

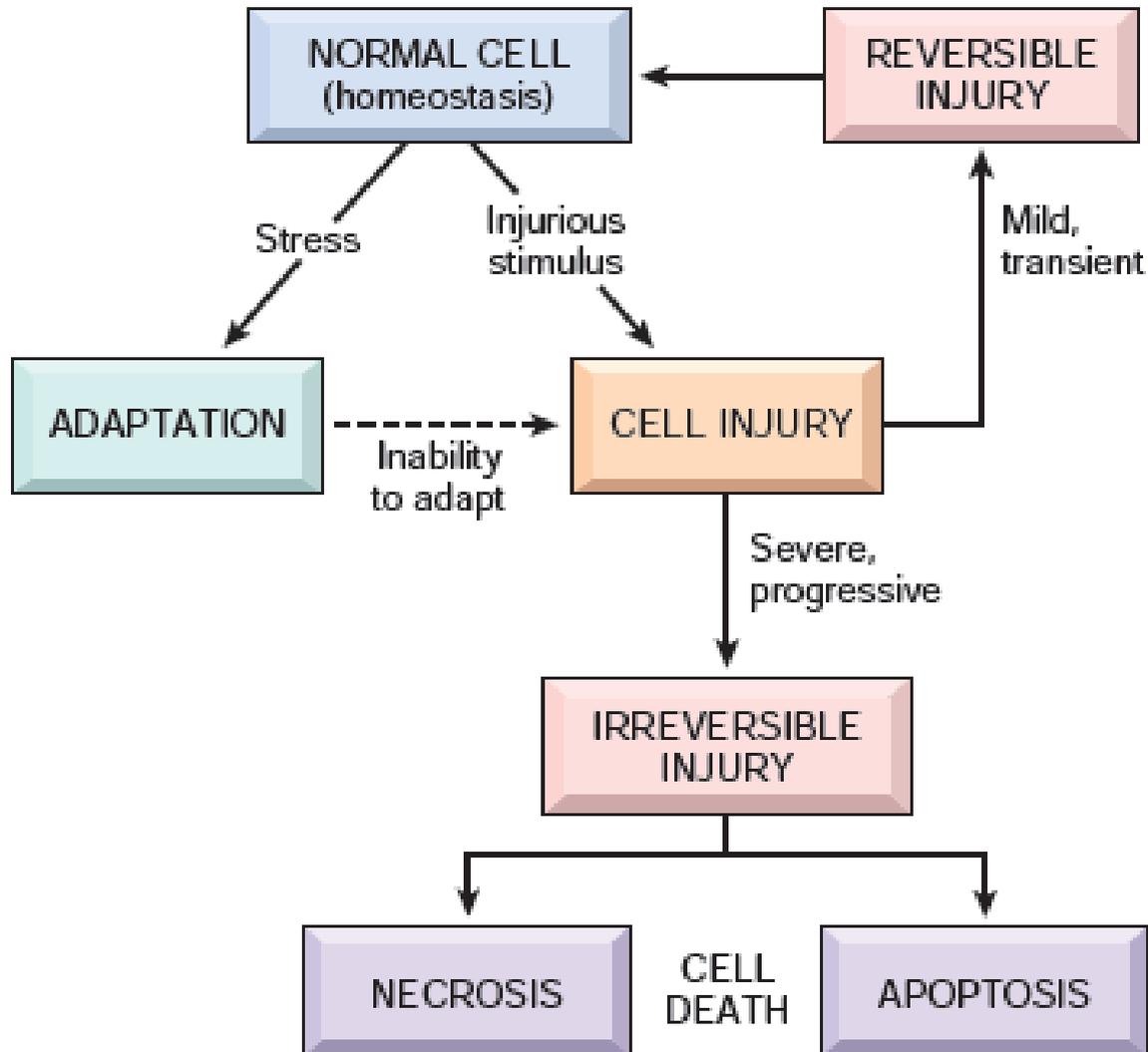


*Lethal cell damage.  
Necrosis. Apoptosis.*

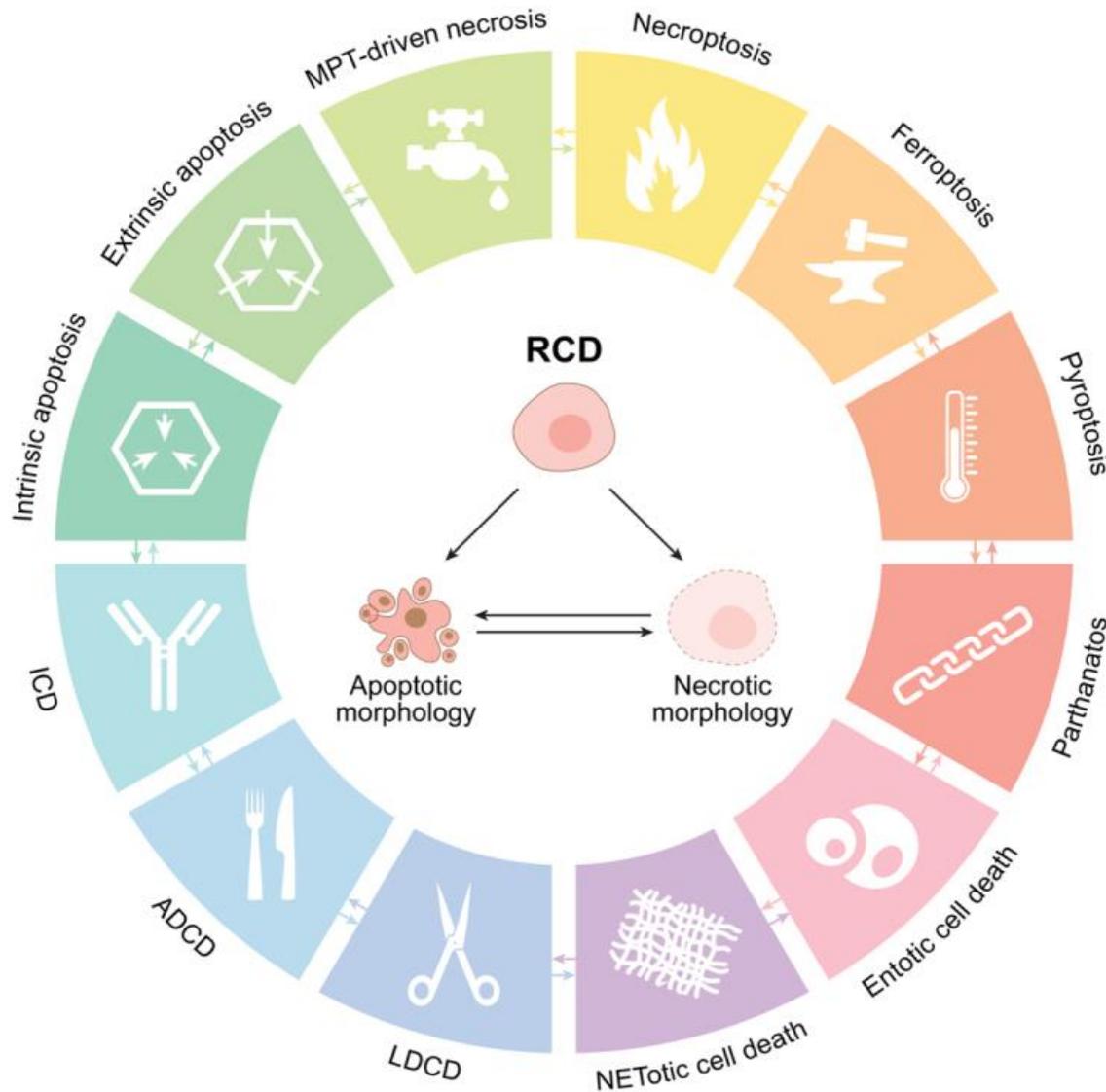
**Lecture 3**

**Mavlikeev M.O.**

# Damage (injury)



# Nomenclature Committee on Cell Death 2018



*RCD*: Regulated cell death, *ADCD*: autophagy-dependent cell death, *ICD*: immunogenic cell death, *LDCD*: lysosome-dependent cell death, *MPT*: mitochondrial permeability transition.

