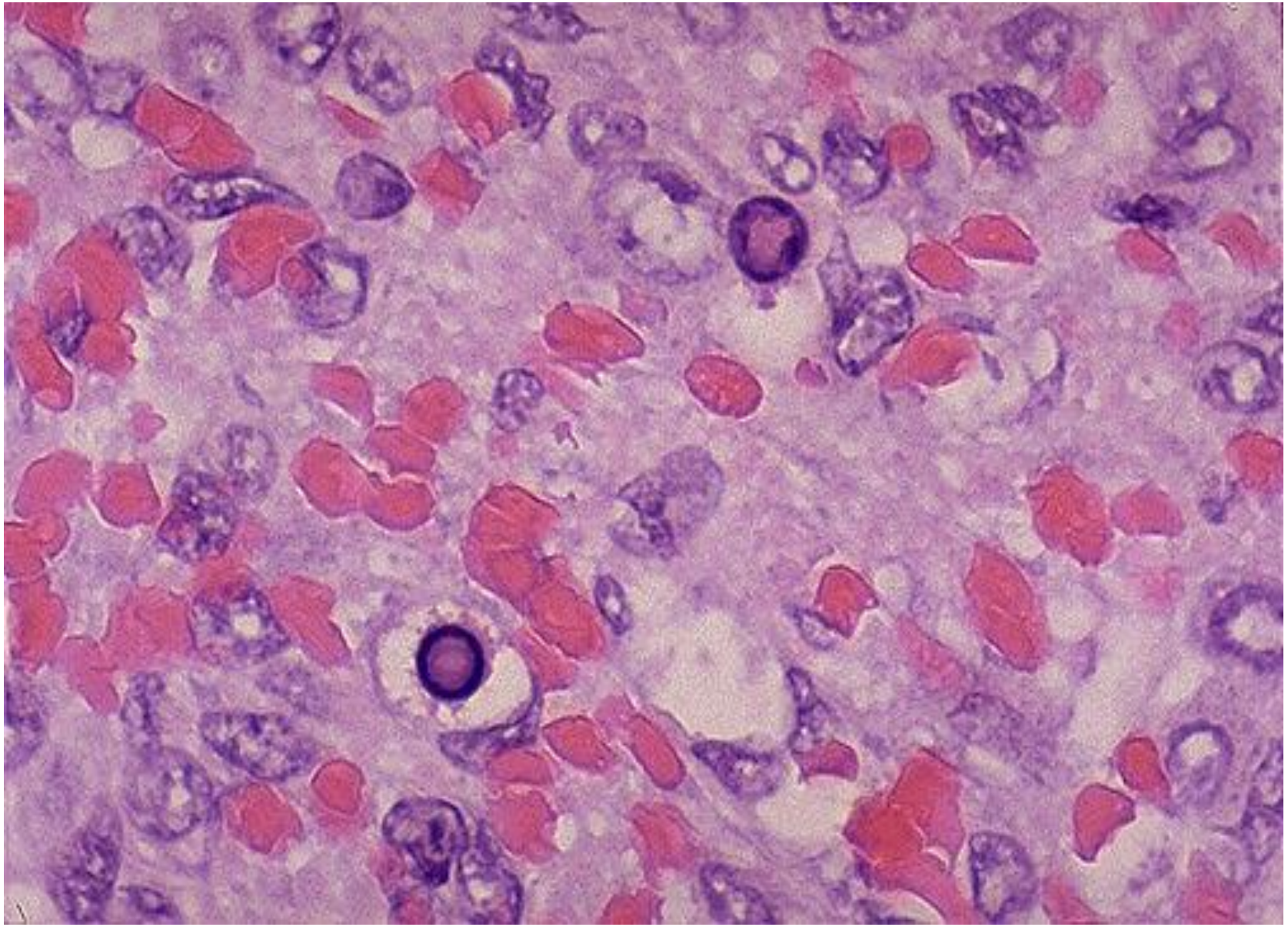
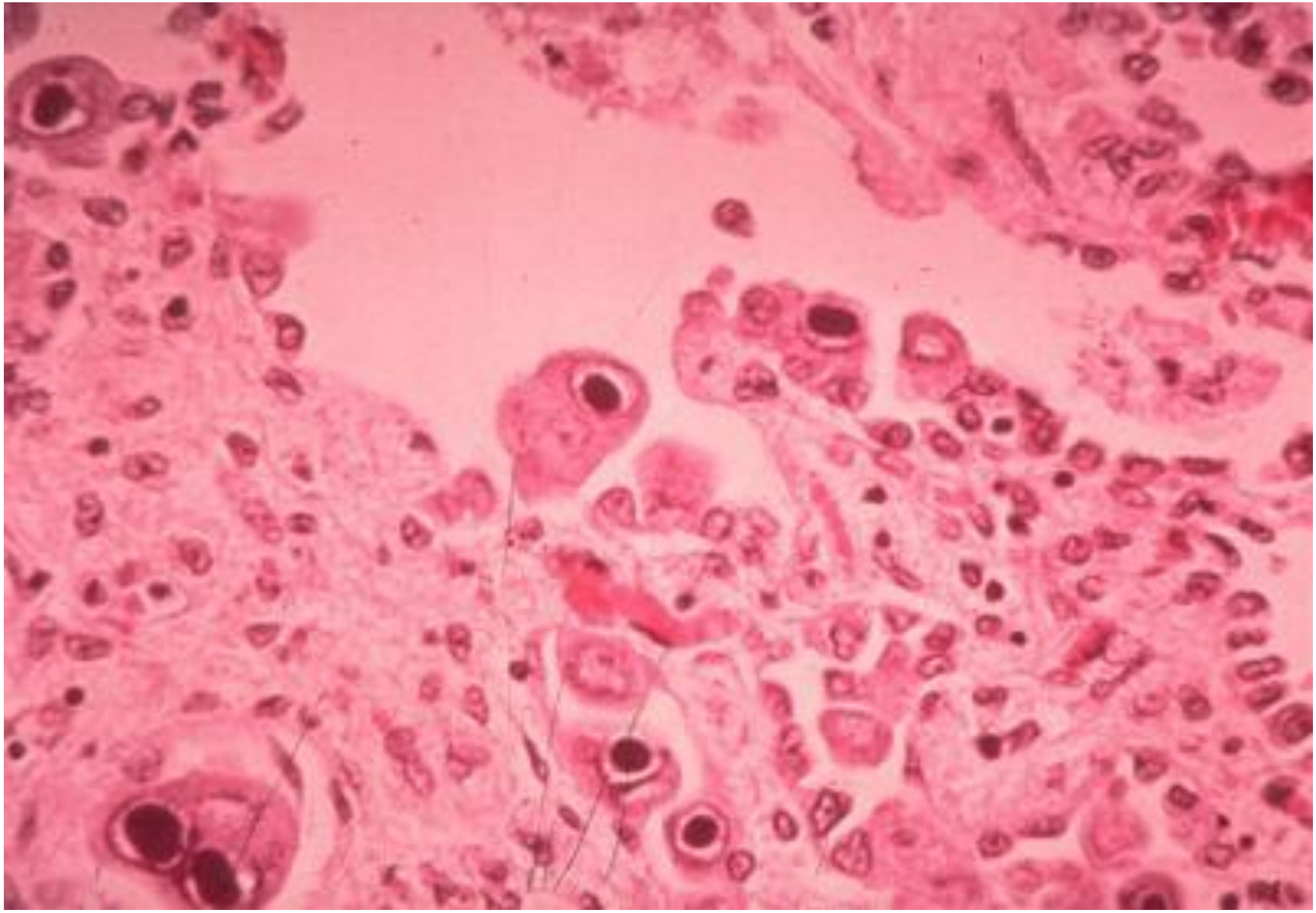
Intracellular Organisms

