The Cellular Basis of Disease

Cell Injury 4B

APPROVED

Intracellular Accumulations

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we will briefly talk about intracellular accumulations and clinico-pathological implications.

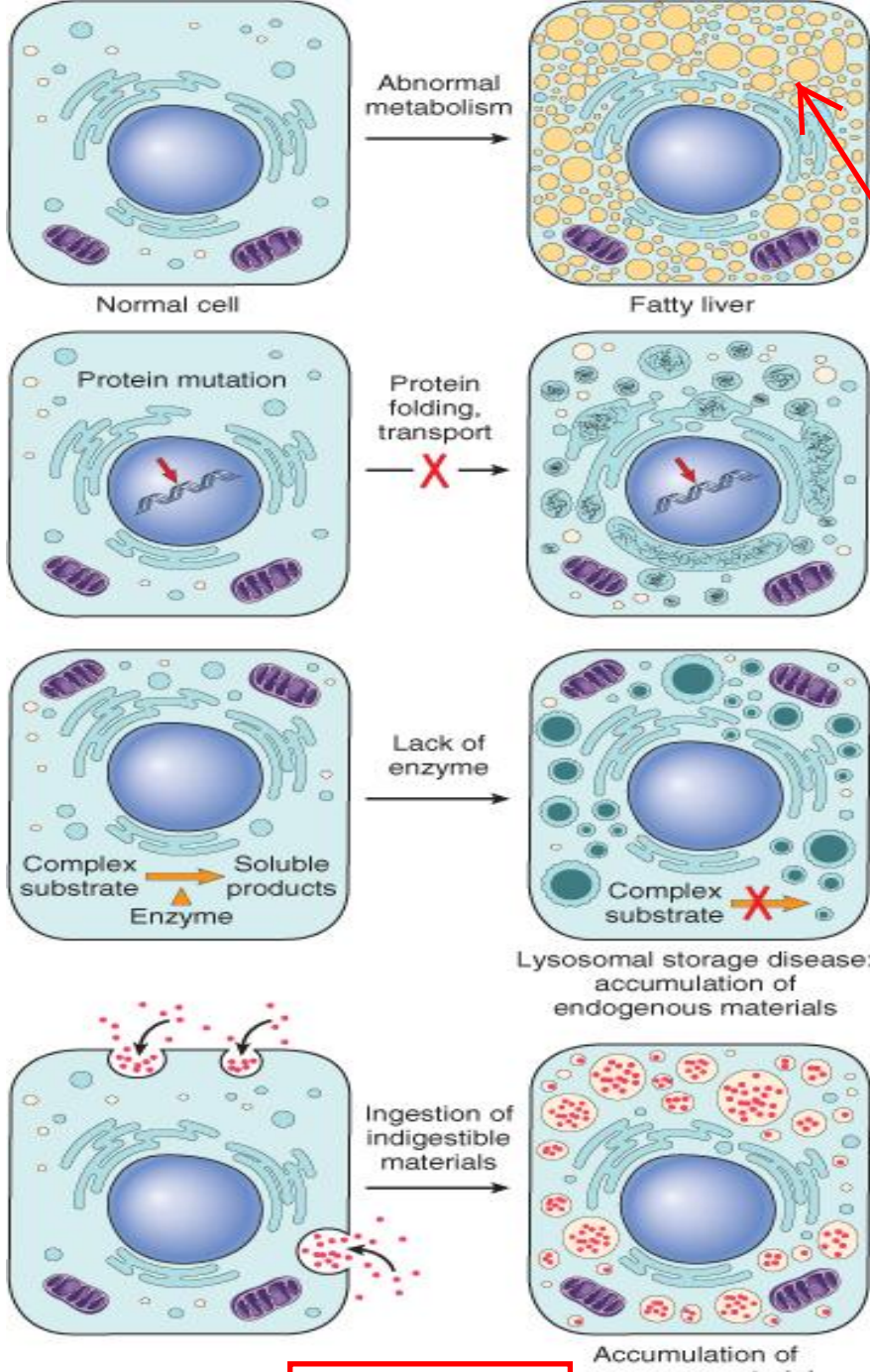
Objectives

- Identify sub lethal cell injury caused by lysosomal accumulation of endogenous and exogenous material.
- Explain the etiology, pathologic and clinical manifestations of lysosomal storage diseases.
- Describe and understand the pathophysiology and clinical implications of intracellular accumulations including Lipids, Proteins, Glycogen, Pigments
- Describe and understand Pathologic Calcification and differentiate between dystrophic and metastatic calcification.

Intracellular accumulations

4 different intracellular accumulations

- **Lipids**
  - **Steatosis**
  - **Cholesterol and Cholesterol Esters**
- **Proteins**
- **Glycogen**
- **Pigments**



Abnormal metabolism – Steatosis (Fatty change)

usually affect the liver, sometimes the heart

accumulation of lipid particles

Abnormal protein folding – Alpha 1 antitrypsin deficiency

misfolded proteins accumulate in the ER

Lack of enzyme – Lysosomal storage disease

blockage in the digestion pathway, causing accumulation of product upstream of the blockage

Indigestible material – Carbon or heme

coal miners get a lot of this

Causes of Steatosis (Fatty Liver)

2 major causes of steatosis

Alcohol is a hepatotoxin that leads to **increased synthesis and reduced breakdown of lipids.**

Nonalcoholic fatty liver disease is associated with **diabetes and obesity**.

this is becoming more common, though the mechanism remains unknown. It also leads to cirrhosis and liver failure