# Local death

- **There are two types of the local death, i.e. destruction of structures in the living organism:**
  - necrosis (of cell and tissues),
  - apoptosis (of cell).

# Necrosis

- **Necrosis - one type of local death, which can involve cells, groups of cells, tissues, organs, and occurs in the presence of strong disturbing factors.**
- **The concept of "necrosis" is a subtype of the more general concept of "death".**

# Etiological types of necrosis

## ■ Traumatic necrosis

- Occurs by the action of physical (mechanical, thermal, radiation) and chemical (acids, alkalis, etc.) factors.

## ■ Toxic necrosis

- Occurs by the action of bacterial toxins and toxins of other origins.

## ■ Trophoneurotic necrosis

- Associated with the violation of microcirculation and innervation of the tissue in chronic diseases (bedsores).

## ■ Allergic necrosis

- Develops in immunopathological reactions (Arthus phenomenon).

## ■ Vascular (ischemic) necrosis

- It is connected with the violation of the blood supply to an organ or tissue.

# Subtypes of necrosis

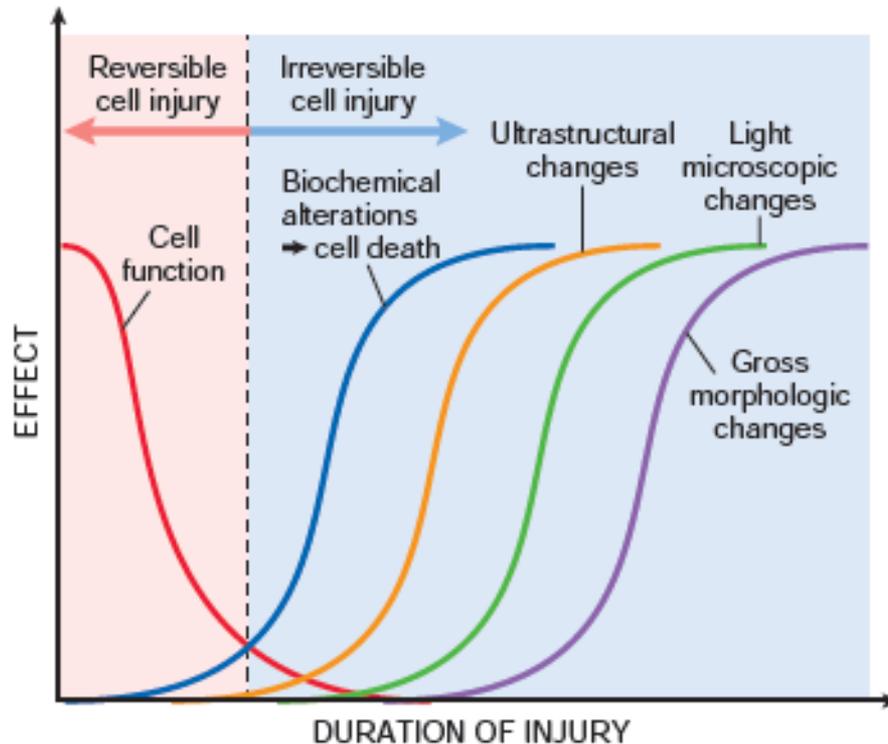
- **Depending on the mechanism of action of the etiological factors there are the following types of necrosis:**
- **Direct necrosis**
  - direct action on the tissue in traumatic and toxic damage.
- **Indirect necrosis**
  - Indirect effects through the vascular, nervous and immune systems.

