Волгоградский государственный медицинский университет

Кафедра патологической анатомии

LECTURE:
INTRODUCTION TO PATHOLOGY. REVERSIBLE AND IRREVERSIBLE CELL INJURY. PROTEINS INTRACELLULAR ACCUMULATIONS. HYALINOSIS. AMYLOIDOSIS.

Pathology

- Pathology literally is the study (logos) of suffering (pathos). More specifically, it is a bridging discipline involving both basic science and clinical practice and is devoted to the study of the structural and functional changes in cells, tissues, and organs that underlie "diseases".

By the use of

molecular,

microbiologic,

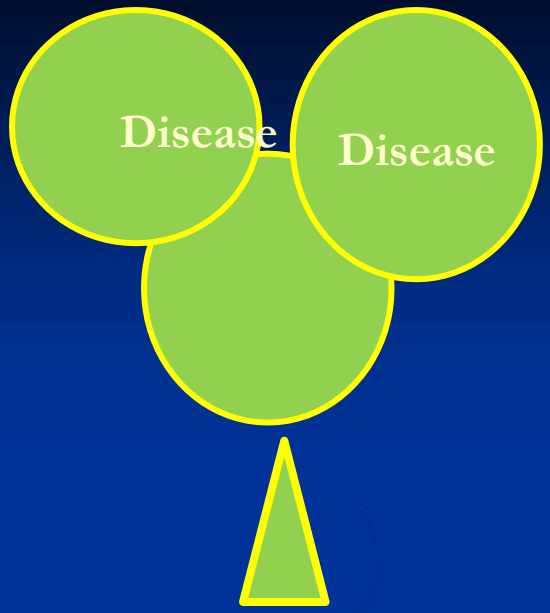
immunologic,

morphologic techniques,

pathology attempts to explain the "whys" and "wherefores" of the signs and symptoms manifested by patients while providing a sound foundation for rational clinical care and therapy.

Core of pathology

1) Cause (etiology),
2) The mechanisms of its development (pathogenesis),
3) The structural alterations induced in cells and organs or the body morphologic changes)
4) The functional consequences of morphologic changes (clinical significance).



One agent → One disease - Malaria

Several agents → One disease - Diabetes

One agent → Several diseases - Smoking

Pathogenesis: Development

- Sequence of events in the response of cells & tissues to a stimulus/pathogen"starting from the initial stimulus to the ultimate expression of disease.

Morphology: Structure Change

- **Structural changes in disease.**
  - Tumor in a cancer.
  - Ulcer in a infection.
  - Atrophy is dementia.
- **Gross & Microscopic.**

Clinical Significance:

- Patient Signs and symptoms are related to underlying pathology…
  - Why a malaria patient has fever?
  - Why not diarrhea?
- Prognosis of disease depends on inside pathology.
- What treatment is suitable for this patient?
- Is he going to recover or die soon?

Classification of Diseases:

- **Developmental** – genetic, congenital.
- **Inflammatory** – Trauma, infections, immune, etc.
- **Neoplastic** – tumors cancers
- **Degenerative** – ageing.

Disease Types:

- **Inflammatory / Neoplastic / Degenerative**
- Acute / Chronic
  - Acute – short days to weeks.
  - Chronic – long – months to years.
- Congenital / Familial / Acquired
- Genetic / Environmental
- Mild / Moderate / Severe

History of Pathology

- **"animism"** – Philosophies of Plato – God/devil
- **Magic** – Primitive thoughts
- **Humors** – Phlegm – excess/def – c300
- **Abiogenesis** – Spontaneous – to c1800
- **Environmental** – Modern - from 1850.
- **Genetic** – Molecular – from 20th century

Scope of Pathology

- Clinical Pathology
- Experimental Pathology
- Molecular Pathology
- Forensic Pathology
- Chemical / Microbiology
- Immunopathology
- Genetics & Disease.

Subdivisions of Pathology:

- Histopathology
- Cytopathology
- Haematology
- Microbiology
- Immunology
- Chemical Pathology
- Genetic Pathology
- Toxicology
- Forensic Pathology

Learning Pathology:

- **General Pathology**
  - Common changes in all tissues.
    - E.g.. Inflammation, cancer, ageing.
- **Systemic Pathology**
  - Specific changes in organs.
    - E.g.. Goiter, pneumonia, breast cancer.

Causes of cell injury and disease

- Oxygen deprivation (hypoxia, ischemia)
- Nutritional imbalances
- Physical agents
- Chemical agents and drugs
- Infectious agents
- Immunologic reactions
- Genetic derangements

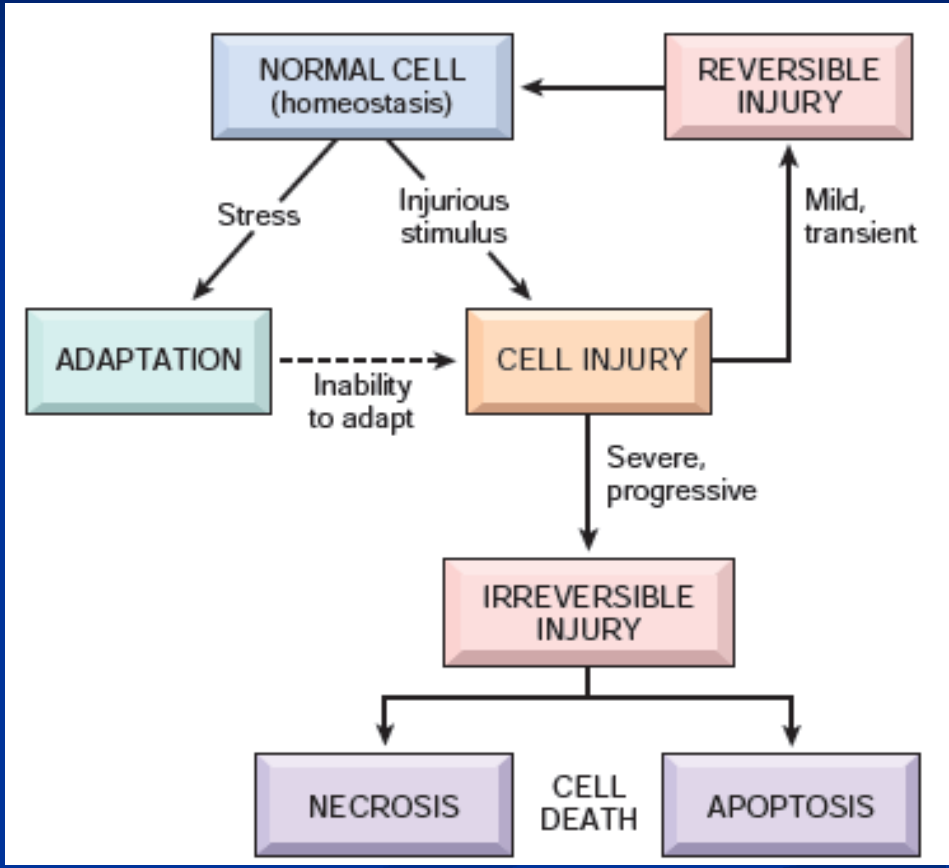
MECHANISMS OF CELL INJURY AND CELL DEATH

- The cellular response to injurious stimuli depends on the type of injury, its duration, and its severity.
- The consequences of an injurious stimulus also depend on the type, status, adaptability, and genetic makeup of the injured cell.
- Cell injury usually results from functional and biochemical abnormalities in one or more of a limited number of essential cellular components

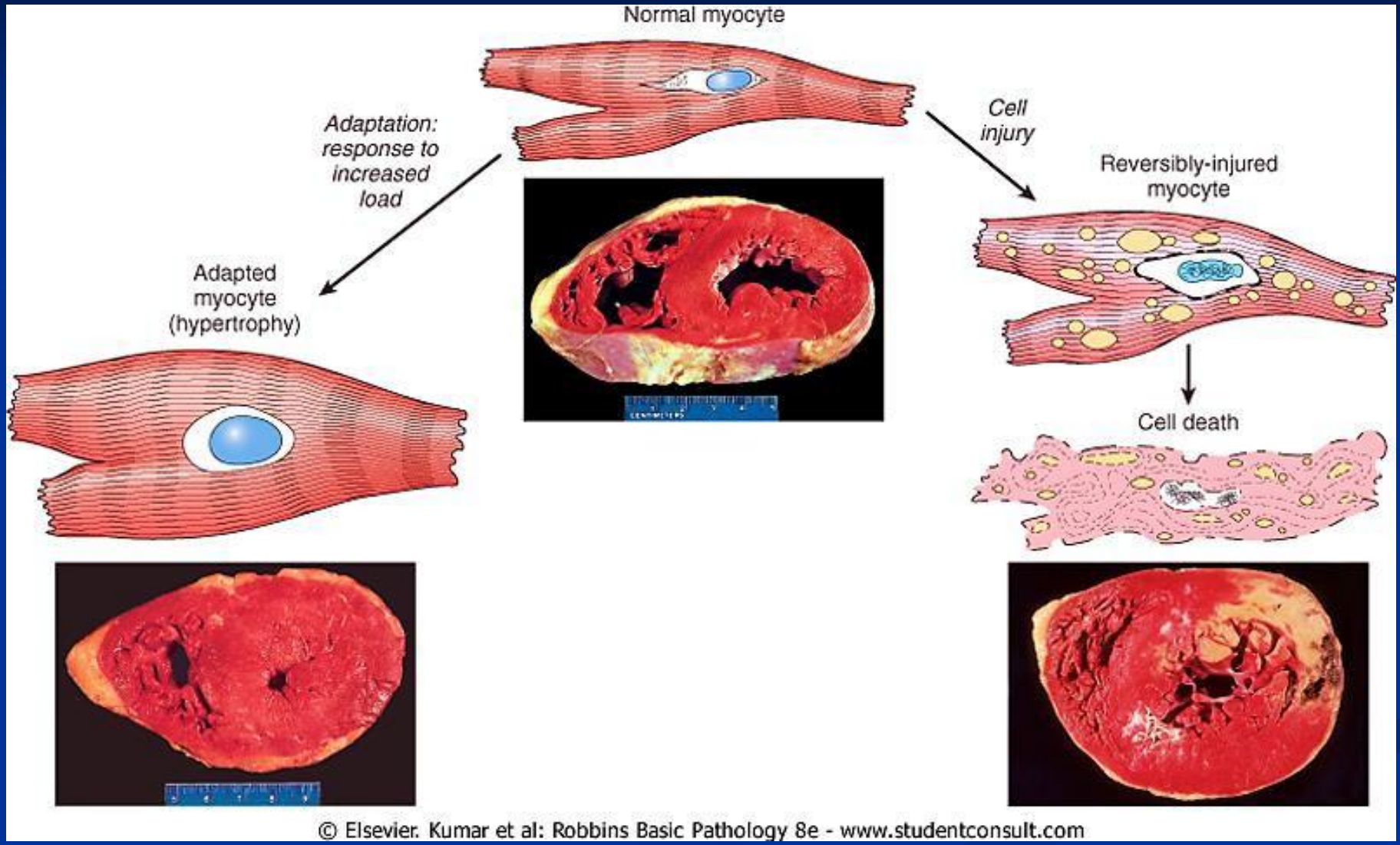
Damage (injury)

Under the influence of excessive physiological andpathological stimuli cellsprocess of adaptation develops.
If the limits of the adaptive response of cells are exhausted, cell damage occurs.

- Up to a certain limit cell damage is reversible.
- If unfavorable factor is permanent or its intensity is very large, it leads to irreversible cell damage and death.



Cell injury


Normal myocyte
Adaptation: response to increased load
Cell injury
Reversibly-injured myocyte
Adapted myocyte (hypertrophy)
Cell death
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Reversible damage

- In the classic pathology reversible (non-lethal) damage is called dystrophy (in english sources - degeneration).
- **Dystrophy - a pathological process (condition), which is based on a violation of the tissue (cell) metabolism, leading to structural changes.**
- This type of cell damage can be manifested by intracellular or extracellular appearance of abnormal substances or accumulation (loss) of various substances in abnormal amount:
  - water, lipids, proteins and carbohydrates;
  - abnormal substances, including exogenous, such as ions, impaired metabolism products;
  - pigments.

INTRACELLULAR ACCUMULATIONS

1)a normal cellular constituent accumulated in excess, such as water, lipid, protein, and carbohydrates;
2) an abnormal substance, either exogenous, such as a mineral, or a product of abnormal metabolism;
3) a pigment or an infectious product.

These substances may accumulate either transiently or permanently, and they may be harmless to the cells, but on occasion they are severely toxic.

Processes of intracellular accumulations divided:

- 1. 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 due to intracellular accumulation of triglycerides.
- 2. A normal or abnormal endogenous substance accumulates because it cannot be metabolized or is deposited intracellularly in an amorphous or filamentous form. One important cause is a genetic enzymatic defect in a specific metabolic pathway, so that some particular metabolite cannot be used. The resulting diseases are referred to as storage diseases.
- 3. An abnormal exogenous substance is deposited and accumulate because the cell has neither the enzymic machinery to degrade the substance nor the ability to transport it to other sites. Accumulations of carbon particles and as silica particles are examples of this type of alteration. Viral inclusions also fall into this category.

Classification of metabolic disorders (dystrophies).

Depending on the localization of deposits:

- Parenchymal dystrophy;
- Stromal-vascular dystrophy;
- Mixed dystrophy.

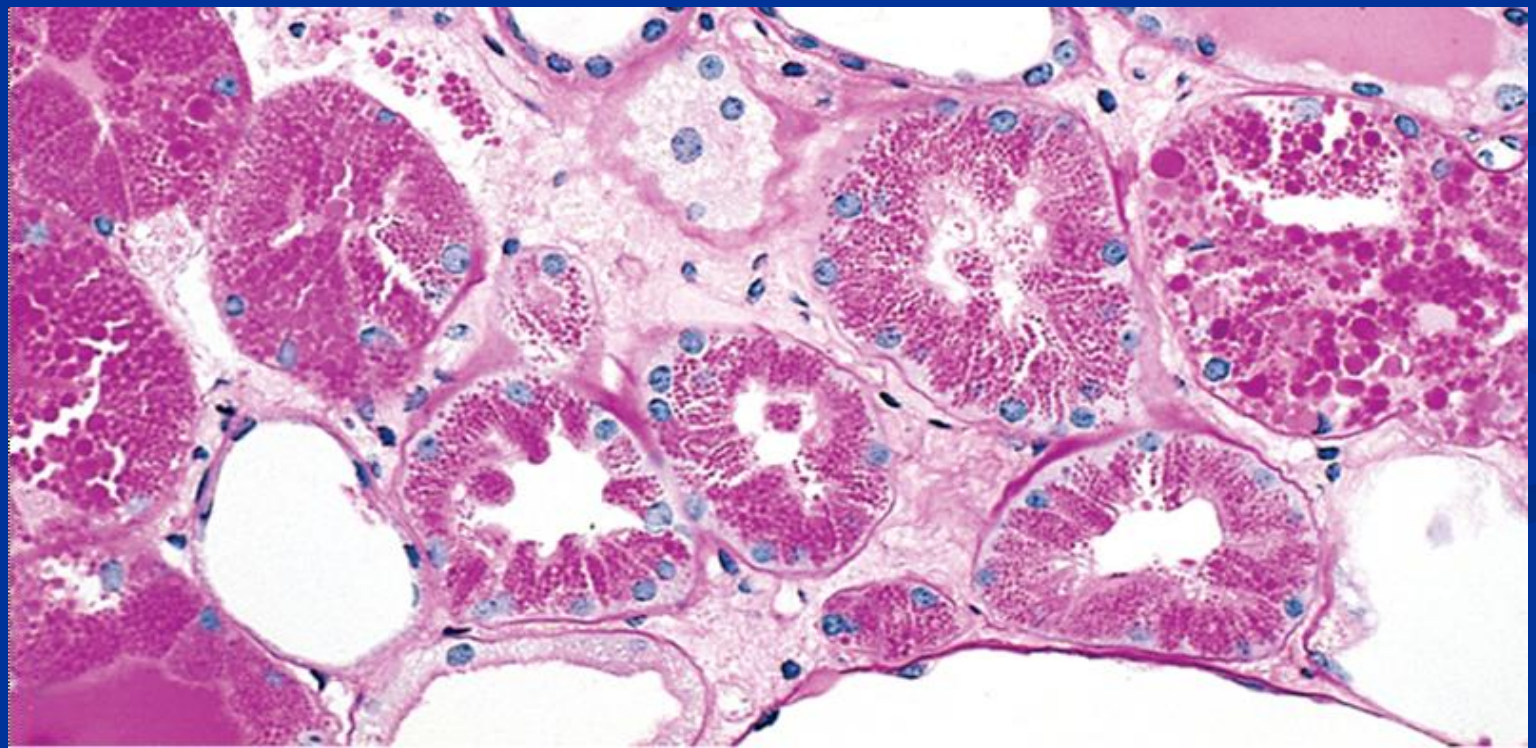
According to the chemical nature:

- Protein dystrophy;
- Fatty (lipid) dystrophy;
- Carbohydrate dystrophy;
- Mineral dystrophy.