- Bacteria
  - Mycobacteria
  - Leishmania
  - Rickettsiae
- Viruses
- Prions

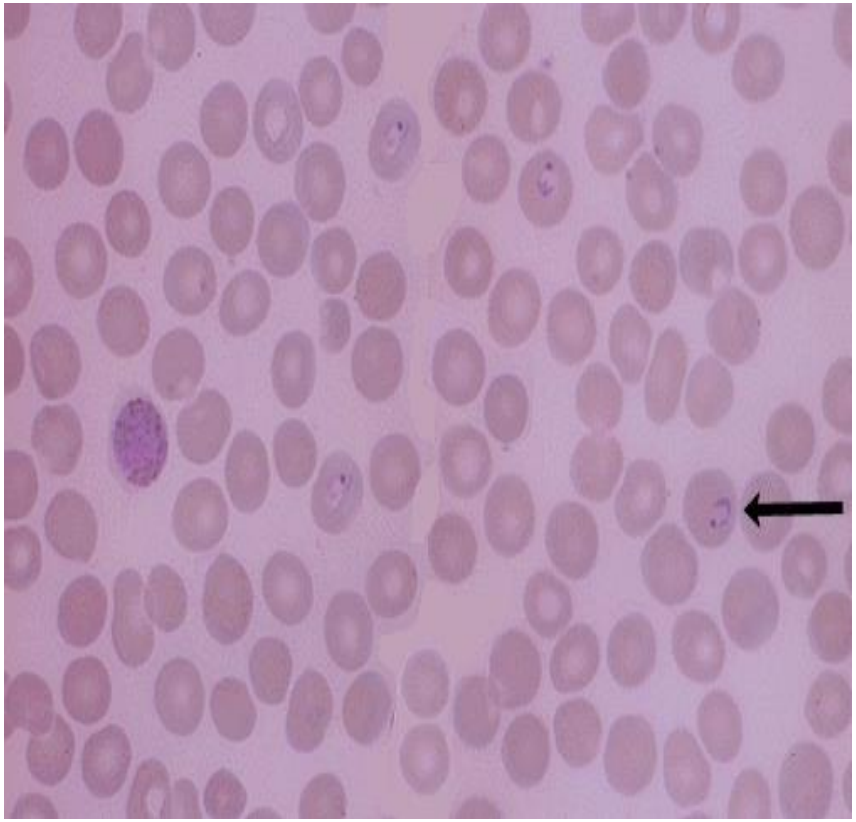






Parasitic infection

- This peripheral blood smear comes from a patient with malaria.
- This infection happens to be with *Plasmodium vivax*. At the arrow is a RBC with a malarial parasite in the shape of a ring.
- Three other RBC's in this smear are also infected with a ring trophozoite.
- At the far left is a gametocyte of this species.



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