dry cleaning

CCl_4 and **protein malnutrition** cause **reduced synthesis of apoproteins.**

apoproteins are required for lipid metabolisms

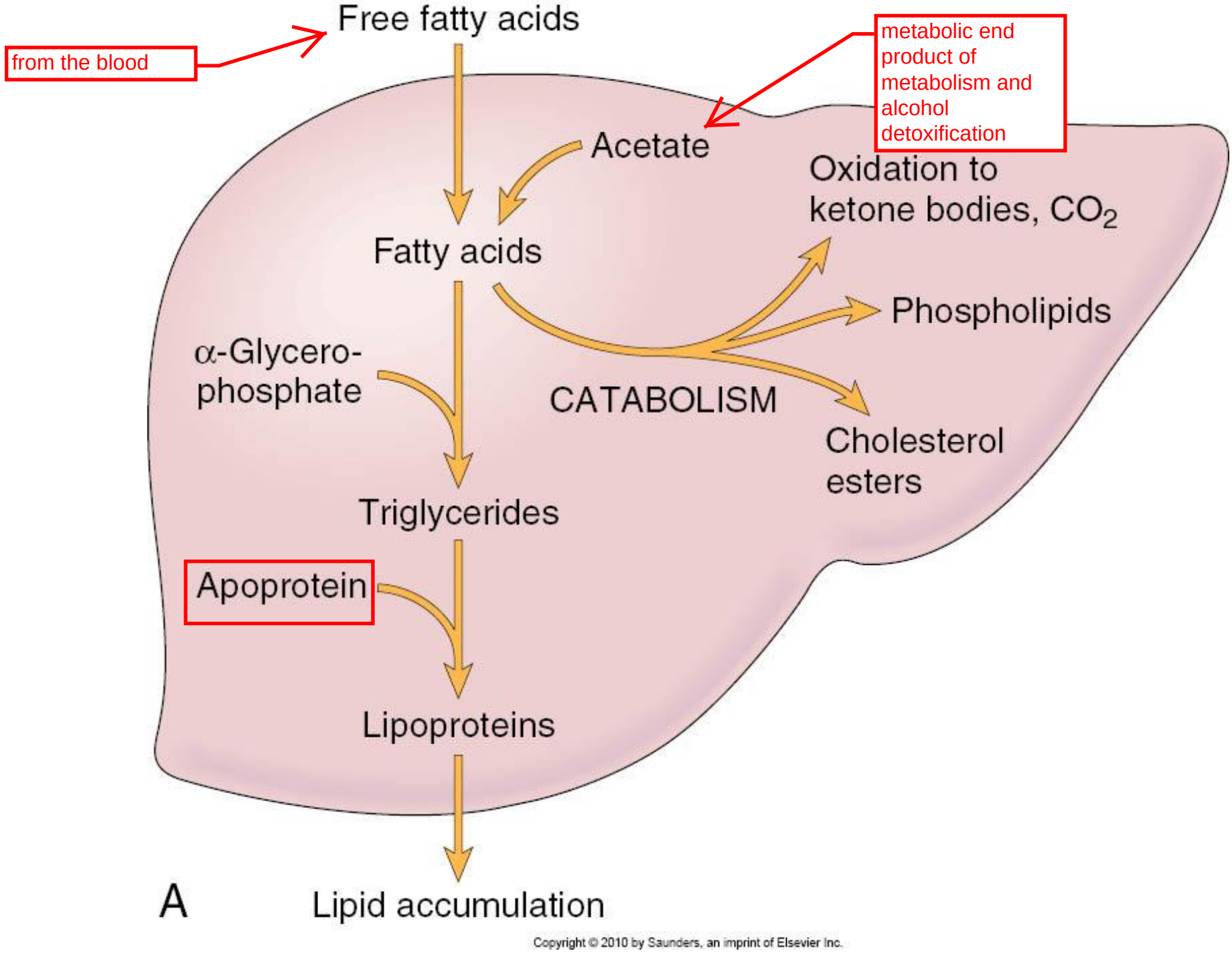
less common

Hypoxia inhibits fatty acid oxidation.

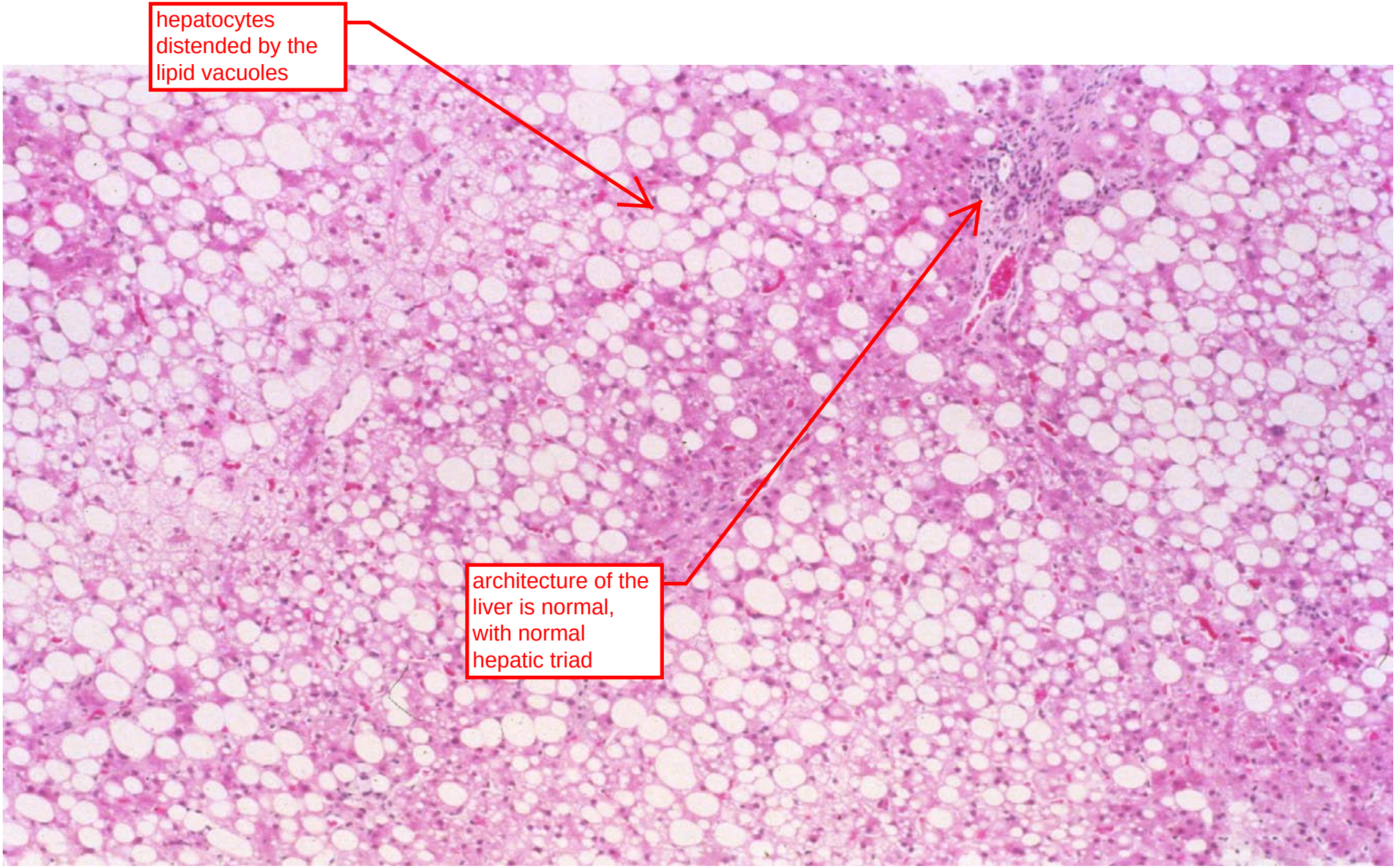
important in fatty deposition in myocardium too