PROTEINS

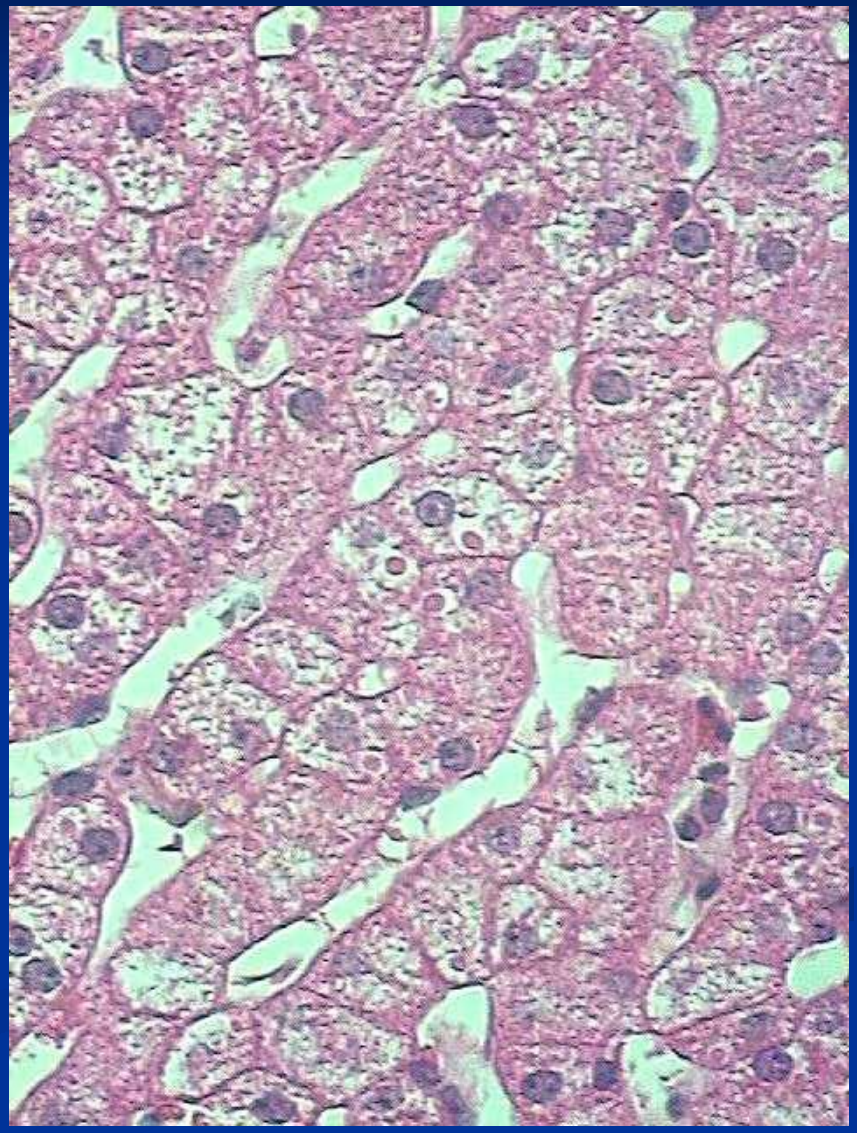
- Excesses of proteins within the cells sufficient to cause morphologically visible accumulation are less common than accumulation of lipids. They usually appear as rounded, eosinophilic droplets, vacuoles, or masses.

1. Reabsorption droplets in proximal renal tubules. This is seen in renal diseases associated with protein loss in the urine. If a protein leaks across the glomerular filter, it passes into the proximal tubule, where it is reabsorbed by the epithelial cell through pinocytosis. Pinocytotic vesicles fuse with lysosomes to produce phagolysosomes, which appear as pink hyaline droplets within the cytoplasm of the tubular cell.

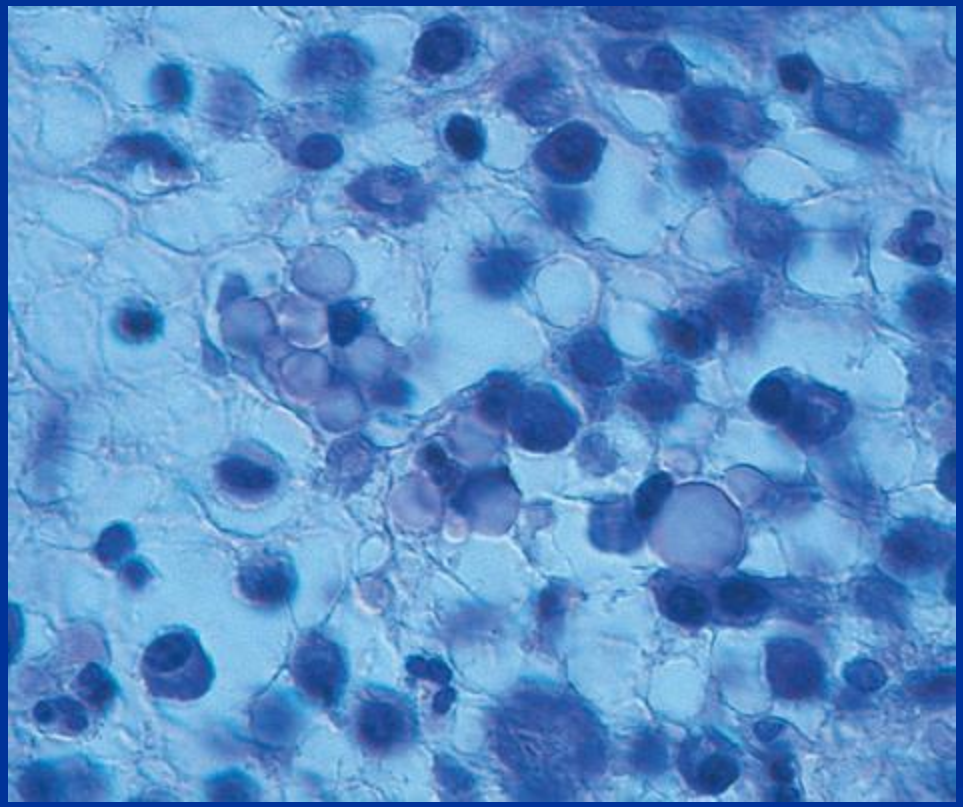


•Cell Injury: Histological expressions

- Hyaline droplet change. Mallory bodies (structural filaments).

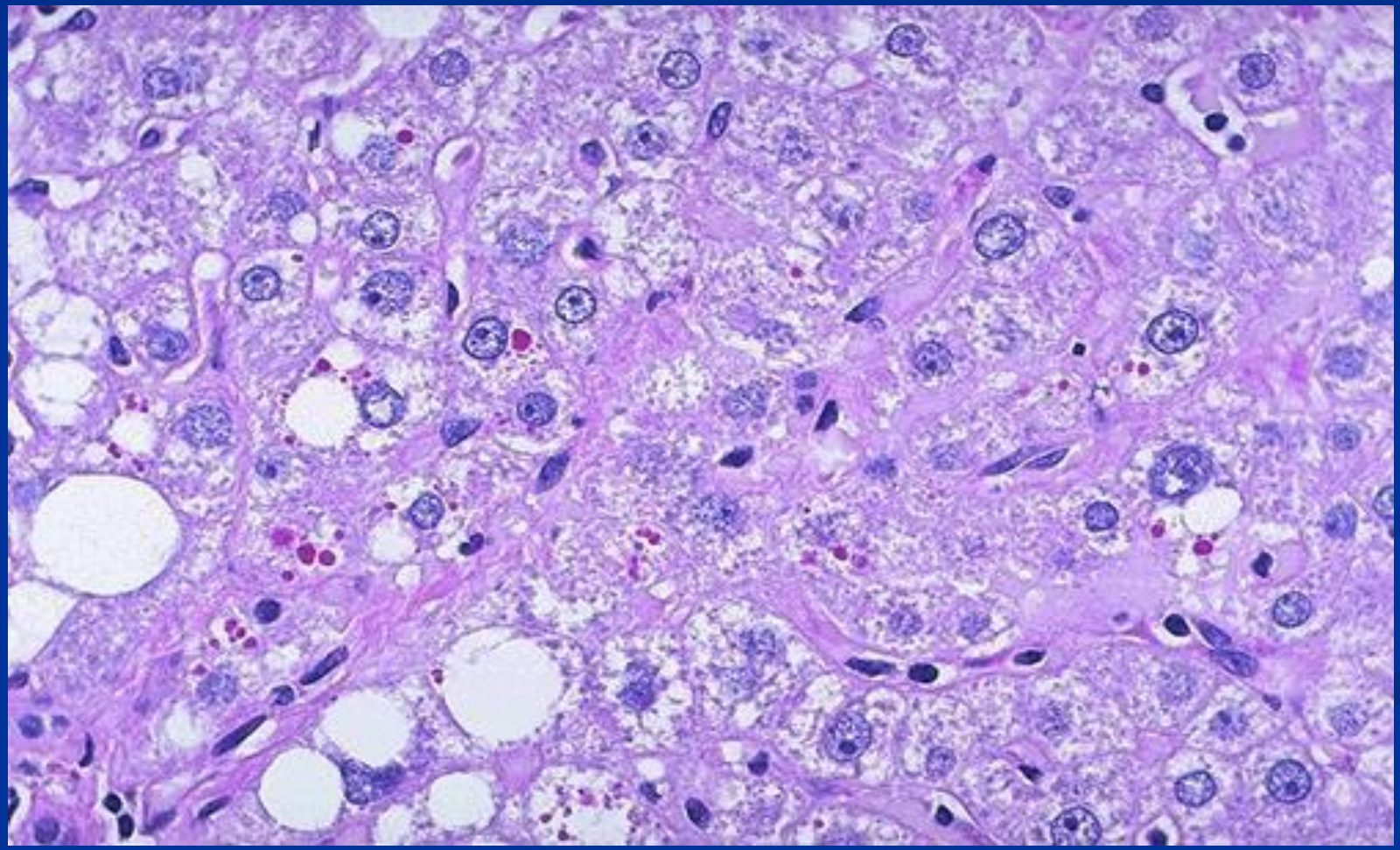


- 2. Immunoglobulin in plasma cells. The endoplasmic reticulum of plasma cells enlarged in active synthesis of immunoglobulins may become hugely distended, producing large, homogenous eosinophilic inclusions called Russel bodies.



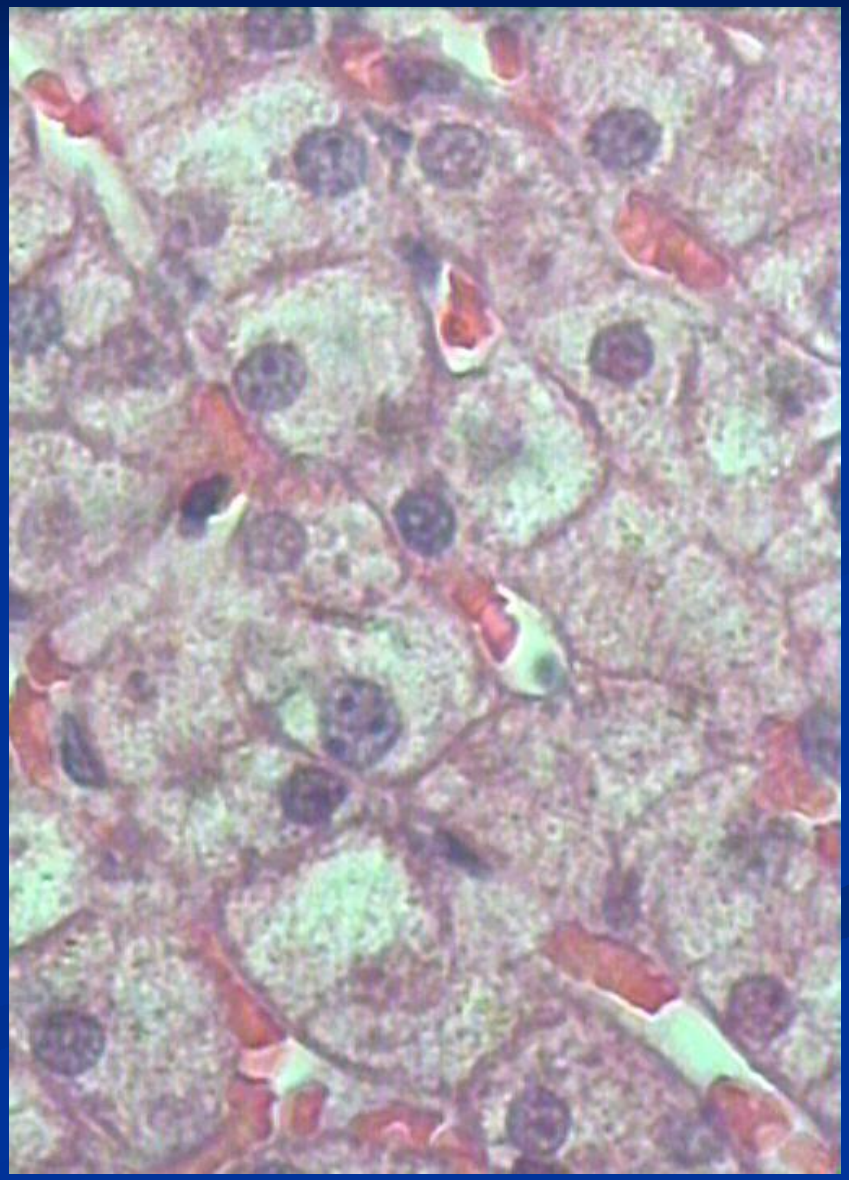
- Crystalline inclusions: Are the consequence of delayed secretion in the presence of enzymopathy or in secreting tumors. In plasmocytoma, a malignant plasma cell tumor, they consist of immunoglobulin chains. In histologic contexts, these inclusions are called Russell bodies

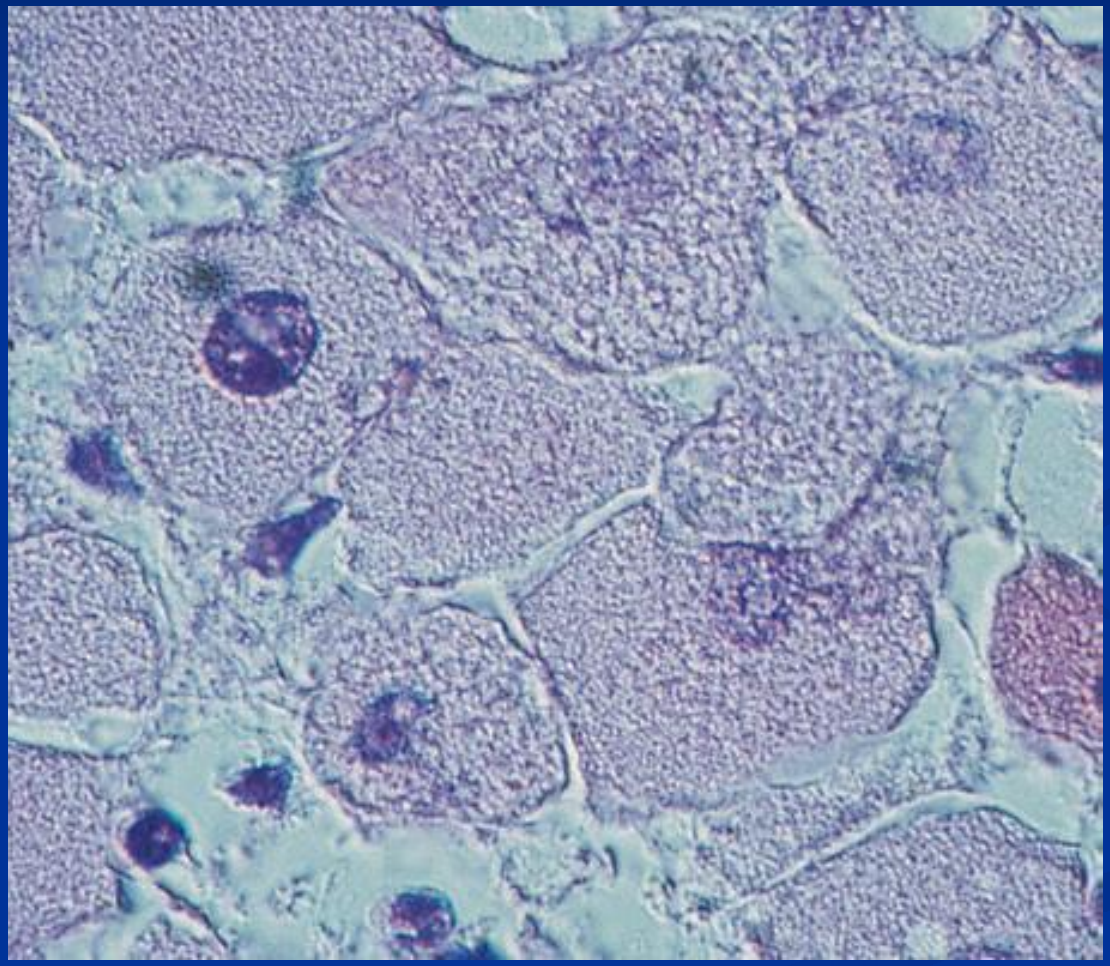
3.Alpha-1-antitrypsin in liver cells. In alpha-1-antitrypsin deficiency, the enzyme accumulates in the endoplasmic reticulum of the liver in the form of globular eosinophilic inclusions.



