Necrosis and apoptosis. Infarction.

Necrosis

- Necrosis is cell death, which is a complex of pathomorphologic changes that follow cell death in living tissue, largely resulting from the progressive degradative action of enzymes on the lethally injured cell.

Classification of necrosis

- Coagulative necrosis
- Liquefactive necrosis
- Caseous necrosis
- Gangrene
- Fat necrosis

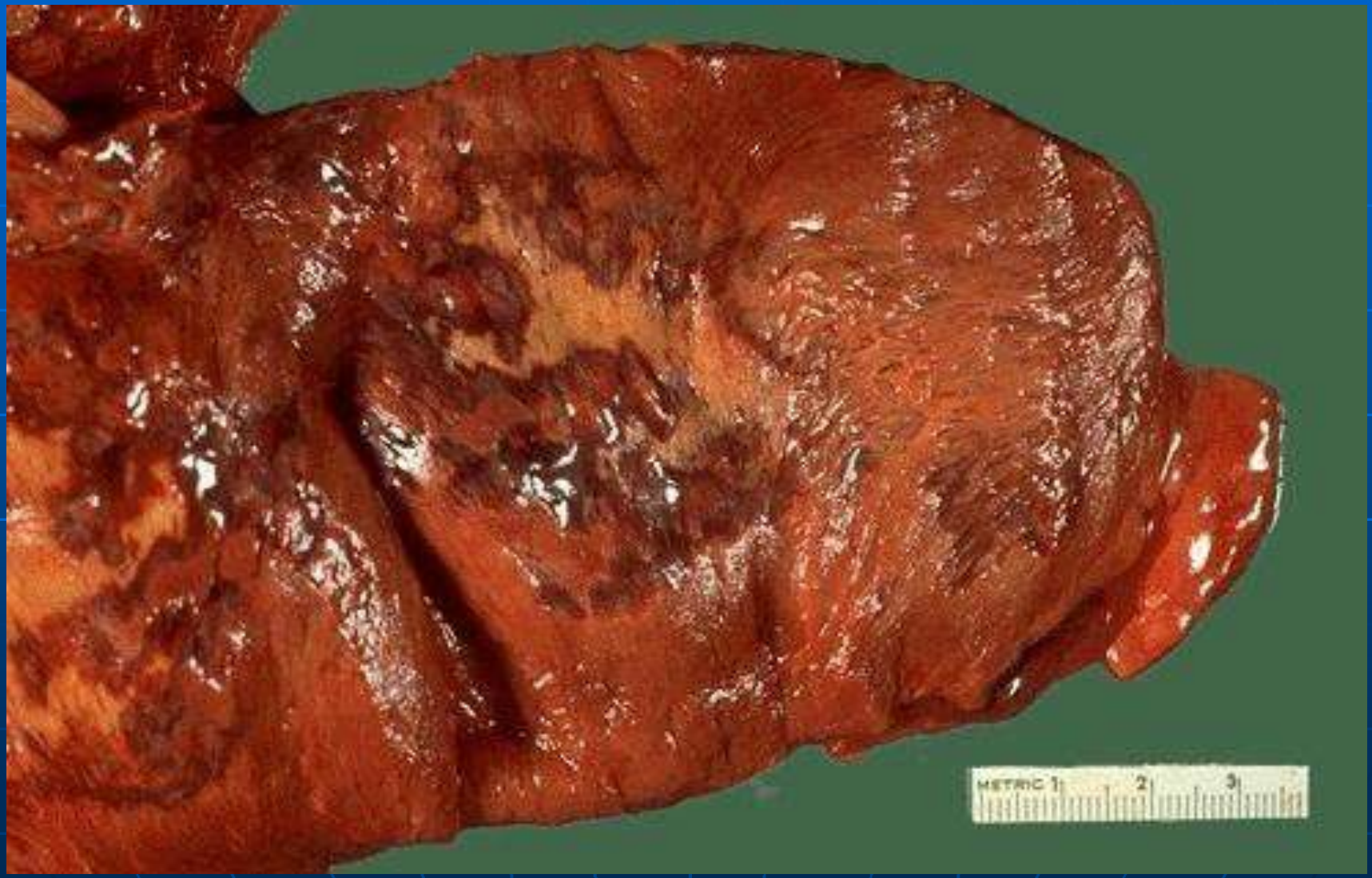
Some additional types of necrosis: fibrinous necrosis, sequestration.

Microscopic appearance: The microscopic changes of necrosis vary with the type of necrosis. Some general changes of necrosis in the cytoplasm are:

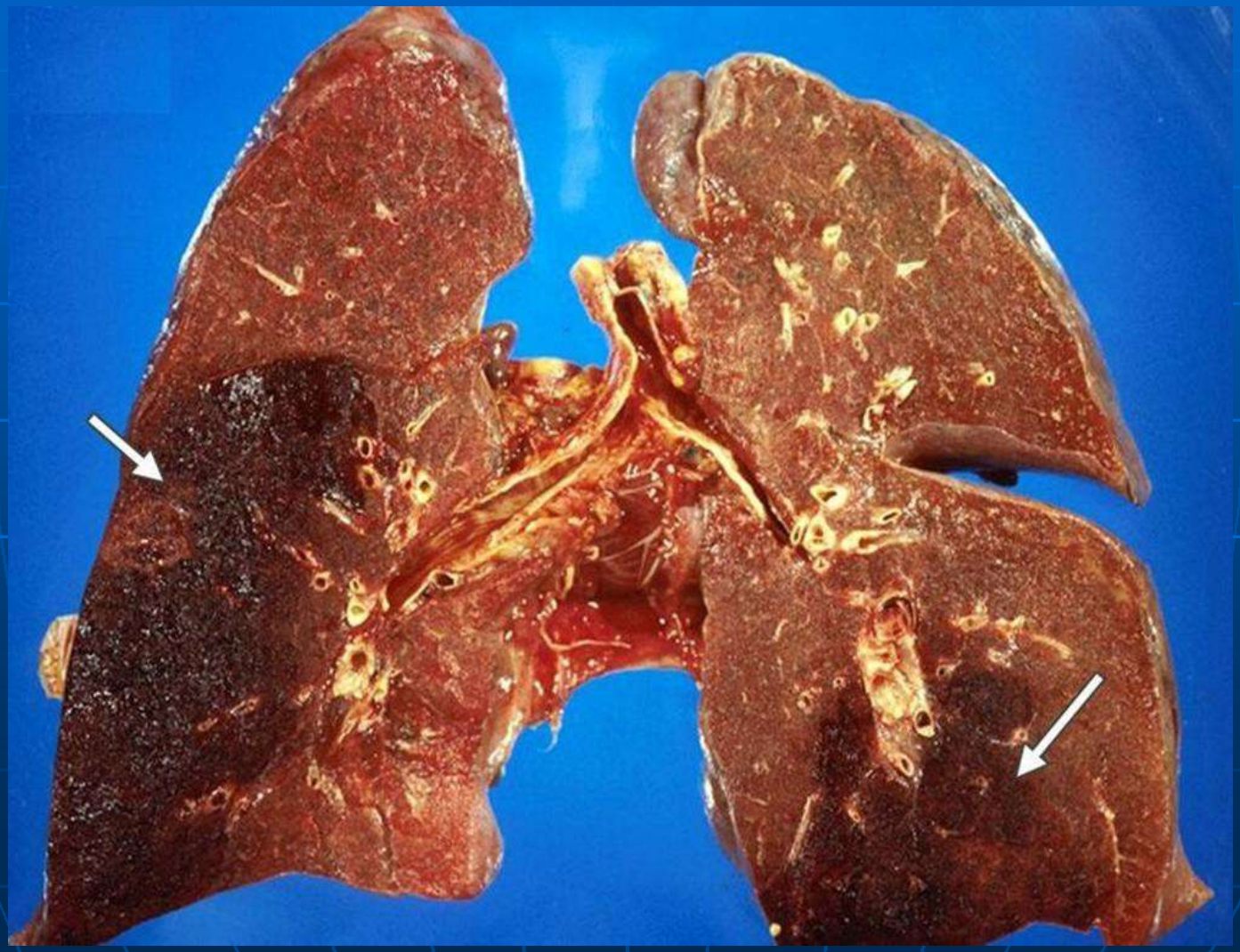
- Eosinophilia: The cytoplasm stains darker red in colour.
- Swelling and vacuolation: The cells are swollen and contain different types of vacuoles.
- Changes in the nucleus: The nucleus may show condensation (Pyknosis), fragmentation (karyorrhexis) and may disappear (karyolysis).

Coagulative necrosis. White infarction.

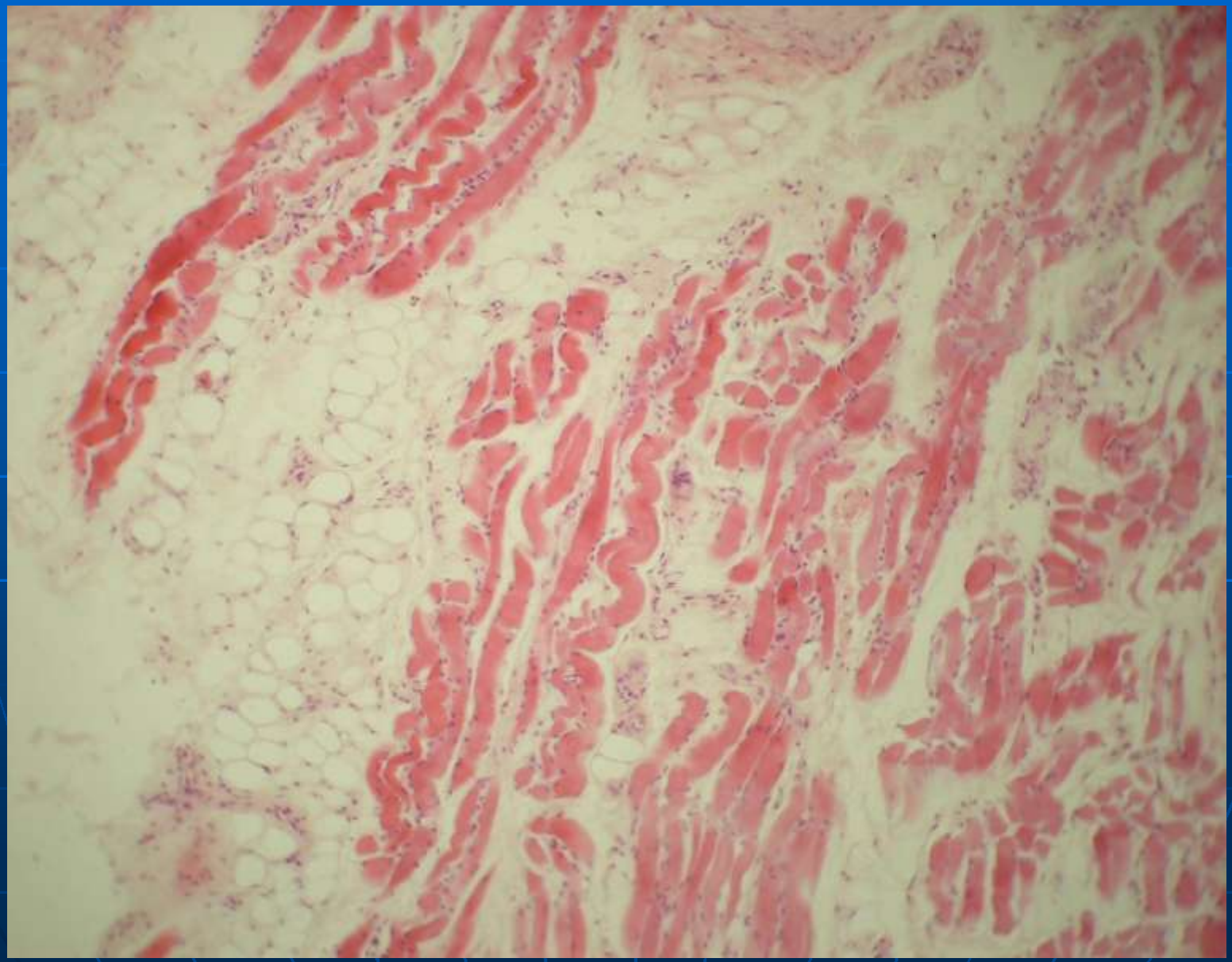
Myocardial infarction.



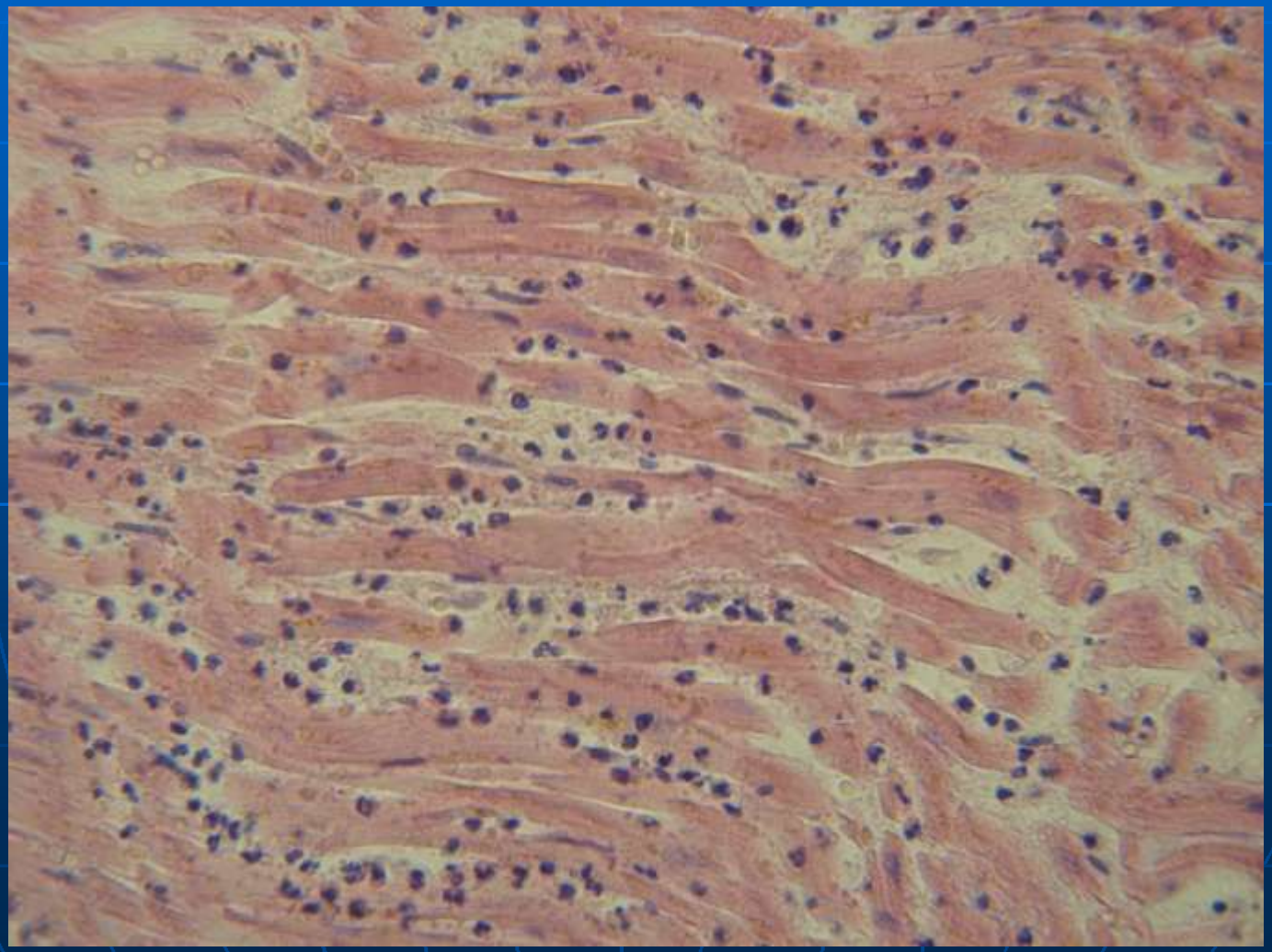
Coagulative necrosis. Red infarction.



