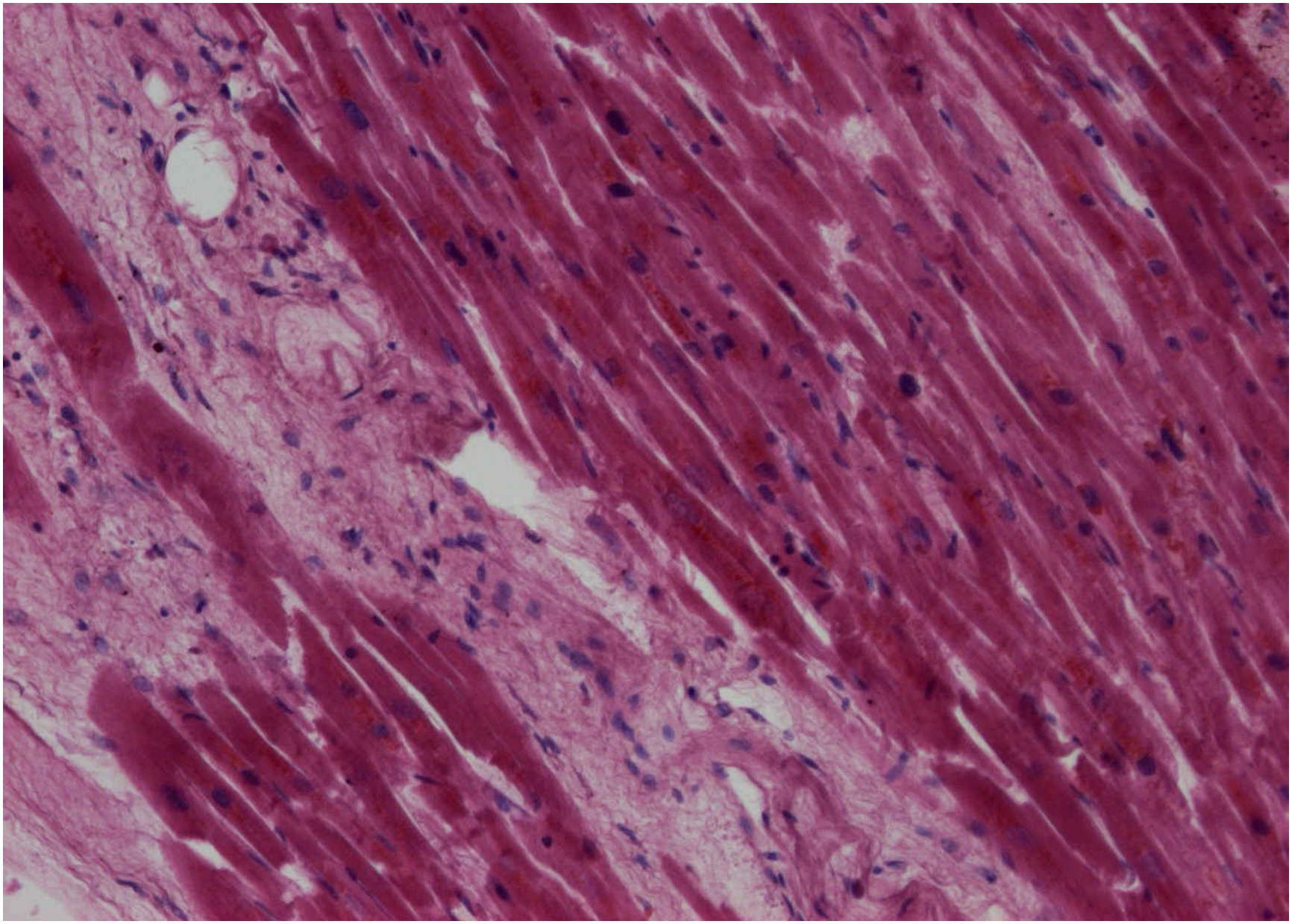
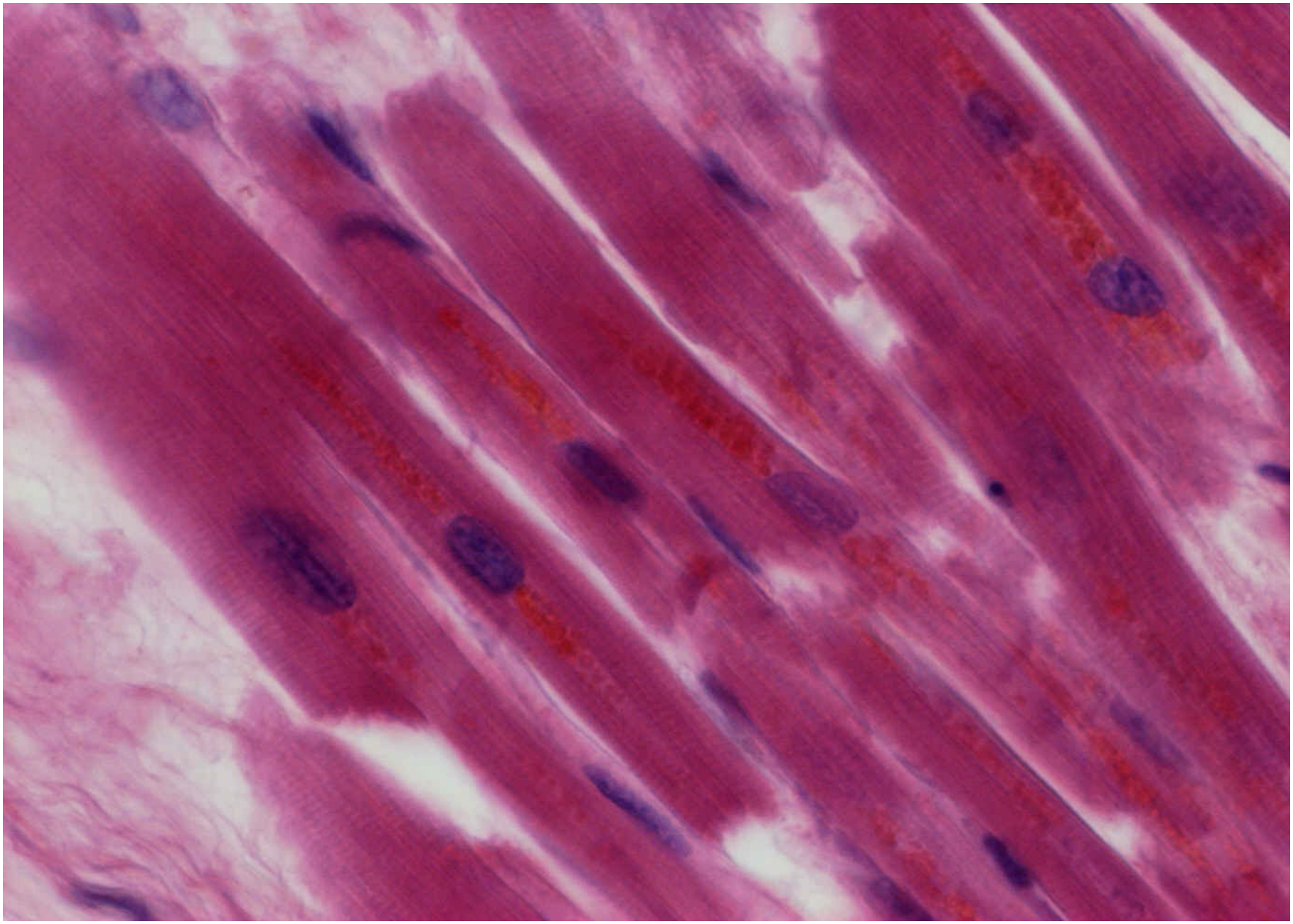
Atrophy, Impaired cell metabolism and - Pathologic Adaptations

Atrophy

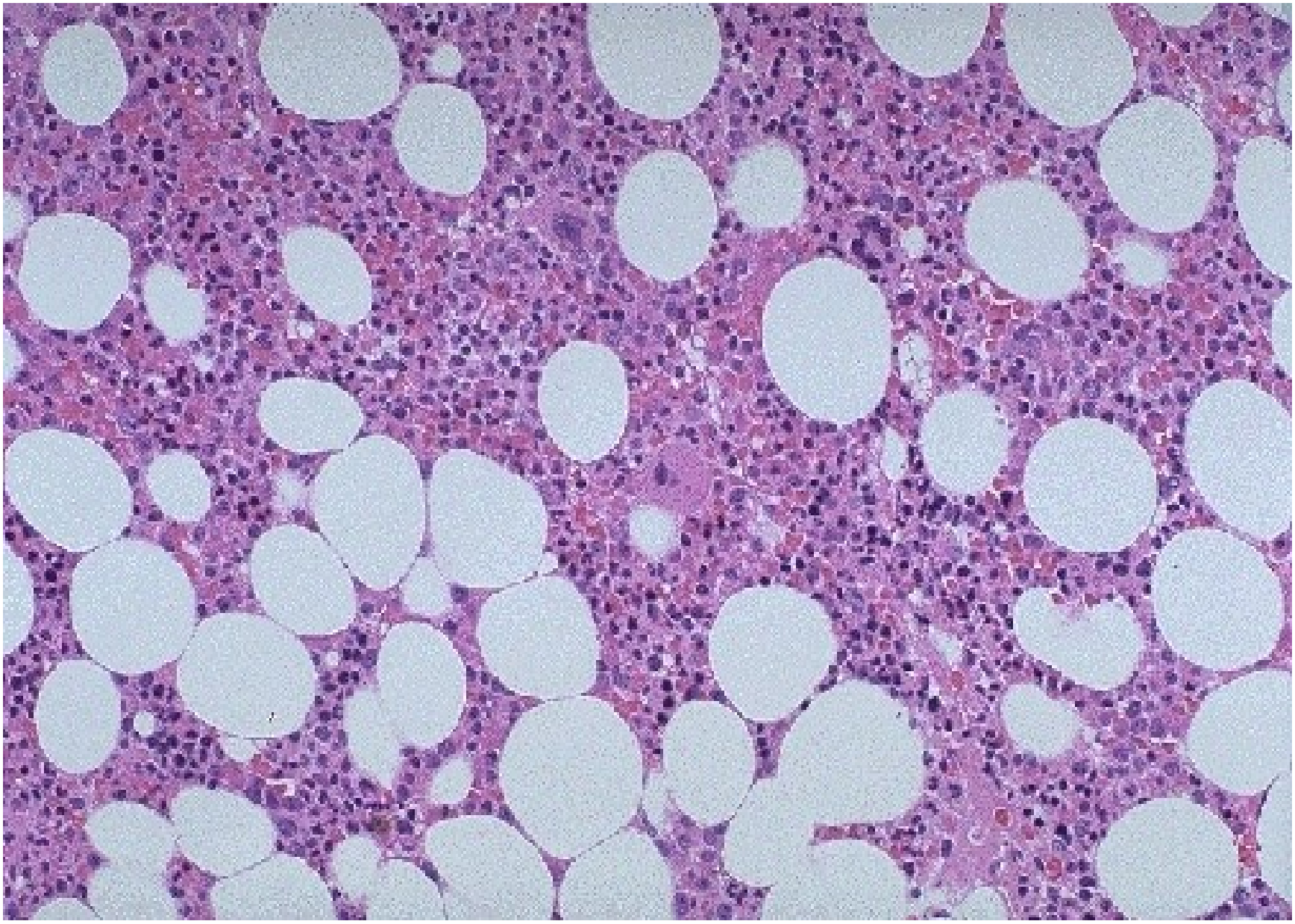
- **Atrophy** – is shrinkage in the size of the cell or the initially normally developed organ (dif.dg. hypoplasia – inborn reduction in the size of the organ, insufficient development of the organ)
- **Simple atrophy of an organ** – shrinkage in the size of cells of an organ whereas the number of cells constituting the organ or a the tissue is preserved – microskopically : pyknotic nuclei, encreased basophilia of cytoplasm, accumulation of lipofuscin, reserve substances are disappearing (lipids, glycogen)
- **Numerical atrophy of an organ** – shrinkage in the size of an organ due to decreasing number of cells constituting the organ (example – atrophy of the red bone marrow in old age)
- **Pseudohypertrophy** – organ seems to be enlarged, but the amount of functional parenchyma is reduced (example – lipomatous atrophy of pancreas)



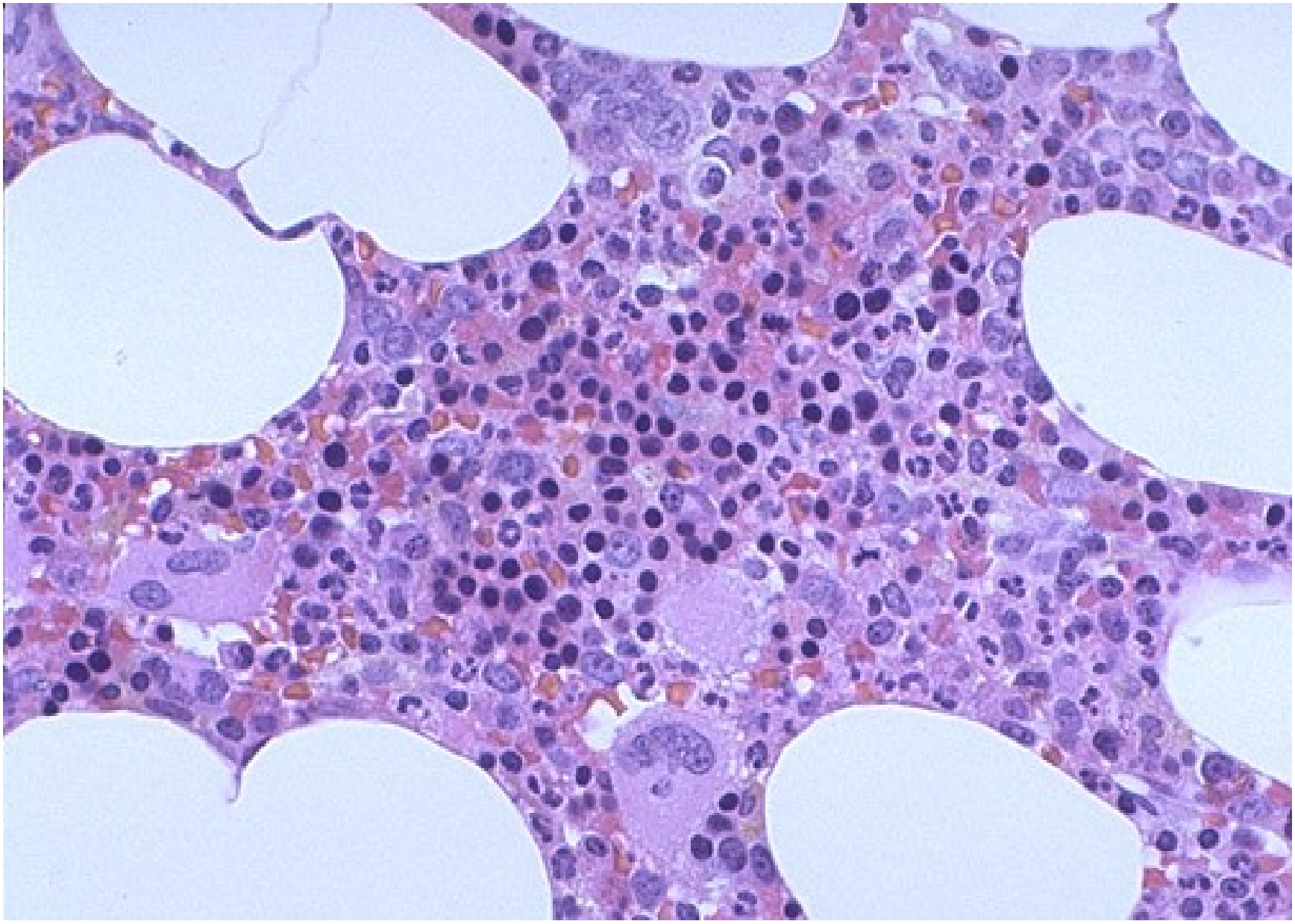
Example of atrophy – myocardium – atrophia fusca (brown atrophy)