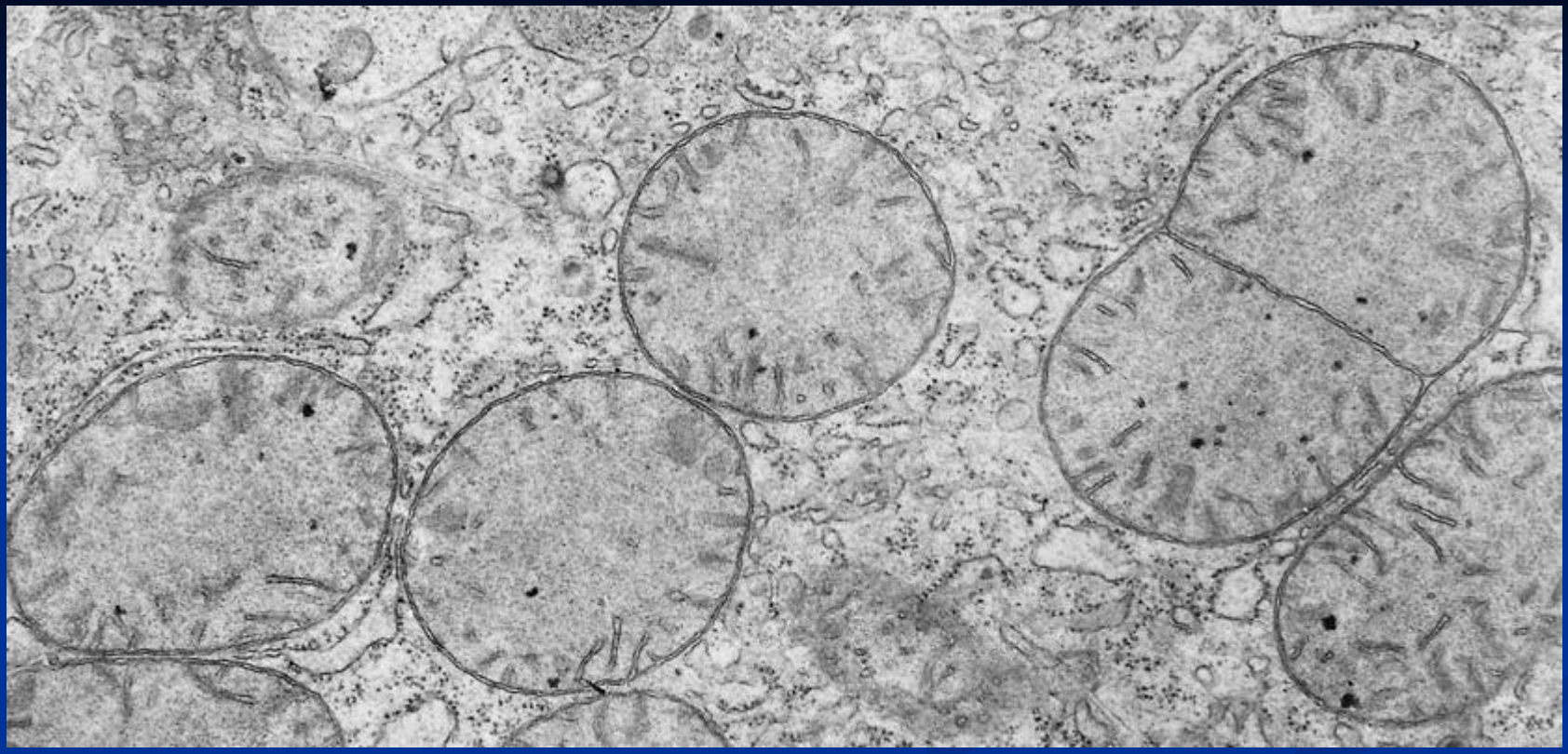
4. Cell swelling (hydropic dystrophy).

- Swelling or hydropic change.





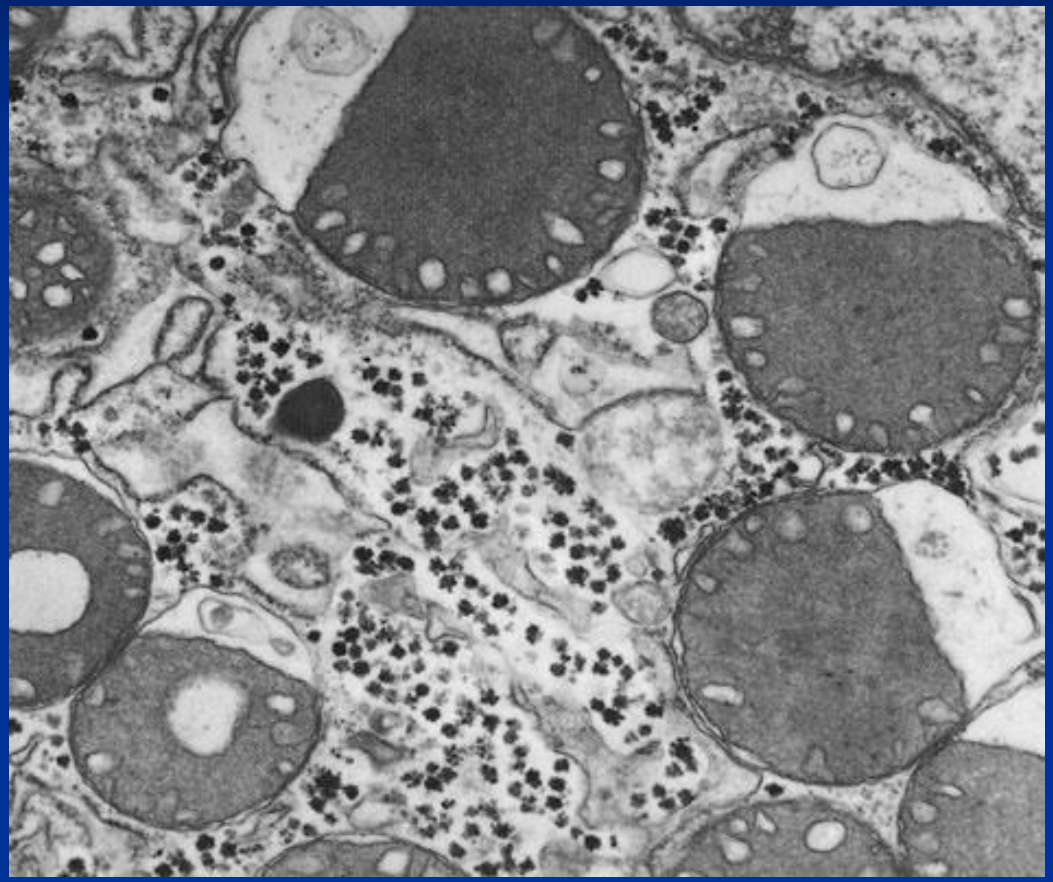
- Microscopic appearance of the cells: characterized by swelling with granular, light cytoplasm



- Mitochondrial DNA mutation disturbs ATP synthesis. This in turn causes compensatory mitochondrial proliferation. The consequence is that the cytoplasm becomes rich in mitochondria and swells, in a process referred to as oncocytic cytoplasm transformation

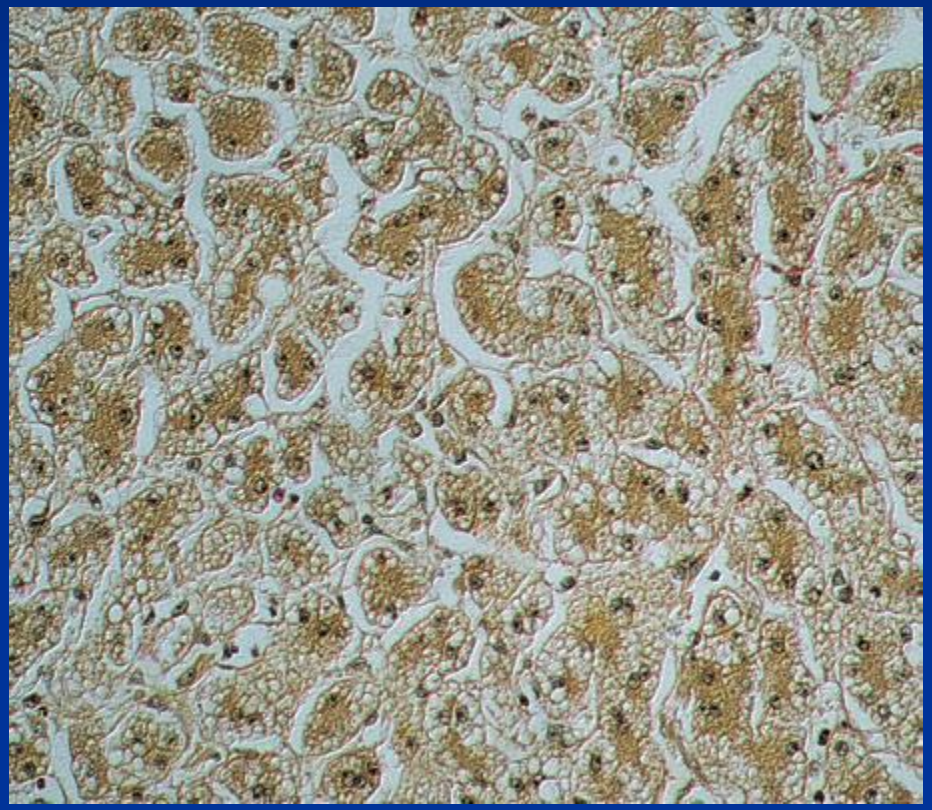
Mitochondrial Swelling

- Mitochondrial swelling is the ultrastructural correlate of the "turbid swelling" of parenchymal organs described by R. Virchow in 1852. It usually occurs together with generalized cytoplasmic degeneration with formation of vacuoles.
- Macroscopic appearance of the organs: characterized by enlargement with a doughy, turbid cut surface.



- Ultrastructural aspect: The swelling begins in response to the change in osmotic pressure with condensation of the matrix and swelling of the space between the cristae (crista type). This is followed by dissolution of the mitochondrial matrix and the mitochondrial cristae (matrix type).

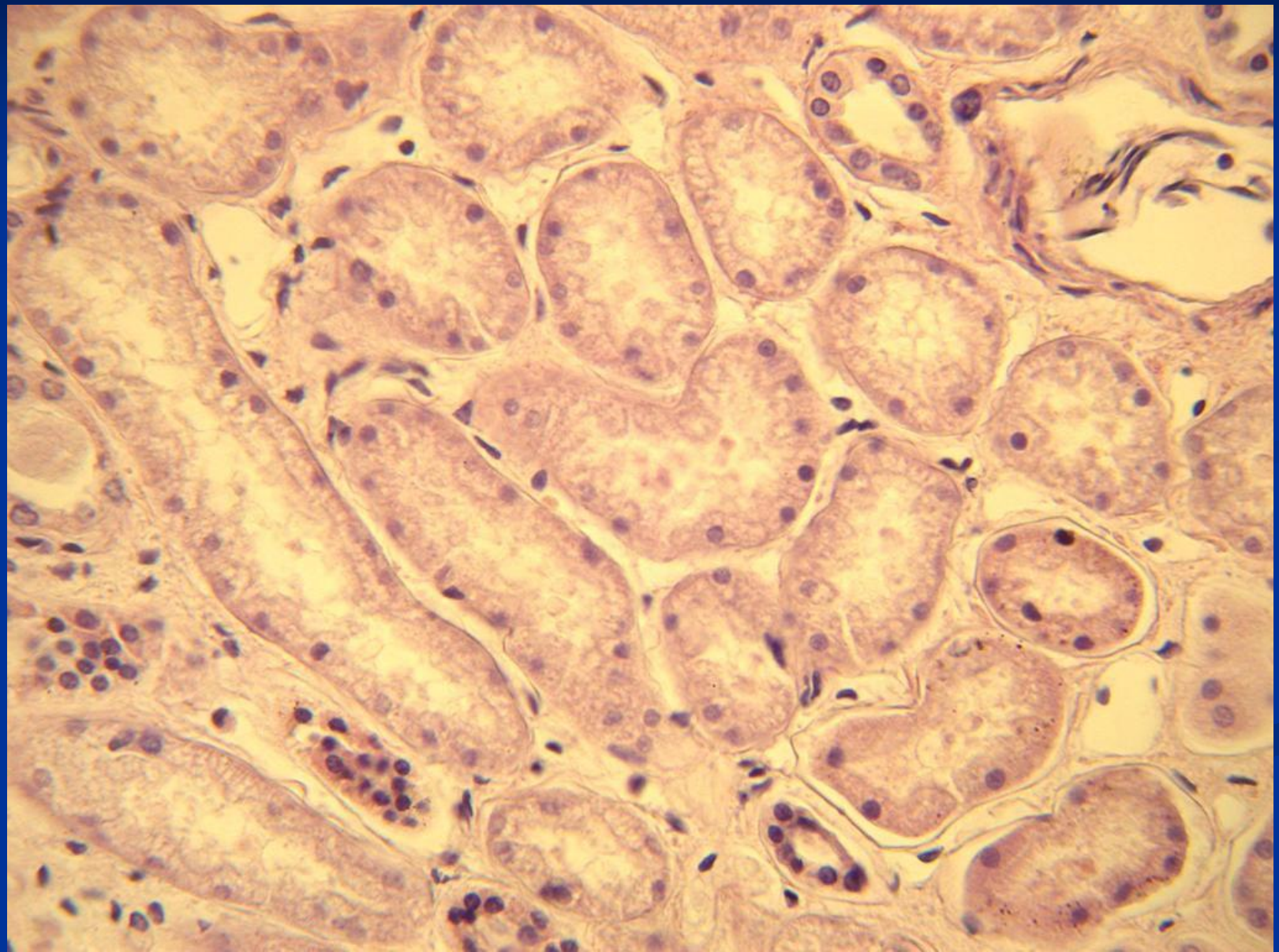
Vacuolization of the RER (liver cells, EvG) x 200



- Formation of vacuoles in the RER: Recognizable under the light microscope, this reversible cell injury is caused by interruption of energy metabolism in which the reaction chain involving Na+, K+-