Coagulative necrosis.



Coagulative necrosis. Myocardial infarction.



Renal cortex and medulla are susceptible to hypoxic injury.

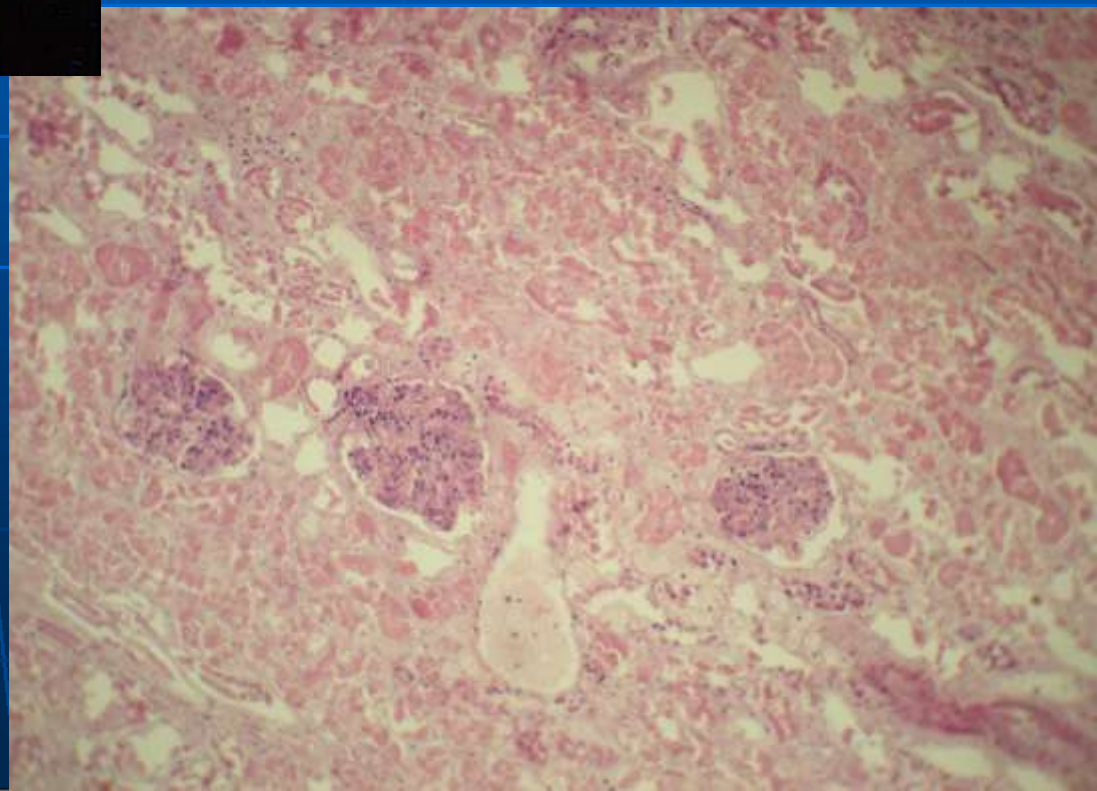
a. The straight portion of the proximal tubule in the cortex is most susceptible to hypoxia.

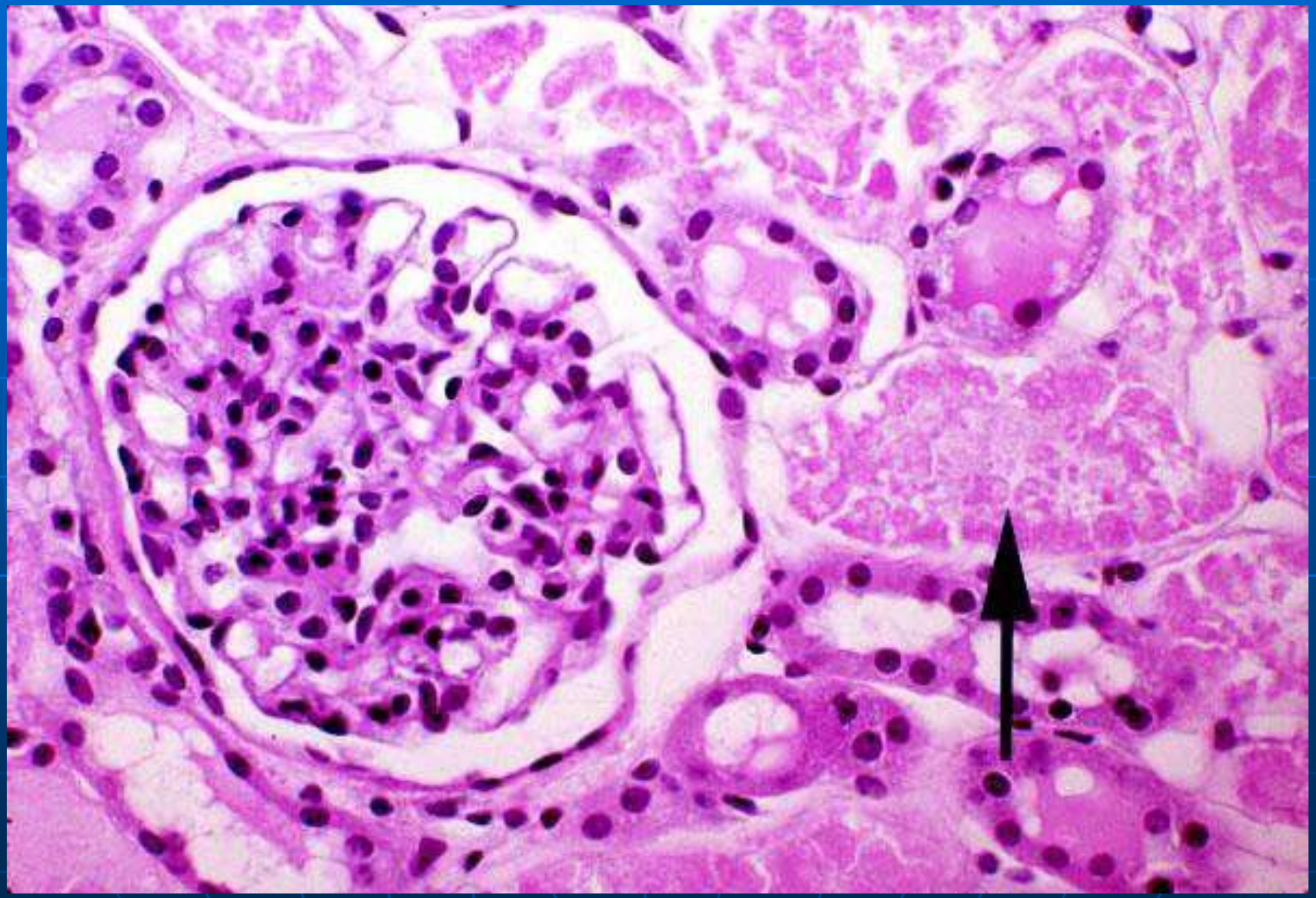
- Primary site for reclaiming bicarbonate and reabsorbing sodium

b. The thick ascending limb of the medulla is also susceptible to hypoxia (location of Na+/K+/2Cl– transporter).

- Primary site for regenerating free water, which is necessary for normal dilution and concentration of urine

Coagulative necrosis.





Liquefactive necrosis: There is digestion and liquefaction of necrotic tissue.

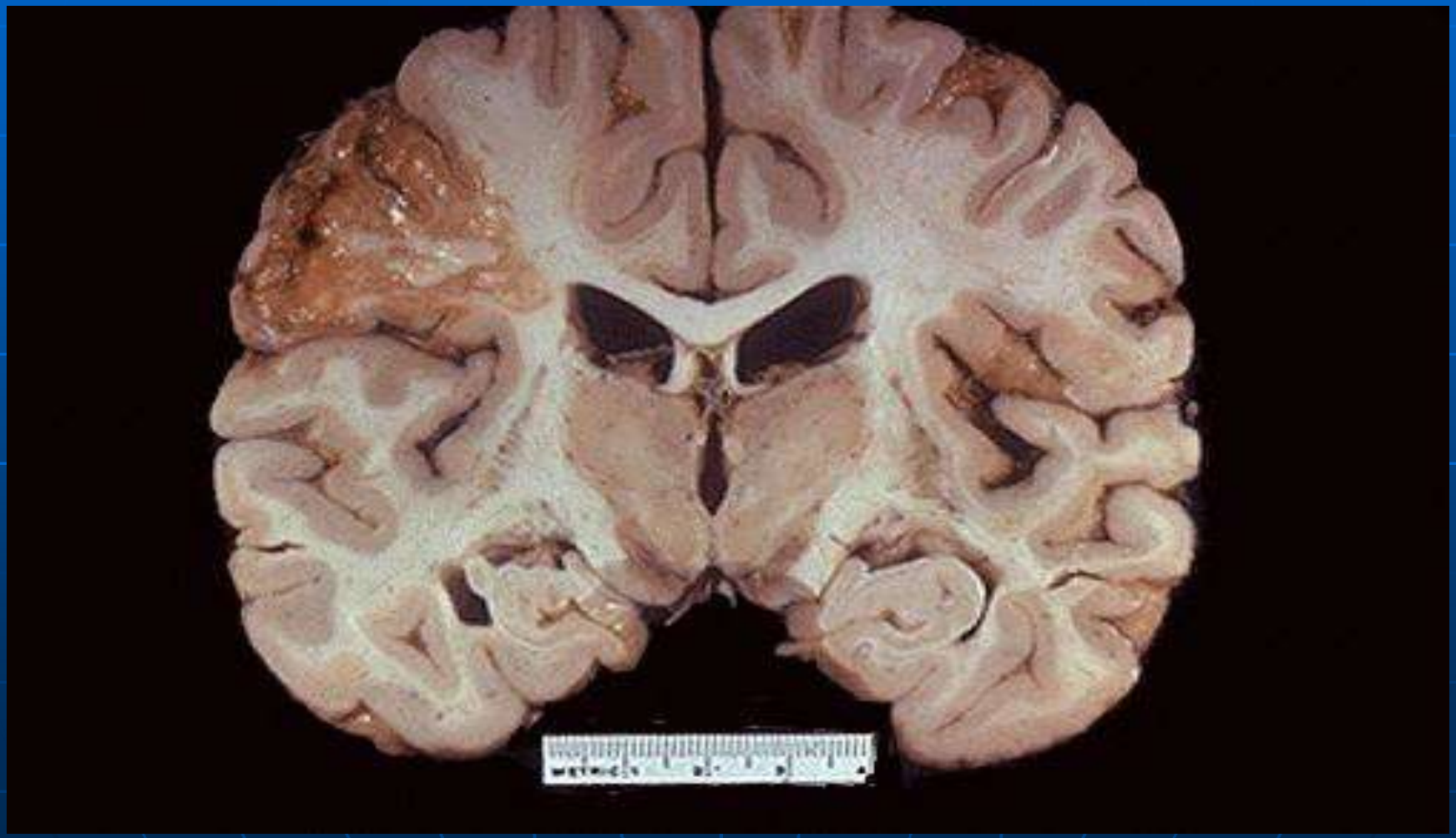
- Causes:

1. Pyogenic bacterial infections attract neutrophils. Bacterial and leukocytic enzymes liquefy dead cells and tissues.

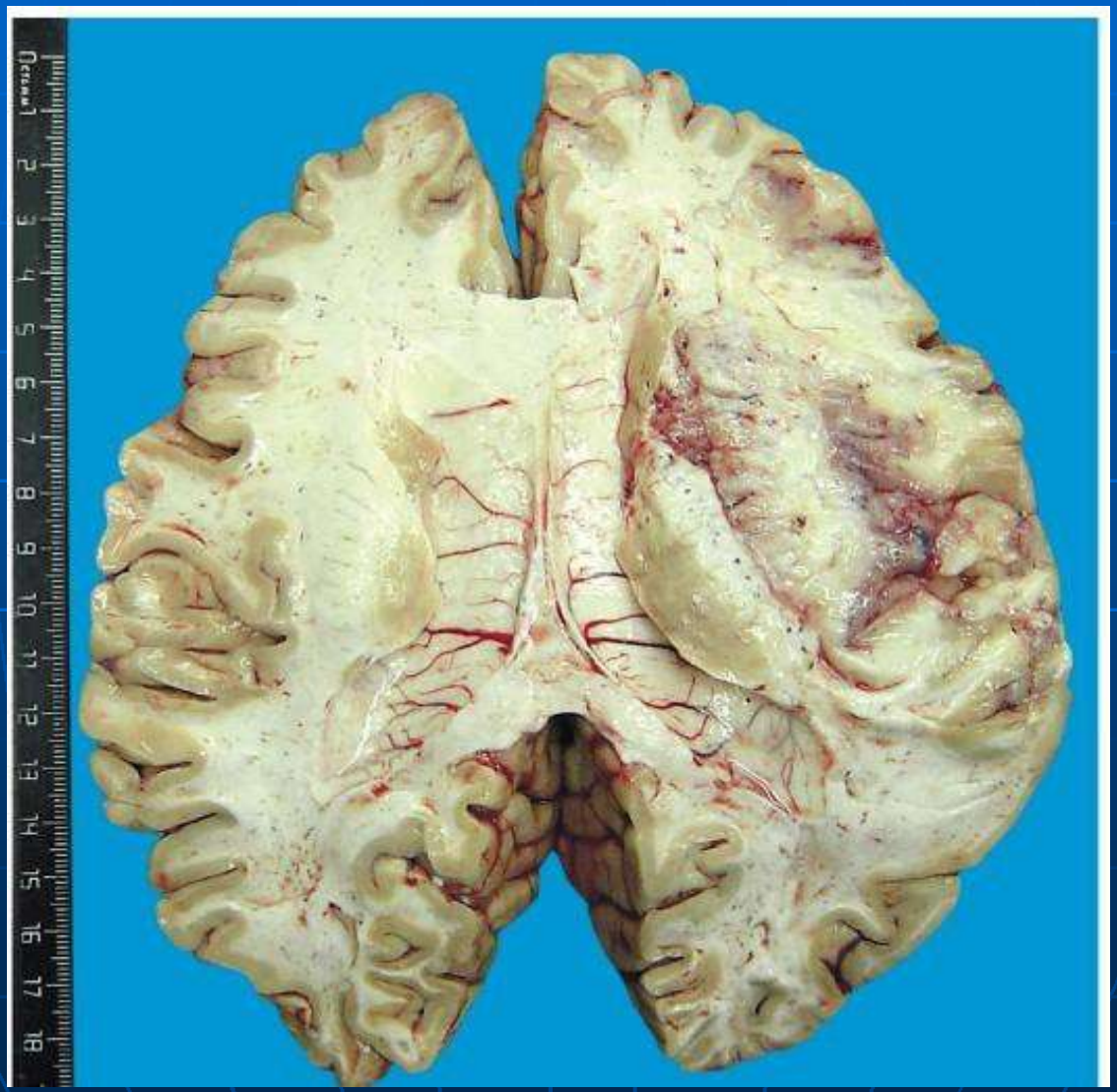
2. Some chemicals like turpentine oil also attract neutrophils and cause pus formation and liquefactive necrosis.

3. The necrosis in the nervous tissue is mostly liquefactive due to high content of lipids and water.

Liquefative necrosis. Cerebral infarction.



Liquefative necrosis. Cerebral infarction.



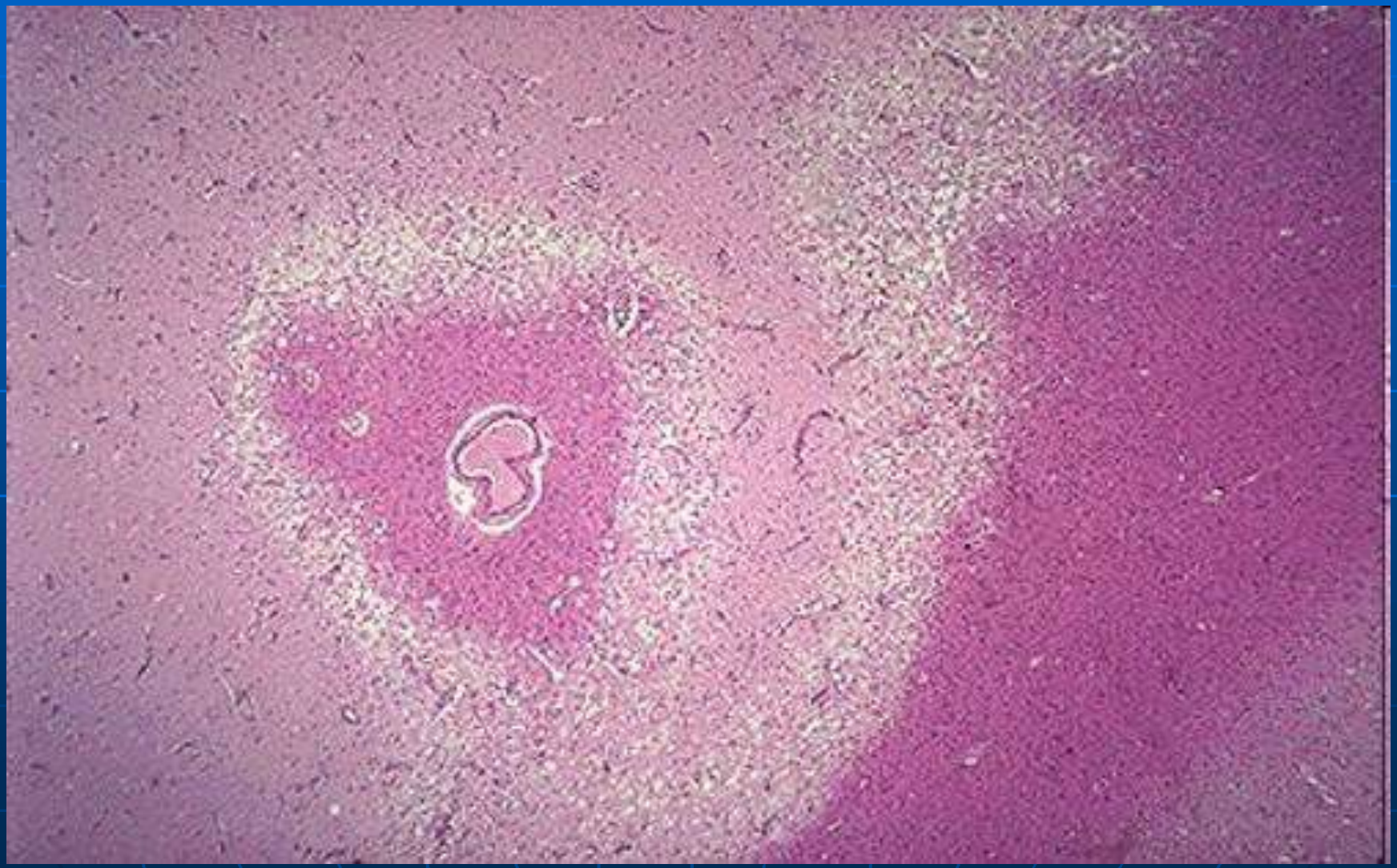
Neurons in the central nervous system are susceptible to hypoxic injury.

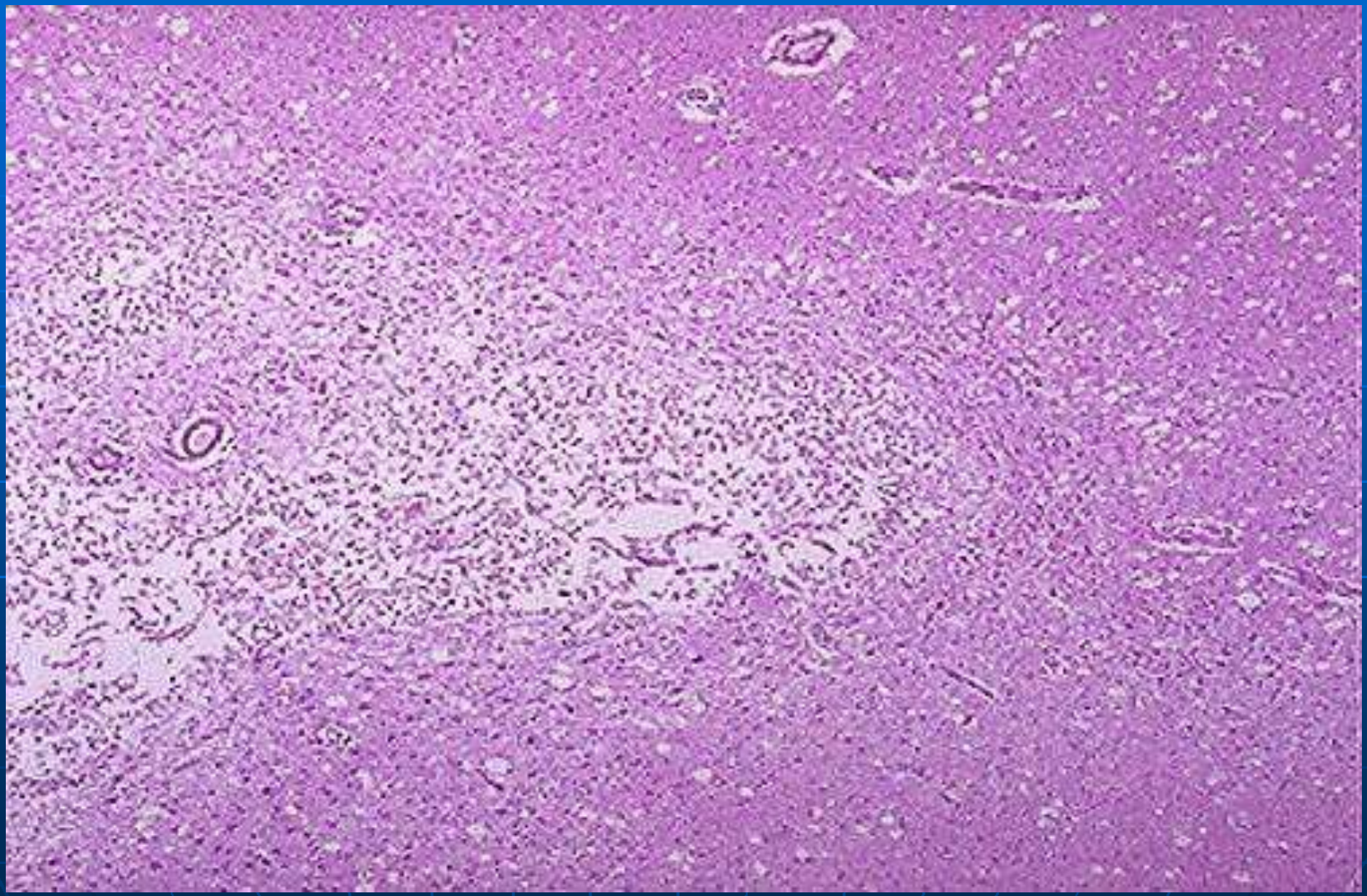
a. Examples—Purkinje cells in cerebellum and neurons in the cerebral cortex

b. Irreversible damage occurs ~5 minutes after global hypoxia (e.g., shock).

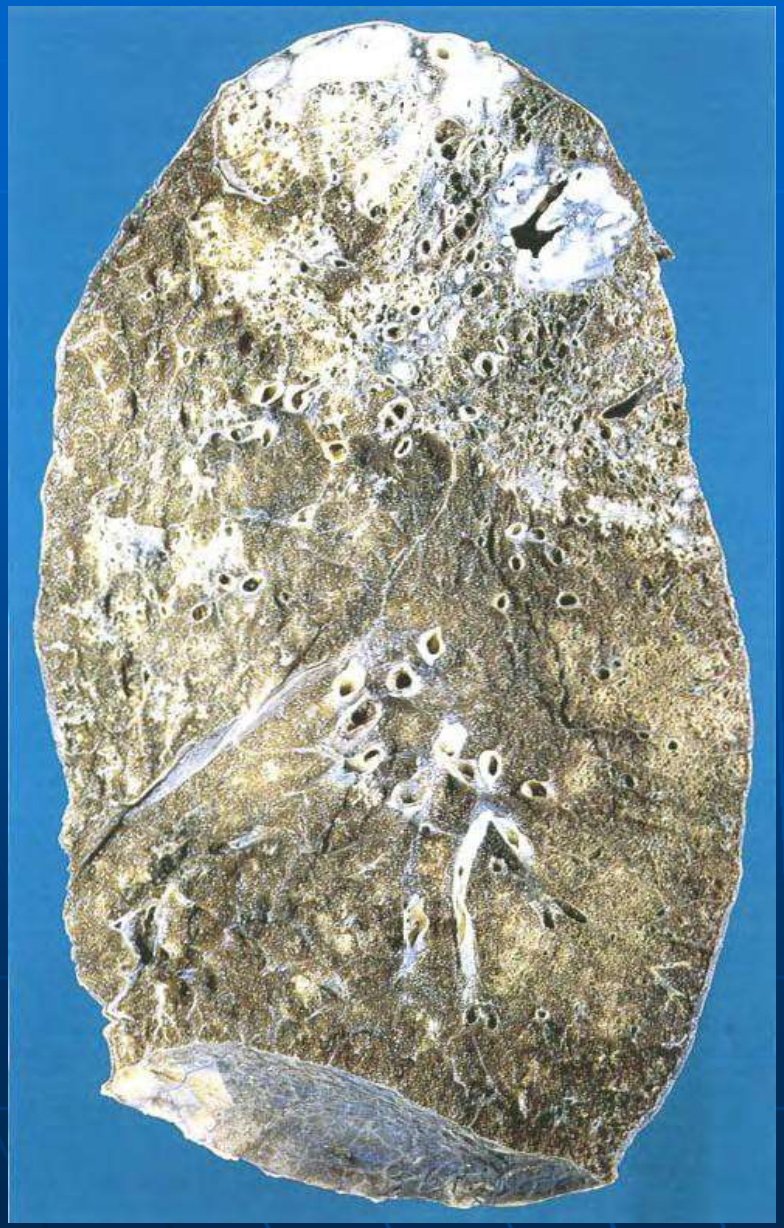
- Most adversely affected cell in tissue hypoxia

Liquefative necrosis. Cerebral infarction.





Caseous necrosis.