Starvation increases mobilization of fatty acids from peripheral stores.

usually seen in patients with other underlying illness, such as cancer



an example of fatty liver
- smooth surface: important distinction from other liver diseases where livers develop irregular surfaces
- cut surface is shiny: greasy and yellow


hepatocytes distended by the lipid vacuoles
architecture of the liver is normal, with normal hepatic triad

Intracellular Lipid Accumulation

Cholesterol and cholesterol esters

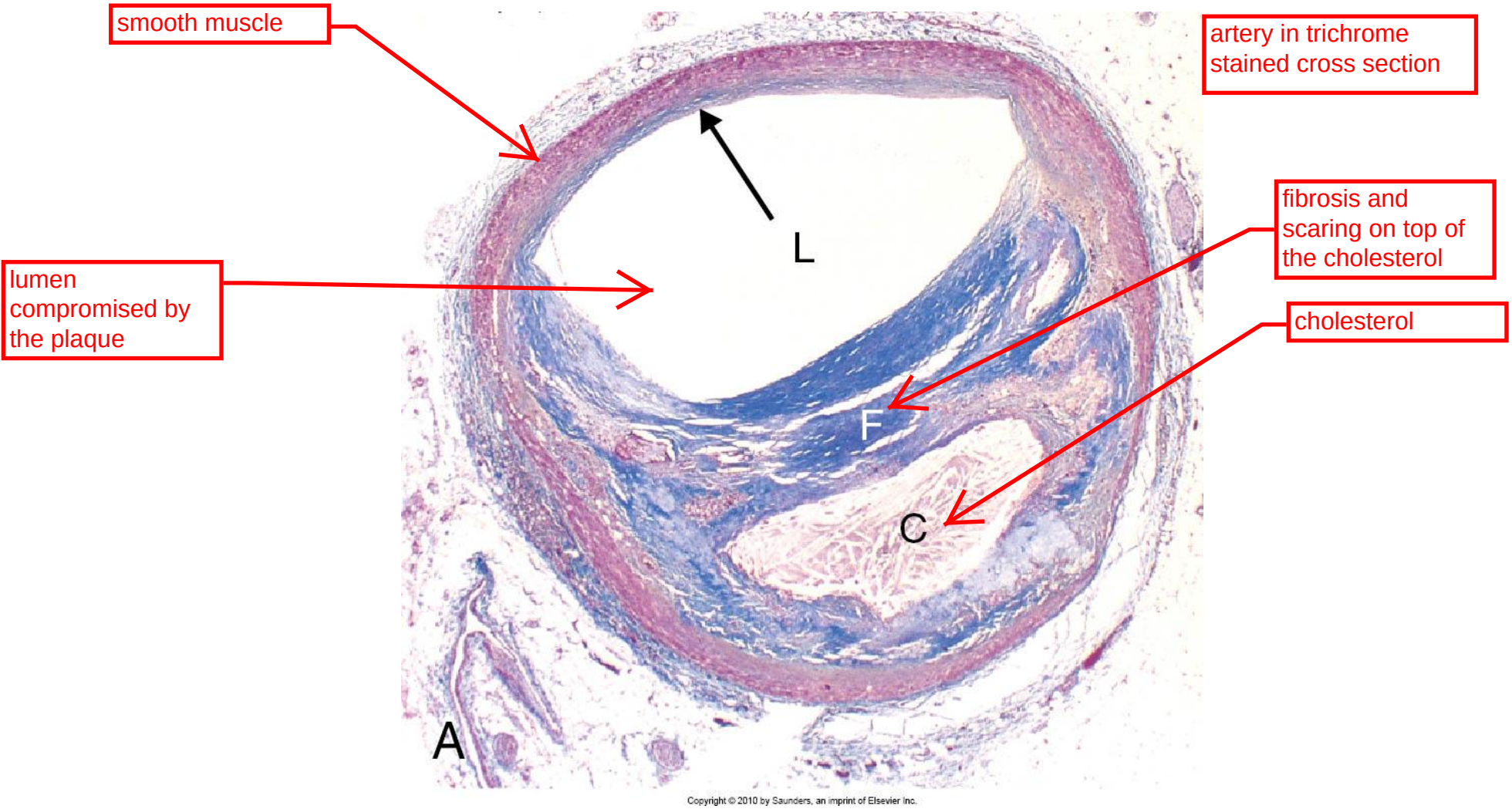
Atherosclerosis — common causes of many diseases