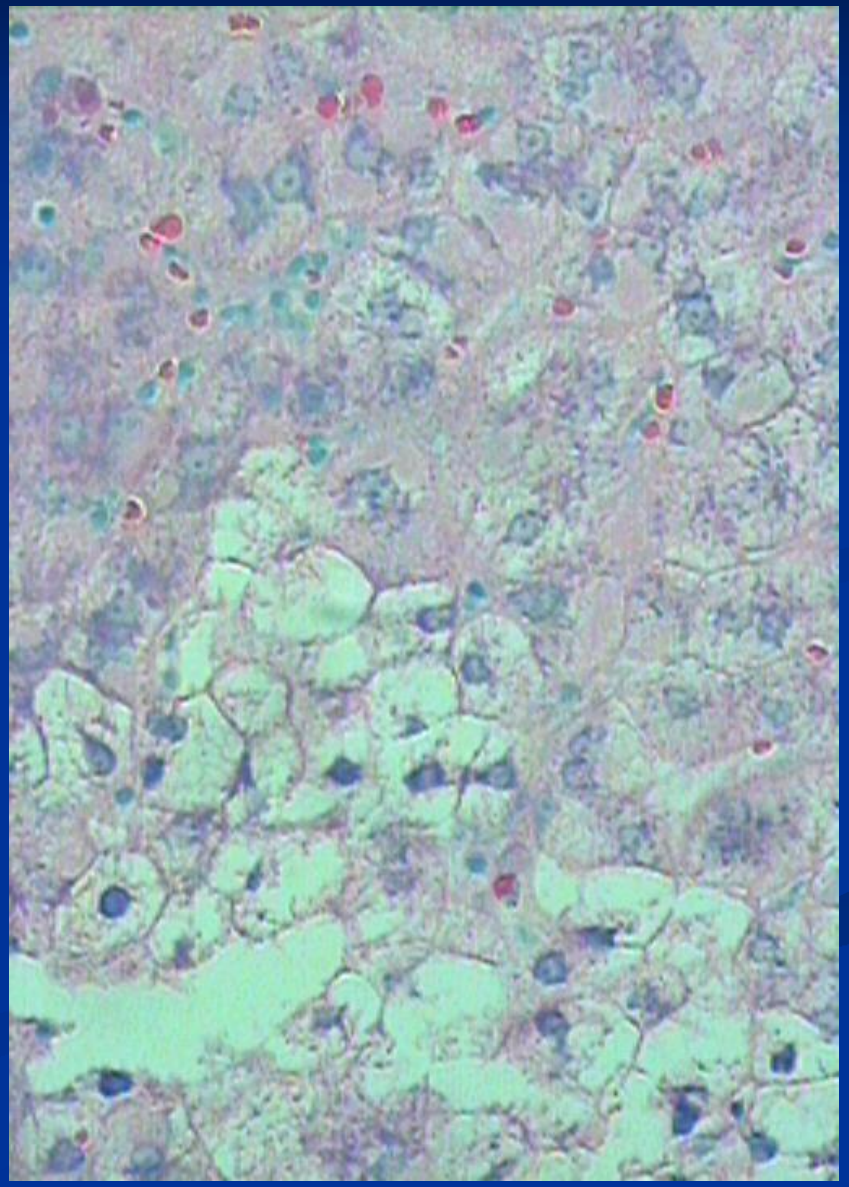
ATPase fails. This causes water to flow into the cell and the cisterns of the rough endoplasmic reticulum. Where accompanied by swelling of the smooth endoplasmic reticulum and mitochondria, it results in cytoplasmic degeneration with formation of vacuoles

Swelling or hydropic change. H & E. X 100.



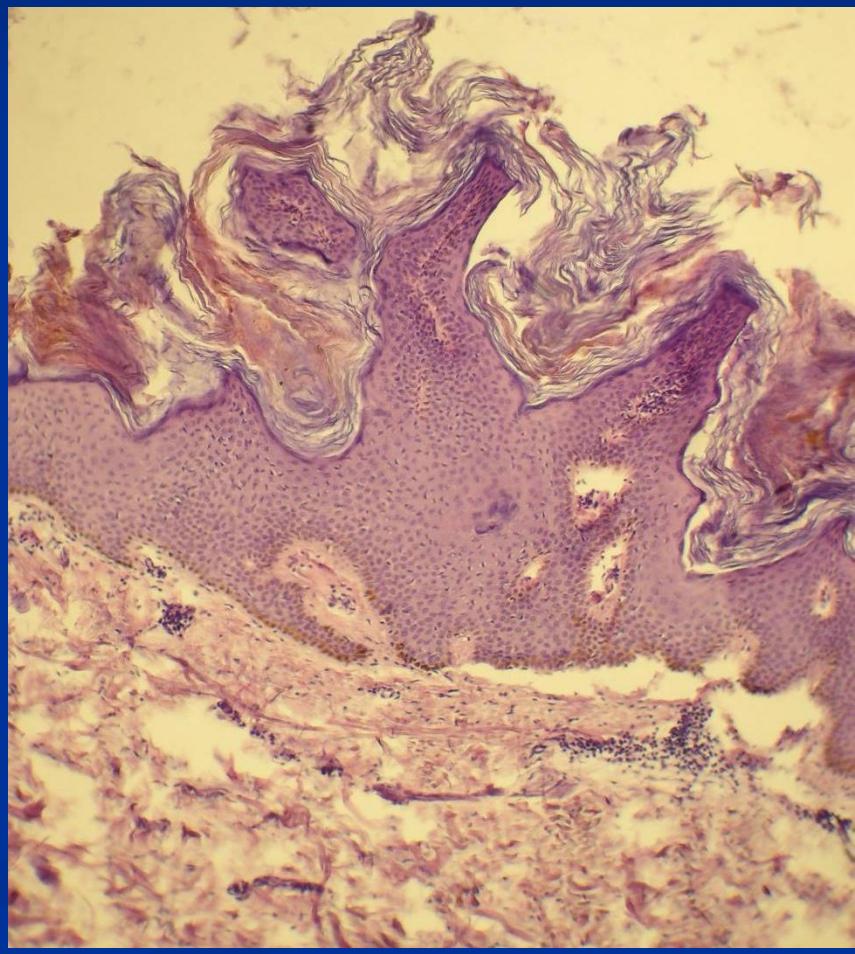
•Cell Injury: Histological expressions

•Swelling or hydropic change. Probably the result of defects in membrane and/or mitochondrial function. This is common to many hepatic injuries.



Hyperkeratosis

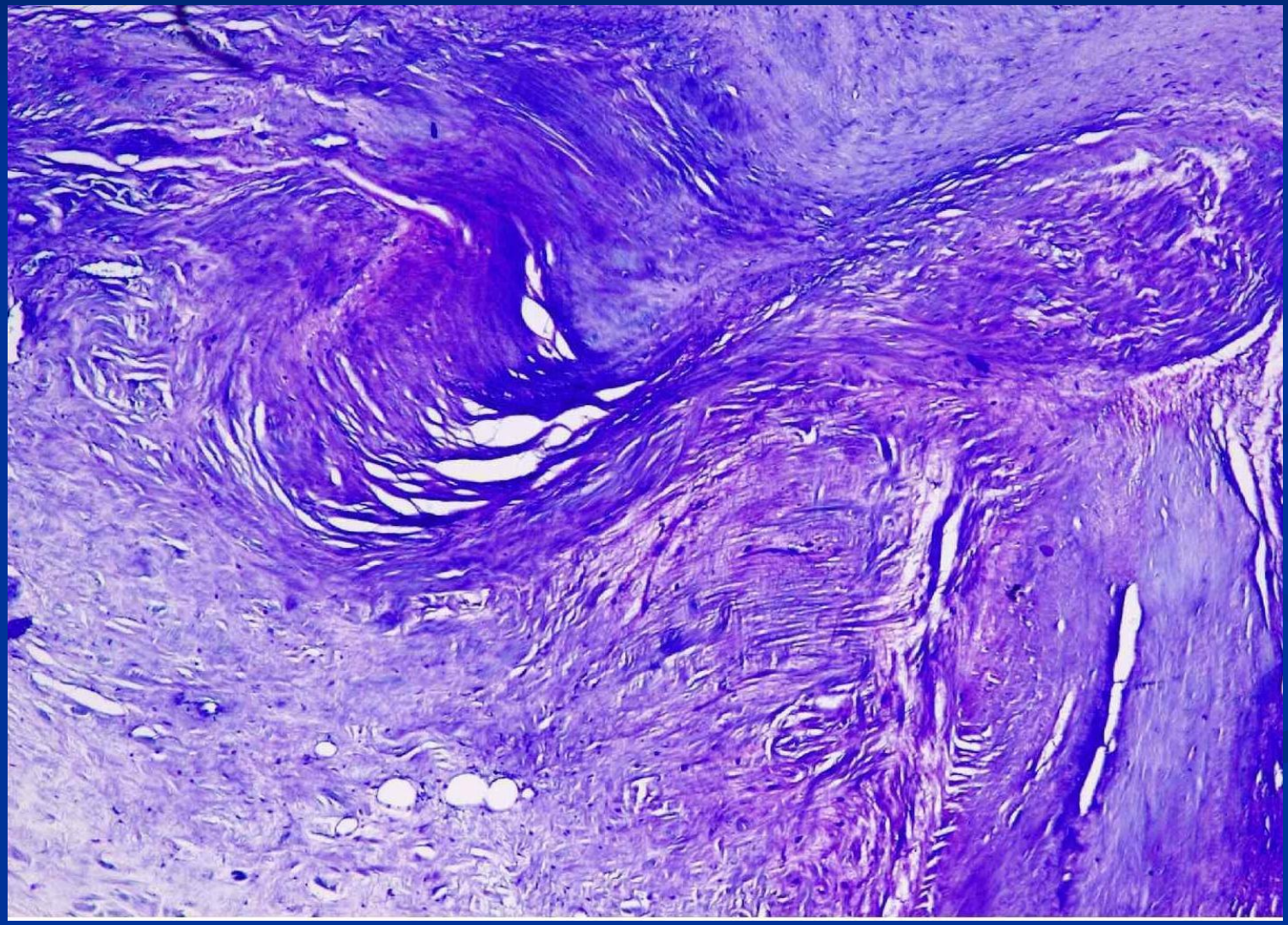
Hyperkeratosis is thickening of the stratum corneum of epidermis, occurs in the epithelium with an increase in its natural deposition of keratin (on the skin) or with the pathological appearance of keratin masses (mucous membranes). Perhaps in the thickness of cancerous tumors ("cancerous pearls").



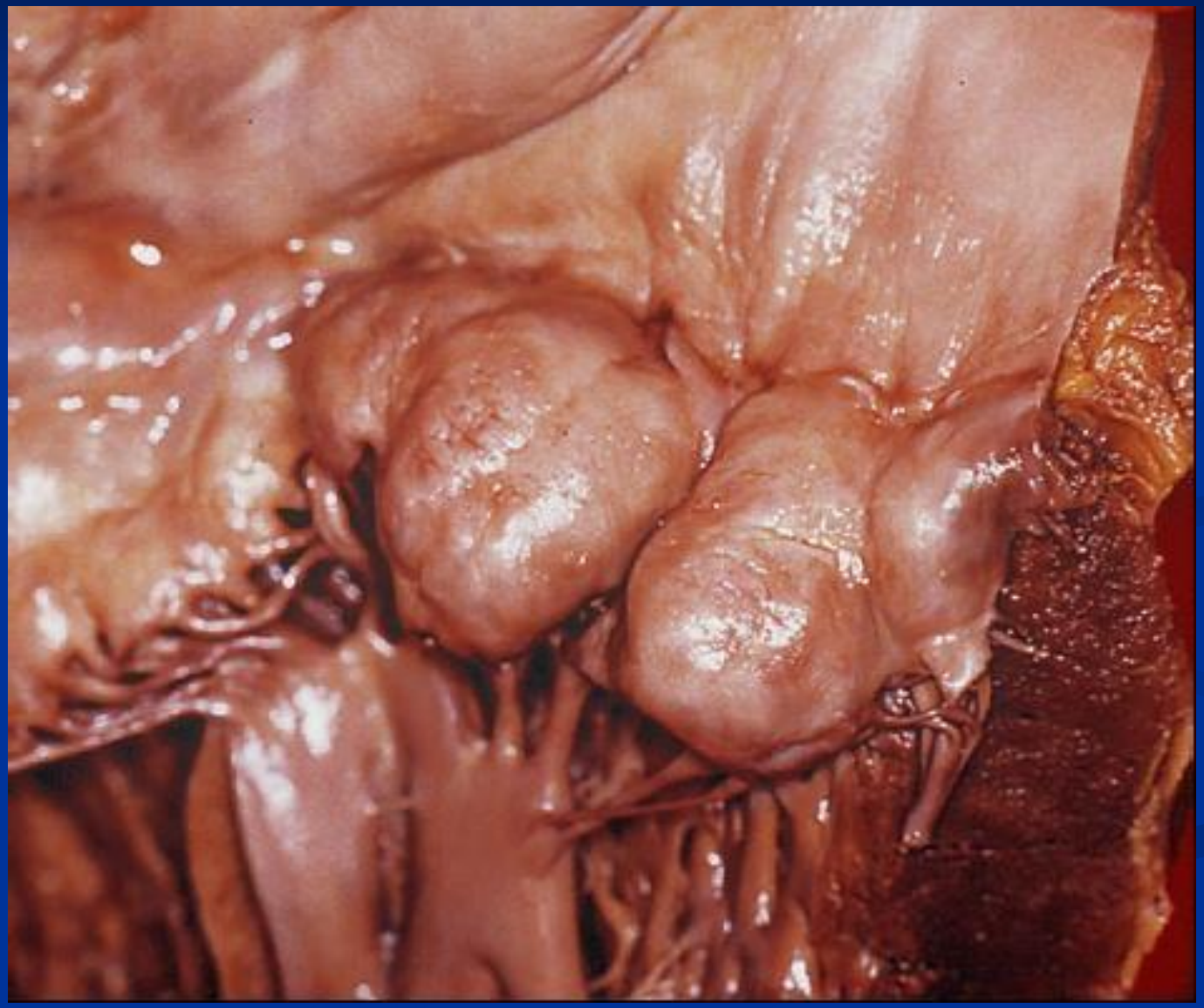
Stromal-vascular proteinosis

- mucoid swelling;
- fibrinoid swelling (necrosis);
- hyalinosis;
- amyloidosis.

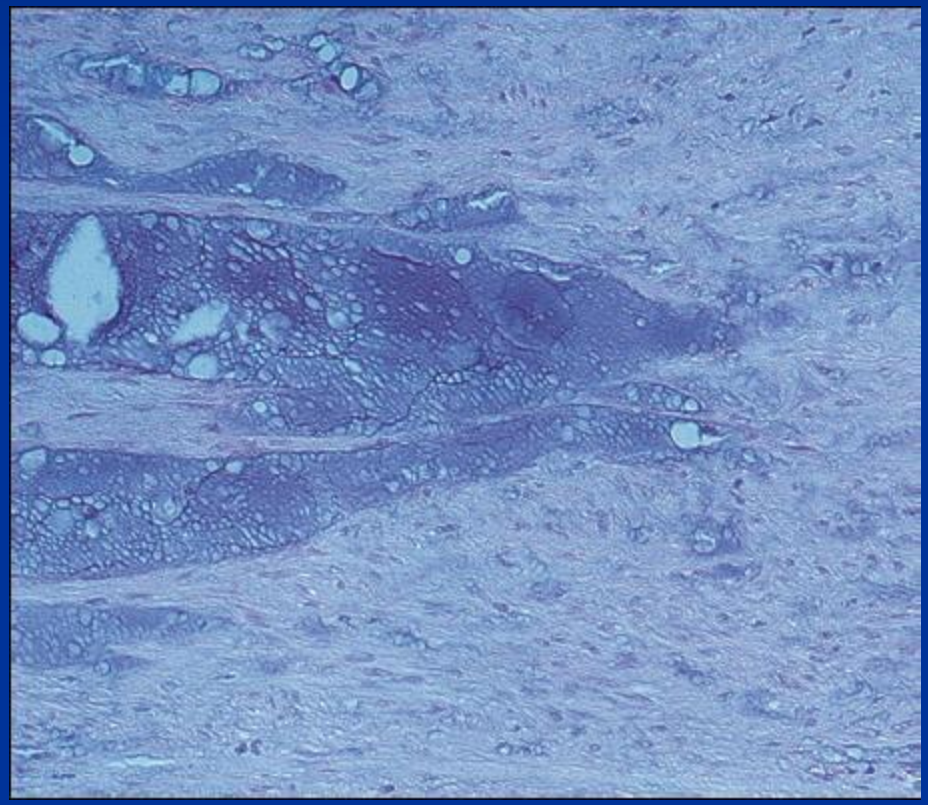
Mucoid swelling of the valve with rheumatism. Toluidine blue. Magn. x40.