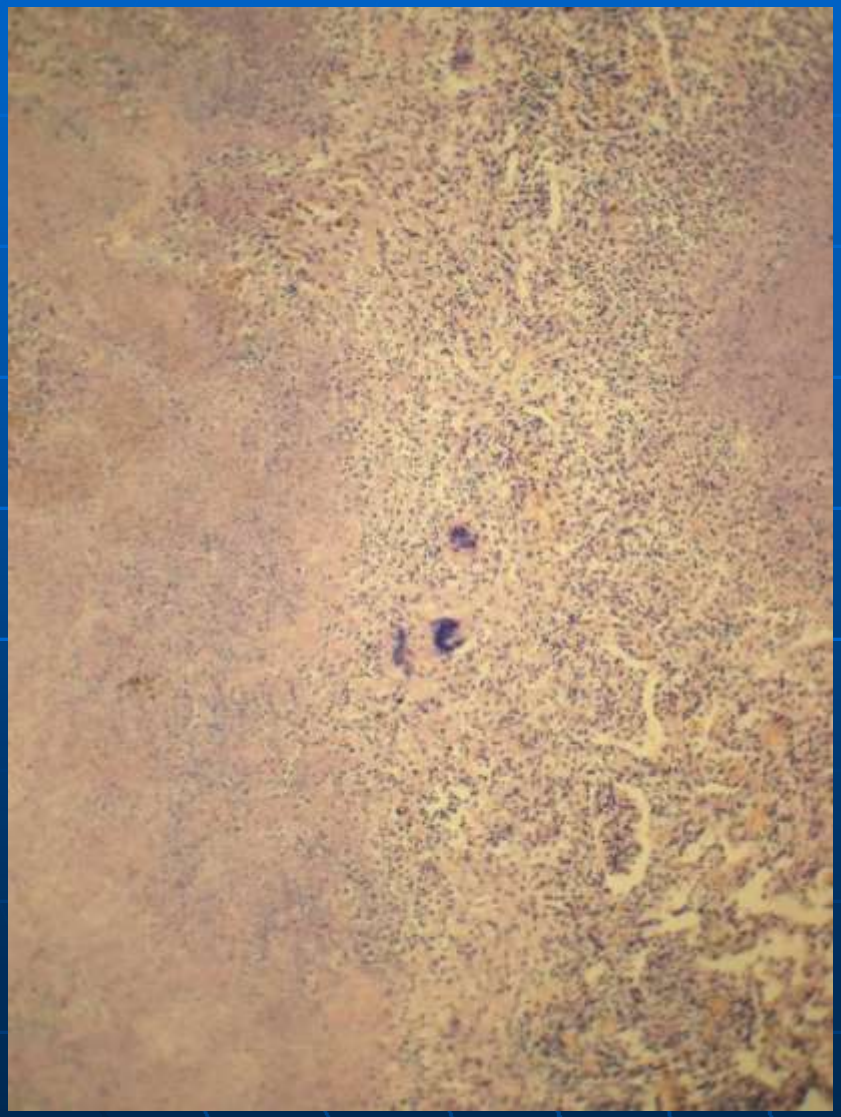
- **Caseous necrosis:**
Dead tissue is converted into a homogenous, granular mass resembling cottage cheese.
- Cause: Associated with lesions of *Mycobacterium tuberculosis, fungal infections ets.*

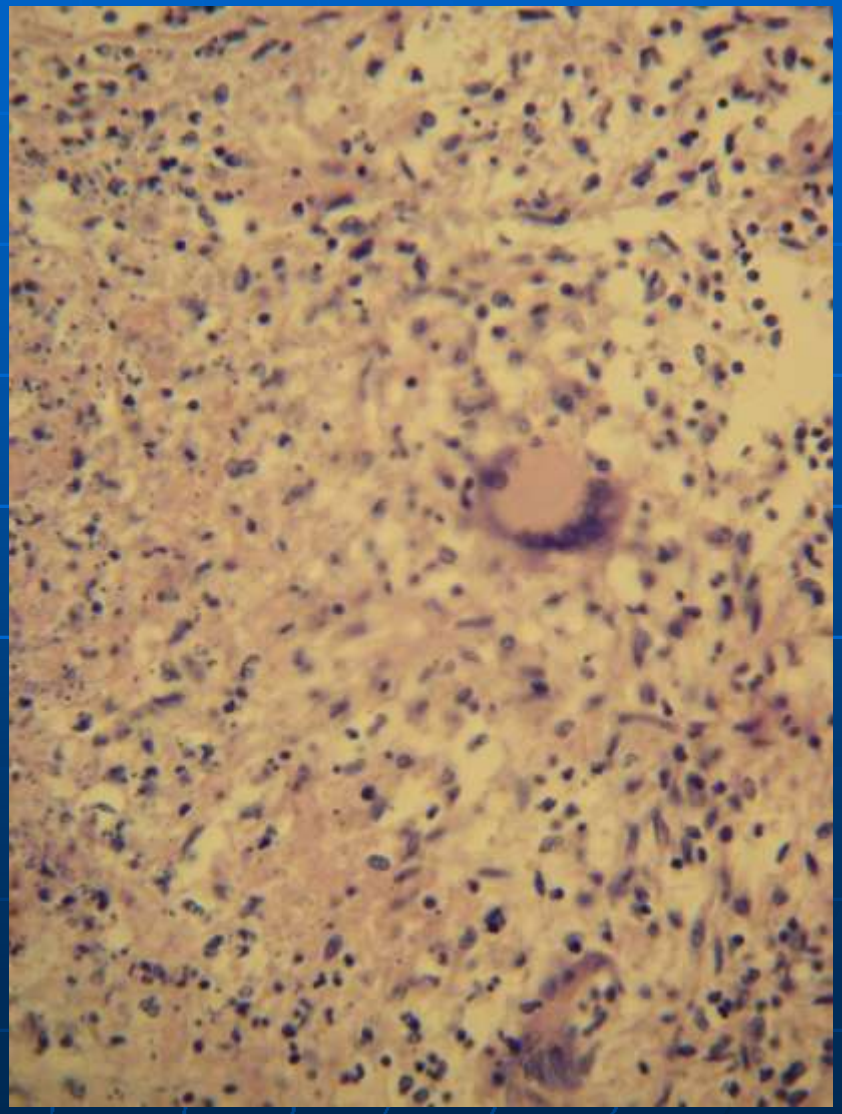
- **Pulmonary tuberculosis.**

Caseous necrosis.

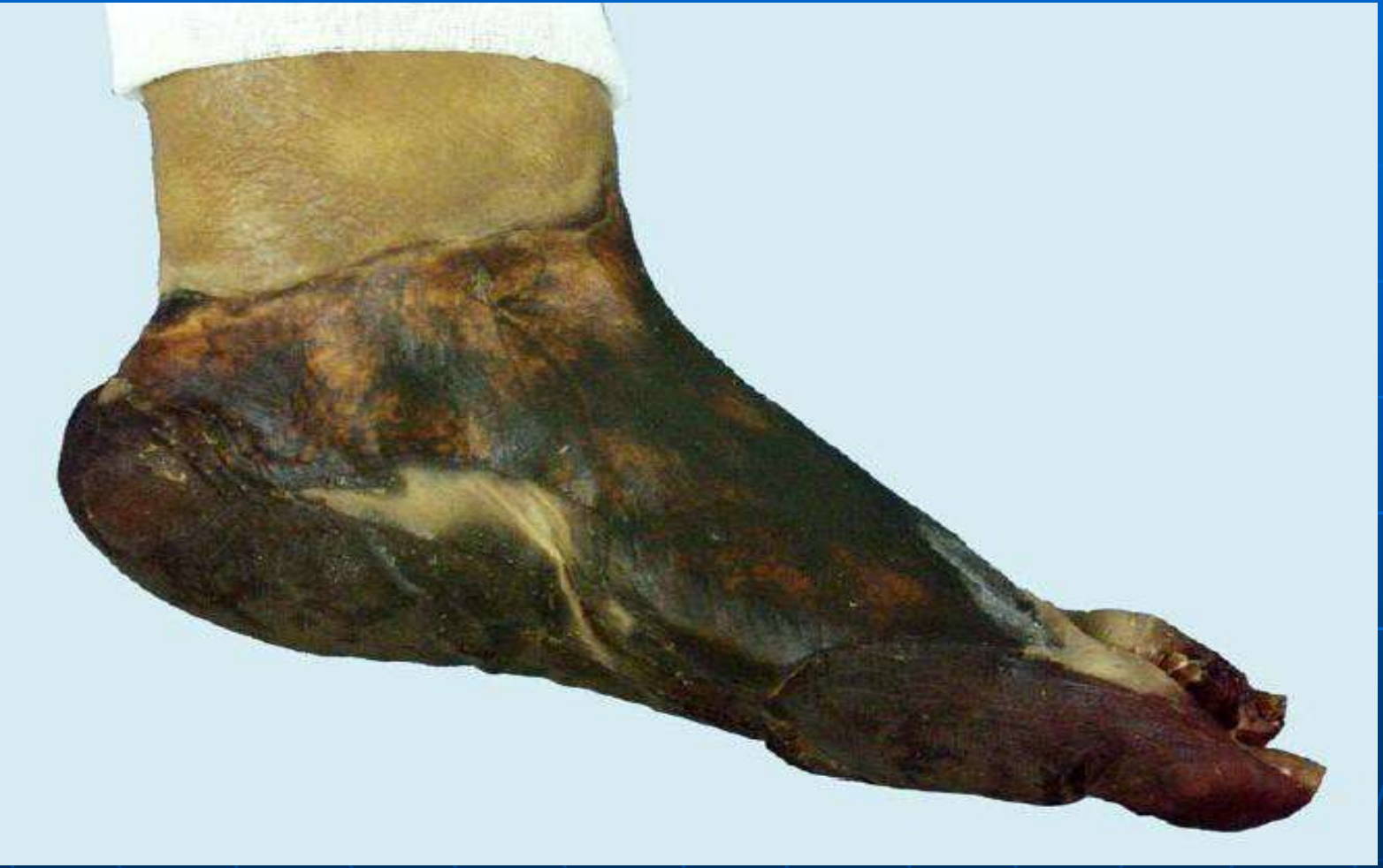
Old, healed, calcified tuberculous lesion in the lung. This patient had been followed for many years with serial chest X-rays. The lesion had not changed in size, and repeated sputum examinations were negative for acid-fast bacilli.

Caseous necrosis.