Example of atrophy – myocardium – atrophia fusca (brown atrophy) - detail

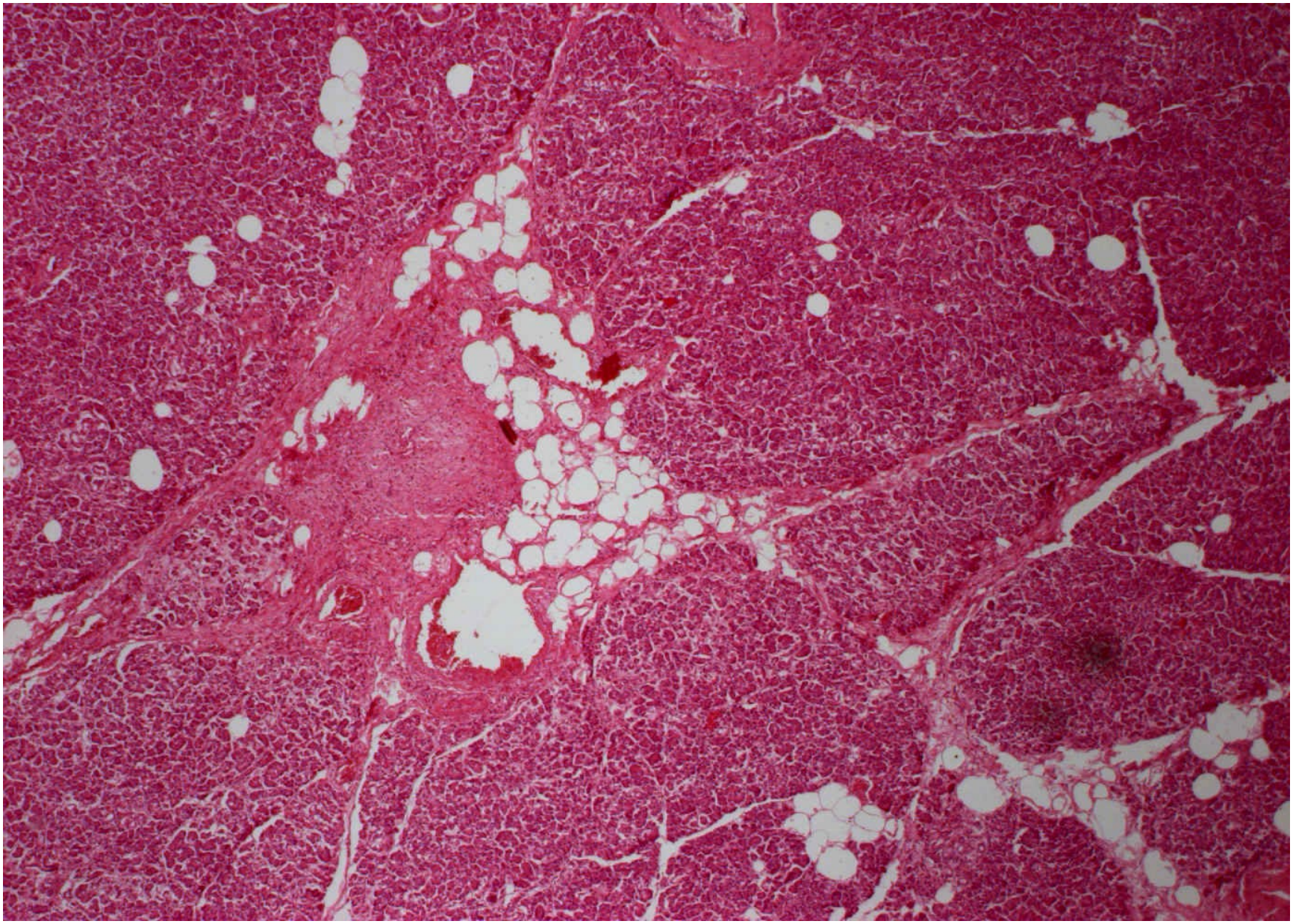


Normal bone marrow in a 5O year-old person

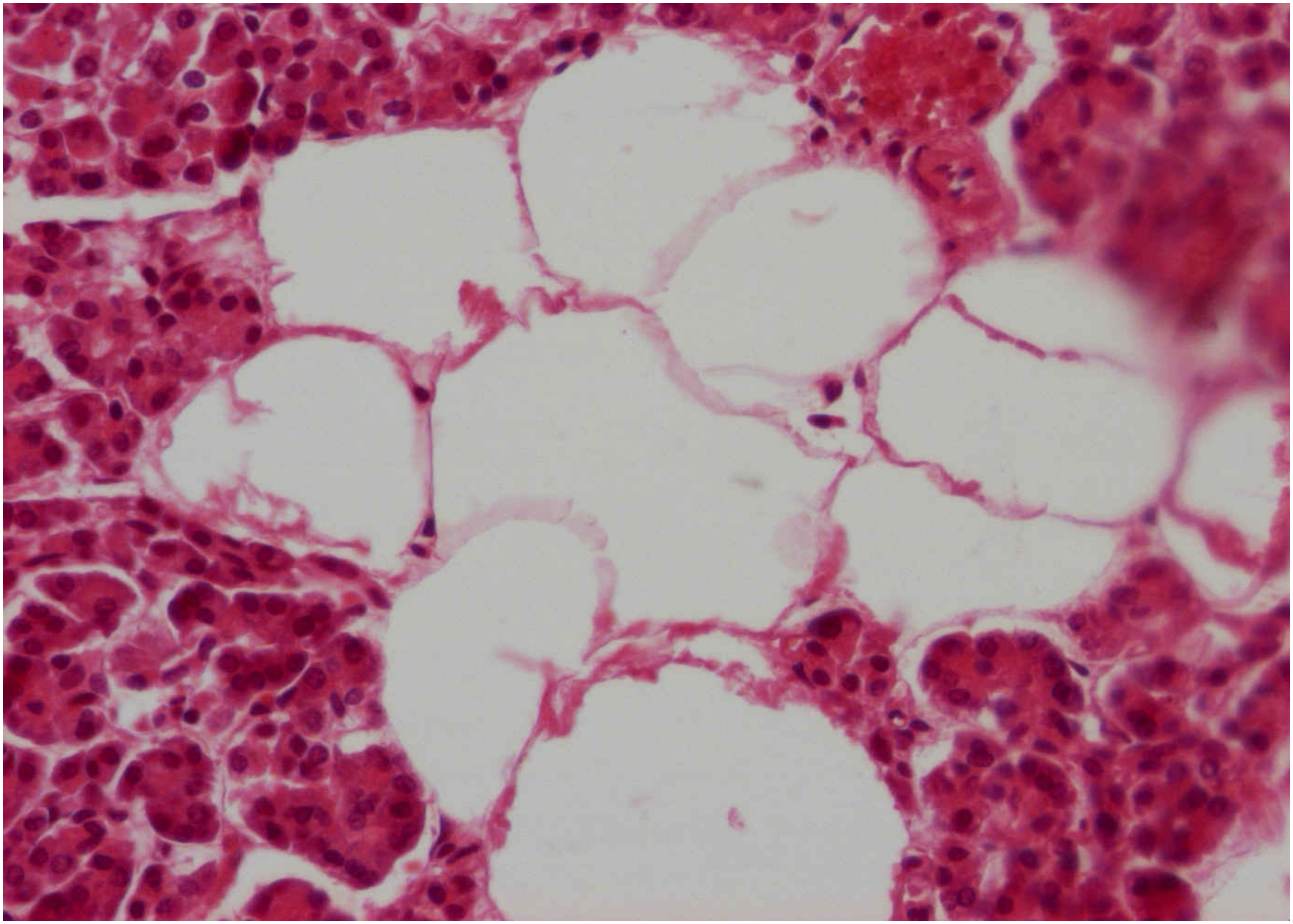


Normal bone marrow in a 50 year-old person – detail

Example of pseudohypertrophy – lipomatous atrophy of pancreas



Lipomatous atrophy of pancreas – ingrowth of fatty tissue



Lipomatous atrophy of pancreas – ingrowth of fatty tissue

Atrophy – common causes

- Aging – senile atrophy – particularly the brain and heart
- Inadequate nutrition – marasmus – atrophy of skeletal muscles (precedes the parenchymatous organs atrophy)
- Pressure atrophy – ex. compression of gingiva by false denture
- Inactivity atrophy – ex. broken limb immobilised in a plaster cast
- Denervation atrophy – ex. polyomyelitis – loss of motor neurons in the anterior horns of the spinal cord – neurogenic atrophy of denervated muscle
- Loss of endocrine stimulation – ex. osteoporosis in postmenopausal women, iatrogenic impact!!

Impaired cell metabolism

(intracellular accumulations)

- Moderate degree of cellular regression (impaired cell metabolism – atrophy – necrosis)

- Inborn – caused by genetic defects – lysosomal enzymatic defects, ex. glycogenosis…
- Acquired – acquired metabolic defects of different substances : : proteins, lipids, glycids, water a electrolytes

Intracellular accumulations - mechanisms

- A normal endogenous substance is produced at a normal or increased rate, but the rate of metabolism is inadequate to remove it (ex. fatty change in the liver because of intracellular accumulation of triglycerides)
- A normal or abnormal endogenous substance accumulates because of genetic or acquired defects in the metabolism, packaging, transport, or secretion of these substances. (ex. „storage diseases“ – lysosomal enzymatic defects)

Defects in protein metabolism

(accumulation of proteins)

- **1) Hyaline droplets**

  Hyaline – a. The uniform matrix of hyaline cartilage.

  b. A translucent product of some forms of tissue degeneration. Homogenous, eosinophilic substance – this concept HAS NOT!! the exact chemical definition
- *Mallory bodies* – accumulation of tangled skeins of cytokeratin filaments in cytoplasm of alcohol-damaged hepatocytes
- *Russell bodies* – distended ER in plasma cells in case of excessive synthesis of immunoglobulins
- *Alfa1-antitrypsin deficiency* – accumulation of A1AT intermediates in the ER of hepatocytes

Defects in protein metabolism

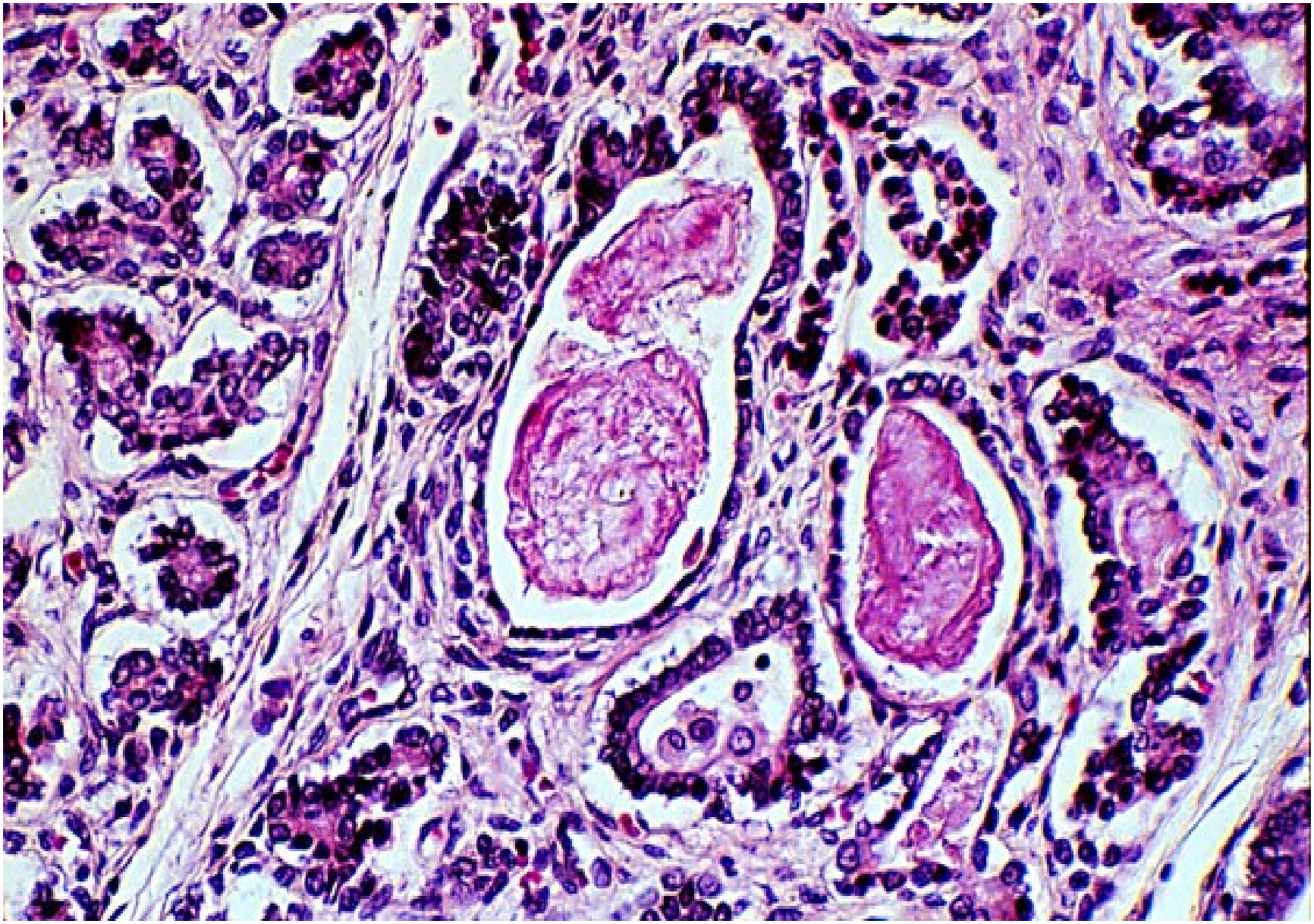
- **2) Depositions of mucosubstances**

- Accumulation of epithelial mucosubstances – ex. cystic fibrosis (mucoviscidosis)
- Accumulation of connective tissue mucosubstances – ex. myxedema, mucopolysaccharidosis