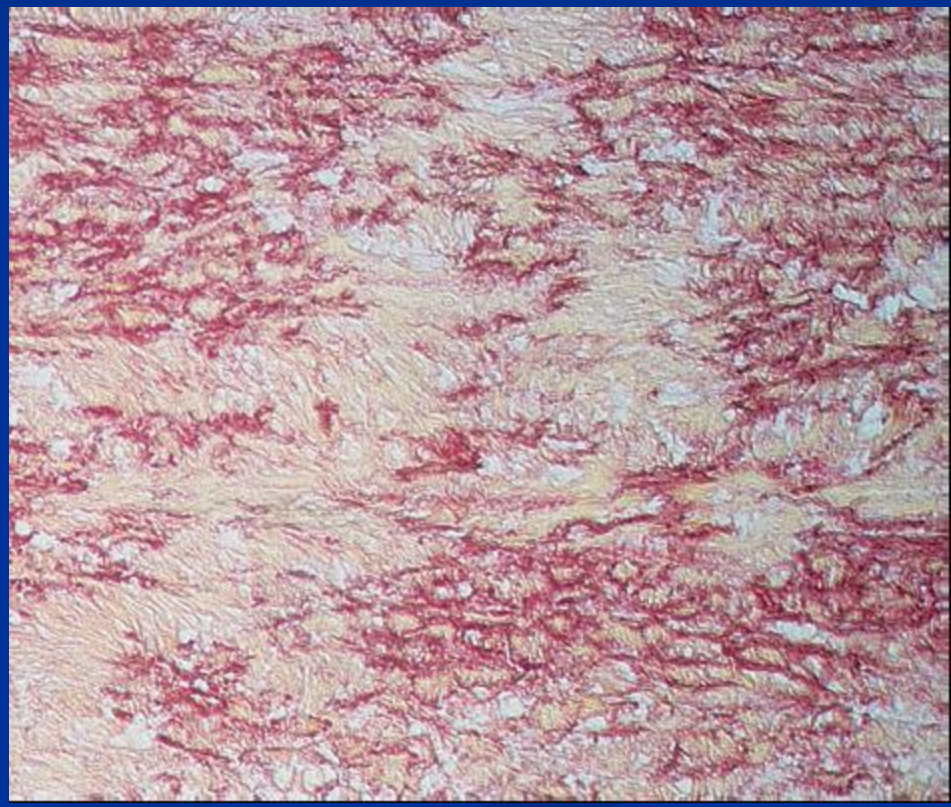


Mitral valve prolapse



Mucoid degeneration (aorta) (HE) x 150 (aorta; EvG) x 150

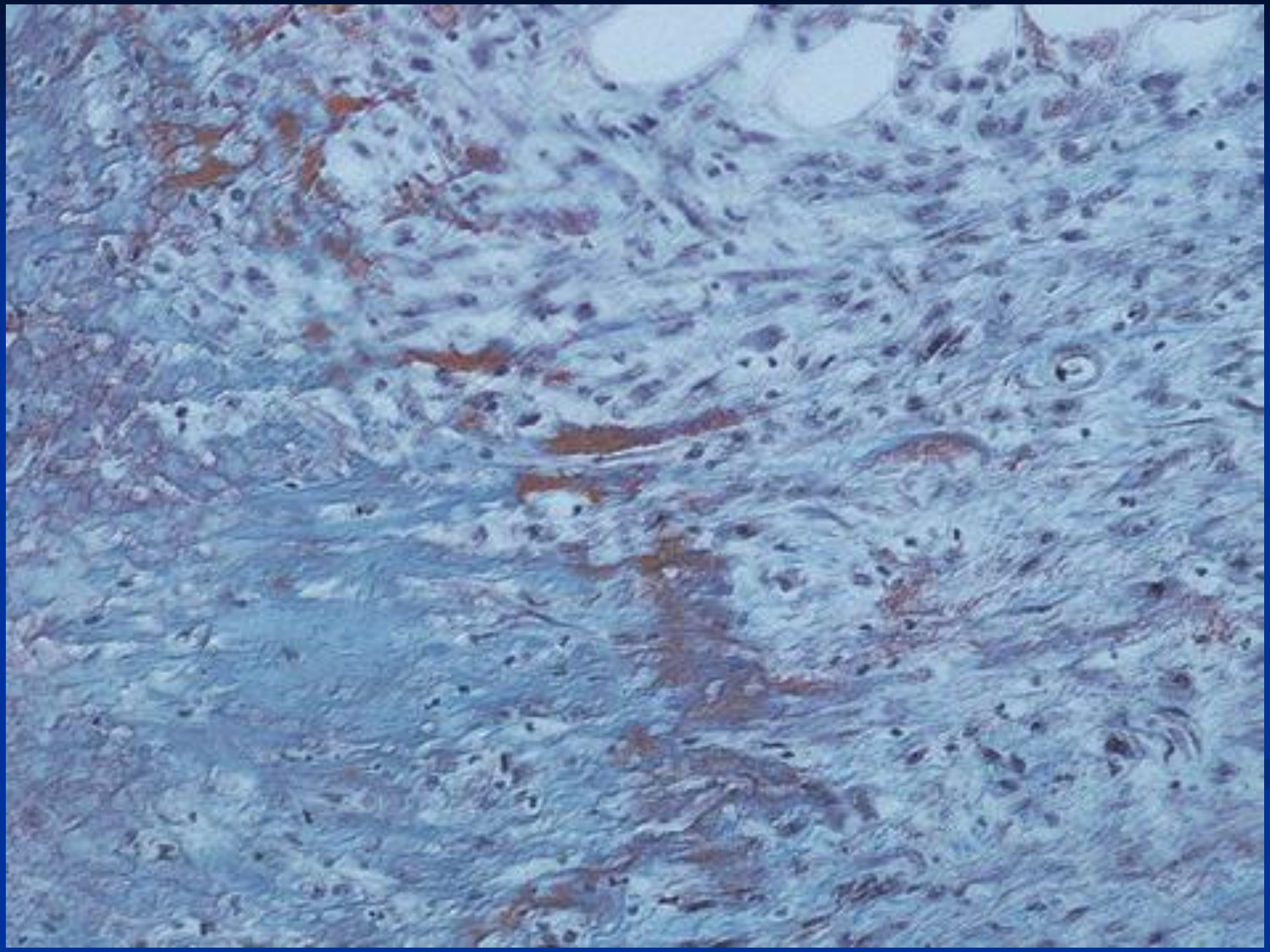




Fibrinoid swelling

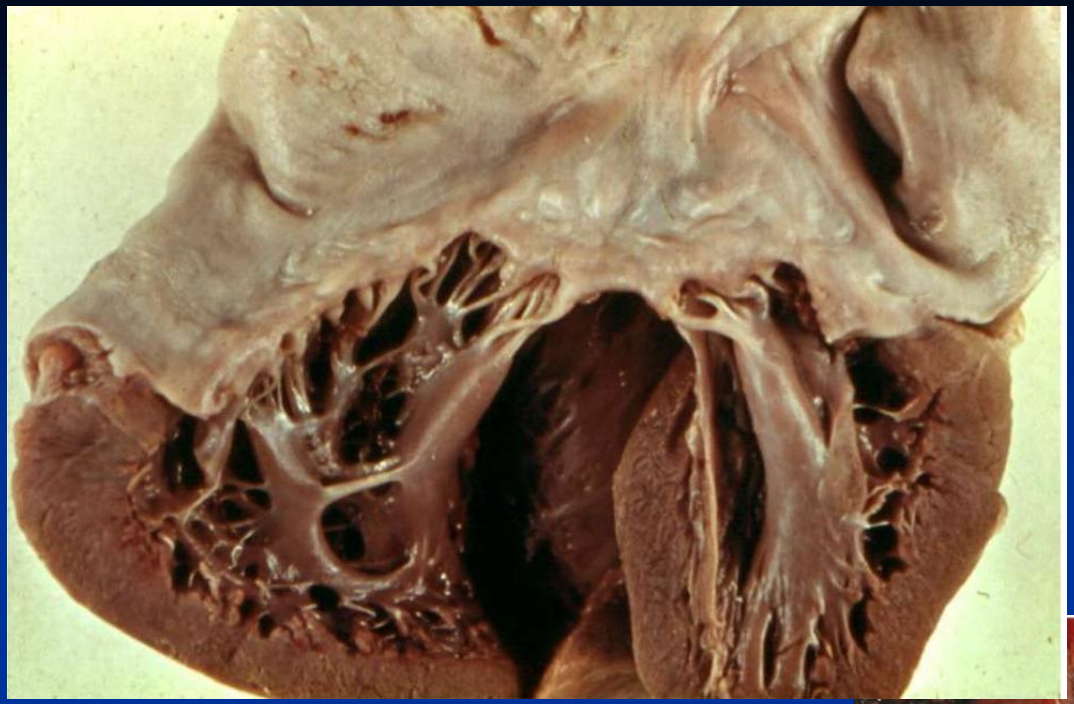
- Fibrinoid swelling is a deep and irreversible disorganization of connective tissue, which is based on the breakdown of protein (collagen, fibronectin, laminin) and GAG depolymerization, which leads to the destruction of its ground substance and fibers, accompanied by a sharp increase in vascular permeability and the formation of fibrinoid.
- A fibrinoid is a complex substance formed by proteins and polysaccharides, decaying collagen fibers and the ground substance, as well as plasma blood proteins and nucleoproteins of destroyed cells of connective tissue. An essential component of fibrinoid is fibrin.

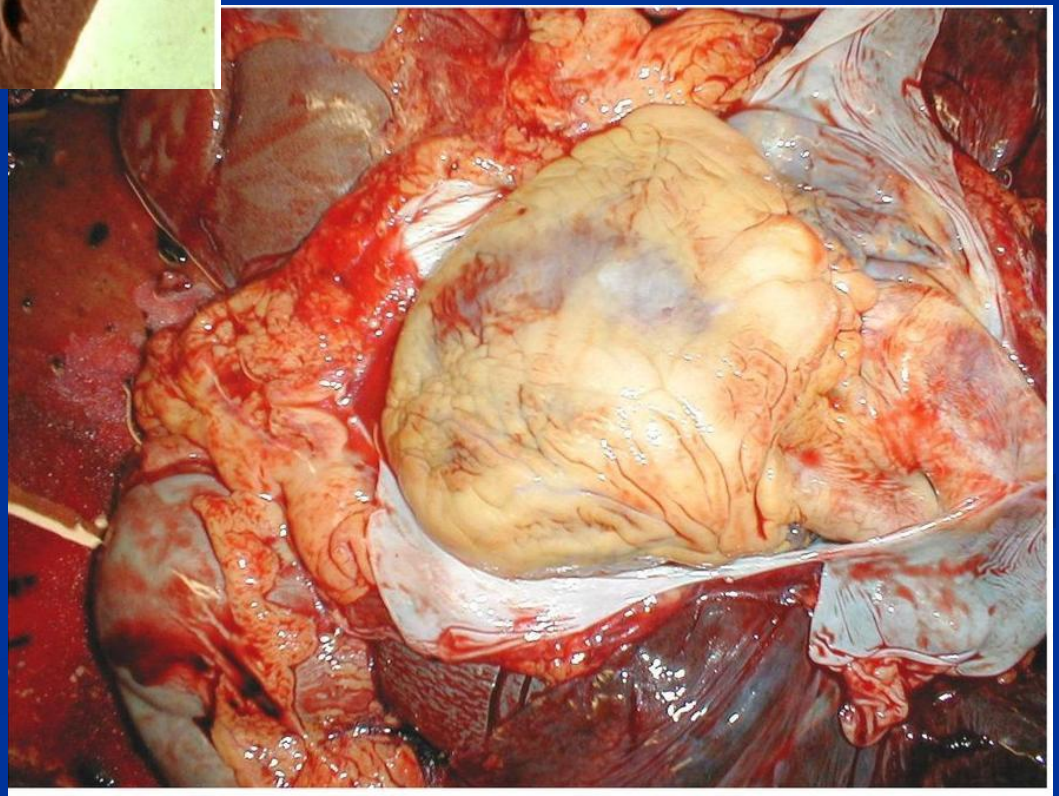
Fibrinoid necrosis



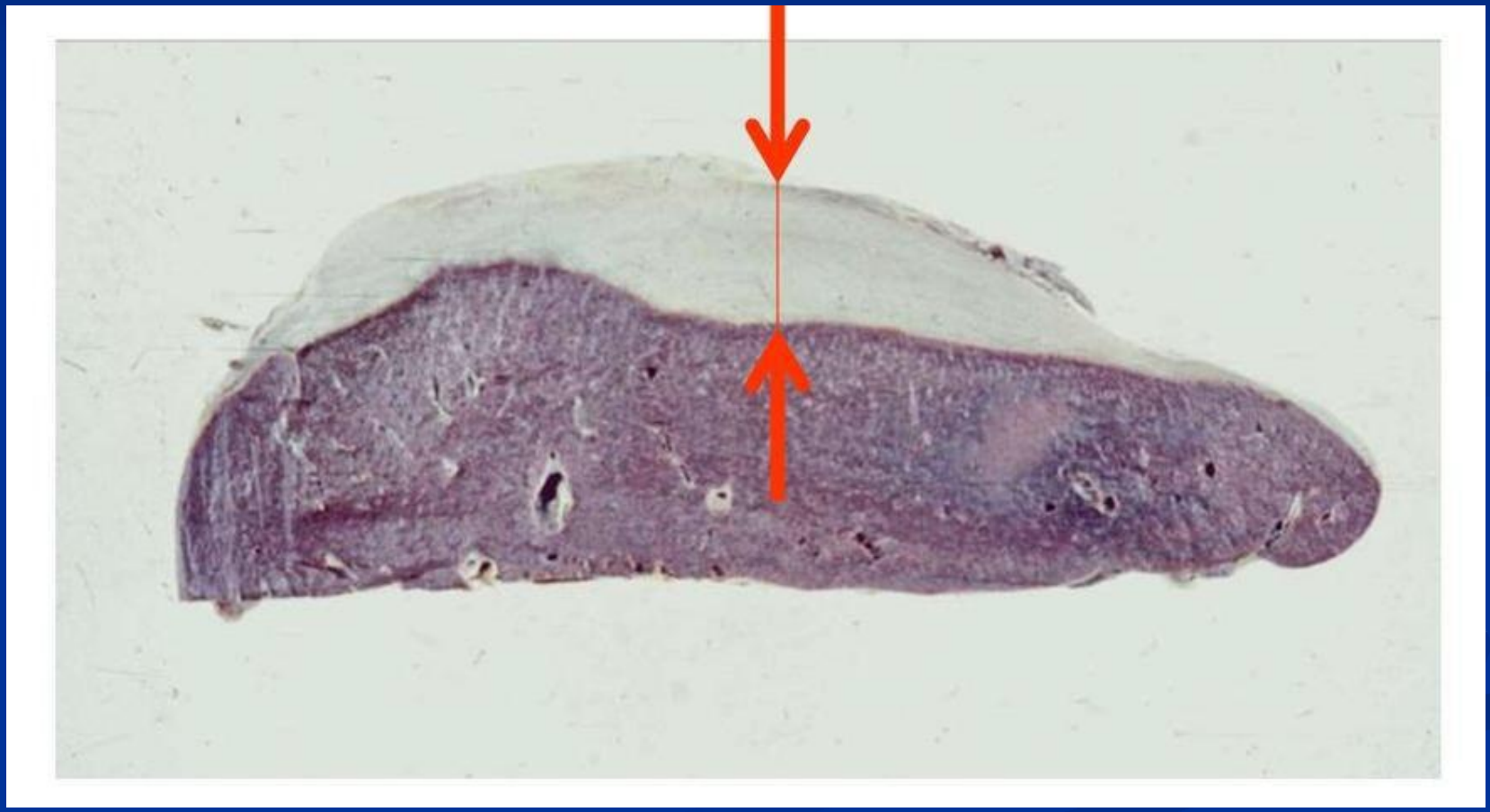
HYALINE CHANGE

- The term "hyaline" is widely used as a descriptive histologic term rather than a specific marker for cell injury. It usually refers to an alteration within cells or in the extracellular space, which gives a homogenous, glassy, pink appearance in routine histologic sections stained with hematoxilin and eosin.
- Exracellular hyaline has been somewhat more difficult to analyze. Collagen fibers tissue in old scars may appear hyalinized, but the physicochemical mechanism underlying this change is not clear. In long-standing hypertension and diabetes mellitus, the walls of arterioles, especially in the kidney, become hyalinized, owing to extravasated plasma protein and deposition of basement membrane material.