Xanthomas — less common

Cholesterolosis — lipid storage disease

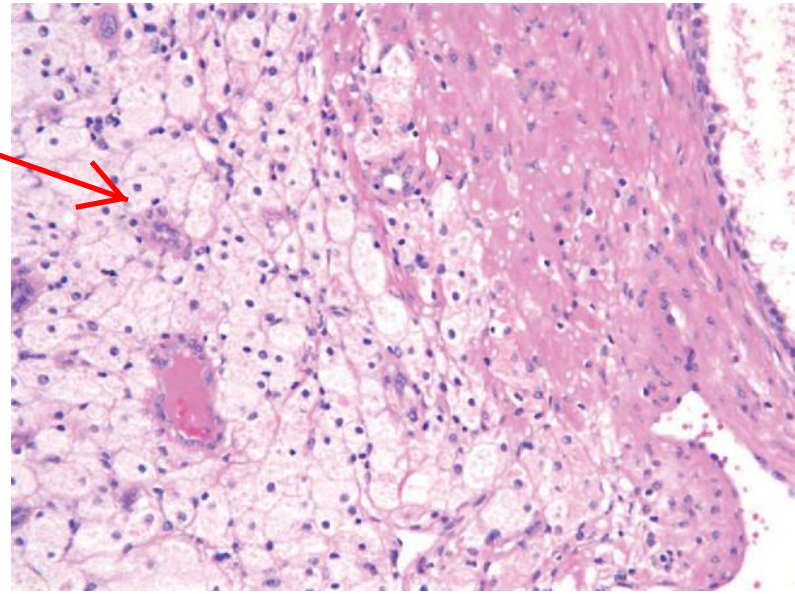
Niemann-Pick Disease Type C

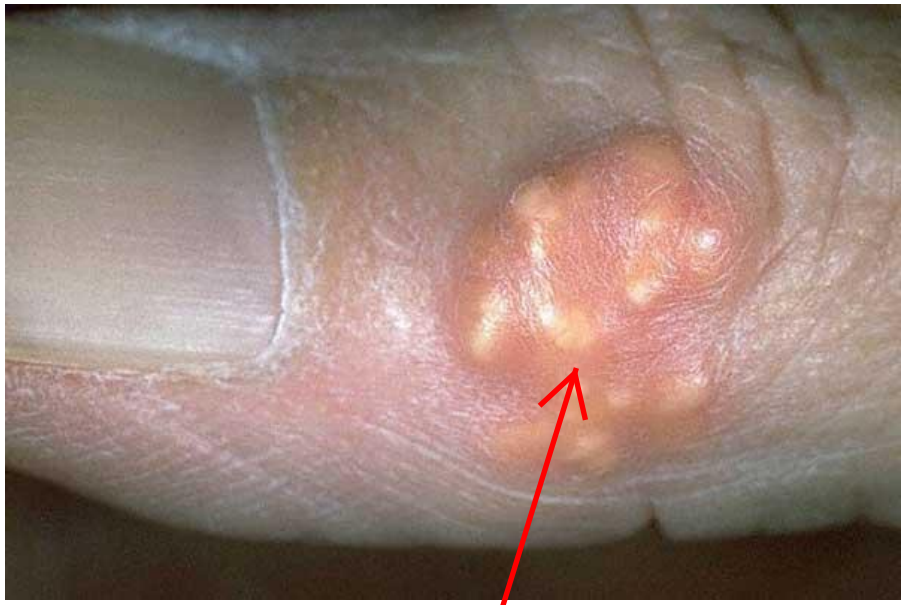
Atherosclerotic Plaque



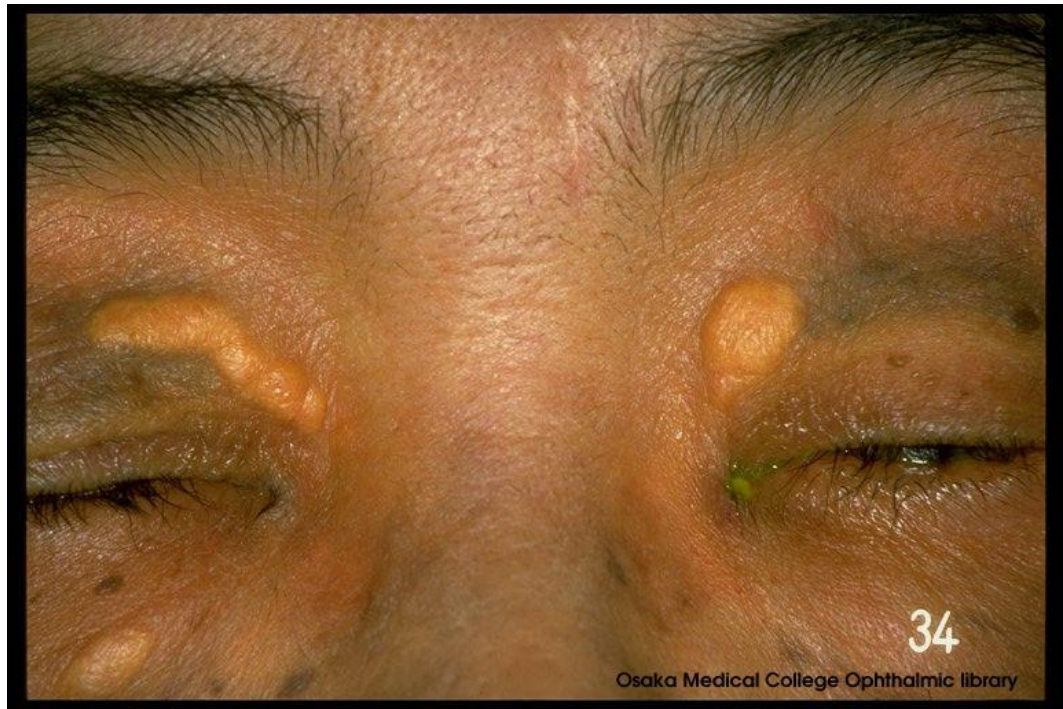
Xanthoma

lipid accumulation in the dermis





knobby appearance--> clue that the patient may have defect in lipid metabolism



Cholesterolosis

ciliated epithelium

accumulation of lipid in gall bladder submucosa
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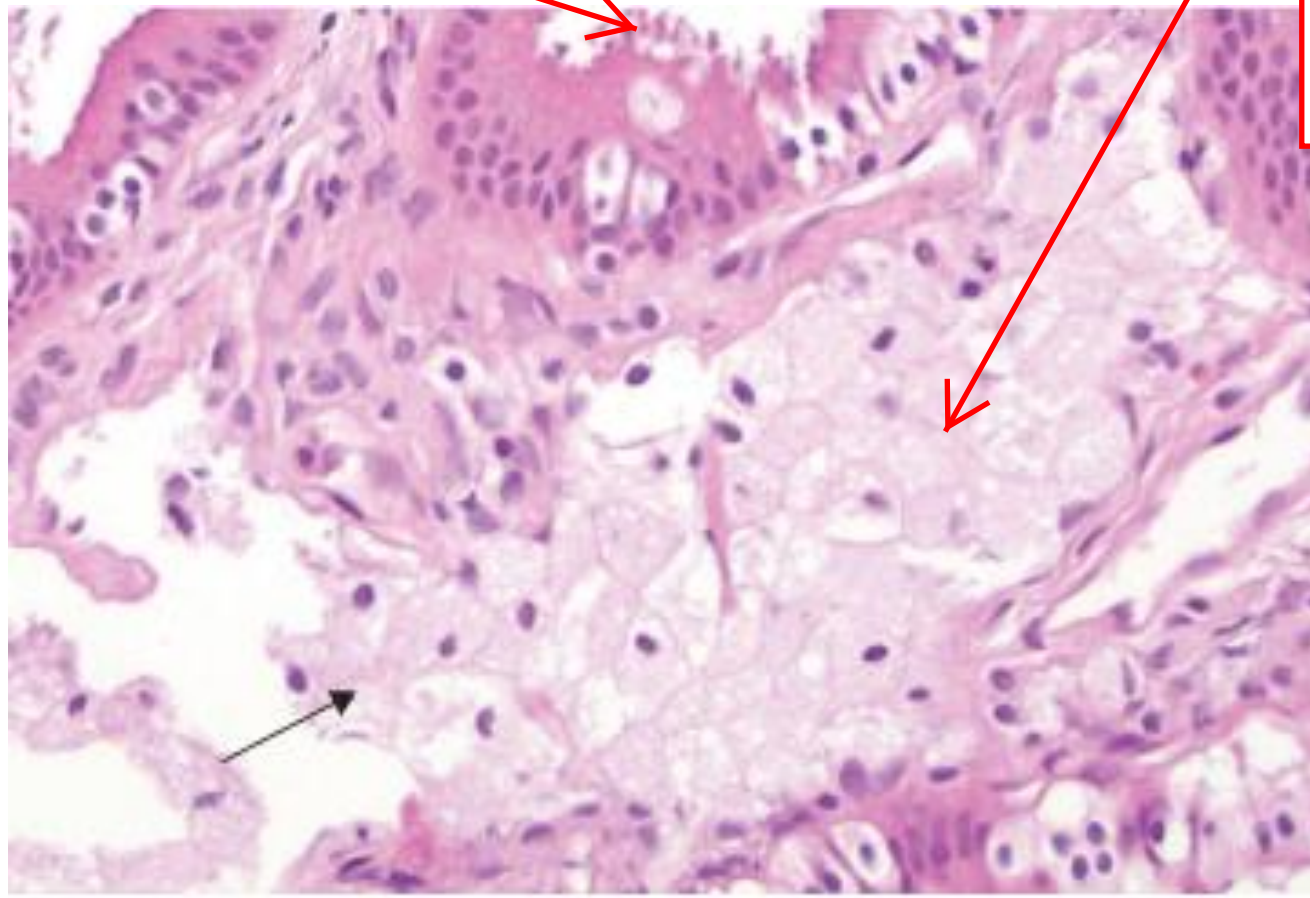
may be an indicator of other underlying diseases