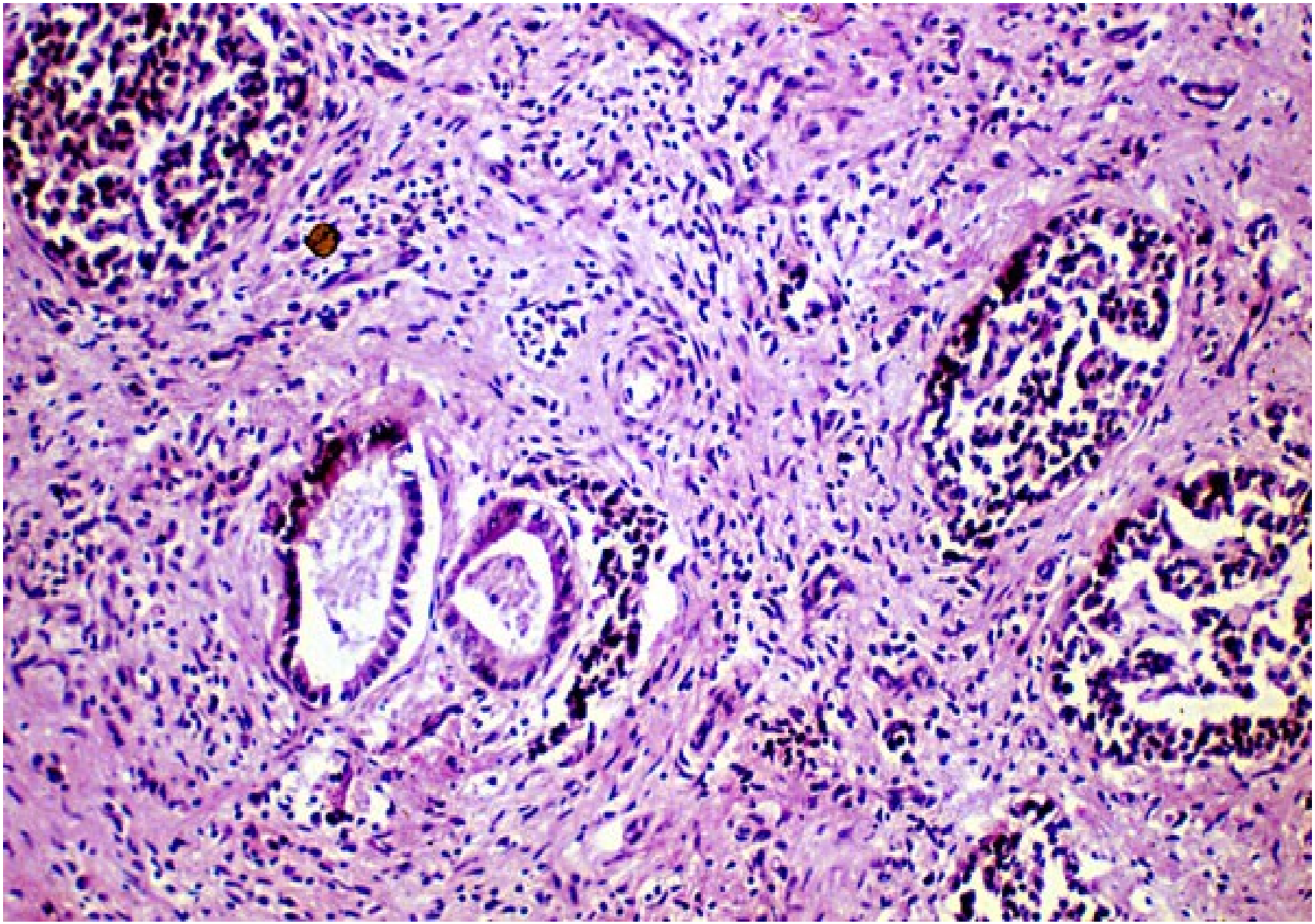
Defects in protein metabolism

cystic fibrosis

- AR transmission, defect of gene encoding a chloride channel protein CFTR
- In normal conditions – chloride channels open after their activation and permit the secretion of chloride ions (and water) to EC surroundings
- In CF – chloride channels are only partially active or inactive – increased viscosity of mucus
- Affected organs – lungs, pancreas, liver, intestines, sweat glands
- !!! Increased concentration of salt in the sweat (the basis for the sweat test) !!!



Cystic fibrosis in pancreas – initial stage



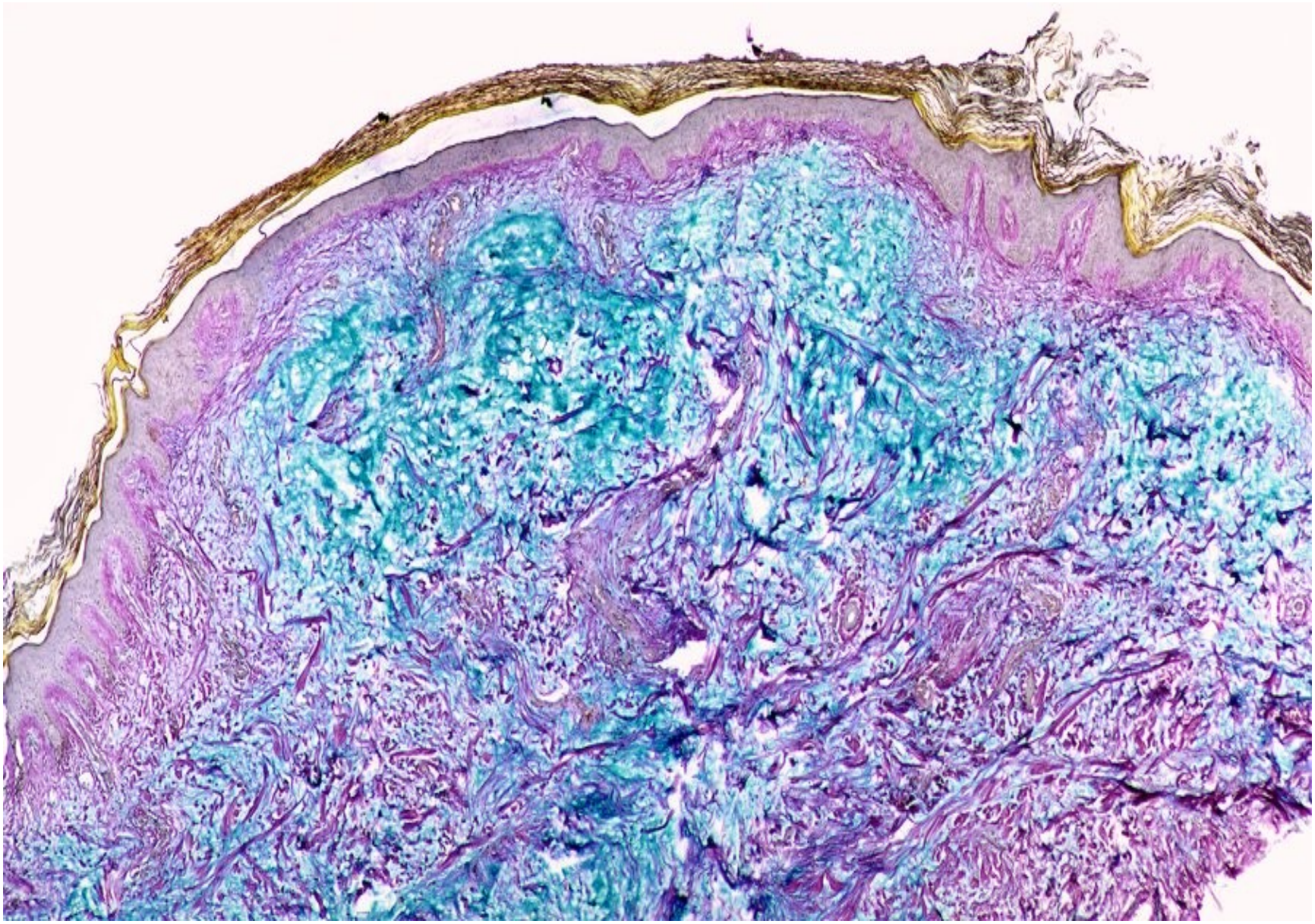
Cystic fibrosis in pancreas – advanced stage – atrophy of parenchyma, fibrosis

Defects in protein metabolism

cystic fibrosis

- Lungs - clogging the airways due to mucosa build-up and resulting inflammation.
- GIT – meconium ileus, volvulus, rectal prolaps…
- Pancreas – maldigestion, malabsorption, steatorrhea, deficiency of the fat-soluble vitamins → poor growth and development
- Liver - cirrhosis
- Skin – salty sweat

- Dg. – clinical signs, sweat testing, genetic testing



Pretibial myxedema – alcian blue stain

Defects in protein metabolism

mucopolysaccharidoses

- Group of related syndromes that result from genetically determined deficiencies of lysosomal enzymes involved in the degradation of mucopolysaccharides
- Glycosaminoglycans (GAG) – long-chain complex carbohydrates linked with proteins to form proteoglycans – they are abundant in the ground substance of connective tissue
- Accumulating metabolites – keratan sulfate I+II, heparan sulfate, dermatan sulfate, chondroitin sulfate

Defects in protein metabolism

mucopolysaccharidoses

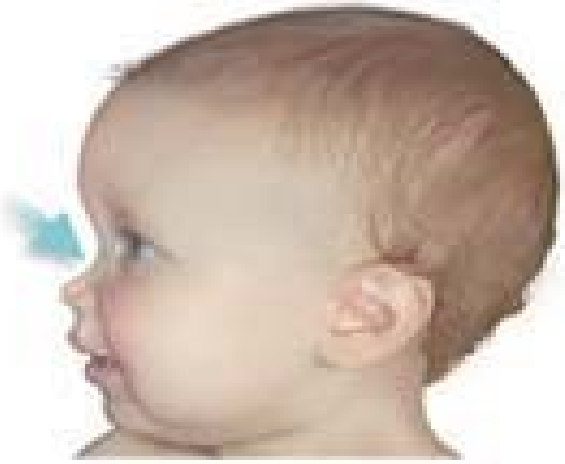
- Accumulated GAG are found in mononuclear phagocytic cells, intimal smooth muscle cells, endothelial cells, fibroblasts.
- Involved organs – spleen, liver, bone marrow, lymph nodes, blood vessels and heart → hepatosplenomegaly, subendotelial arterial deposits (particularly in the coronary!! arteries), valvular lesions, skeletal deformities, lesions in the brain…
- Microscopically – cells are distended with clearing of the cytoplasm, minute vacuoles with PAS-positive material

Defects in protein metabolism

mucopolysaccharidoses - examples

- Hurler syndrome (MPS I) – AR, deficiency of α-L-iduronidase – one of the most severe forms of MPS, developement of hepatosplenomegaly by 6 to 24 months, retarded growth, mental retardation, clouding of the cornea, deafness, coarse facial features as a „low nasal bridge“, skeletal deformities (joint stiffness), death by 6 to 10 years of age
- Hunter syndrome (MPS II) – X-linked, milder clinical course, mental retardation, agresivity, hyperactivity (juvenile form), absence of corneal clouding.

Normal nasal bridge



Low nasal bridge

Defects in protein metabolism

amyloidosis

- **Amyloid** – amorphous, eosinophilic, hyaline substance, chemically heterogenous, deposited between cells extracelullarly! in various tissues in a wide variety of clinical settings
- *Physical nature of amyloid* – amyloid fibrils, β-pleated sheet conformation (95%) + P component and other nonfibrillary glykoprotein (5%)
- *Chemical nature of amyloid*
  - AL-amyloid – immunoglobulin light chains
  - AA-amyloid – SAA-protein synthesized by the liver, acute-phase protein
  - Hemodialysis-associated amyloidosis – β2-mikroglobulin
  - …

Defects in protein metabolism

AL amyloidosis

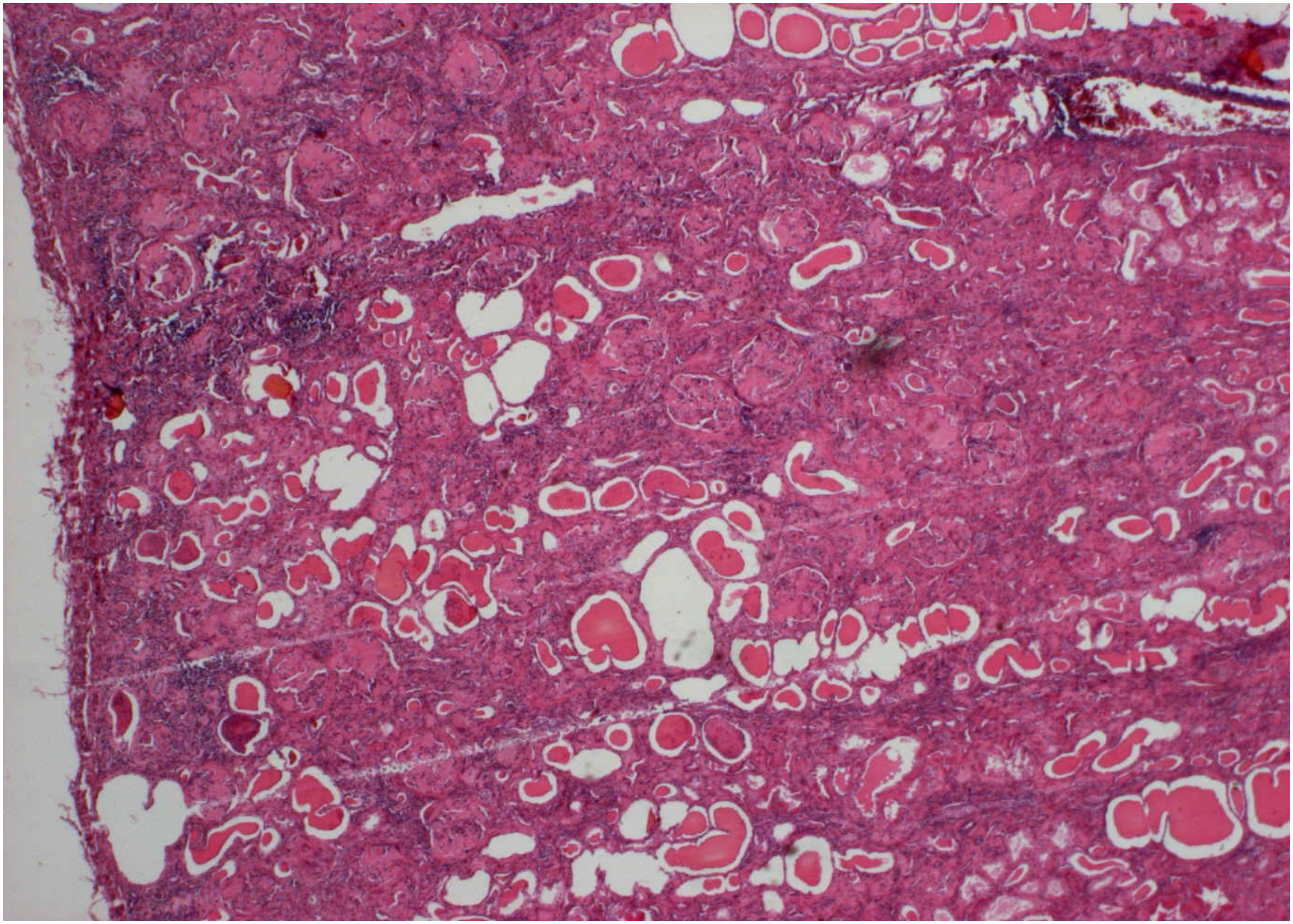
- Pathogenesis – ex. multiple myeloma (MM)