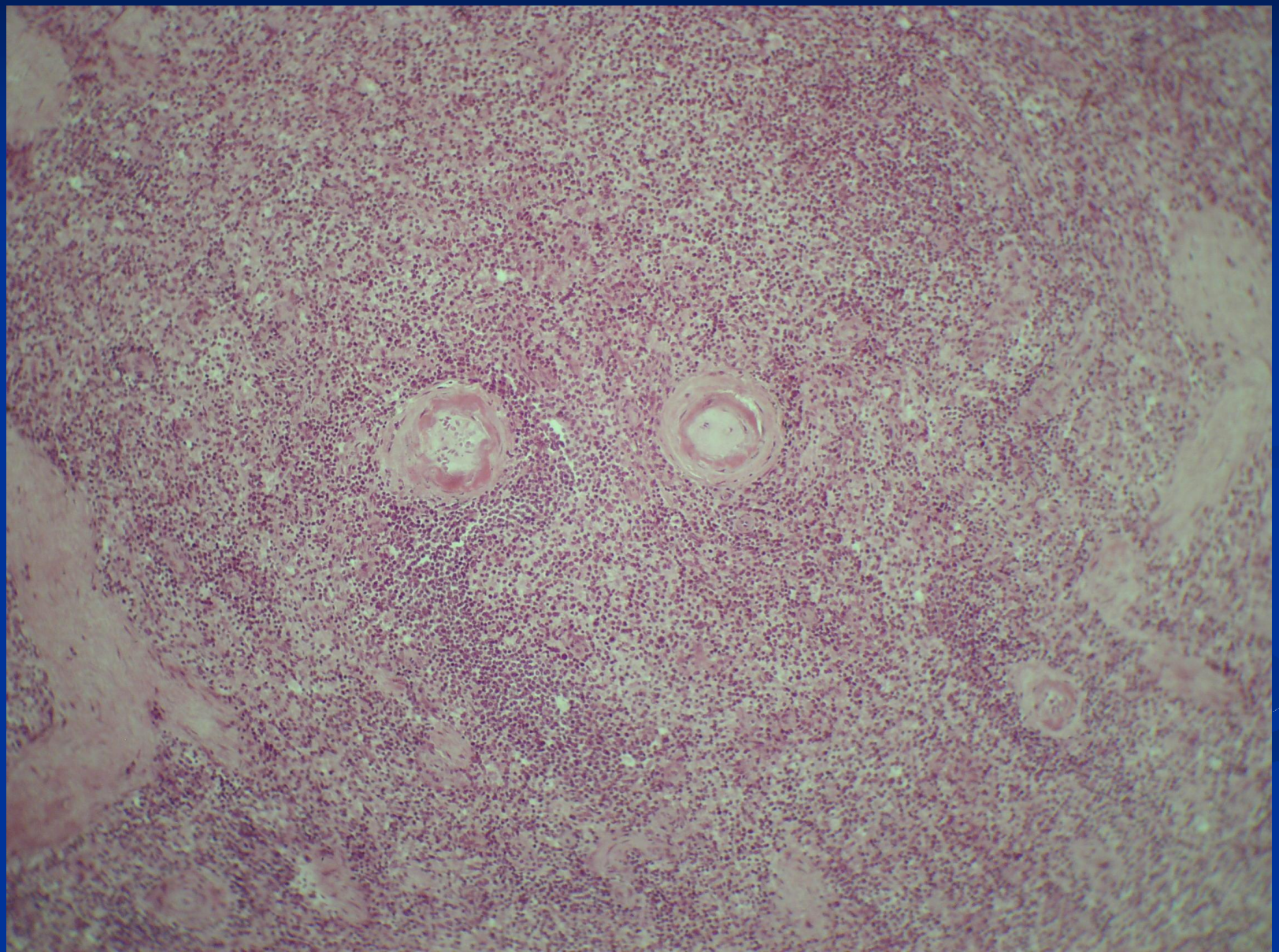


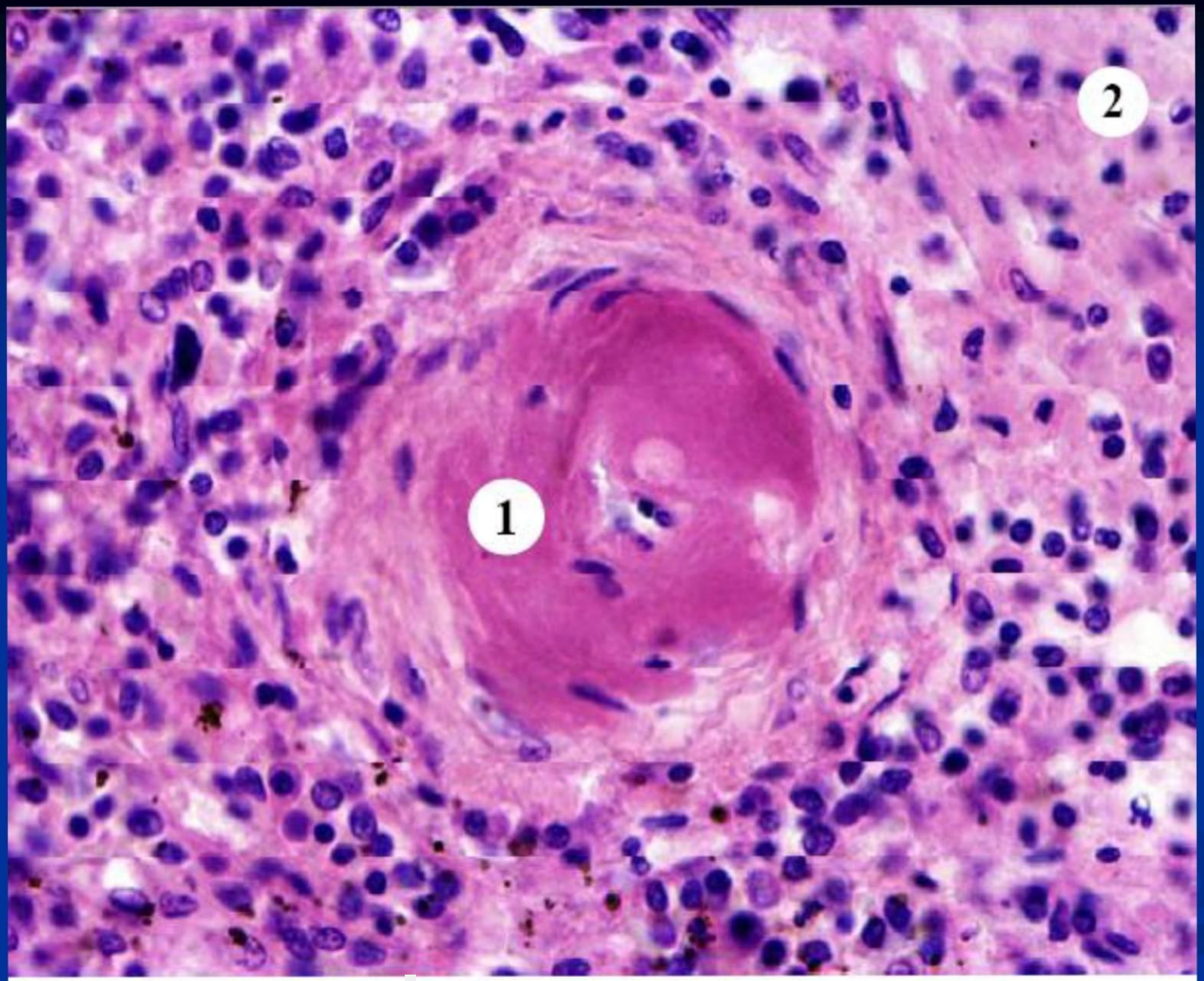
Hyalinosis of spleen capsule.



Hyalinosis of arteries in the spleen.

Hematoxilin and eosin. X 100.





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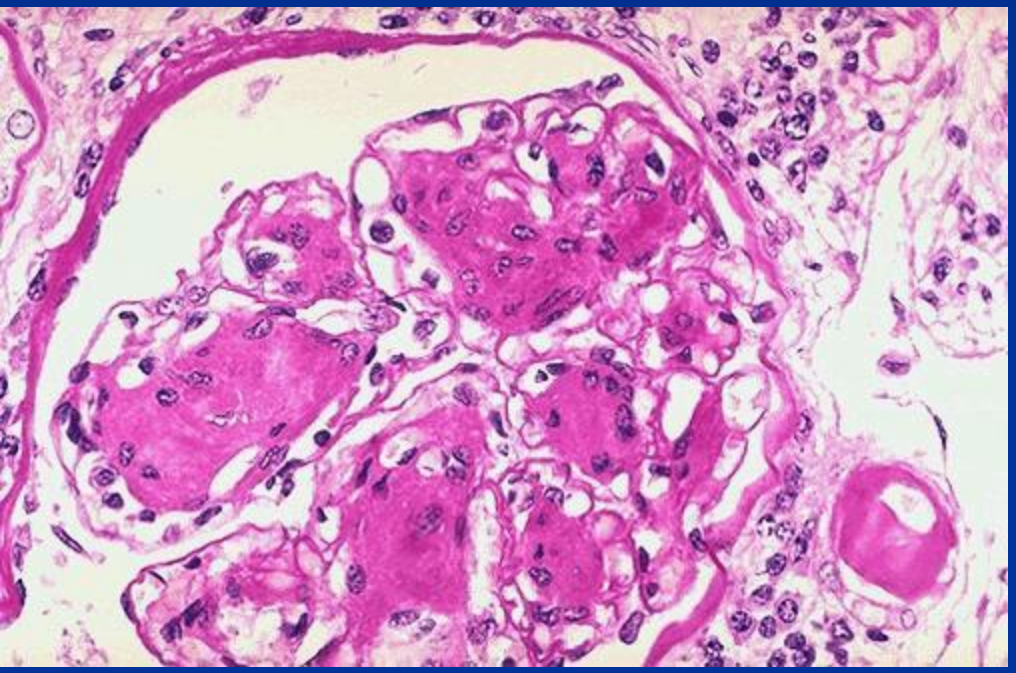
Hyalinosis

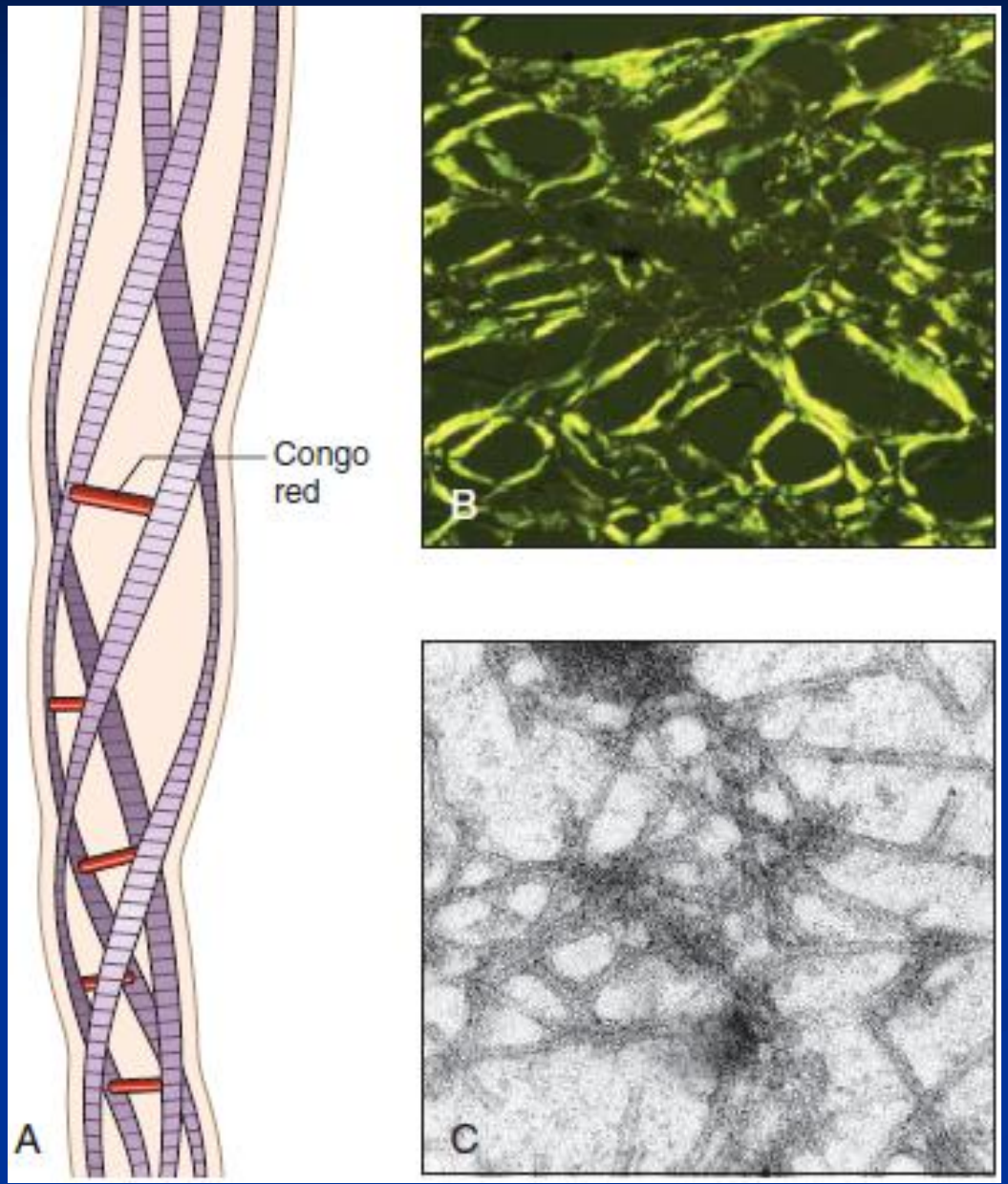


- Hyaline arteriolosclerosis is demonstrated by the markedly thickened arteriole to the lower right of this glomerulus with PAS stain. Hyaline arteriolosclerosis is seen in the elderly, but more advanced lesions are seen in persons with diabetes mellitus and/or with hypertension.

AMYLOIDOSIS

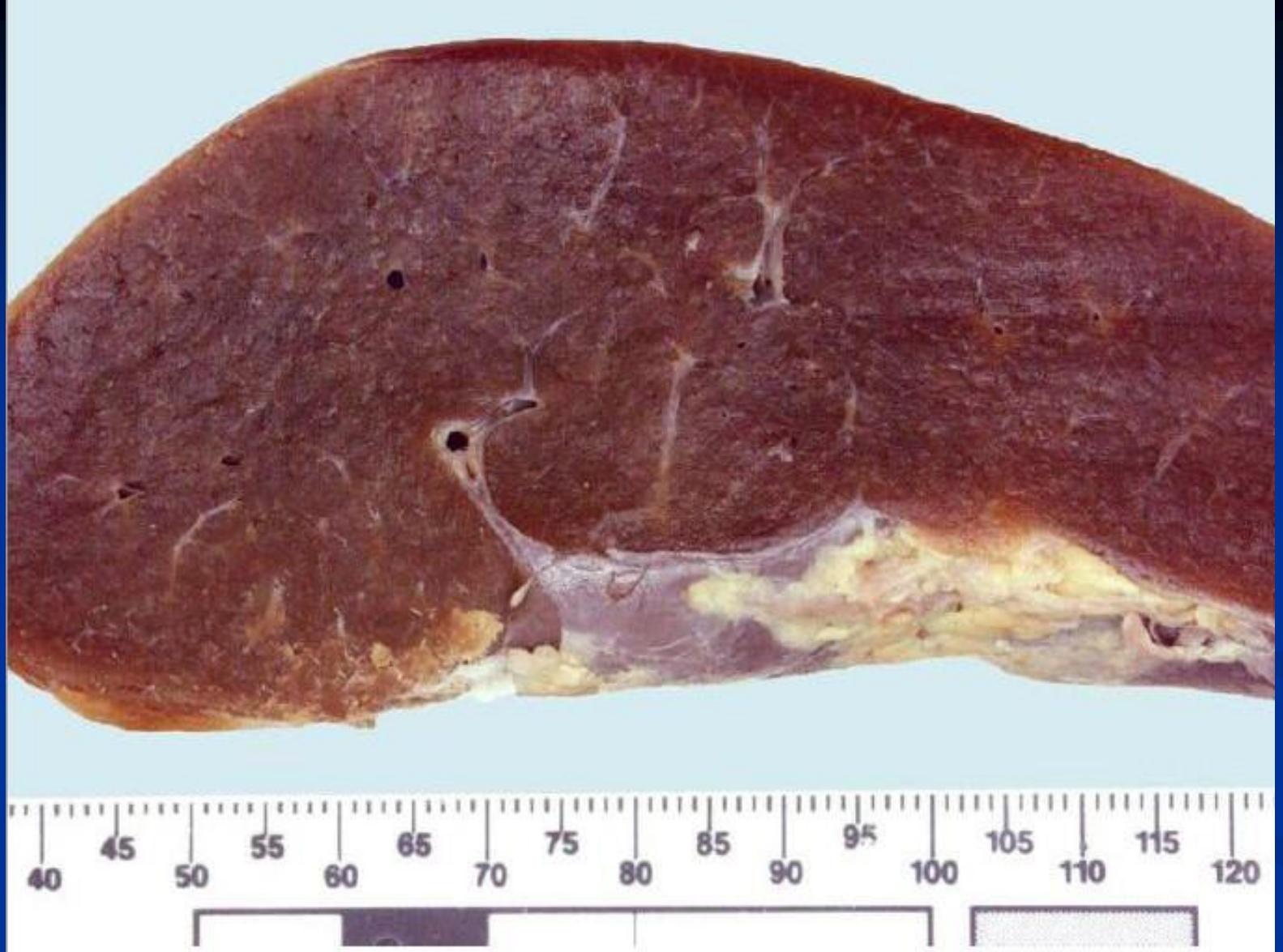
is a condition associated with a number of disorders in which extracellular deposits of fibrillar proteins are responsible for tissue damage and functional compromise.