Intracellular Protein Accumulations

Excessive amounts of normal proteins
(Multiple myeloma -Russell Bodies)

proliferation of plasma cells, causing accumulation of immunoglobin

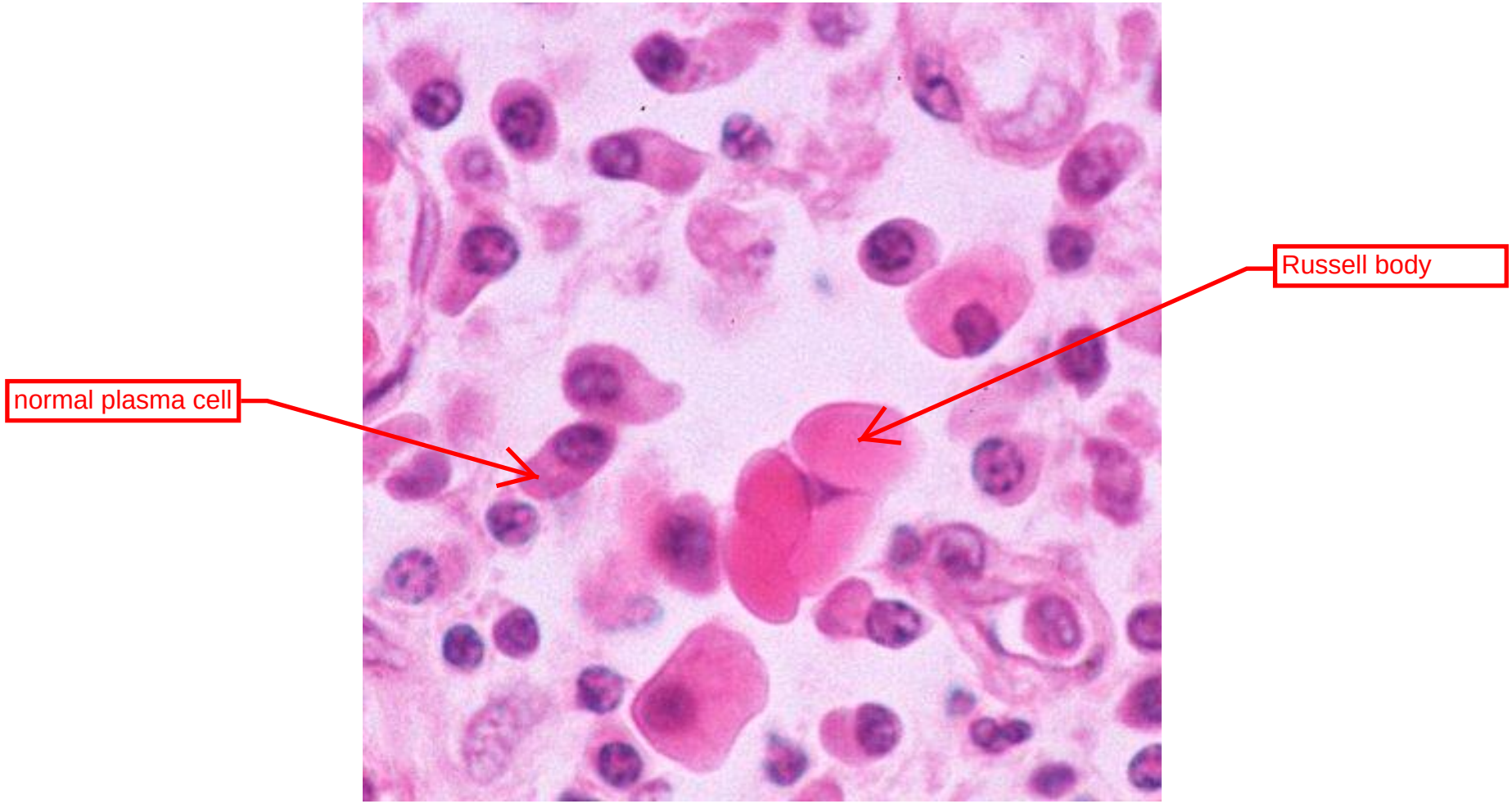
Defective intracellular transport and secretion
(Cystic fibrosis)