- MM – clonal proliferation of plasma cells, myeloma cells are then able to synthesize monoclonal immunoglobulins (either whole molecule or less often only light chain)
- Symptoms of MM
  - Myeloma cells cytokines – osteolytic lesions throughtout of skeletal system, immunosuppression
  - Monoclonal immunoglobulin (myeloma nefropathy „myeloma kidney“)
  - Repression of hematopoesis

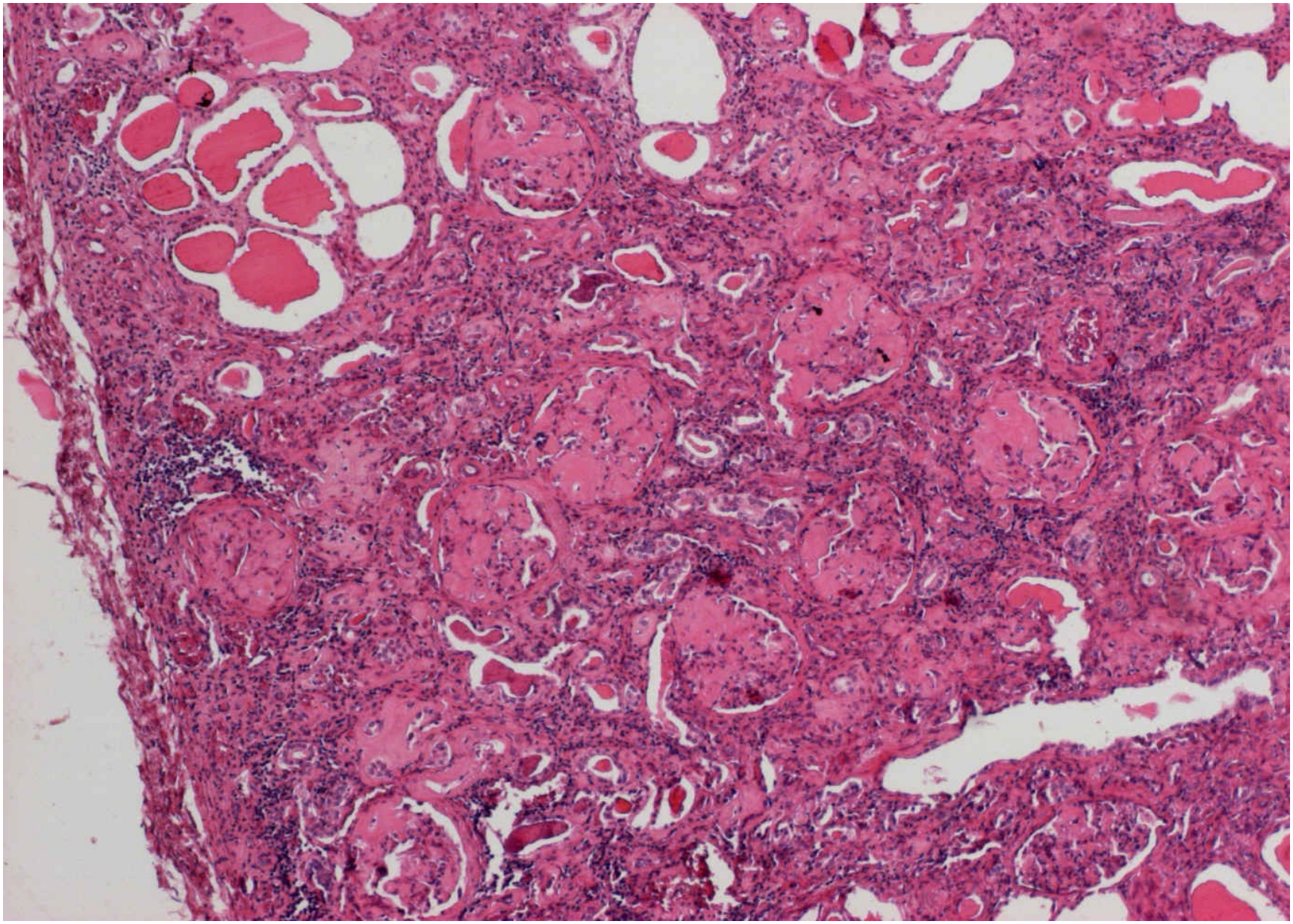
Defects in protein metabolism

AL – amyloidosis – myeloma kidney

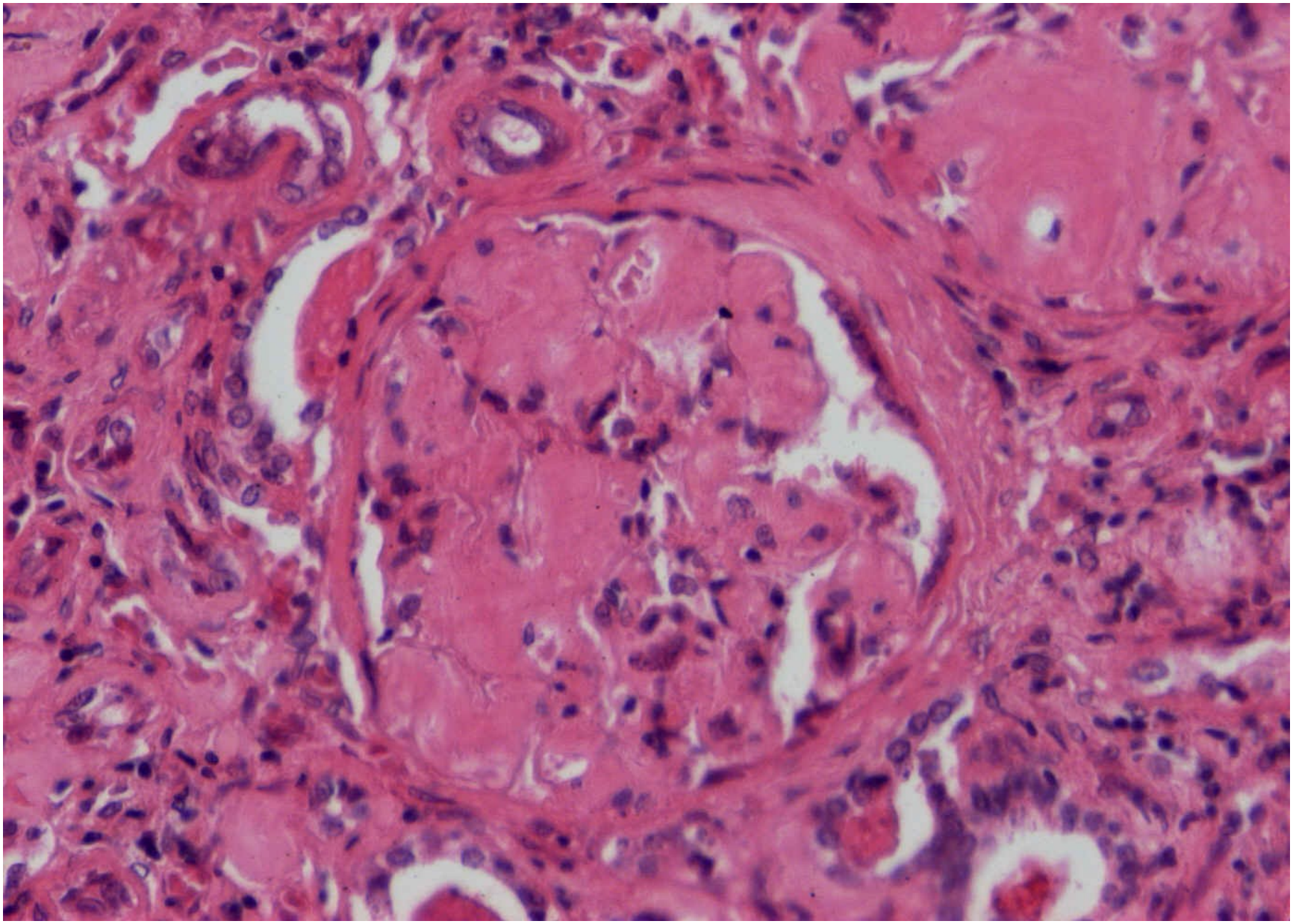
- Deposition of immunoglobulin light chains in the glomeruli or around tubules (light-chain nephropathy)
- Bence Jones proteinuria and cast nephropathy - formation of histologically distinct tubular casts in the distal tubuli and collecting ducts that obstruct the tubular lumina and induce a peritubular inflammatory reaction
- Amyloidosis
- Result is irreversible damage of renal functions with the renal failure and a necessity of hemodialysis!!!