Structure of amyloid.



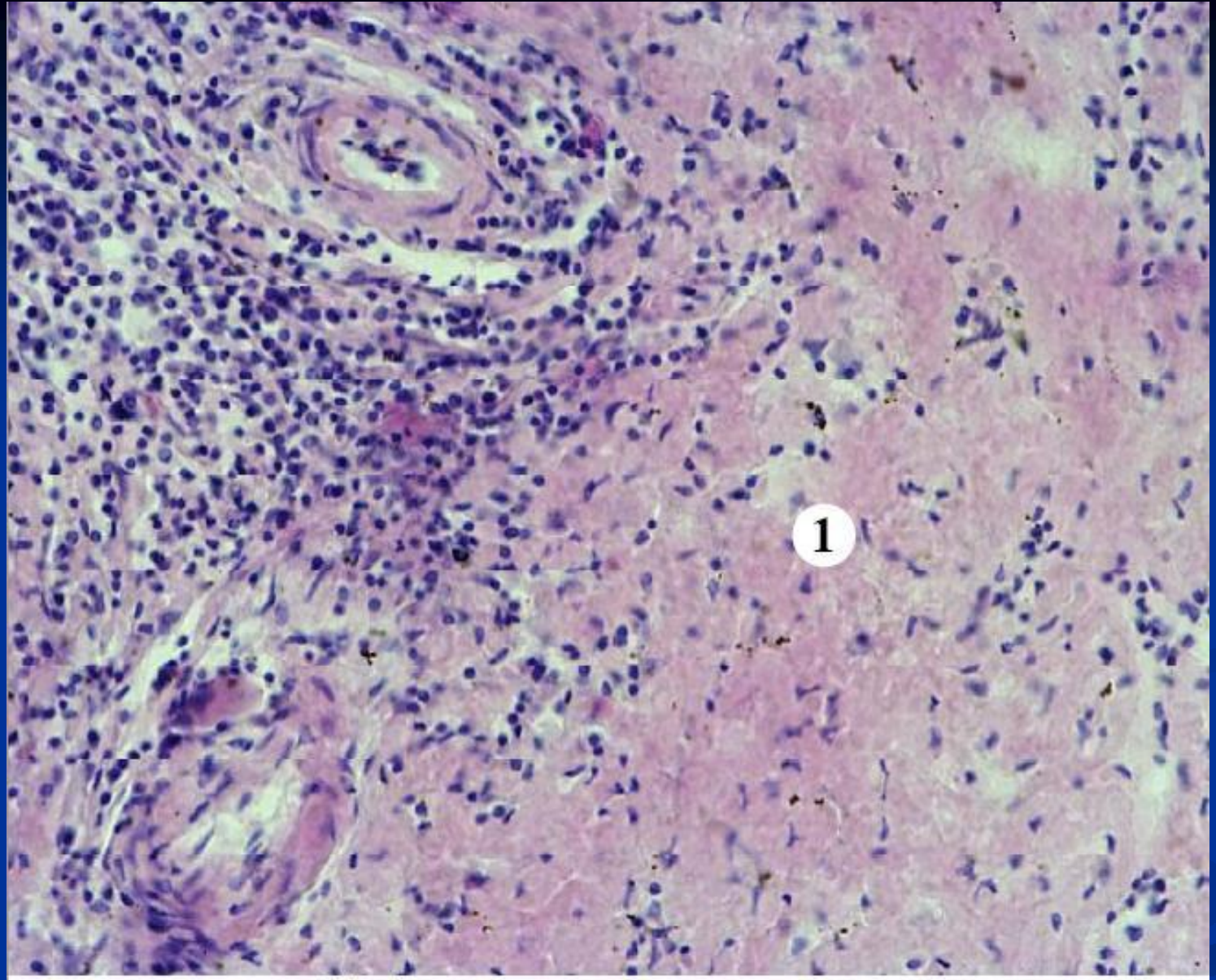
Classification of Amyloidosis

Clinicopathologic Category	Associated Diseases	Major Fibril Protein	Chemically Related Precursor Protein
Systemic (Generalized) Amyloidosis			
Plasma cell proliferations with amyloidosis (primary amyloidosis)	Multiple myeloma and other monoclonal plasma cell proliferations	AL	Immunoglobulin light chains, chiefly λ type
Reactive systemic amyloidosis (secondary amyloidosis)	Chronic inflammatory conditions	AA	SAA
Hemodialysis-associated amyloidosis	Chronic renal failure	$A\beta_2m$	β_2-microglobulin
Hereditary Amyloidosis			
Familial Mediterranean fever		AA	SAA
Familial amyloidotic neuropathies (several types)		ATTR	Transthyretin
Systemic senile amyloidosis		ATTR	Transthyretin
Localized Amyloidosis			
Senile cerebral	Alzheimer disease	Aβ	APP
Endocrine	Type 2 diabetes		
Medullary carcinoma of thyroid		A Cal	Calcitonin
Islets of Langerhans		AIAPP	Islet amyloid peptide
Isolated atrial amyloidosis		AANF	Atrial natriuretic factor



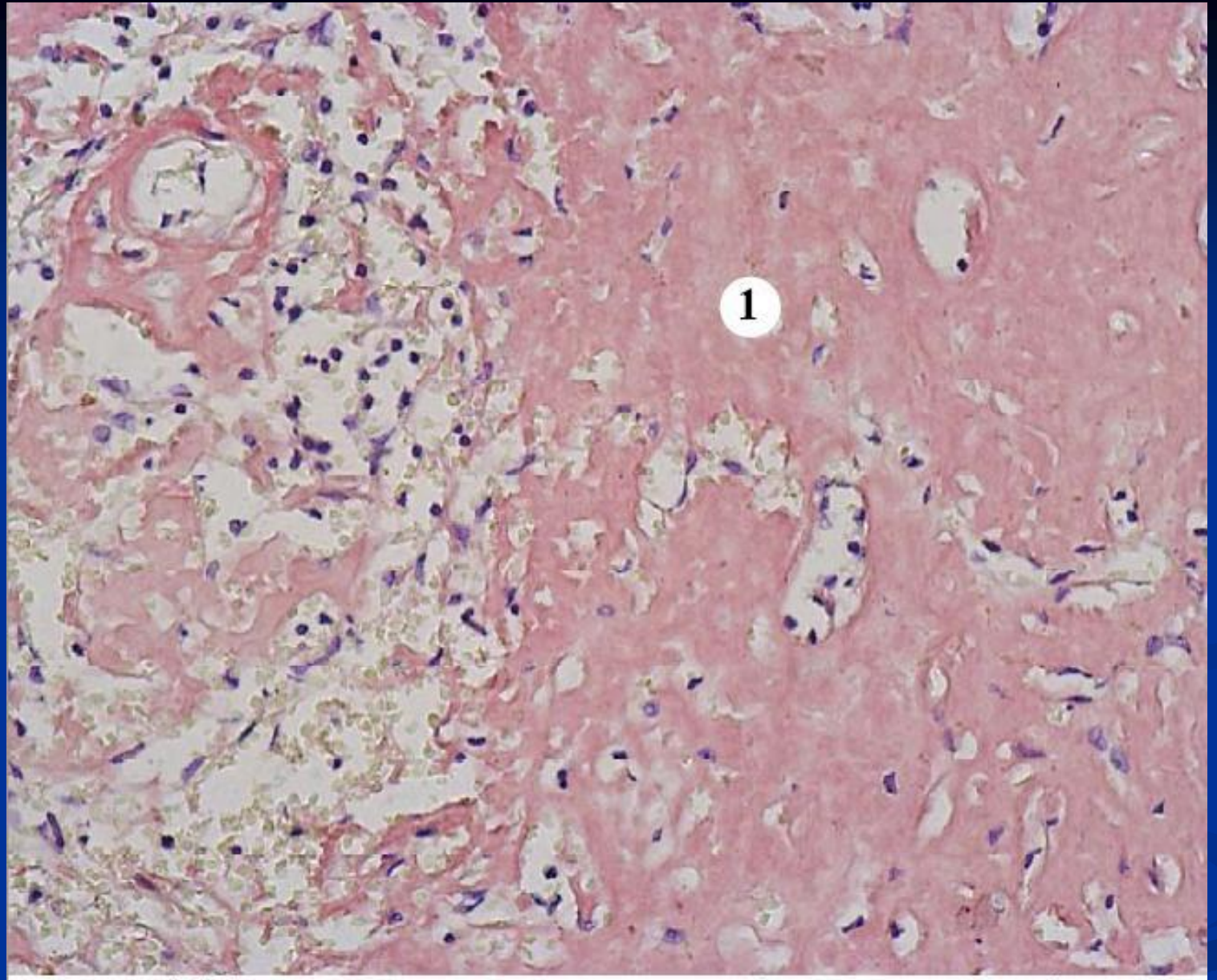
4.15. Амилоидоз селезенки, сальная селезенка.
Селезенка увеличена, плотная, ее поверхность гладкая, капсула напряжена.
На разрезе пульпа коричневатая, с сальным блеском

Amyloidosis of the spleen, "lardaceous" spleen.



4.16. Амилоидоз селезенки, сальная селезенка.
В лимфоидных фолликулах, интиме артерий и красной пульпе по ходу ретикулярных волокон – отложения розовых масс, вытесняющих ткань селезенки (1).

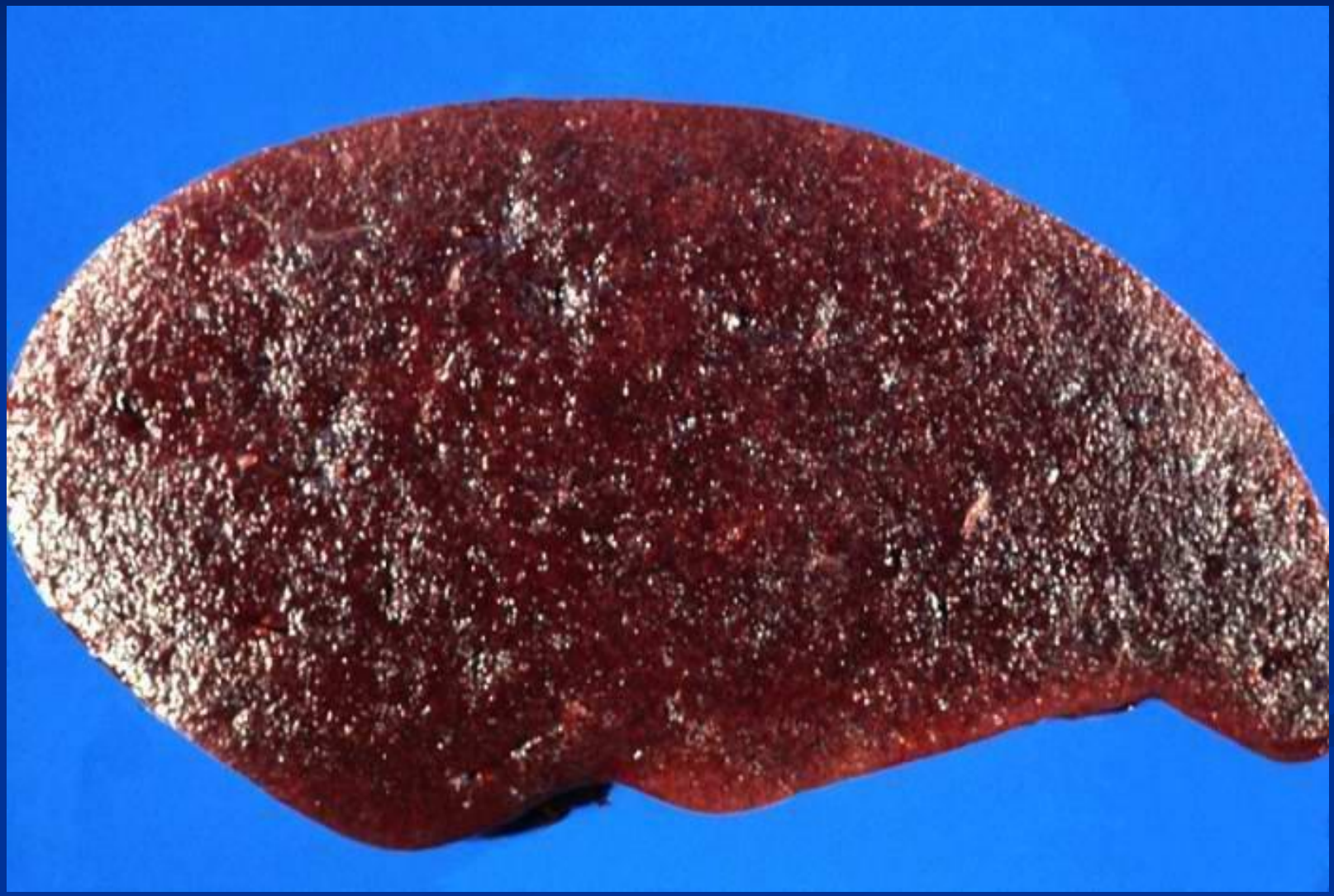
Amyloidosis of the spleen, "lardaceous" spleen

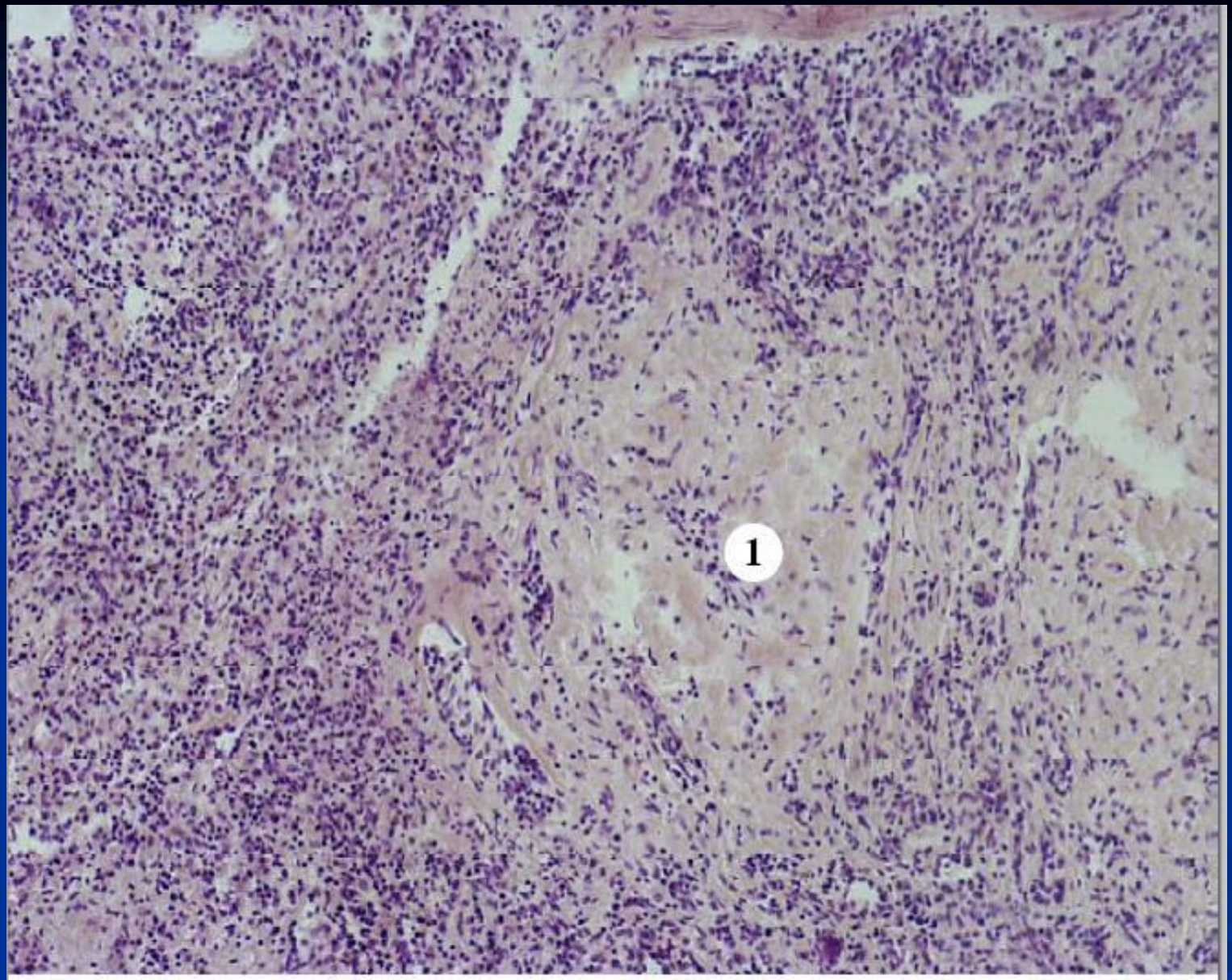


4.17. Амилоидоз селезенки, сальная селезенка (окраска конго красным).
В лимфоидных фолликулах, интиме артерий и красной пульпе по ходу ретикулярных волокон – отложения масс амилоида коричнево-красного цвета (1).