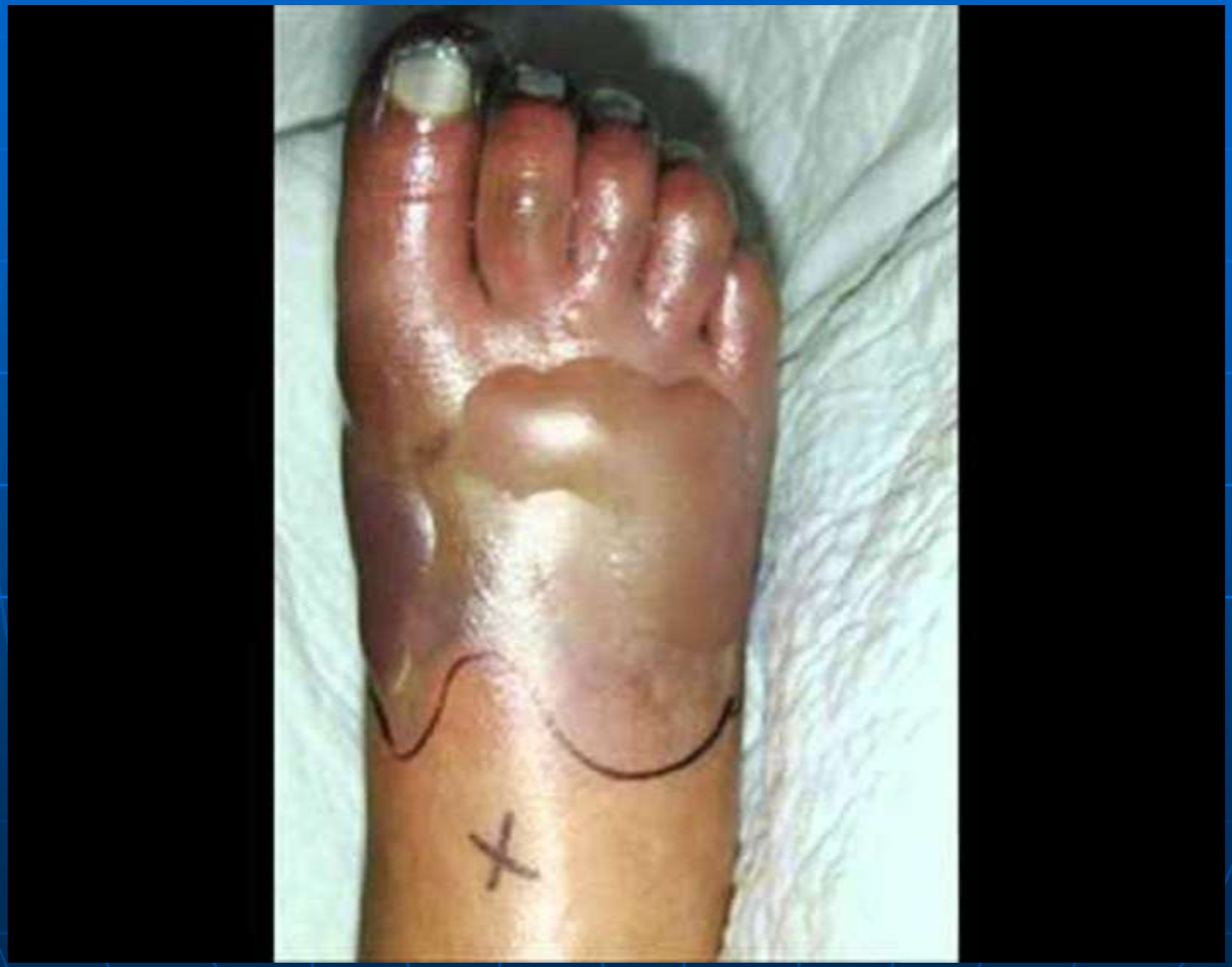


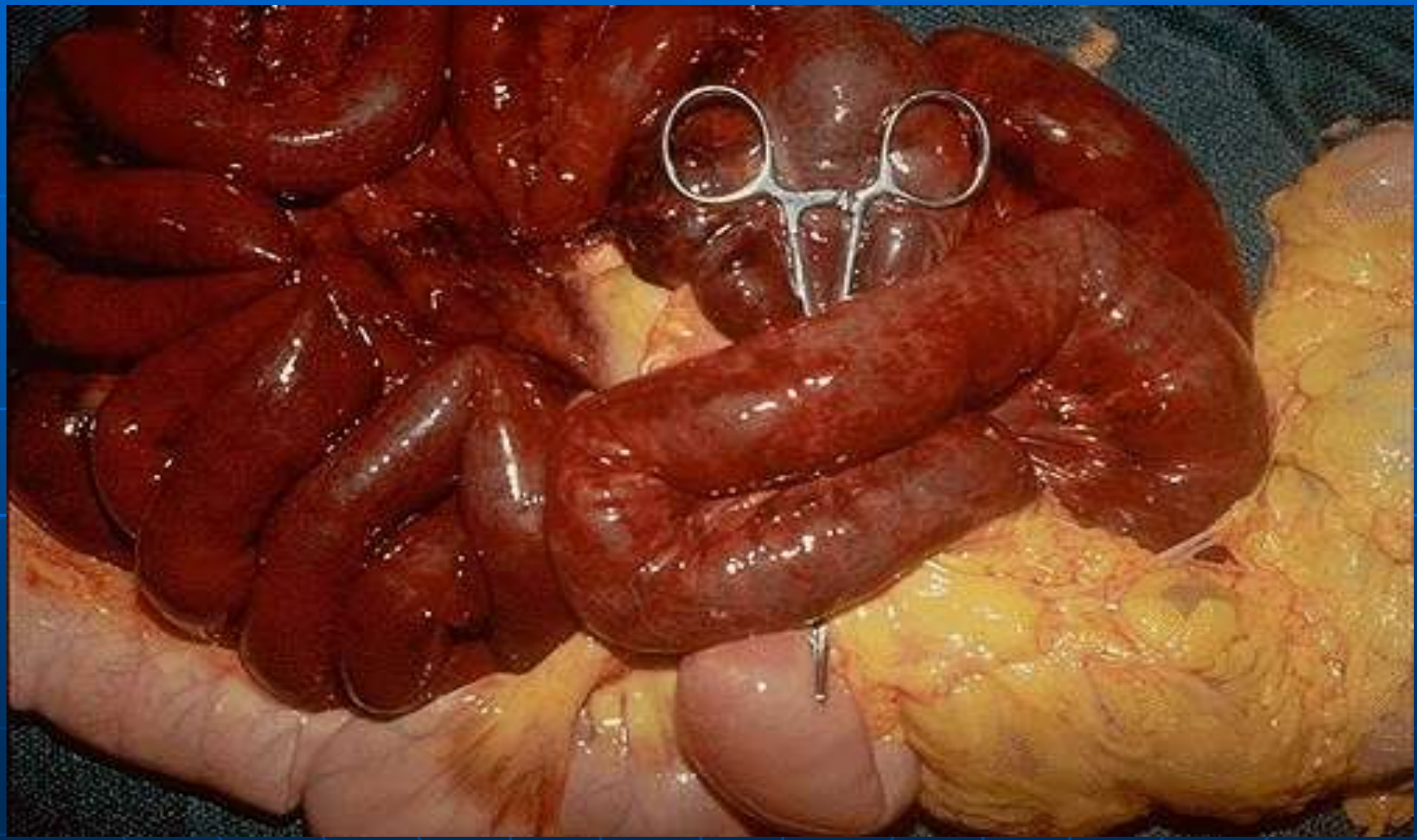
Gangrene



Gangrene: dry, wet, gas; decubituses (pressure sores).

Wet gangrene





Pancreatic fat necrosis:

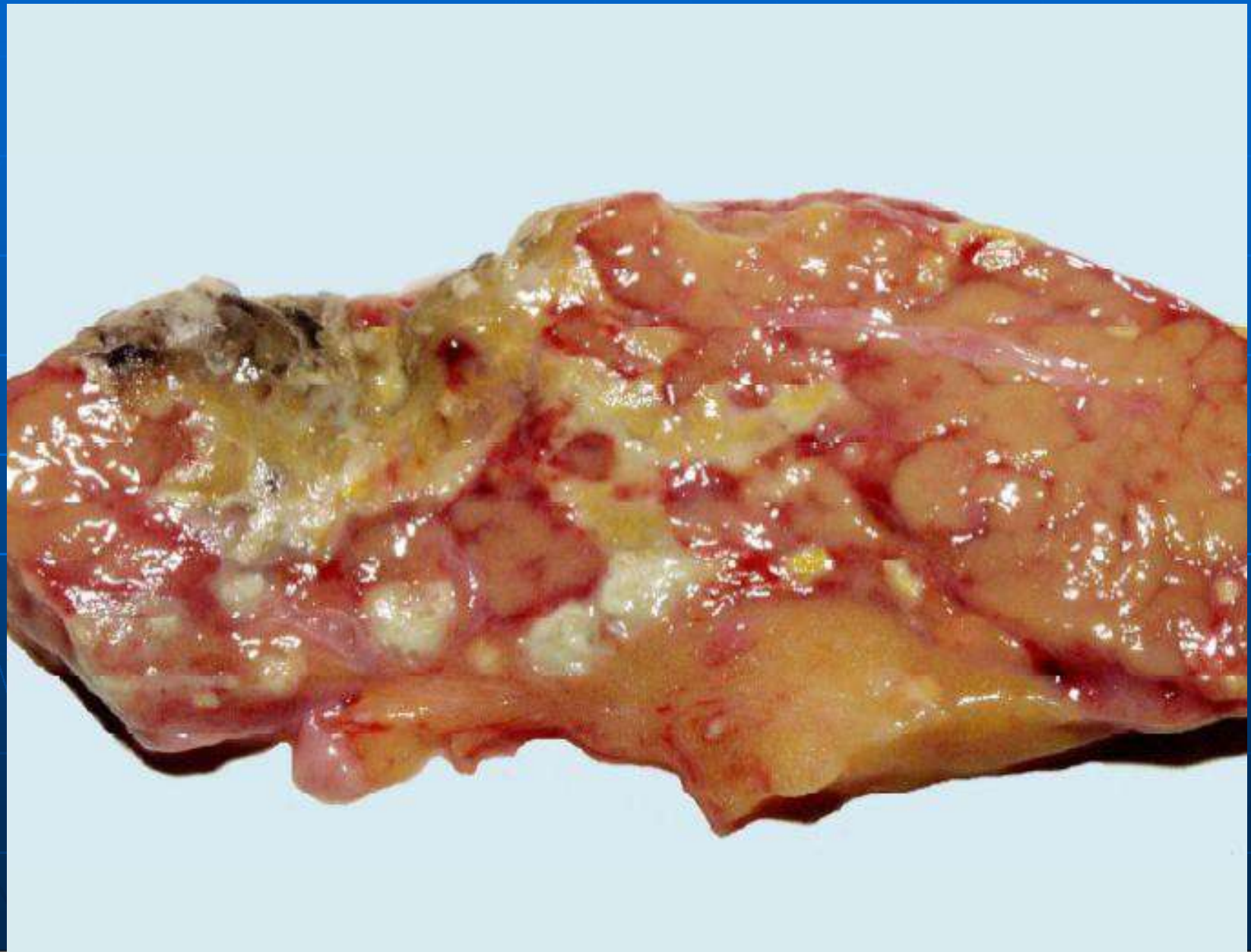
Death of adipose tissue in and around pancreas.

Causes: Pancreatitis and/or injury to pancreas and its ducts release lipases which attack adipose tissue in the peritoneum.Hydrolysis of triglycerides releases fatty acids which combine with calcium to produce chalky white areas (saponification).

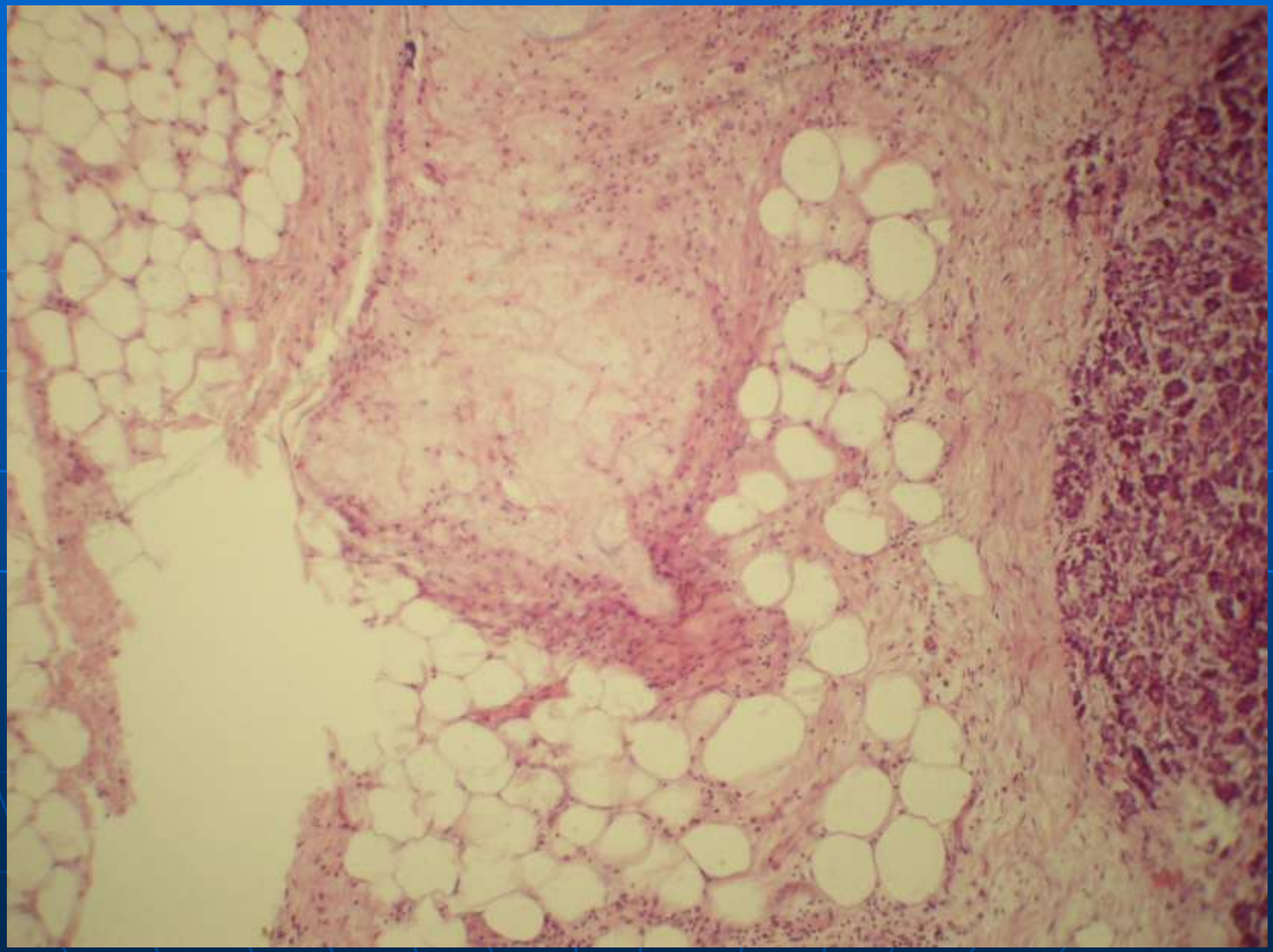
Gross appearance: Necrotic fat appears as white or yellowish chalky masses. A zone of inflammation appears around the necrotic areas.

Microscopic appearance: The necrotic tissue is solid and homogenous and there arenumerous small needle-shaped clefts occupied by fatty acid crystals.

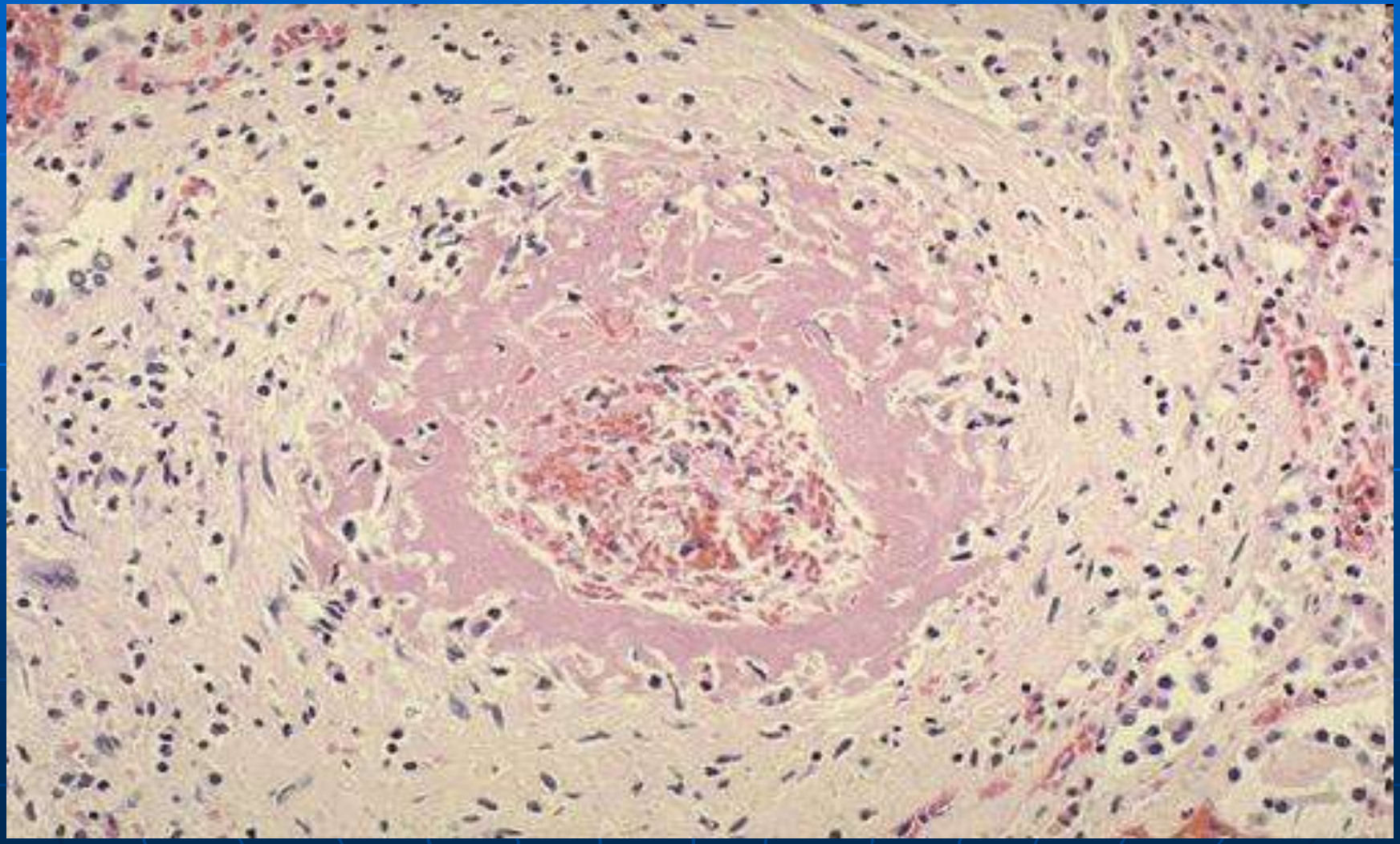
Fat necrosis in pancreas.