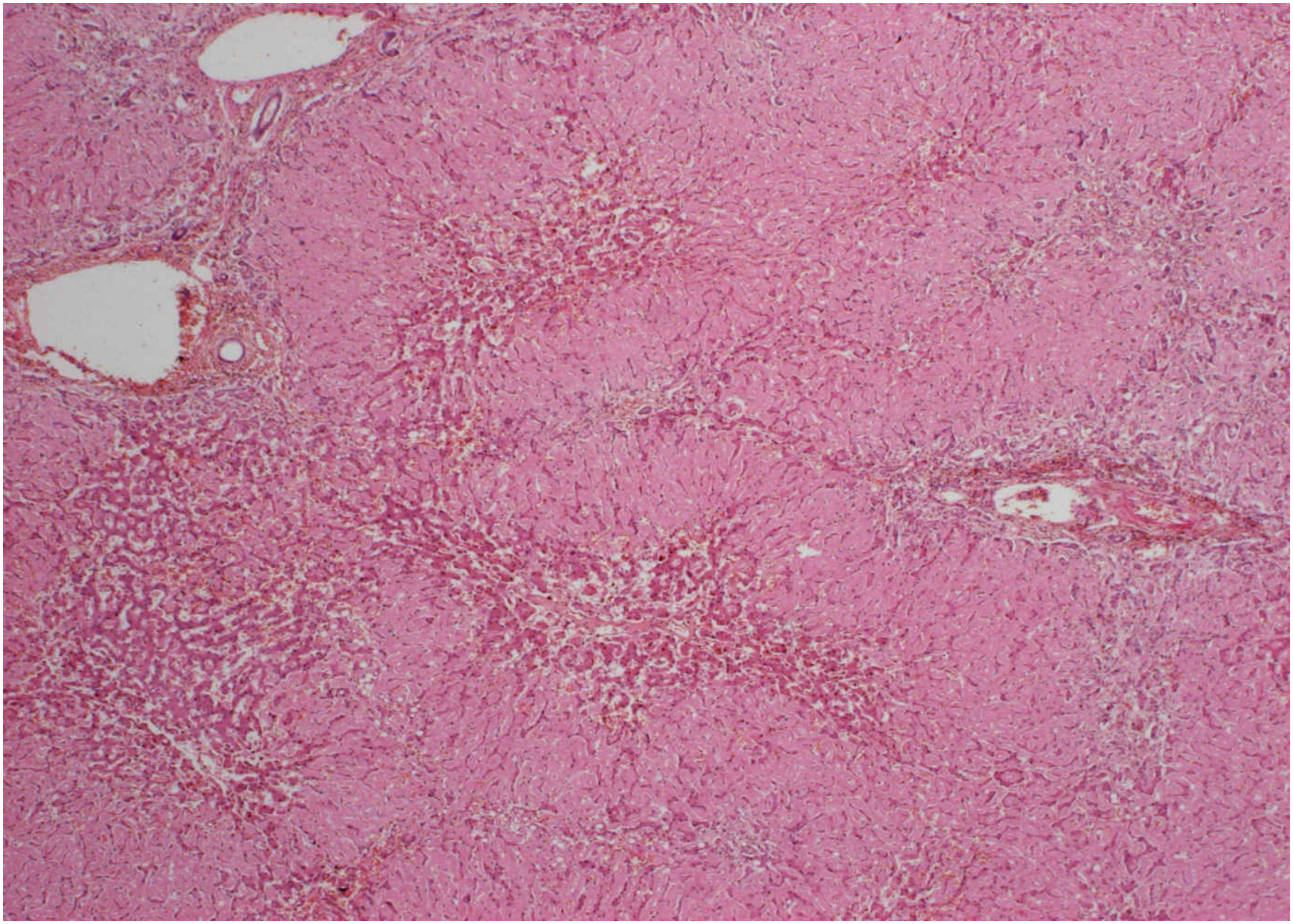
Secondary AL amyloidosis- tubular casts



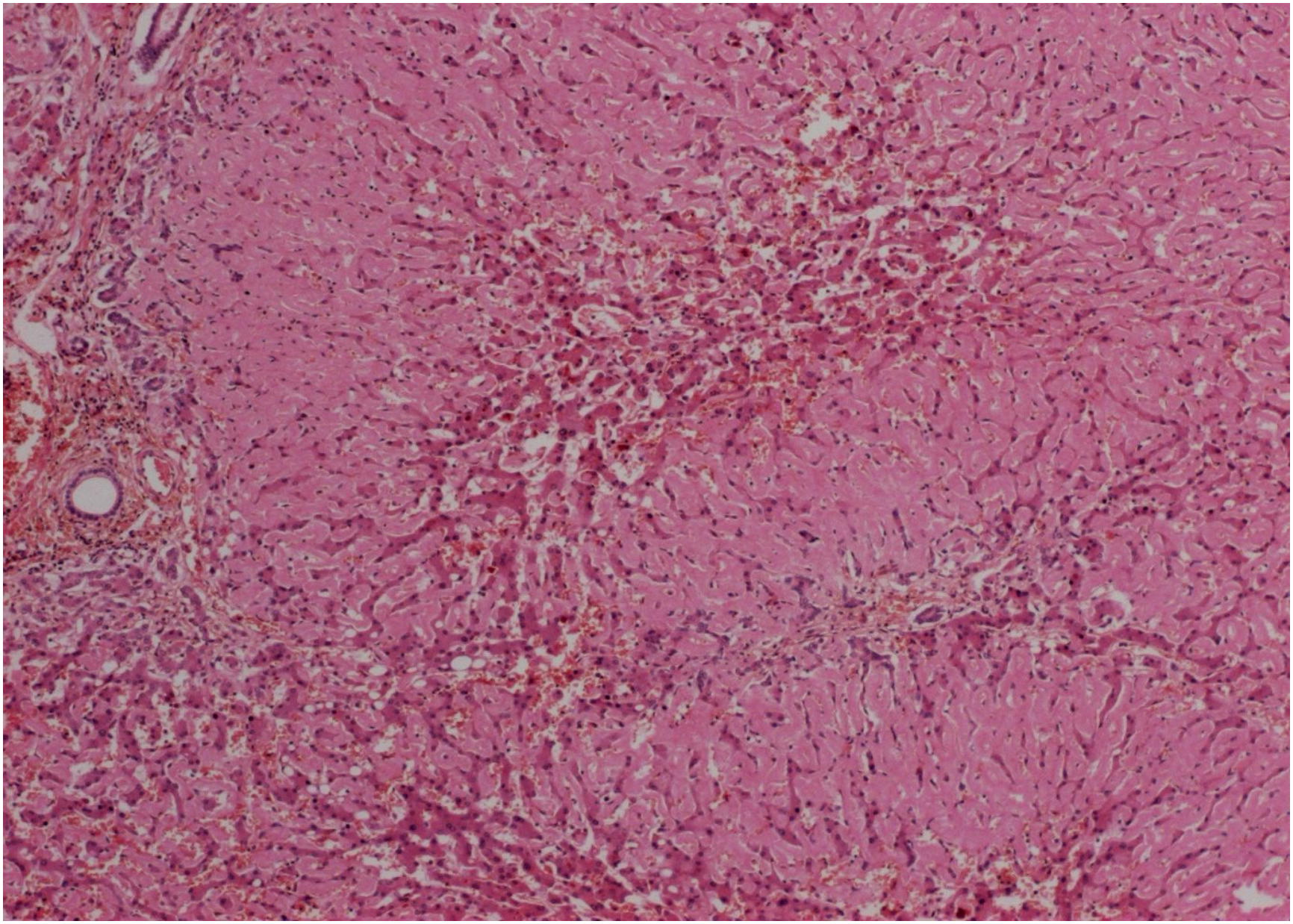
Secondary AL – amyloidosis, kidney



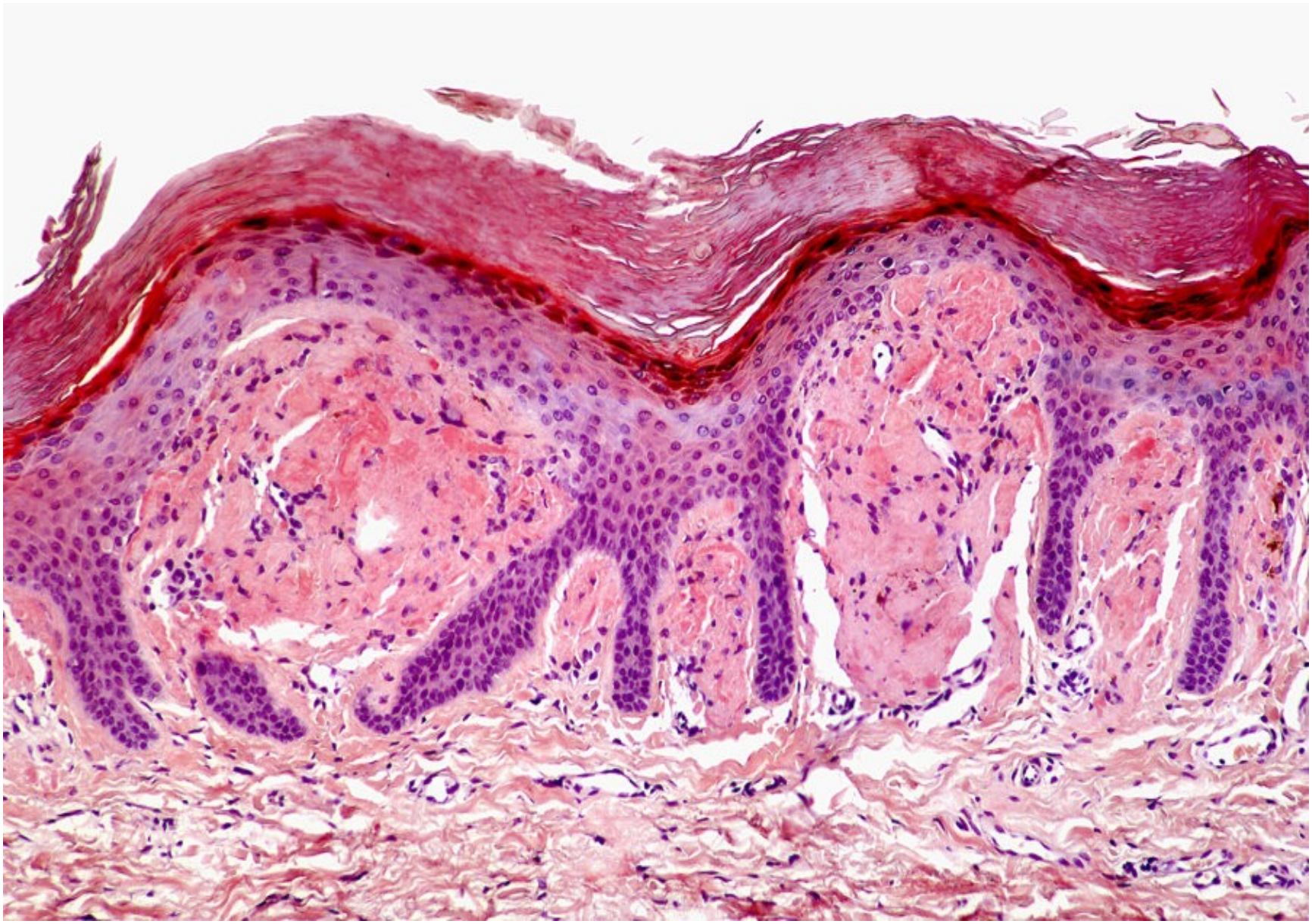
Secondary AL – amyloidosis,MM, kidney



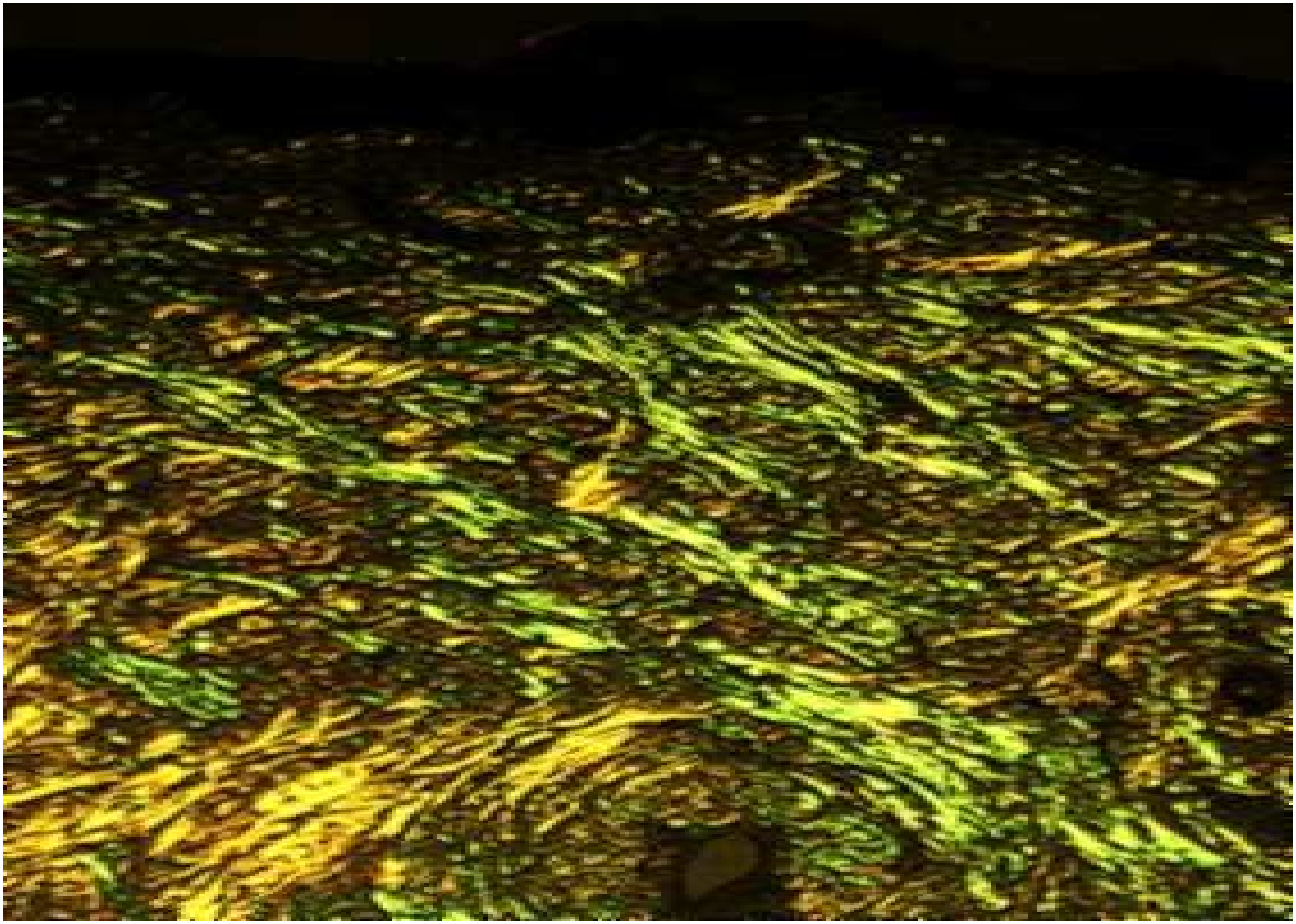
Amyloidosis of liver



Amyloidosis of liver - detail



Skin amyloid – Congo red stain



amyloid – Congo red stain – green birefringence under polarized light

Defects of lipid metabolism

- Intracelullar accumulation of lipids – mitochondrial dysfunction, lysosomal dysfunction
- Extracellular accumulation of lipids – lipomatosis
- Hyperlipoproteinaemia

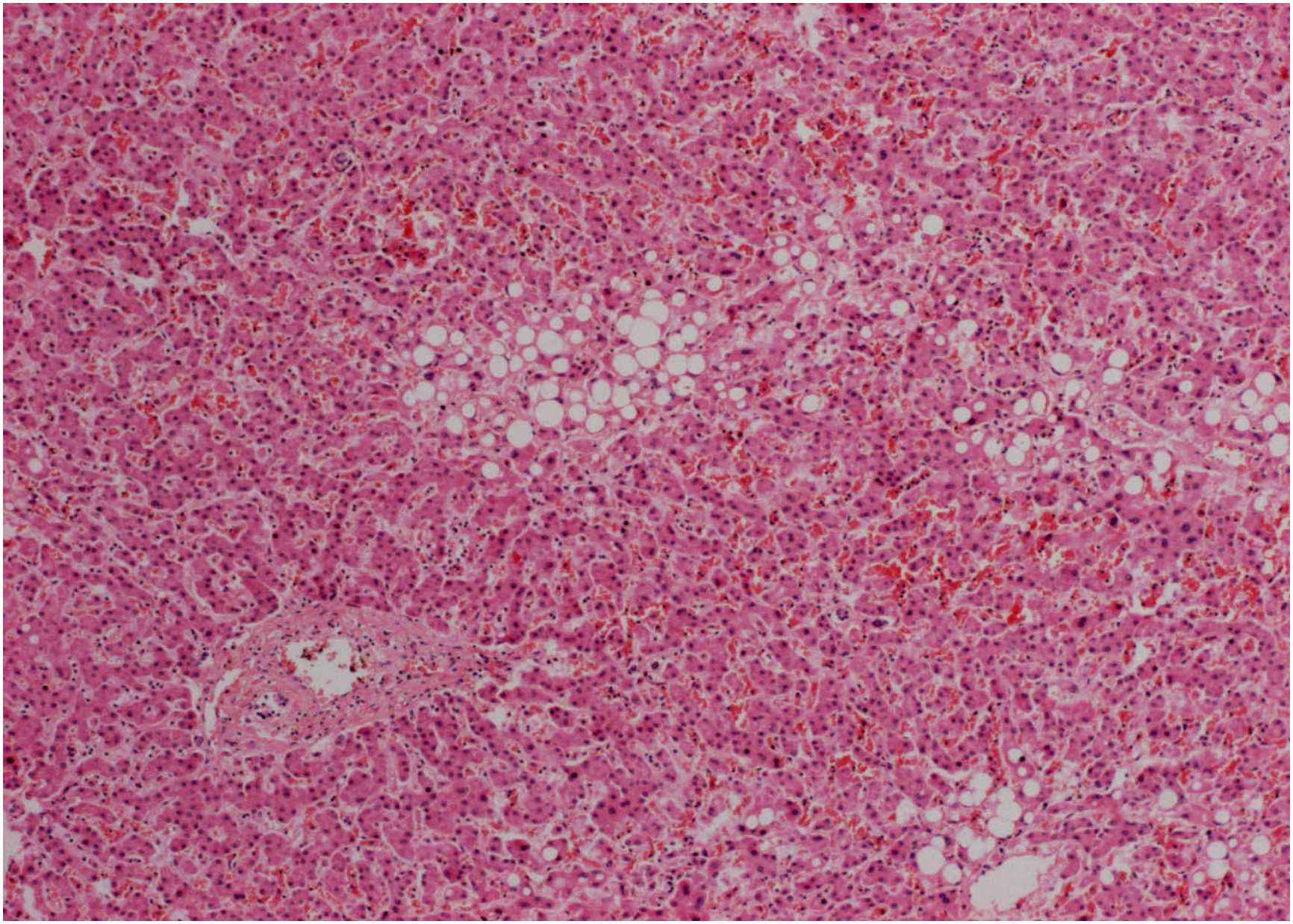
- Triglycerides
- Cholesterol esters
- Fatty acids