accumulation of mucin

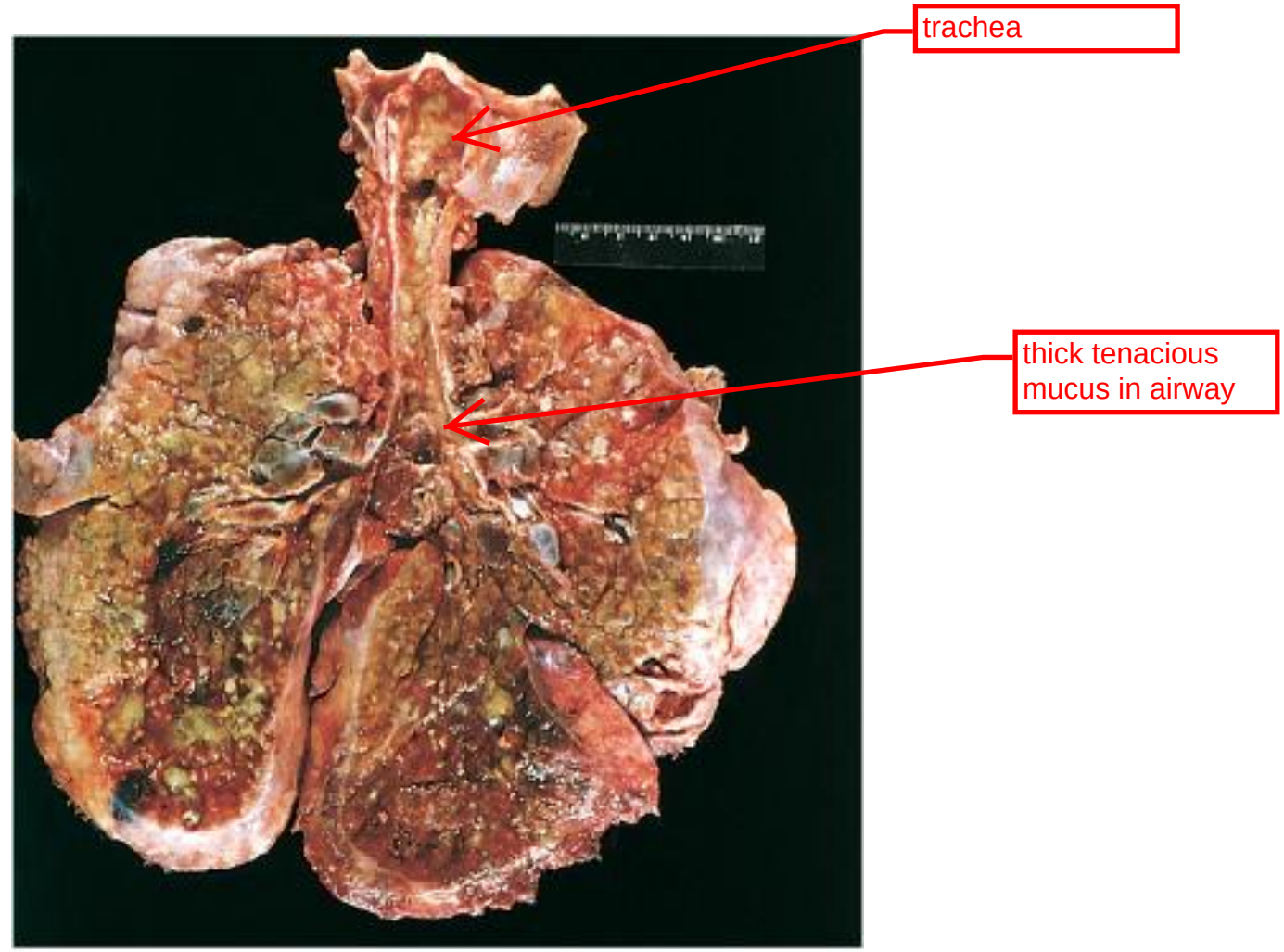
Aggregation of abnormal proteins (Alpha-1 Antitrypsin deficiency; Systemic Amyloidosis)

Excessive normal proteins (Russell bodies)

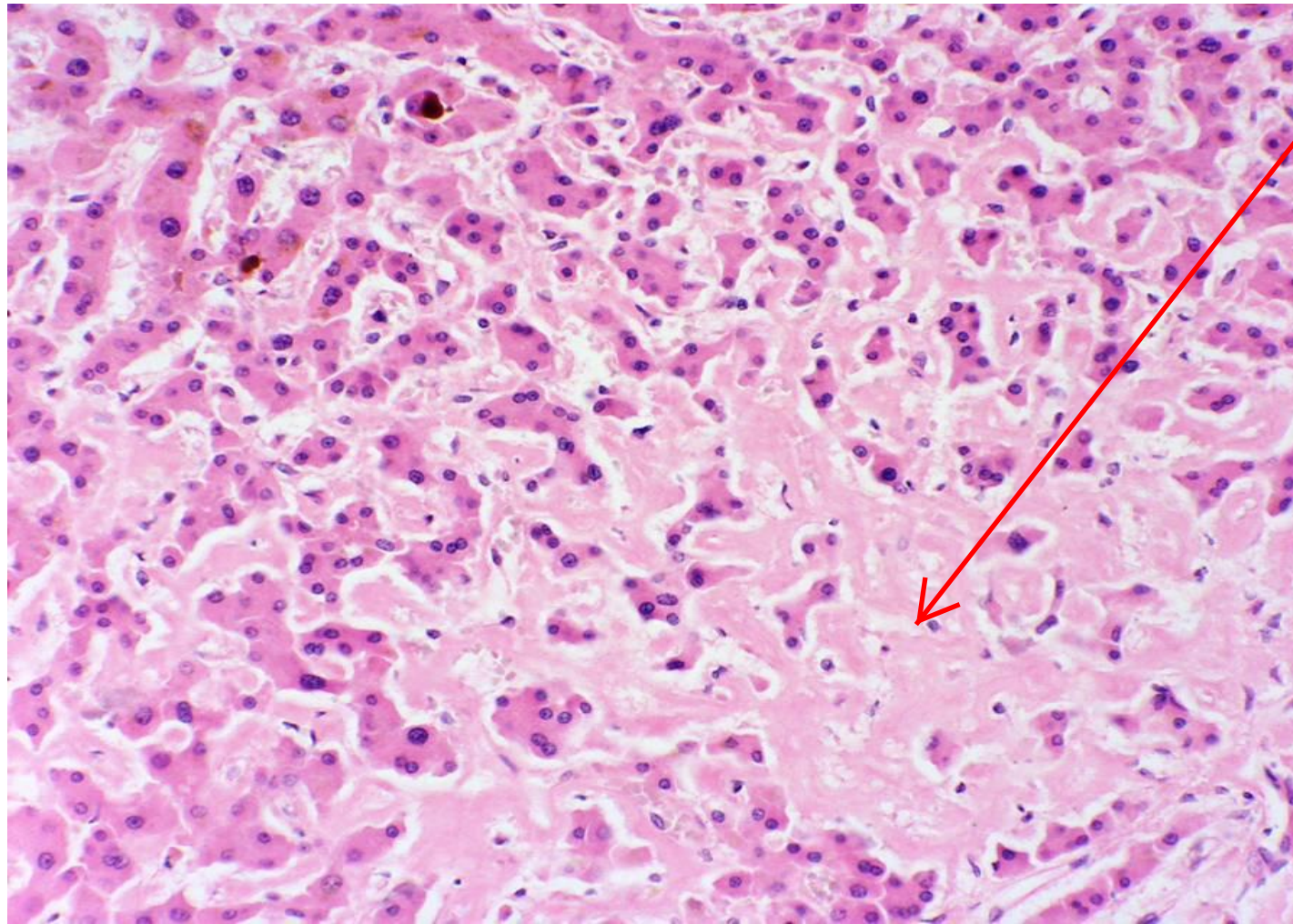
PathGuy



Defective intracellular transport and secretion (Cystic fibrosis)