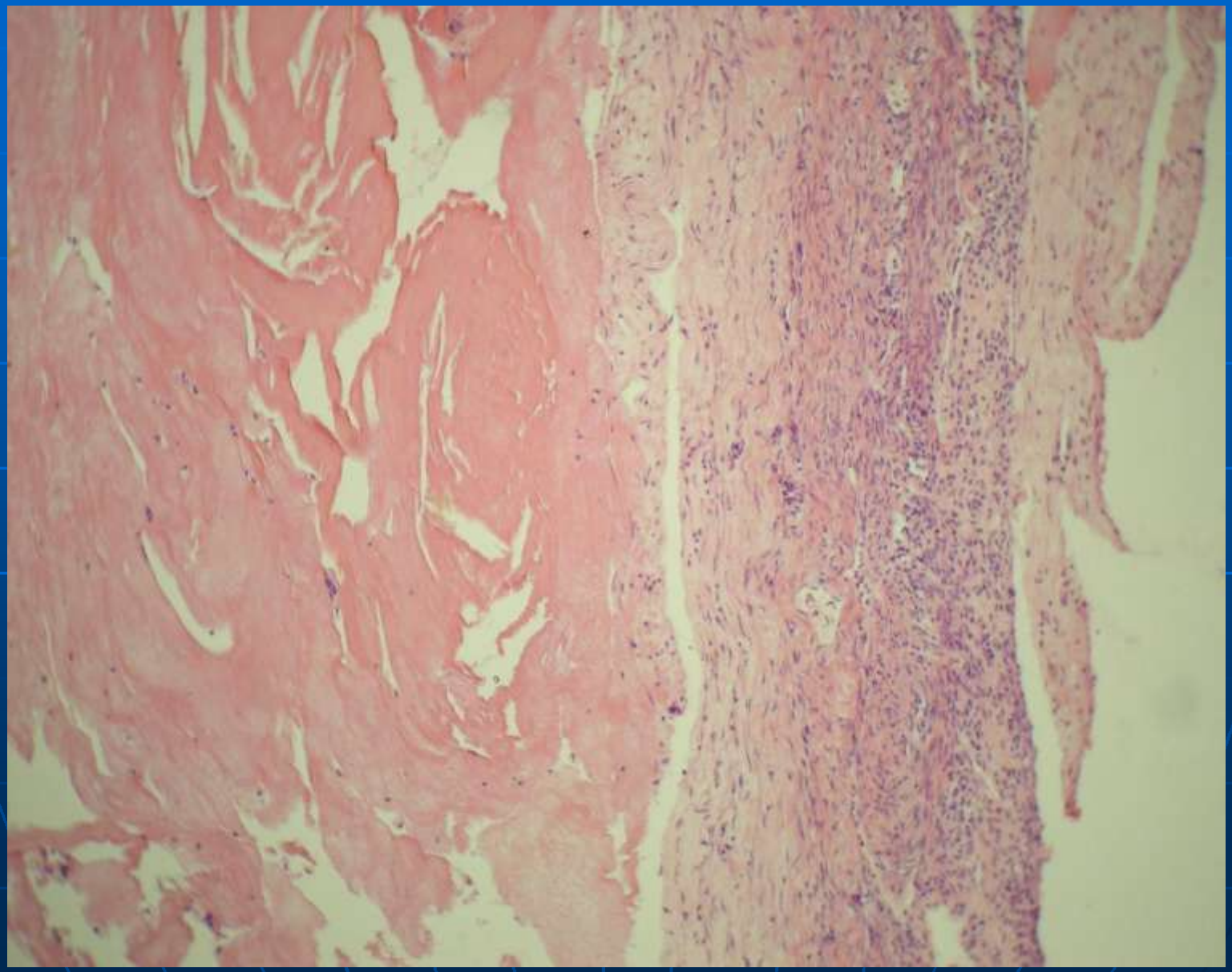
Fat necrosis.



Fibrinoid necrosis. Artery.



Fibrinoid necrosis.



Apoptosis

- Definition: In this genetically mediated programmed cell destruction, cells die, shrink, and disintegrate in the absence of any reactive inflammation.

- **Number of mitoses:** cells in embryonic tissue have a "mitosis counting" gene which introduces the cell death program once a certain number of mitoses has been reached. In postnatal tissues not possessing telomerase, the chromosomal telomeres are minimally eroded by each mitosis cycle until normal DNS replication can no longer be guaranteed. At this point, the "genome guardian protein" p53 clears the way for apoptosis.

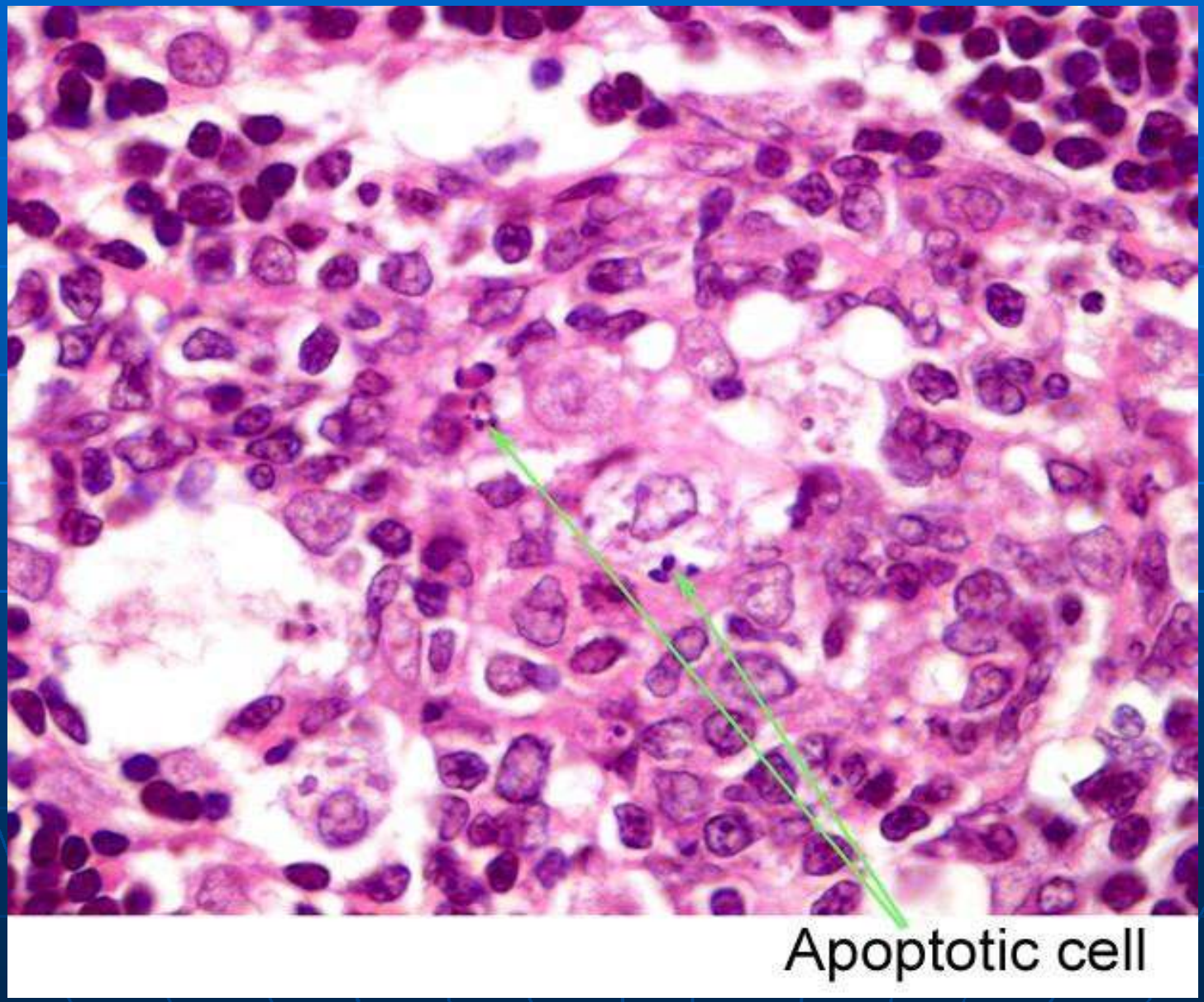
- **Cell age:** once cells have reached a certain age their cell death program is triggered. This is particularly the case for erythropoiesis, endochondral ossification, and molting tissue.

- **Function-sustaining signal substance loss**, i.e., hormones or growth factors: when their threshold level falls in those tissues dependent on them, the relationship of antiapoptotic bcl-2 proteins (the B-cell lymphoma oncogene) is shifted, inducing the mitochondrial apoptosis path. This is exemplified in involution atrophy and cyclical endometrial rejection.

- **Cell communication:** When cells lose their cadherin-mediated cell-to-cell communication, or their integrin-mediated anchorage in the extracellular matrix, the “focal adhesion kinase” is deactivated in the non-tumorous cells, DNA is blocked, and apoptosis begins.

- **Contact-less cytotoxic lymphocytes:** As these cells track down foreign cells, they also express Fas-ligand (FS7-associated surface antigen = CD95) and thereby bind onto thier Fas receptors. Apoptosis begins. Alternatively, they can secrete the pore-forming protein perforin, with which they “inject” serin-protease granzyme-B into the target cell; they then activate the cysteine aspartate-protein-cleaving enzyme system (CASPASE). Apoptosis begins.

Apoptosis



- Initial (early) phase:

In this phase, programmed cell death starts, but cell can stop this process.

- Execution (final, late) phase:

In this phase, programmed cell death progresses until the cell is irreversably damaged. The core element in programmed cell death’s efficacy is the system of cell death proteases in the form of CASPASEs.

The intrinsic way for apoptosis

- Heat, radiation, and/or cytostatics cause DNA damage, whereby the p53 genomic guardian protein clears the way for apoptosis. Nitrogen and oxygen radicals can directly trigger the mitochondrial pathway of apoptosis by oxidative stress.

Mitochondrial path: begins with the release of mitochondrial apoptosis factor (= AIF) and/or the cytochrome-c from damaged mitochondria; both trigger the CASPASE cascade. This path is activated by a series of inhibitors (primarily bcl-2). It prevents the release of cytochrome–c and AIF.

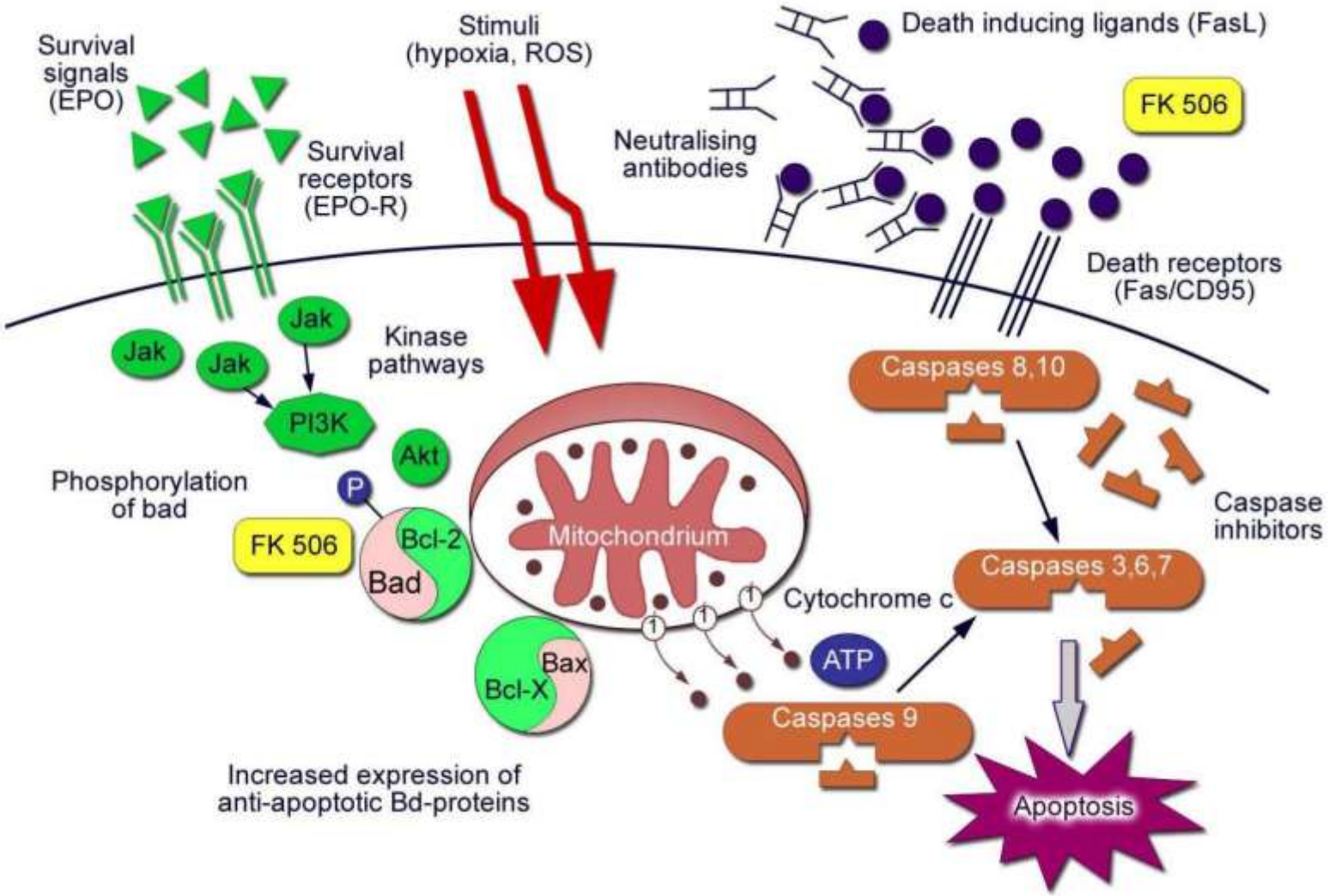
- Targets of executing CASPASEs: these enzymes attack at the following death substrata, among others:
- Focal adhesion kinase: Its inactivation triggers the loss of the cell's cytoskeletal cell to cell cohesion.

The extrinsic way for apoptosis

- Signaling paths: Triggering signals can engage the cellular execution mechanism indirectly with the aid of receptors (the transmembrane-signaling, or death receptor path), or directly in cytoplasm (the intracellular-signalling or mitochondrial path).