Defects of lipid metabolism

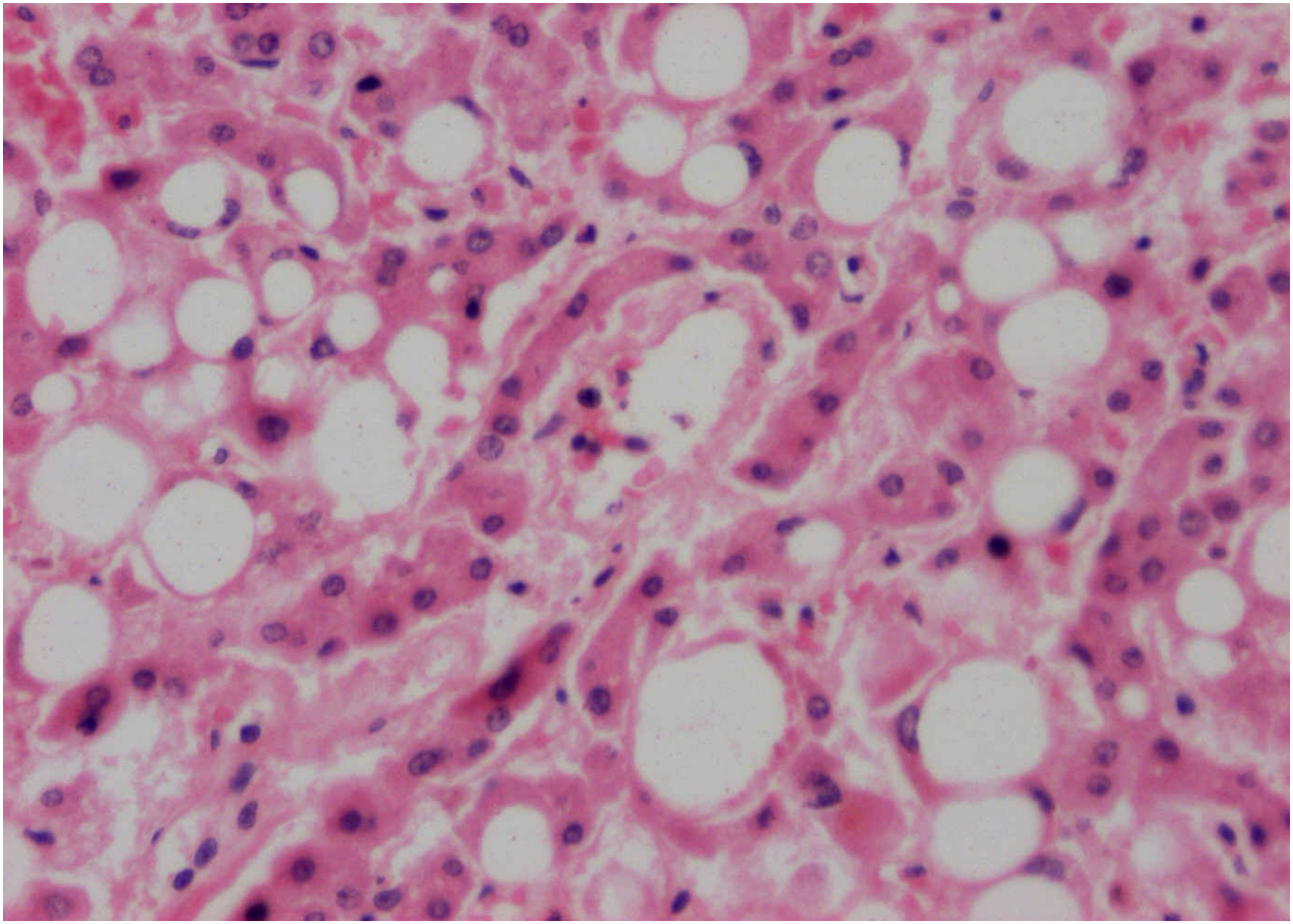
steatosis, fatty change

- Abnormal triglycerides accumulations within parenchymal cells
- Etiology – toxins (alcohol!!), protein malnutrition, diabetes mellitus, obesity…

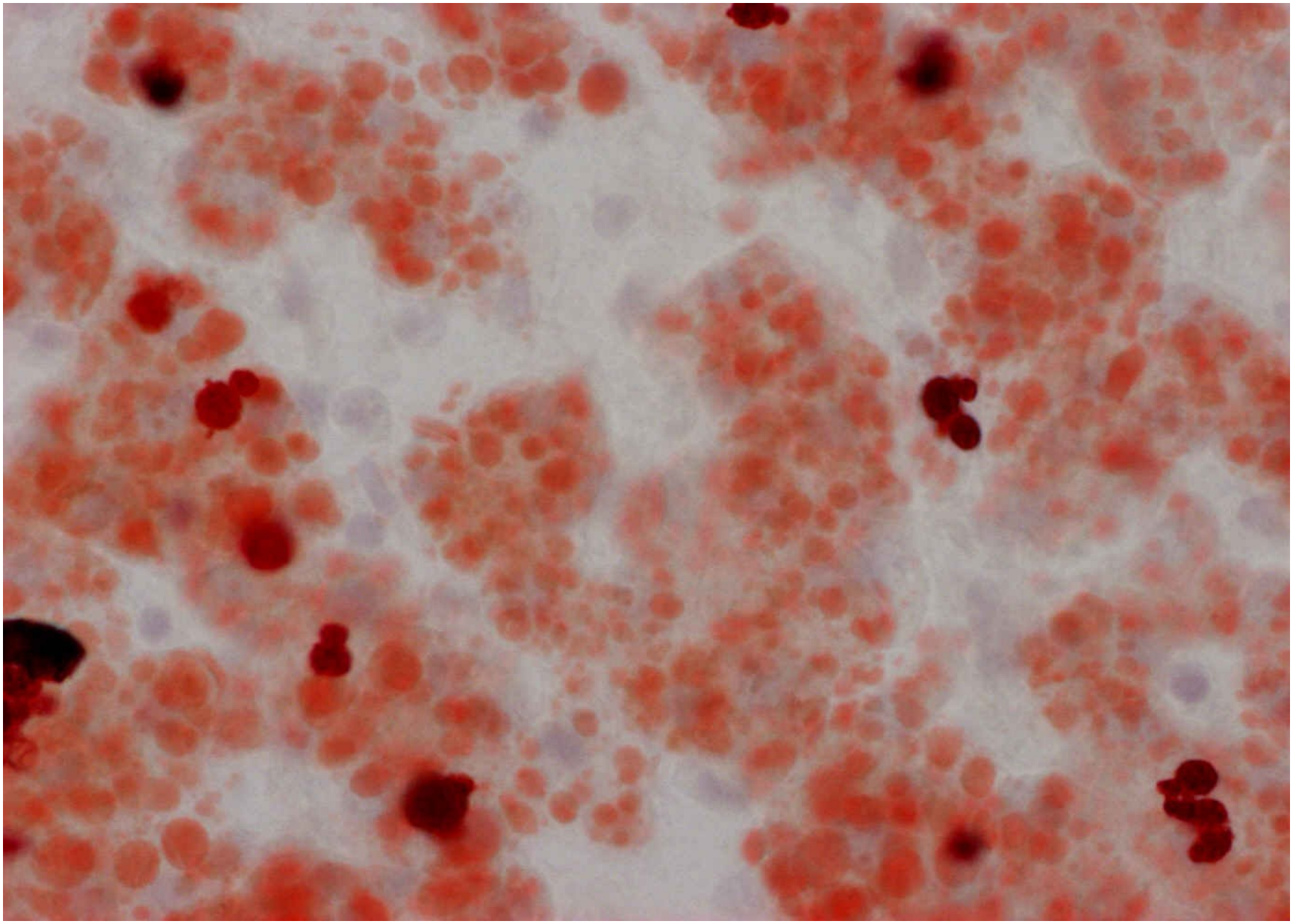
- Mechanisms of alcohol effect – ethanol si oxidised by alcohol dehydrogenase and give rise to the acetaldehyd formation, NADH is produced within this reaction, increased concentration of NADH inhibits the oxidation of fatty acids, and amplify thier esterification to triglycerides



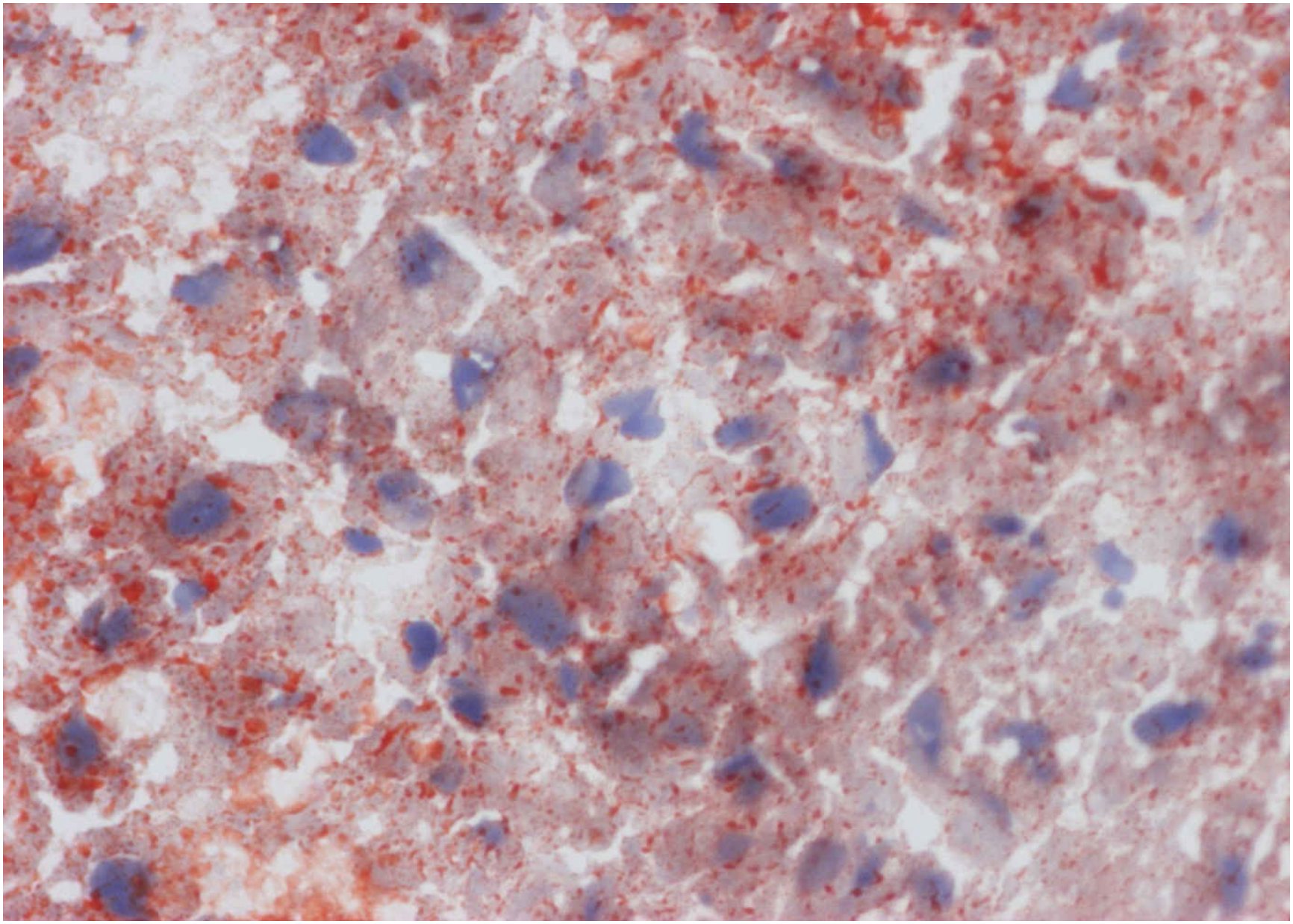
Hepatic steatosis (centrolobular macrovesicular)



Fatty liver, macrovesicular - detail



Fatty liver (mikrovesicular) – frozen tissue section, oil red-O stain



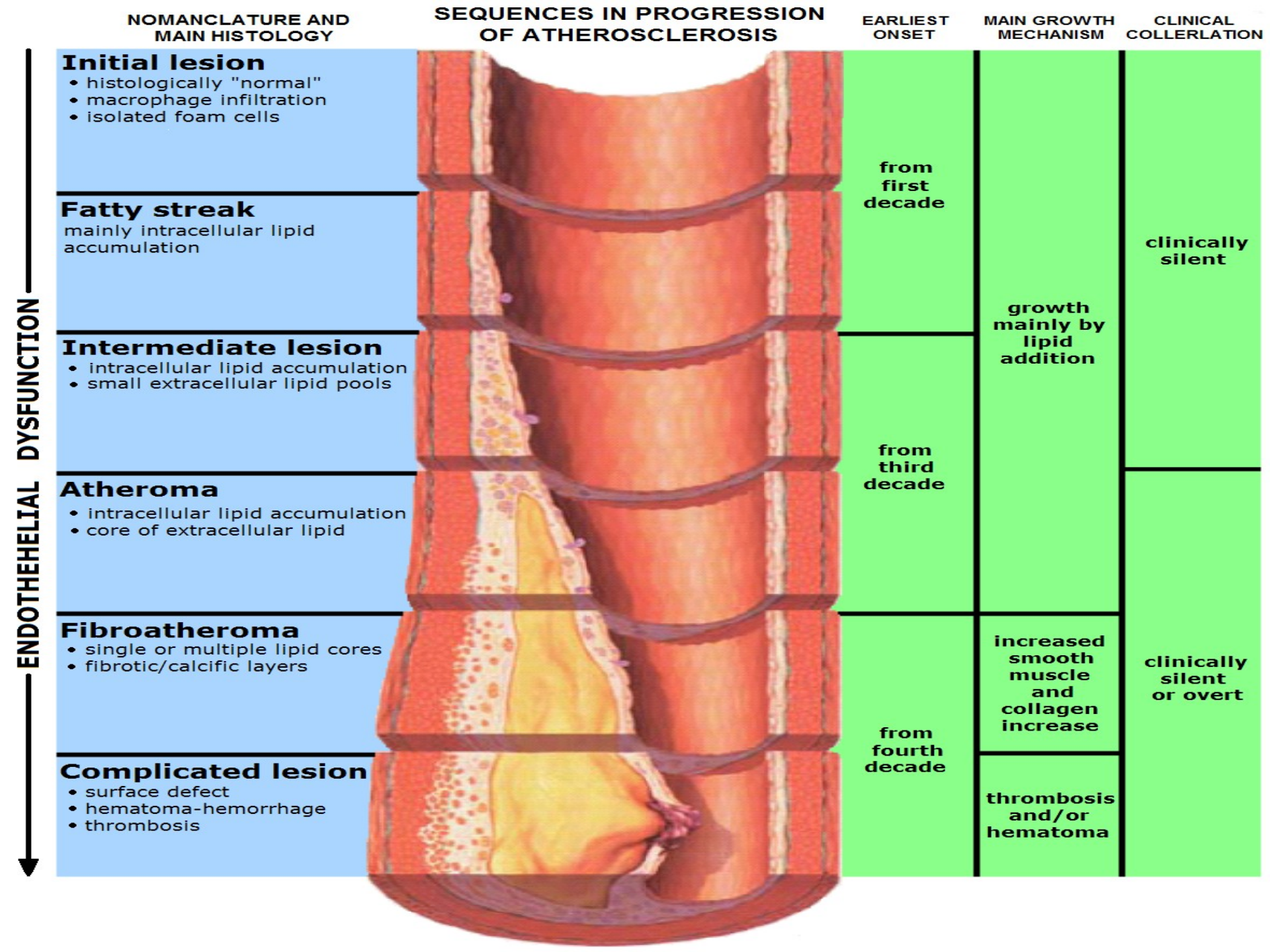
Hepatic steatosis – frozen section, oil red–O stain