# Morphogenesis of necrosis

- There are the following stages of the development of necrosis.
- **I. Paranecrosis**
  - Reversible necrosis-like changes.
- **II. Bionecrosis**
  - Irreversible degenerative changes.
- **III. Cell death**
  - Criteria for establishing the time of cell death currently do not exist.
- **IV. Autolysis**
  - Decomposition of dead substrate under the action of hydrolytic enzymes released from damaged cells.
- **Decomposition of the cells by the action of enzymes released from white blood cells, or from bacteria, is called "heterolysis".**

# Morphology of necrosis

- The morphological features of necrosis (macro- and microscopic) appear only at the stage of autolysis, i.e. a few hours after the onset of cell death.
- Early signs of necrosis are detected by electron microscopy and histochemical studies.



# Morphology of necrosis

- In the heart, for example, the first morphological signs of necrosis are usually detected only after 12 - 18 hours from the time of ischemia, but the disappearance of the enzymes, glycogen in necrotic cells, ultrastructures decay can be detected much earlier.
- **Electron-microscopic picture:**
  - In the ischemic area of the myocardium swelling and vacuolization of the mitochondria, cristae decay are revealed.
- **Histochemical study (PAS-reaction):**
  - disappearance of glycogen from ischemia zone is revealed, it remains stained magenta in intact areas.

# Morphology of necrosis

## ■ Macroscopic signs of necrosis

- Common to all forms of necrosis are changes in color, consistency, and in some cases - the smell of tissue.
- Dense and dry consistency, mummification (coagulation necrosis); loose, contains a lot of liquid, miomalycia (colliquative necrosis).
- Color white or yellowish, reddish-brown surrounded by demarcation inflammation. The foci of necrosis may be soaked with blood, bile.
- In putrid melting of dead tissue – there is a characteristic bad smell.

## ■ Microscopic features of necrosis

- It relates both nucleus and cytoplasm of cells and extracellular matrix.

# Microscopic features of necrosis

## ■ Changes in the nucleus:

- Karyopyknosis - shrinkage of the nuclei with the condensation of chromatin.
- Karyorrhexis - decay of nuclei in the clumps.
- Karyolysis - dissolution of the nucleus (activation of hydrolases).

## ■ Changes in the cytoplasm:

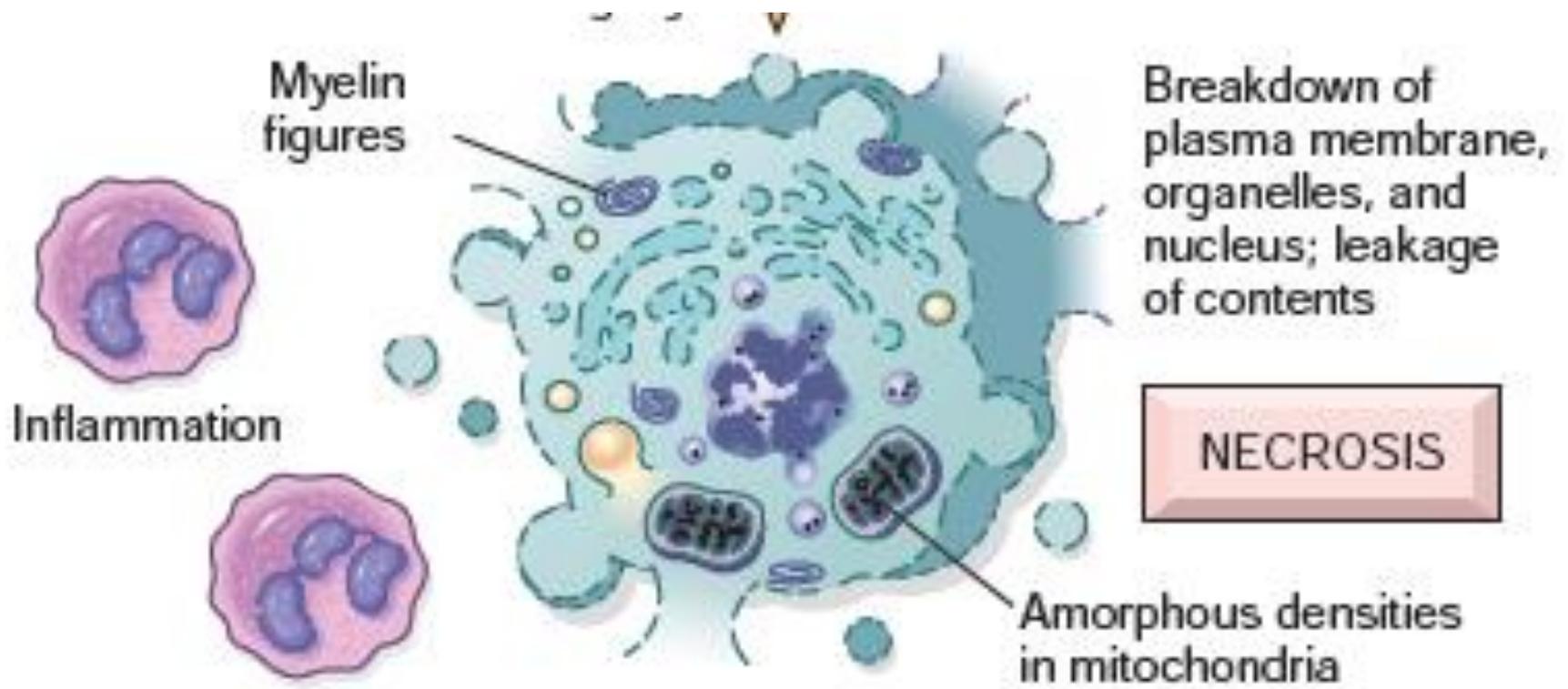
- Plasma-coagulation - coagulation and denaturation of protein and the appearance in the cytoplasm bright pink lumps (hypereosinophilia).
- Plasmorrhaxis
- Plasmolysis