- **Death-receptor path.** It begins by the binding of certain death signals, such as the cytokine TNF (tumor necrosis factor), or the soluble Fas-ligand (FasL/CD95L), formed by immune cells, to the death receptors on the cell such as TNFR-1 or Fas. These receptors then associate with adaptor proteins (TRADD, FADD) in the cell, which bear a "death-effector-domain" with which they bond to homologous CASPASE sites. This is the first CASPASE cascade step that "exe executes" the cell. The suppressor gene p53 furthers apoptosis by depositing CD95 on the cell membrane surface. A "rash" activation of the cell receptor path is halted by a series of inhibitor proteins that intervene at various levels of the CASPASE cascade. This is the mechanism several viruses use to prevent the elimination of infected cells by lymphocytes.

Apoptosis

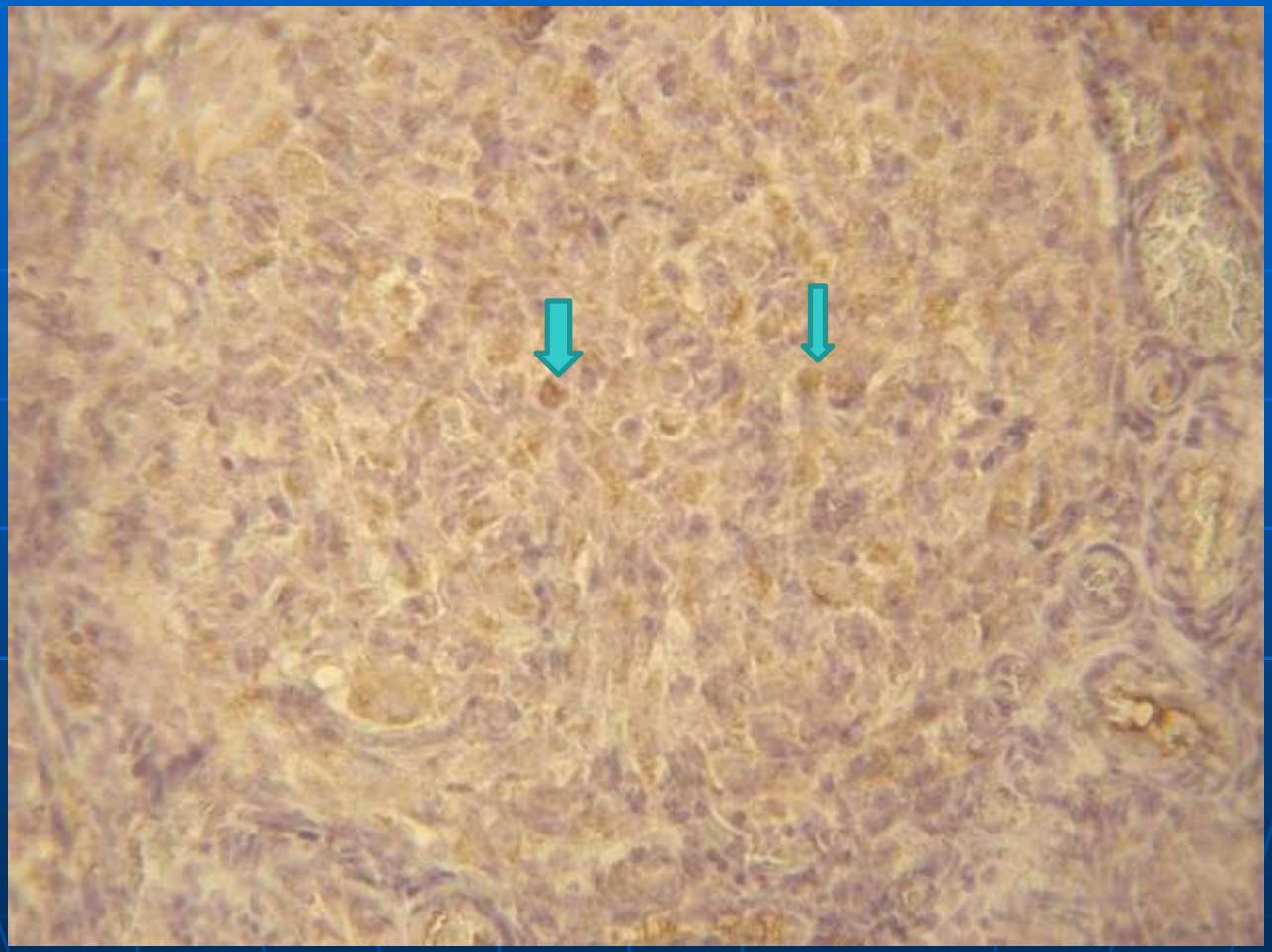

Survival signals (EPO)
Survival receptors (EPO-R)
Stimuli (hypoxia, ROS)
Death inducing ligands (FasL)
Neutralising antibodies
FK 506
Death receptors (Fas/CD95)
Jak
Jak
Jak
Kinase pathways
PI3K
Akt
P
Phosphorylation of bad
FK 506
Bcl-2
Bad
Mitochondrium
Caspases 8,10
Caspase inhibitors
Caspases 3,6,7
Cytochrome c
ATP
Bax
Bcl-X
Caspases 9
Increased expression of anti-apoptotic Bd-proteins
Apoptosis

Morphologic features of apoptosis

1. Cell shrinkage. The cell is smaller in size; the cytoplasm is dense; and the organelles, although relatively normal, are most tightly packed.
2. Chromatin condensation. This is the most characteristic feature of apoptosis. The chromatin aggregates peripherally, under the nuclear membrane, into well-delimited dense masses of various shapes and sizes. The nucleus itself may break up, producing two or more fragments.

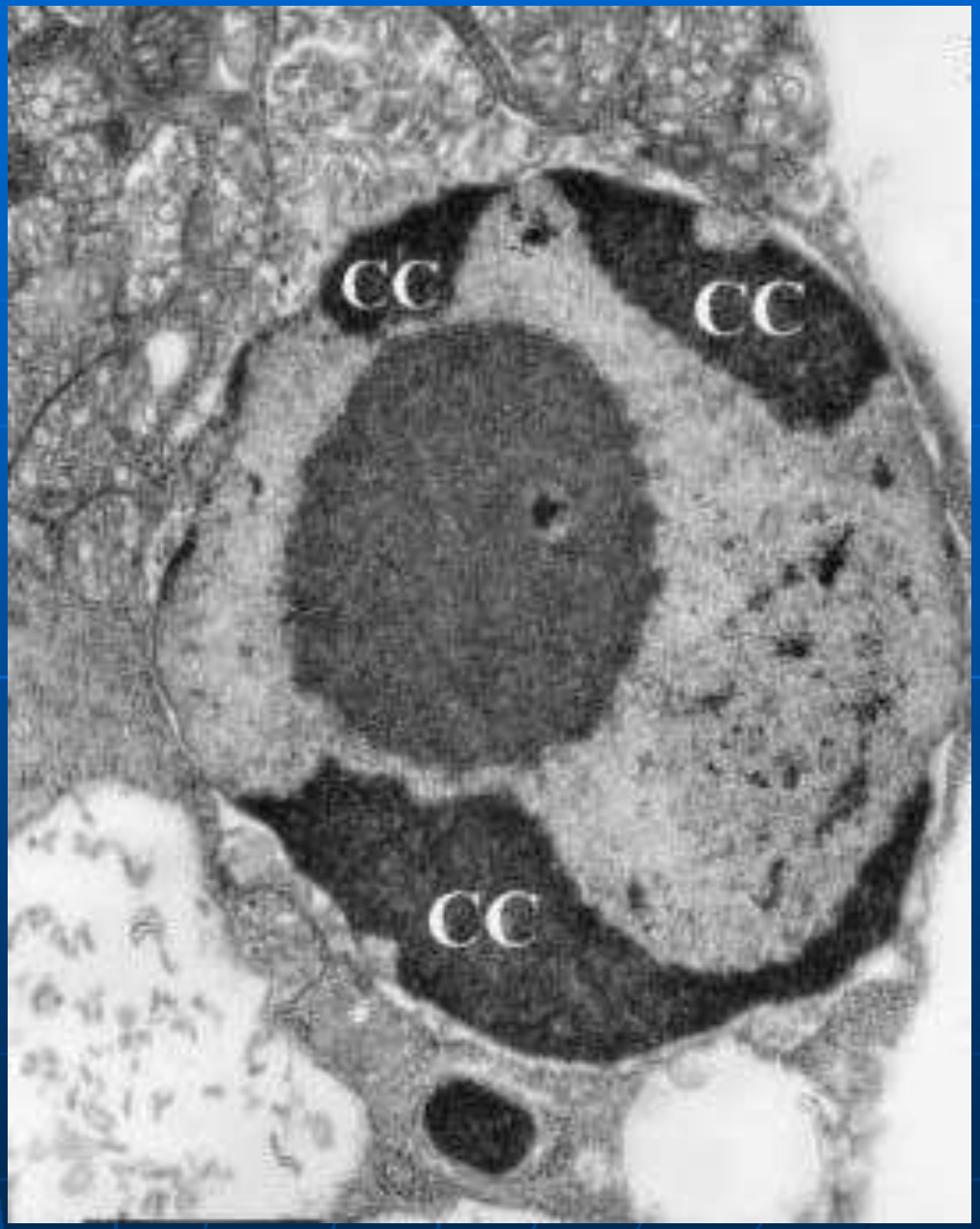
3. Formation of cytoplasmic blebs and apoptotic bodies. The apoptotic cell first shows extensive surface blebbing, then undergoes fragmentation into a number of membrane-bound apoptotic bodies composed of cytoplasm and tightly packed
organelles, with or without a nuclear fragment.
4. Phagocytosis of apoptotic cells or bodies by adjacent healthy cells, either parenchymal cells or macrophages. The apoptotic bodies are rapidly degraded within lysosomes, and the adjacent cells migrate or proliferate to replace the space occupied by the now deleted apoptotic cells.

Apoptosis

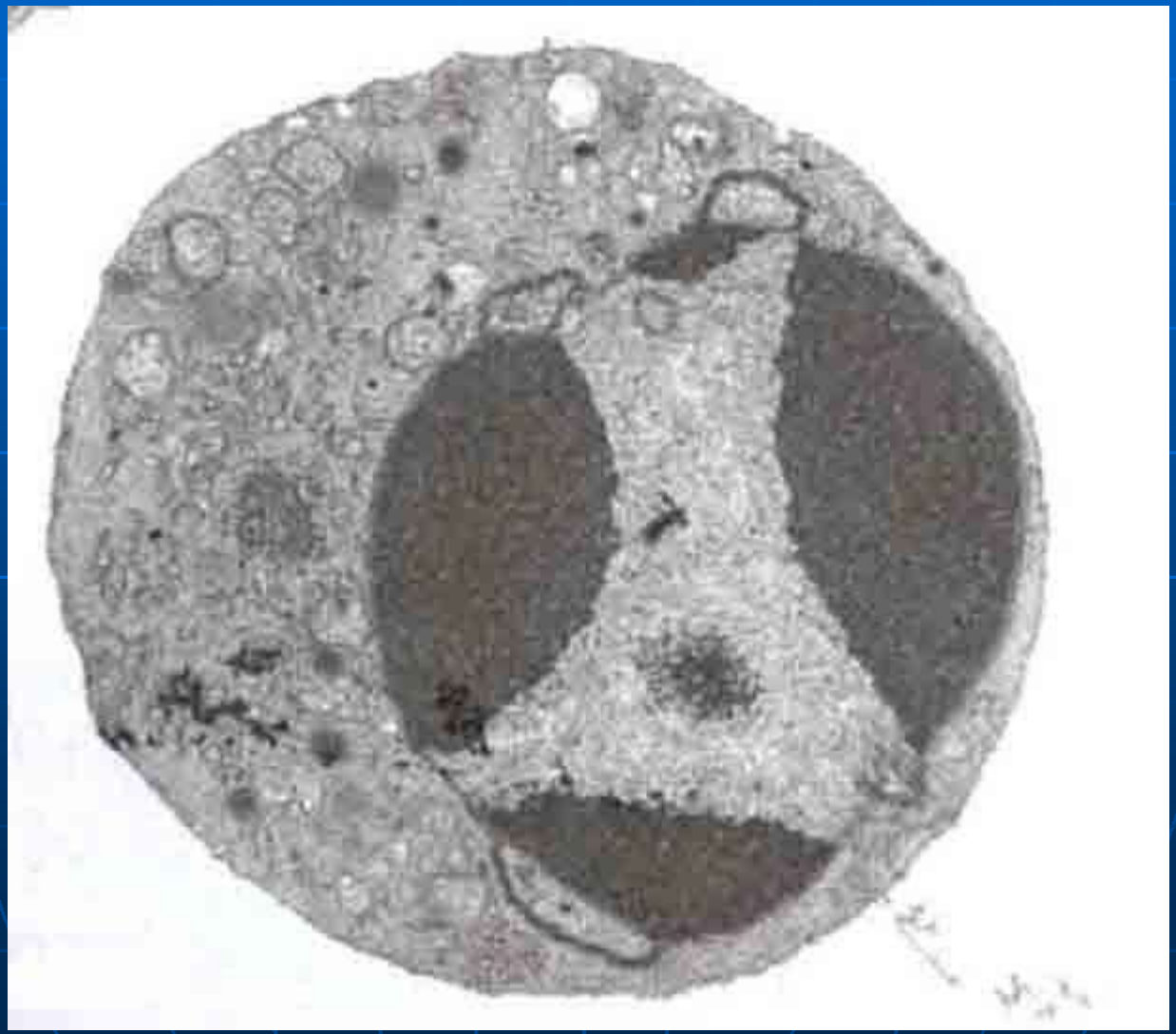


Corpus luteum, peritonitis. IHC, caspasa 3.