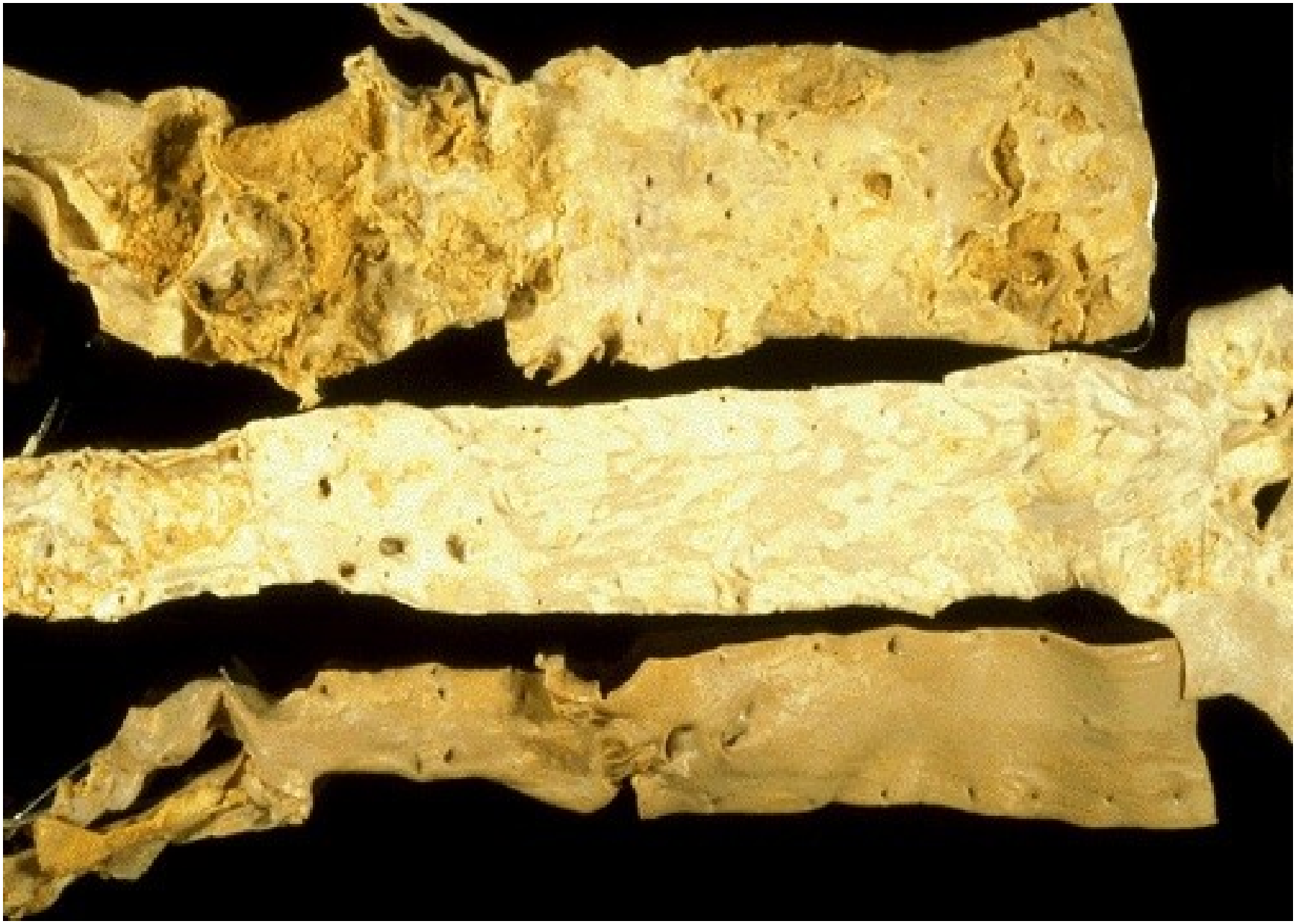
Defects of lipid metabolism

atherosclerosis

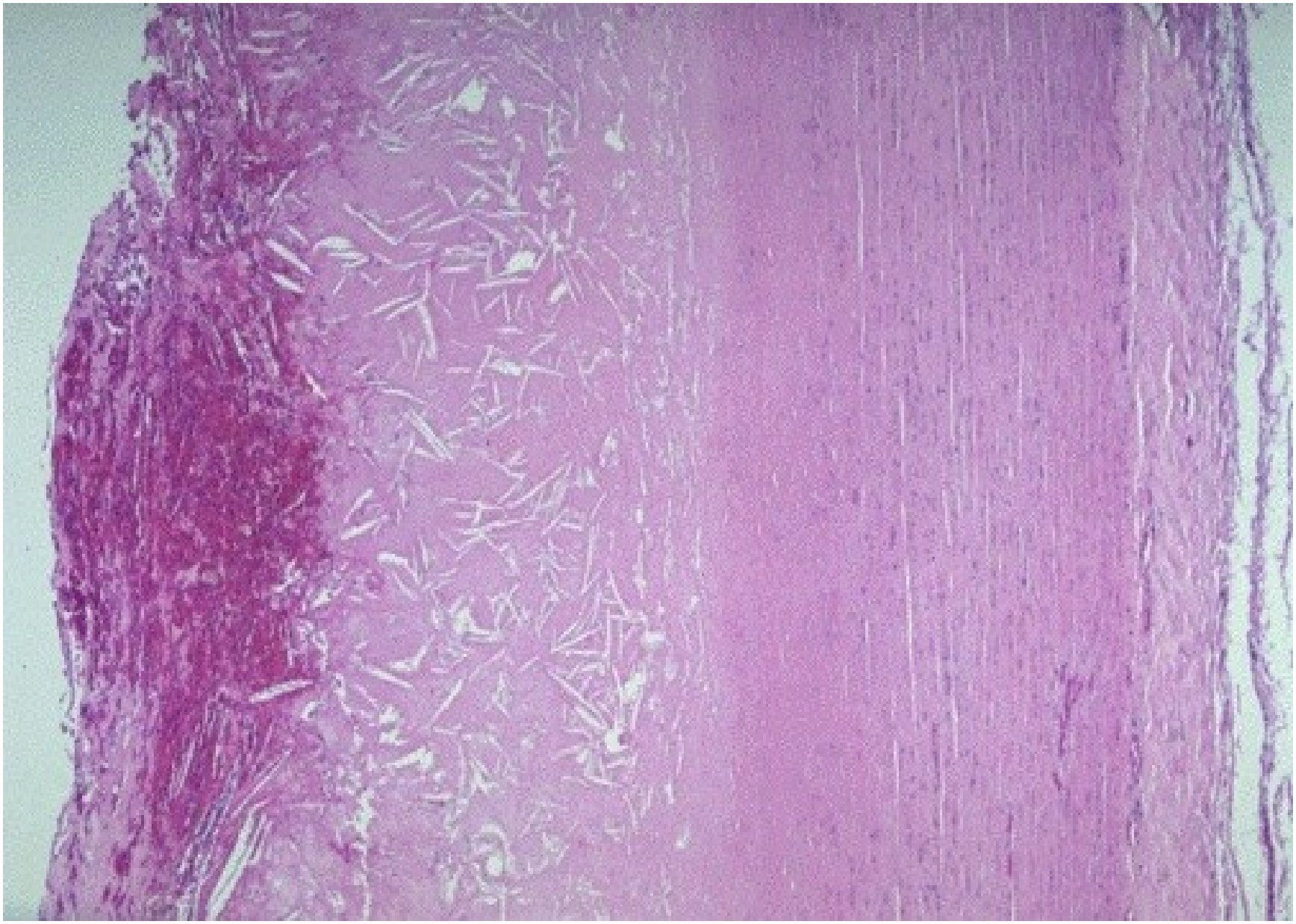
- Atherosclerotic plaques – smooth muscle cells and macrophages within the arterial intima are filled with lipid vacuoles, some of them rupture releasing lipids into the extracellular space – cholesterol esters crystalls

- Xathomas, inflammation, cholesterolosis

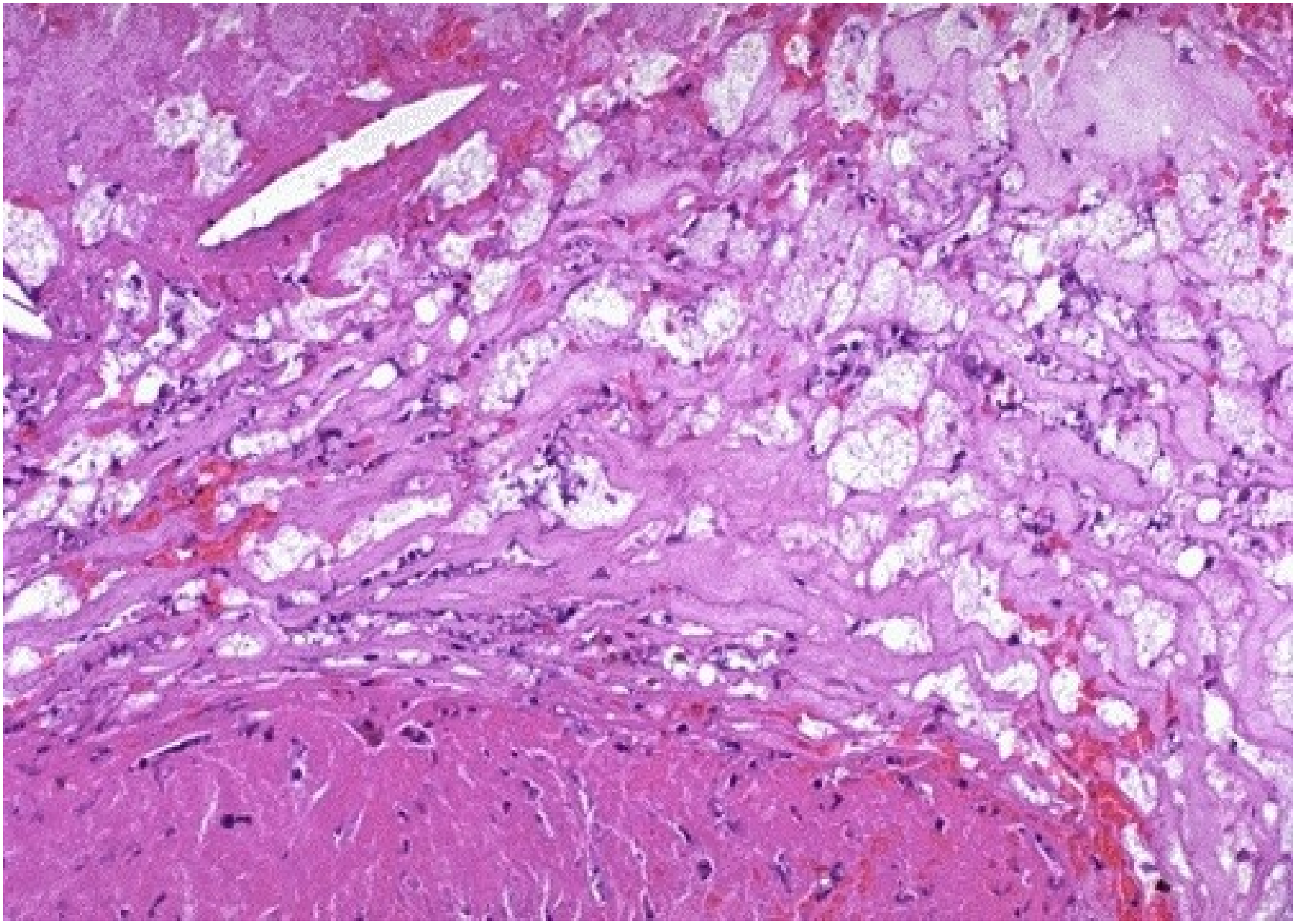

NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt



Mild, moderate and severe atherosclerosis (from the bottom to the top)



Atheroma with a recent hemorrhage



Fibrofatty atheroma – detail of foam cells

Defects of lipid metabolism

lipidoses - examples

- Group of inheredited diseases associated with defects of lysosomal enzymes

- Tay-Sachs disease (GM2-gangliosidosis) – deficiency of hexosaminidase A – involvement of neurons and the CNS with mental and motoric disablement dominates in the clinical picture
- Niemann-Pick disease – deficiency of sphingomyelinase – accumulation of sphingomyelin and cholesterol within lysosomes of macrophages – lipid-laden macrophages are widely distributed in the spleen, liver, lymph nodes, bone marrow, GIT and lungs. Psychomotor retardation, death by 5 years of age.
- Gaucher disease – deficiency of glucocerebrosidase – accumulation of glucocerebroside particularly in the phagocytic cells throughout the body (Gaucher cells) – involvement of the spleen, bone marrow, liver (Kupffer) and lungs.