Aggregation of abnormal proteins (Amyloid in Liver)



Indigestible material Pigments

Exogenous Pigment – Carbon in lung = anthracosis

common to miners and people in urban environment

Endogenous Pigments

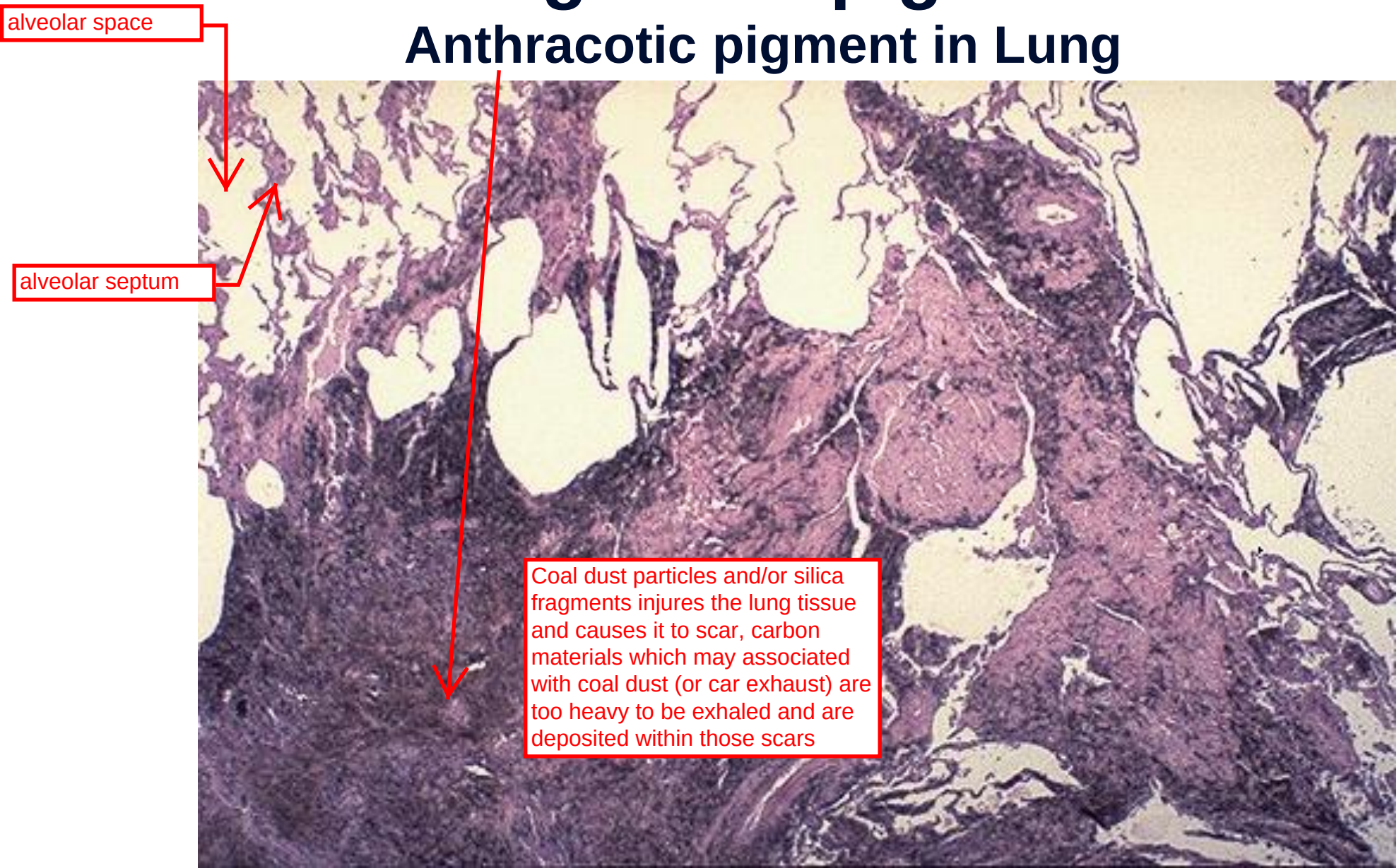
end product of erythrocyte degradation, can lead to impaired liver function

- **Hemosiderin- multiple transfusions**
- **Lipofuscin- aging pigment**
- **Melanin- skin and neurotransmission**
- **Bilirubin-hepatocytes**

ROS causes lipid peroxidation, and the body respond by forming those lipofuscin granules

Exogenous pigment

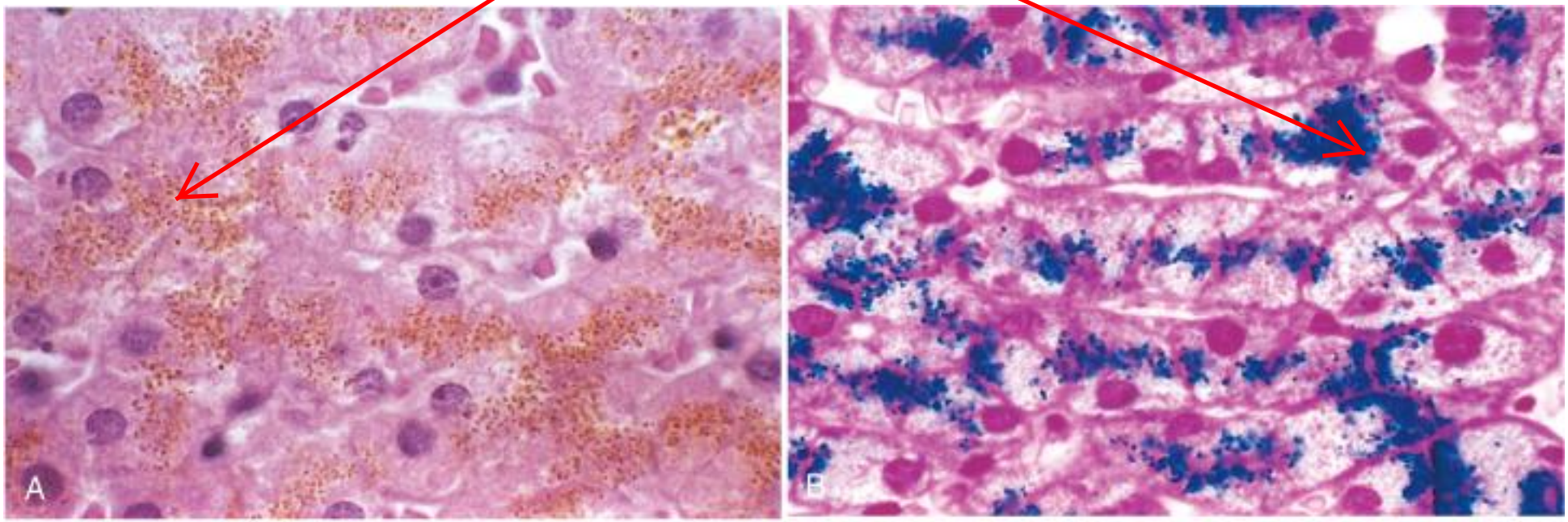
Anthracotic pigment in Lung



same tissue section, different stain

Endogenous pigment

Hemosiderin in Liver



H & E stain

with time, these hemosiderin depsosits will impair hepatic function and lead to cirrhosis