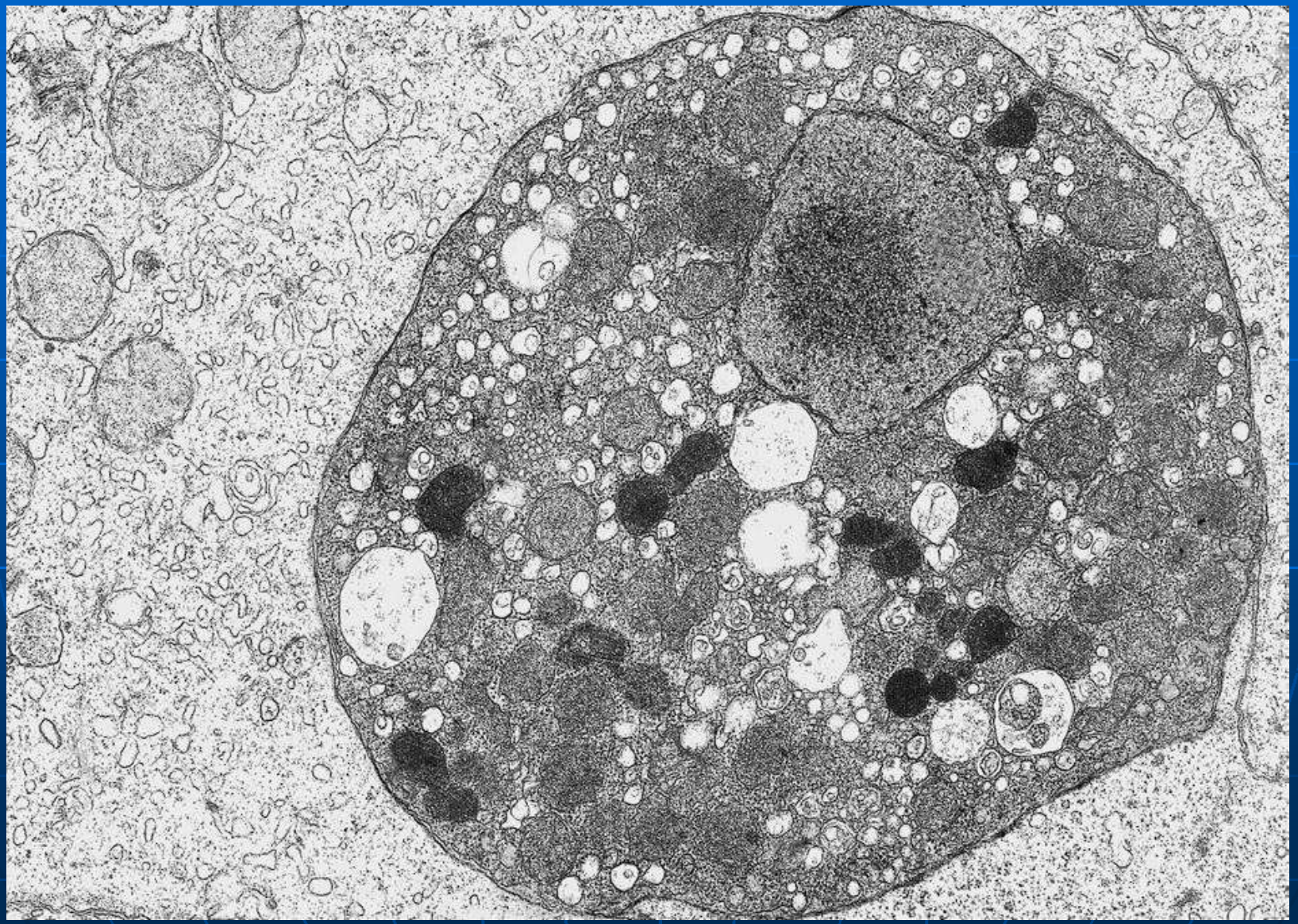
Apoptosis WNF (chromatin condensation)



Apoptosis (chromatin condensation)

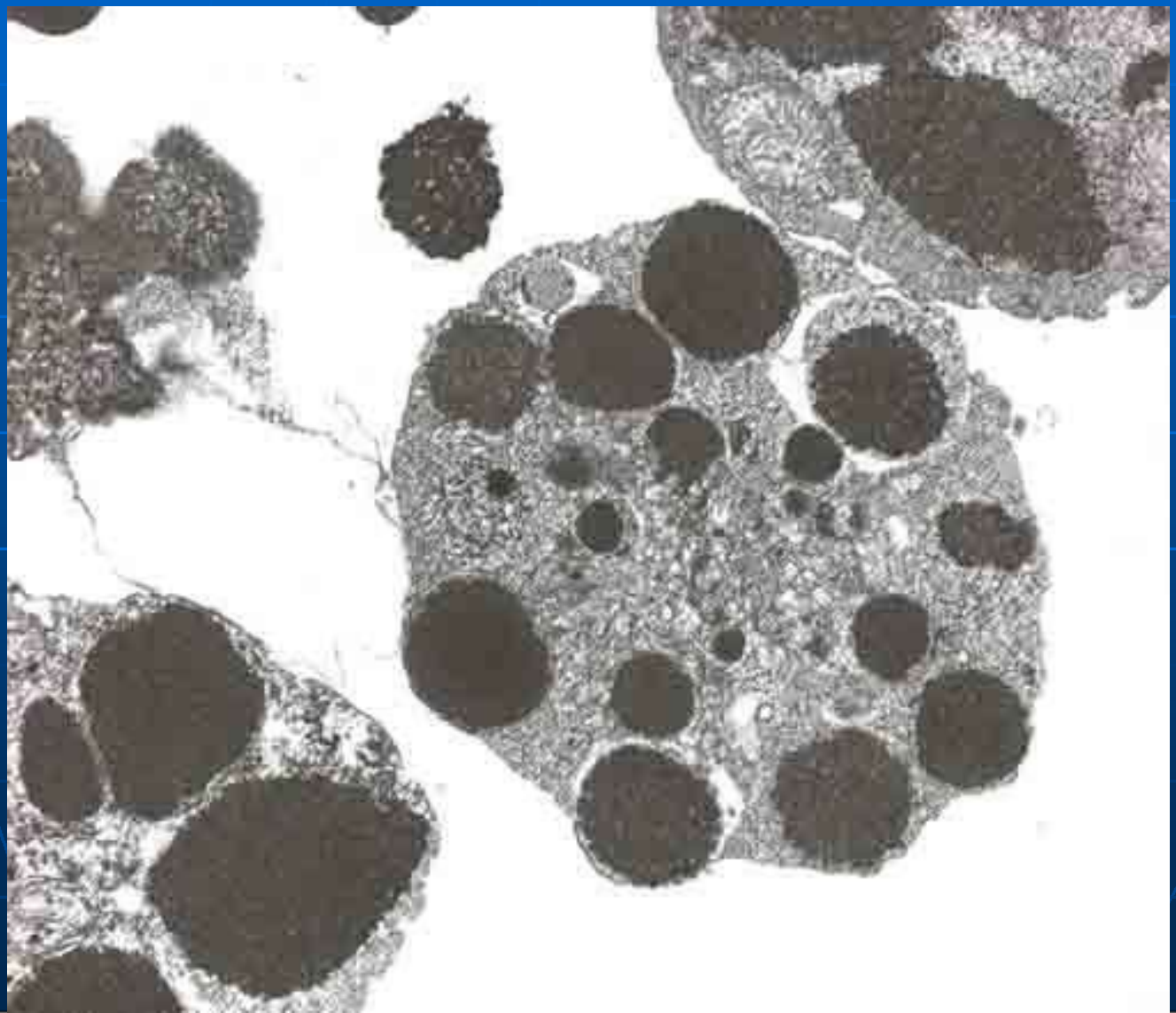


- Apoptotic liver cell (TEM) x 5000



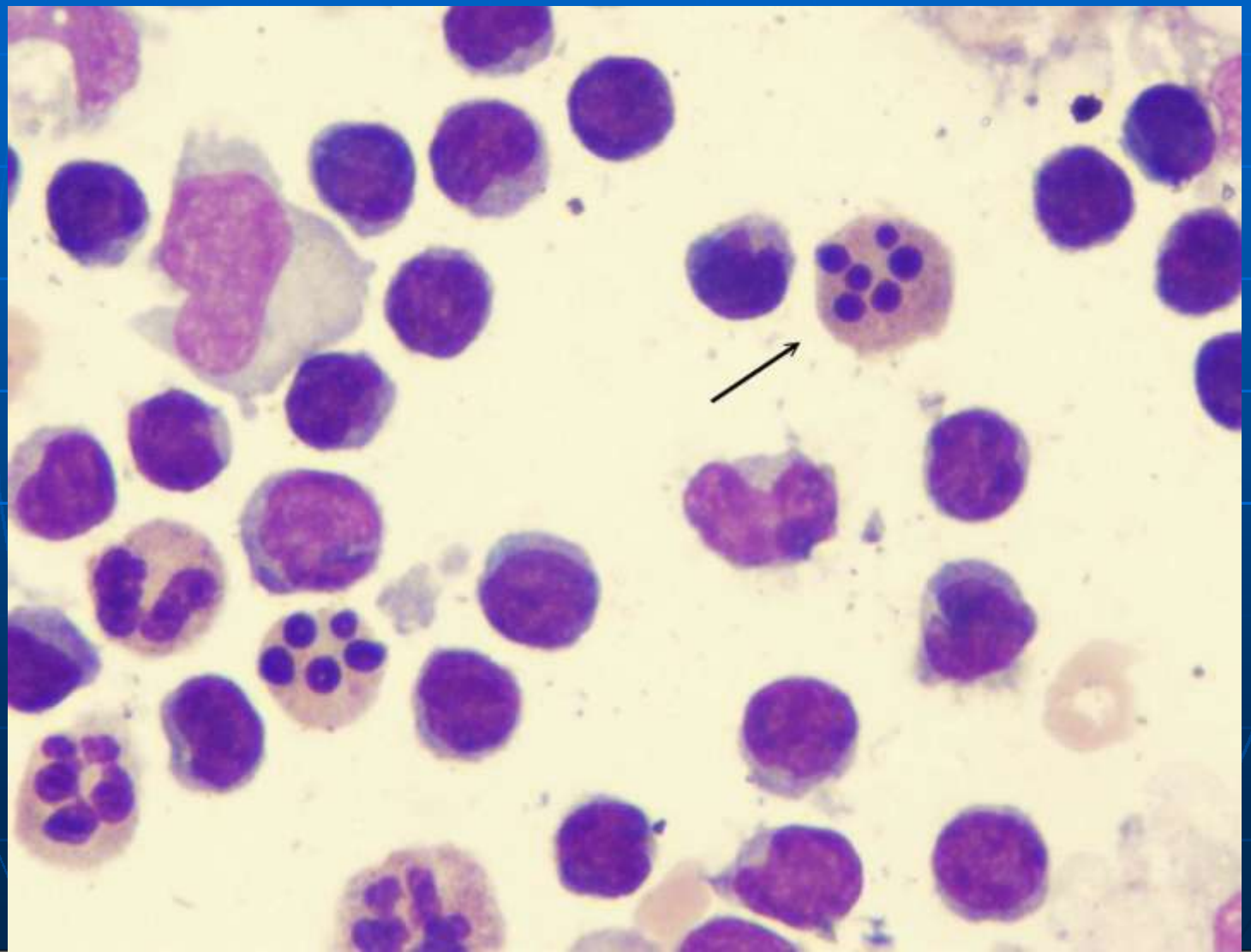
Apoptosis

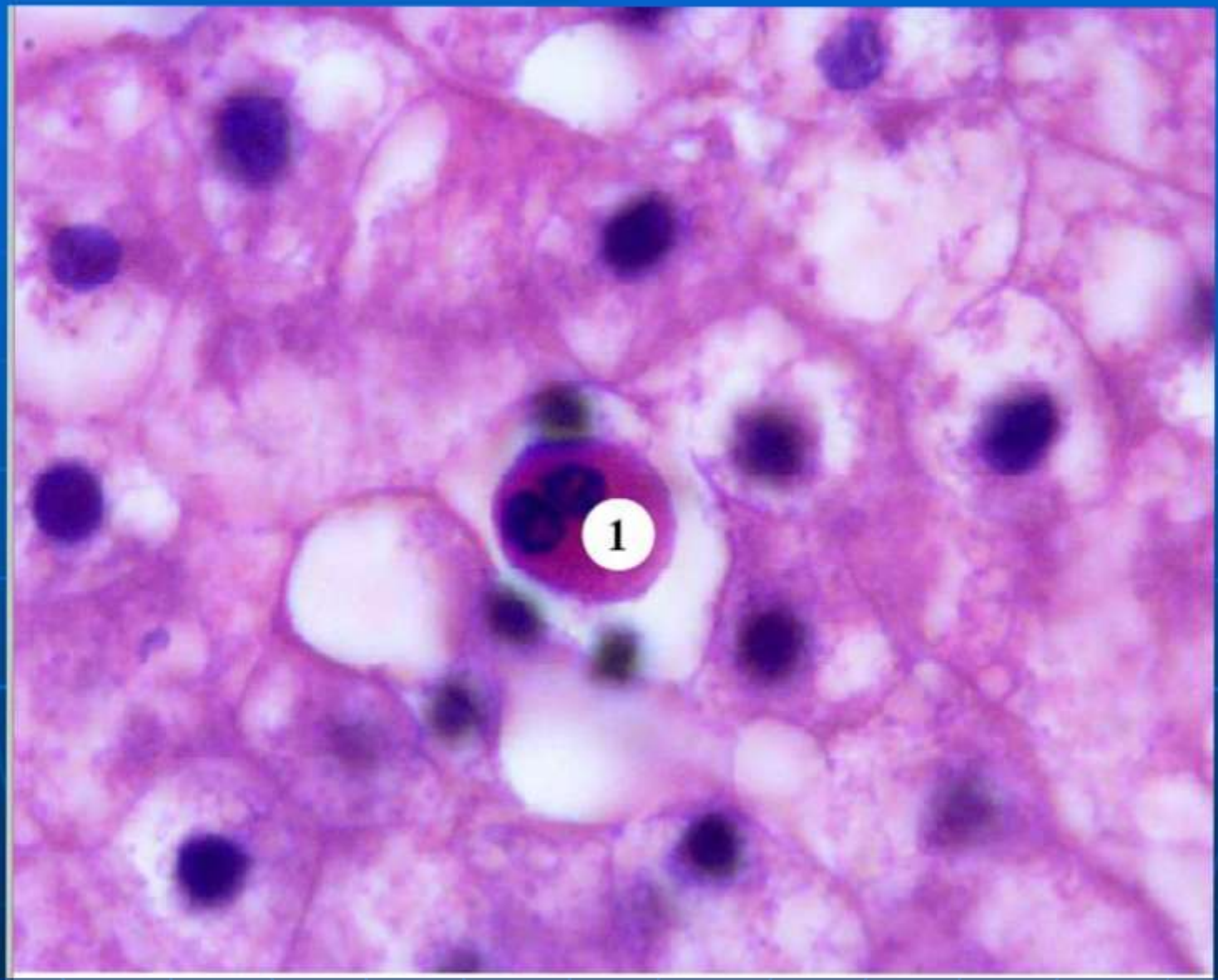
- karyorrhexis



Apoptosis

- karyorrhexis





Apoptosis is programmed cell death.

Thank you!