Defects of glycid metabolism

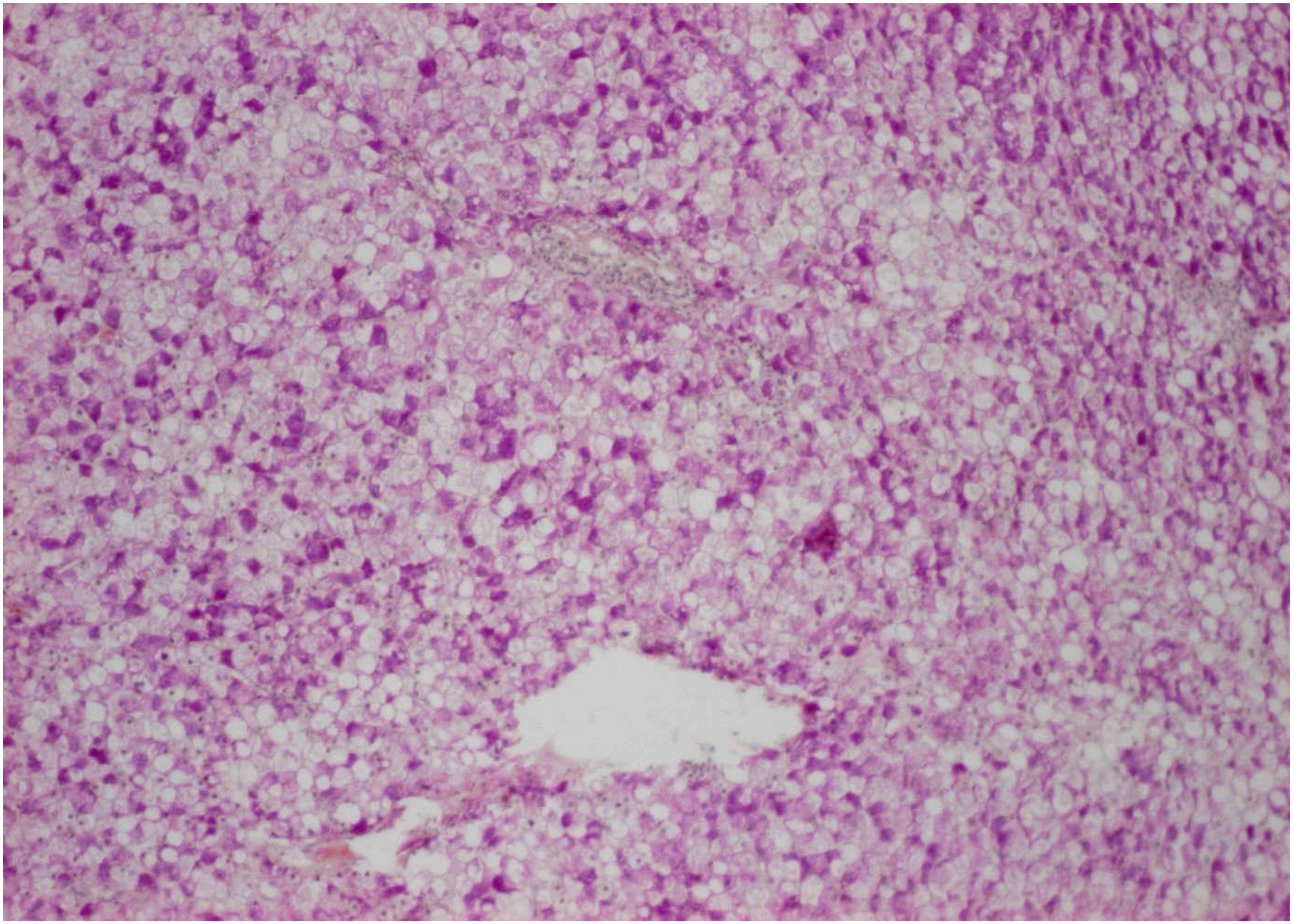
glycogenoses

- Number of genetic syndromes that result from metabolic defect in the synthesis or catabolism of glycogen
- Hepatic forms - von Gierkeho disease (typ I – deficiency od glucose-6-phosphatase) – glycogen is stored in the liver (and kidneys), clinically hepatomegaly, renomegaly, hypoglycemia!!
- Myopathic forms – McArdle disease (typ V - deficit muscle phosphorylase) – involves entirely striated muscles, glycogen accumulation under the sarcolemma, clinical picture: muscular weakness, muscle cramps after exercise, myoglobinuria, failure of exercise-induced rise of blood lactate levels (block in glycolysis)!!

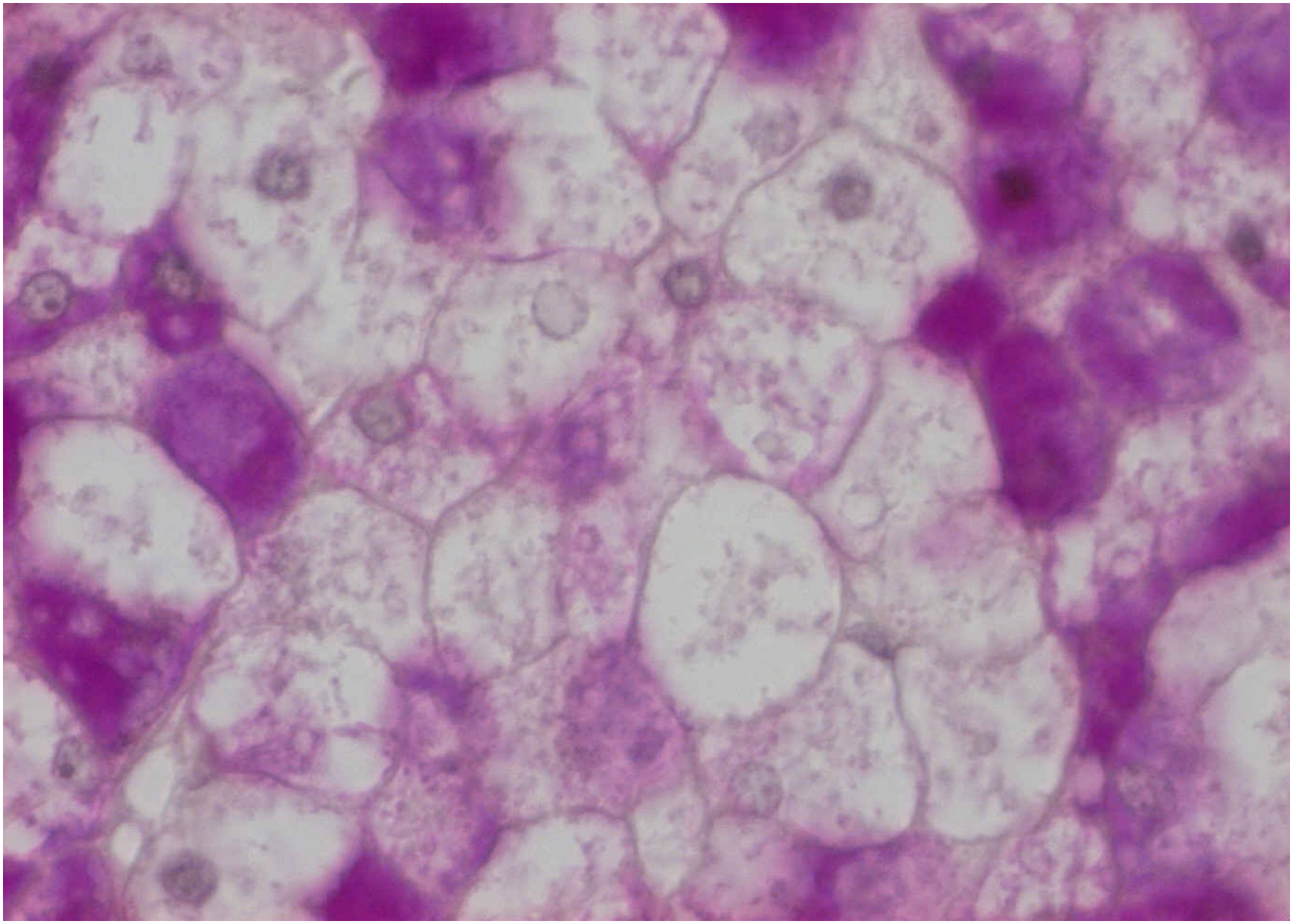
Defects of glycid metabolism

glycogenoses

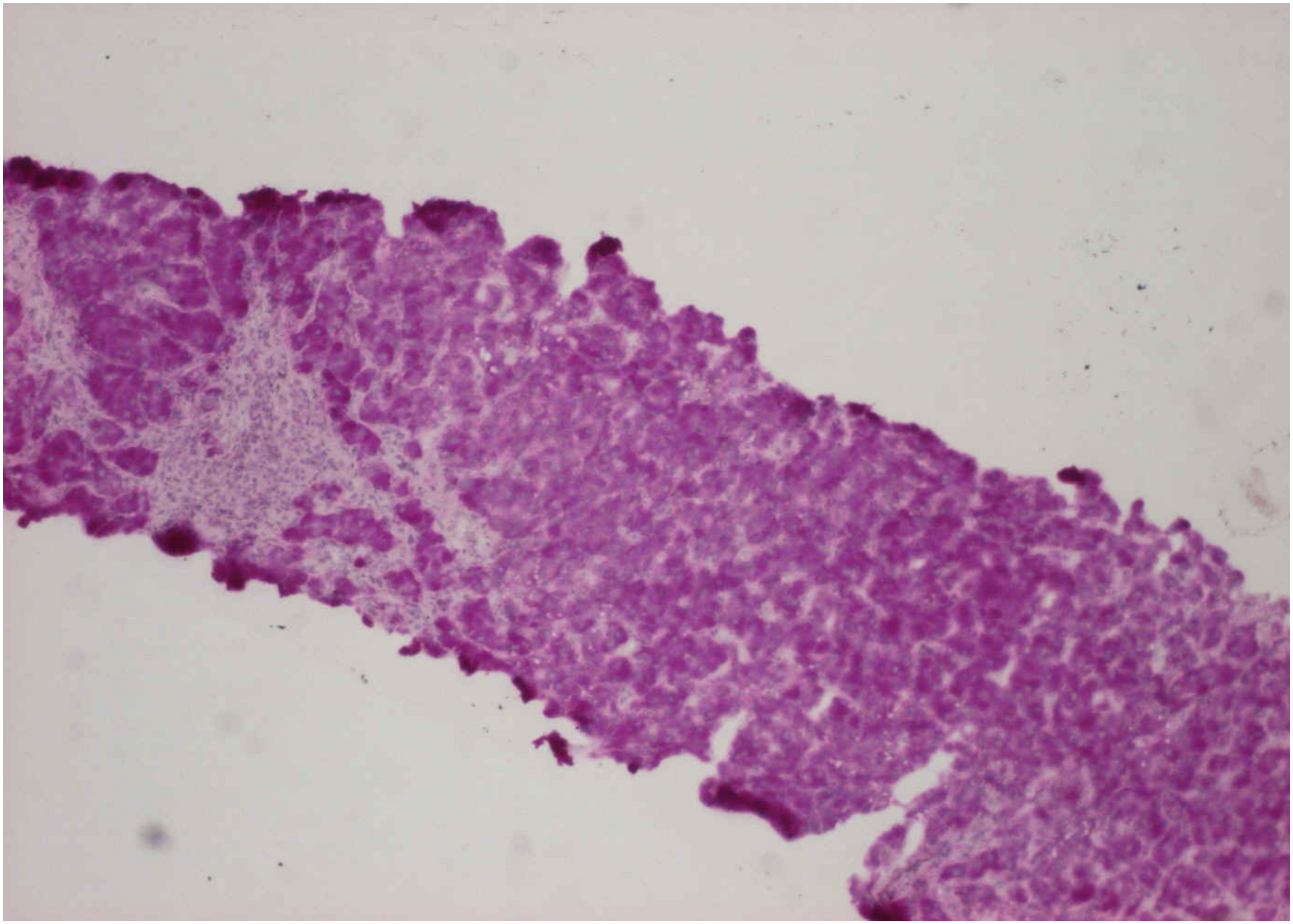
- Other forms – Pompeho disease (typ II – deficiency of α-glucosidase = lysosomal acid maltase) – glycogen storage in many organs: juvenile form - prominent cardiomegaly!!, moderate hepatomegaly, muscle weakness, cardiorespiratory failure and death in early childhood (by 2 years of life), adult form with involvement of only skeletal muscles – chronic myopathy



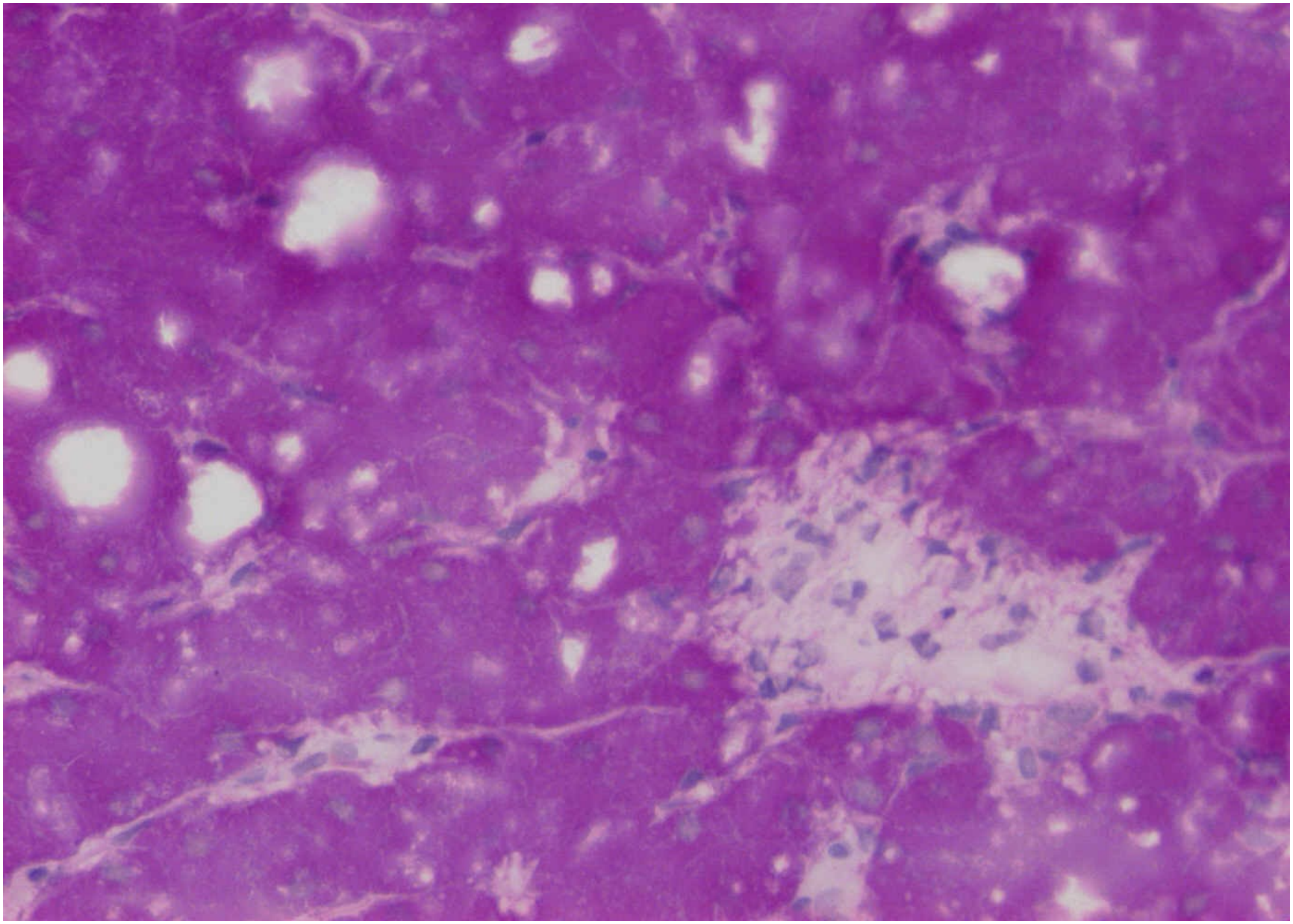
Glycogenosis in liver – PAS, paraffine section



Glycogenosis in liver – PAS, paraffine section- detail



Glycogenosis in liver – PAS, native frozen section, liver tapping



Glycogenosis in liver – PAS – frozen section

"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."

- Thank you for your attention