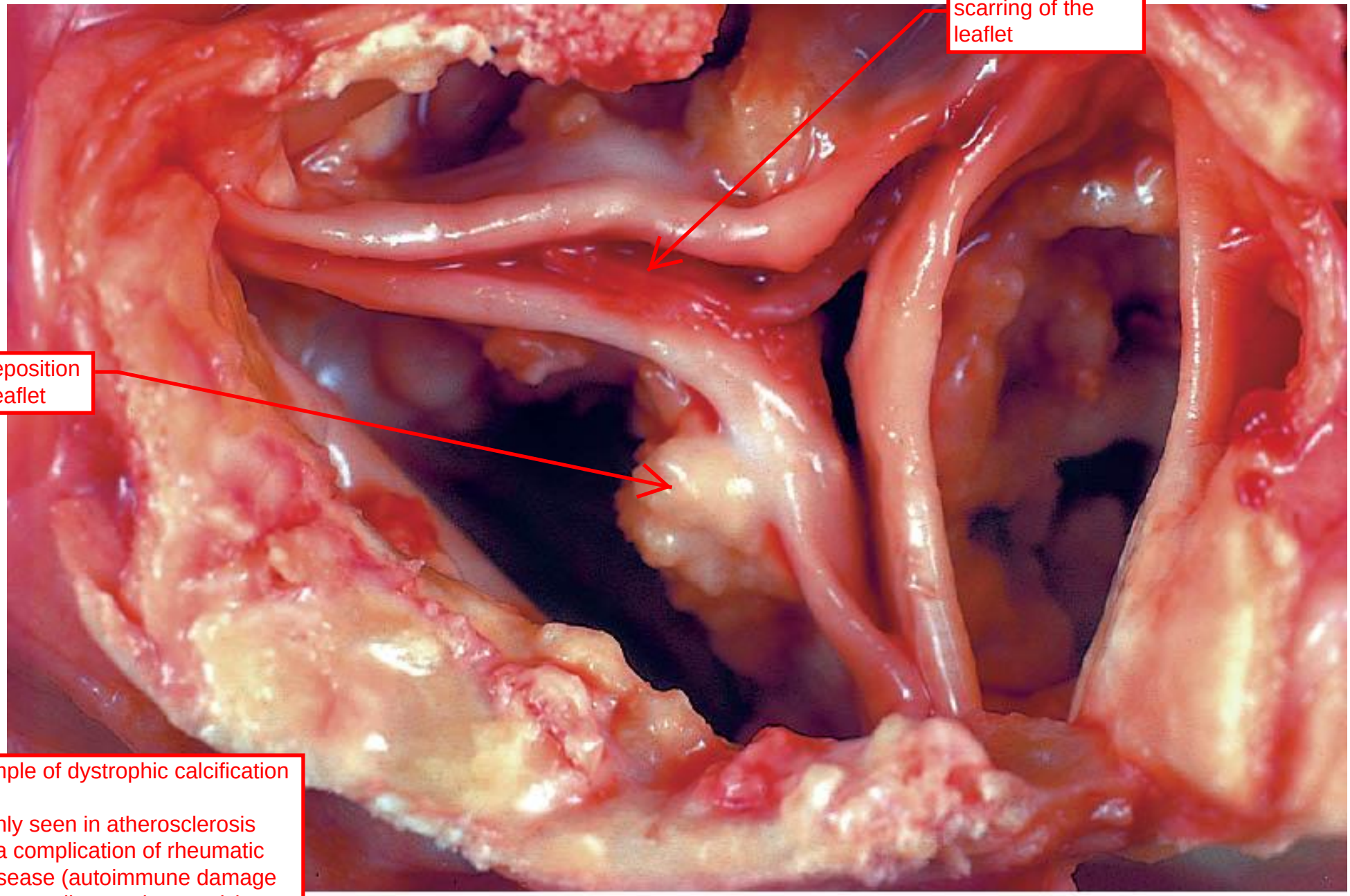
Pathologic Calcification

Dystrophic Calcification – occurs in areas of necrosis and atherosclerosis.

implies there is damage of underlying organ

Metastatic Calcification – occurs in normal tissues when there is hypercalcemia.

implies increased levels of circulating calcium



an example of dystrophic calcification
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commonly seen in atherosclerosis and as a complication of rheumatic heart disease (autoimmune damage to the myocardium and necrosis)

Metastatic Calcification

Excess Parathyroid hormone

Destruction of bone

Vitamin D disorders

Renal failure

increases circulating Ca2+ level and can lead to bone lysis.
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can be caused by vitamin D disorder and renal failure

most common

inadequate control of parathyroid function

A 22 year-old woman has congenital anemia that has required multiple transfusions of RBCs for many years. Which of the following findings would most likely appear in a liver biopsy specimen?

A. Steatosis in hepatocytes

B. Bilirubin in canaliculi

C. Glycogen in hepatocytes

D. Amyloid in the liver

E. Hemosiderin in hepatocytes

possible: bilirubin is a metabolite of hemoglobin, but we often see this in hepatic failure

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Summary

Intracellular accumulations

Lipids — often seen in atherosclerosis

Proteins — associated with neoplastic or genetic disorder

Glycogen — also often associated with genetic disorder

Pigments

Pathologic Calcification — dystrophic or metastatic

Conclusions

Cell injury may occur by a variety of mechanisms and sources - **endogenous (ischemia/inflammation)** or **exogenous (drugs/toxins)**

Cell injury can be **reversible or irreversible.**

Reversible cell injury can result in changes which **may recover** when the cause is removed, **or which may persist**.

Irreversible (lethal) cell injury may cause only **transient functional impairment if the dead cells can be replaced.**

Alternatively, lethal cell injury may lead to **permanent functional impairment if the dead cells can not be replaced.**

Cell death **(apoptosis) is a normal mechanism** to remove damaged cells which can be activated in pathologic conditions.

Substances may be deposited within cells in response to cell injury.

All clinical disease arises from abnormal cell structure and function.