Amyloidosis of the spleen, "lardaceous" spleen

Amyloidosis of the spleen, «sago spleen».

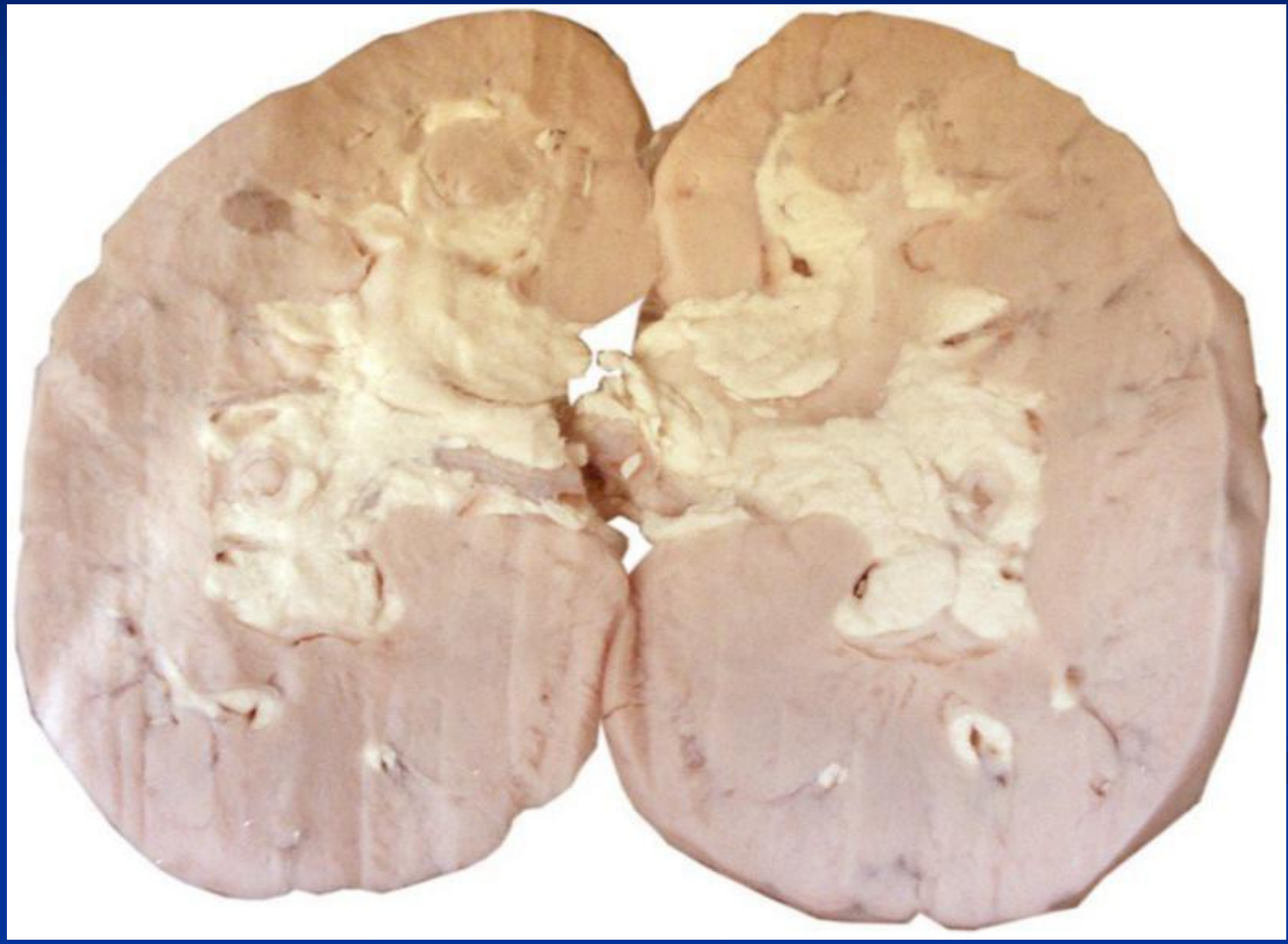




4.18. Амилоидоз селезенки, саговая селезенка.
В интиме центральных артерий и в лимфоидных фолликулах имеются отложения масс амилоида (1).

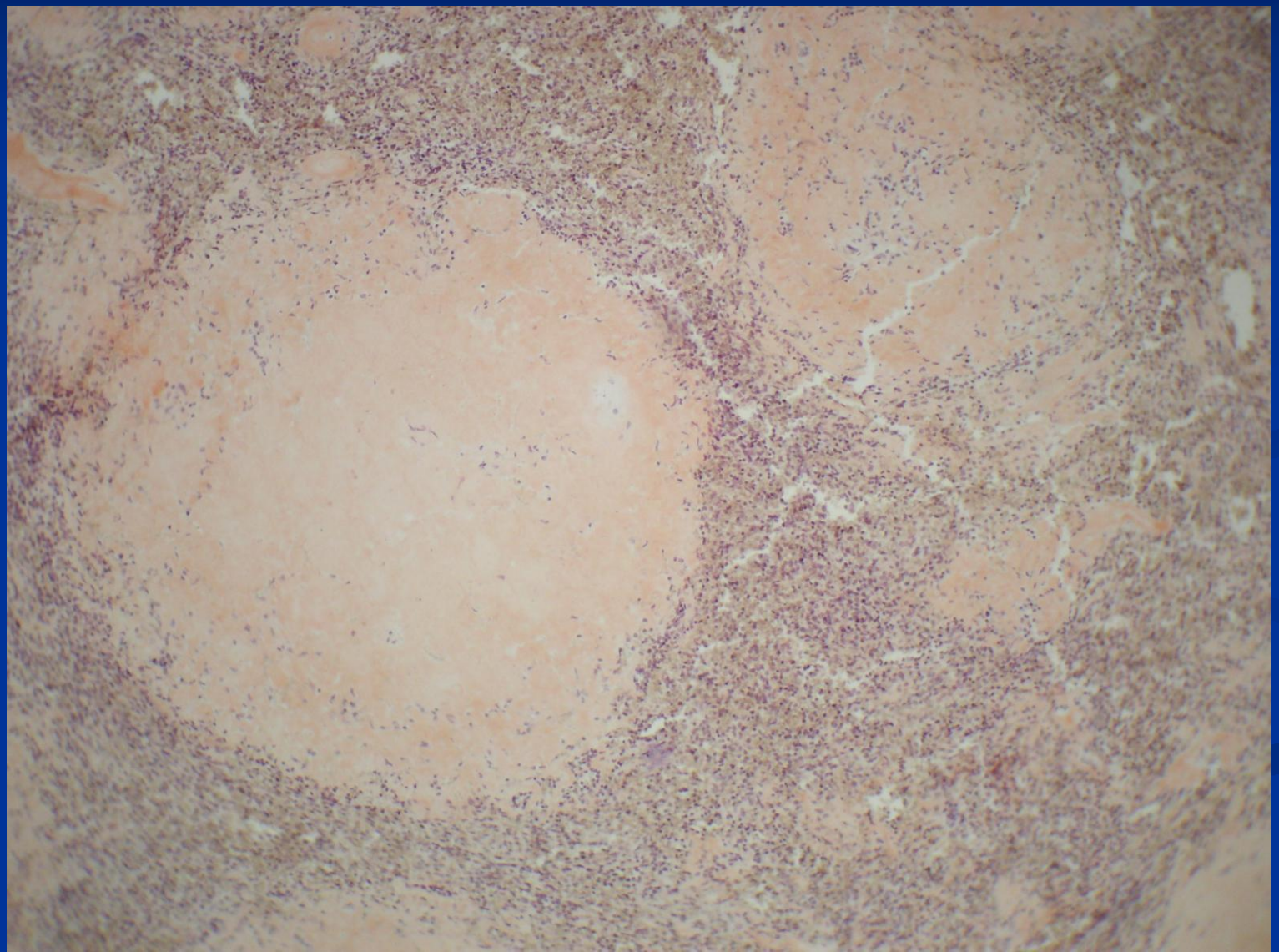
Amyloidosis of the spleen, "sago spleen"

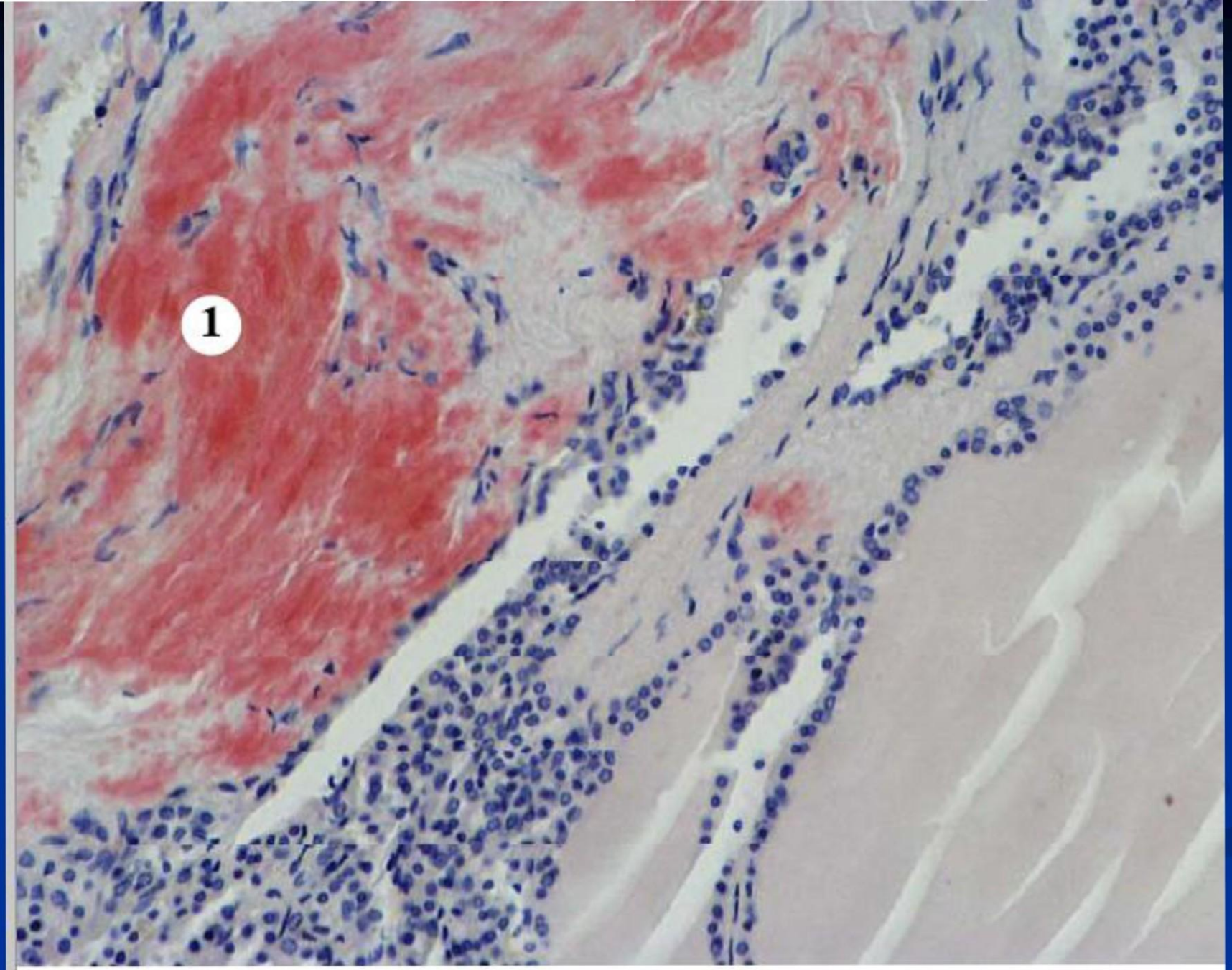
Amyloidosis of kidney



Amyloidosis of kidney.

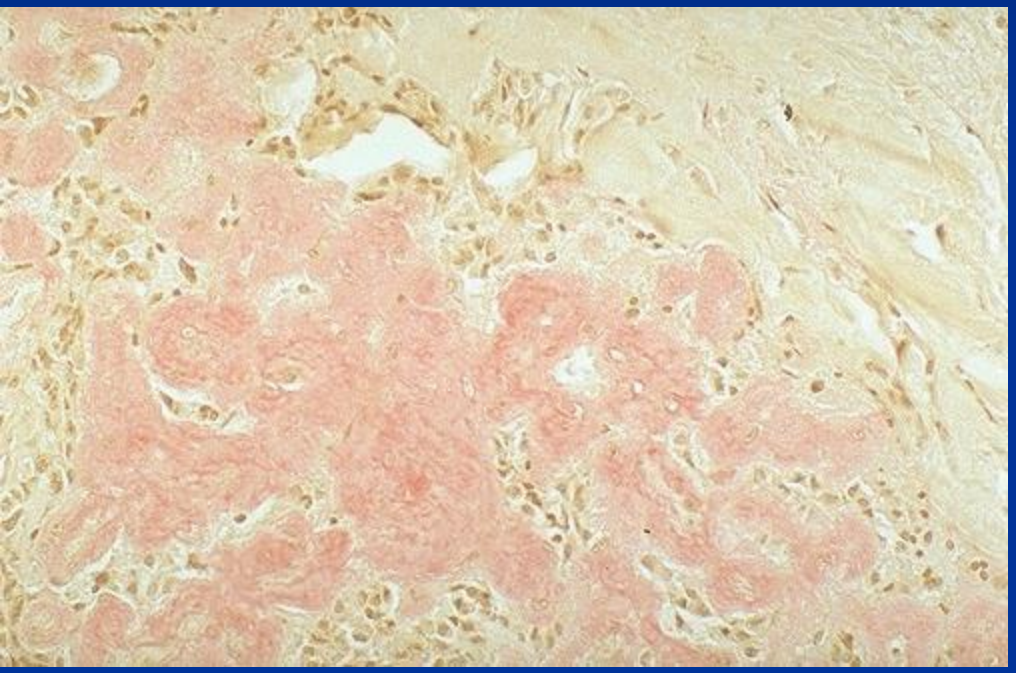
Congo red.X 400.





4.19. AMlt1Jl0"1A03 ITTOB"1AHO >Kene3bl (oKpacKa KOHrO KpaCHblM). AMWIO"'A (1) 06Hapy>t<111BaercH a cocyAax "1 crpoMe

Amyloidosis



- This is a Congo red stain to reveal orange-red deposits of amyloid, which is a proteinaceous material that can collect in cells and tissues.