## ■ Changes in the membrane:

- Loss of integrity
- Formation of myelin figures

## ■ Changes in the extracellular matrix:

- Cleavage of reticular, collagen and elastic fibers by the proteases, lipases.
- Impregnation of necrotic masses with fibrin with the development of fibrinoid necrosis.



# The ultrastructural features of necrosis

## ■ Nucleus:

- The aggregation of chromatin, fragmentation of fibrils, complete destruction.

## ■ Mitochondria:

- Swelling, formation of aggregates of irregular shape in the matrix, the deposition of calcium salts.

## ■ Endoplasmic reticulum:

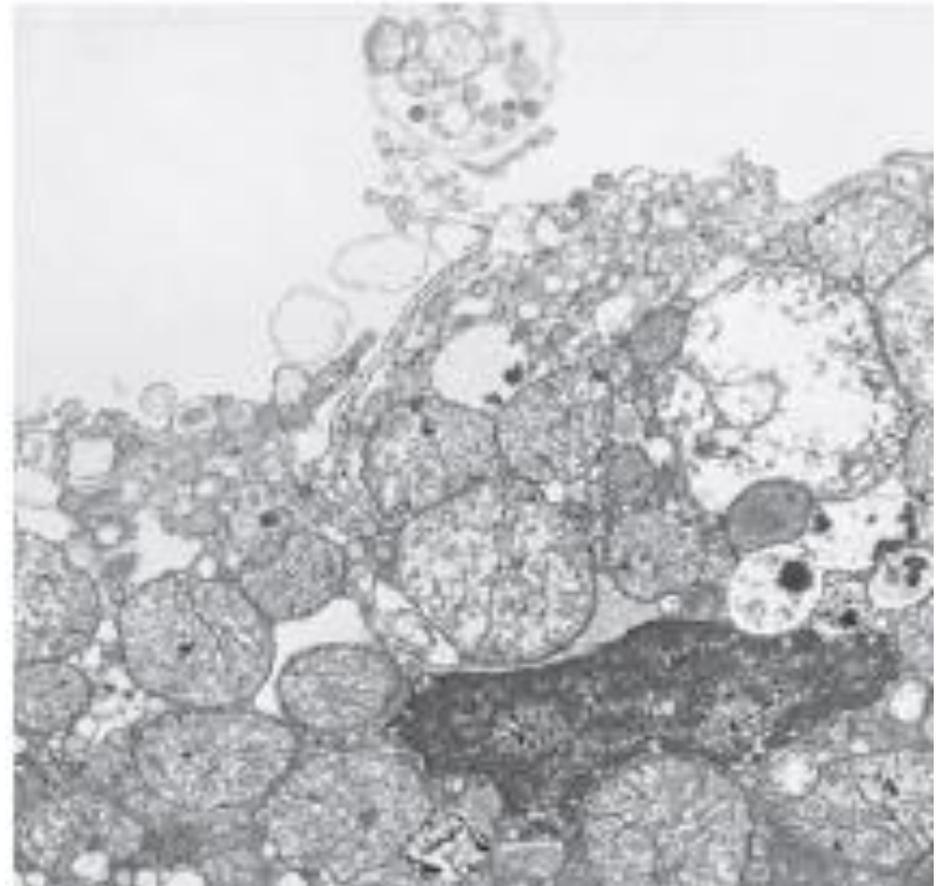
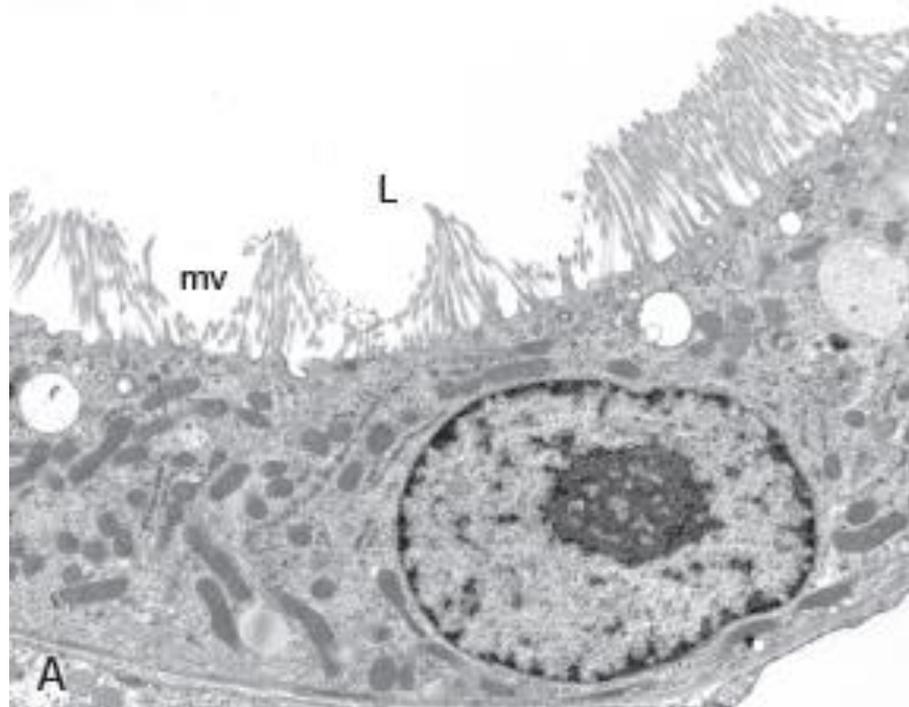
- Swelling, fragmentation and disintegration of the membrane structures.

## ■ Polysomes and ribosomes:

- The collapse of the polysomes, the separation of the ribosomes from the cisternae, reduction in the amount, sharpness of contours and sizes.

## ■ The cytoplasmic matrix:

- The disappearance of glycogen granules, reduced enzymatic activity.



# Reaction to necrosis

- **May be local and systemic.**
- **Local reaction:**
  - Around the area of necrosis demarcation inflammation appears. Its expediency is the delimitation of necrosis focus, participation in the resorption of necrotic masses, followed by the organization, i.e., replacement by connective tissue.
- **Systemic reactions:**
  - Associated with the synthesis of acute inflammation phase proteins - C-reactive protein (CRP) and amyloid-associated plasma protein (AAP) by the liver cells.
  - CRP activates complement by the classical pathway and initiates the demarcation inflammation.
  - AAP can be a precursor of AA-amyloid.

# Clinical-morphologic forms

- **Clinical-morphological forms of necrosis are presented by:**
  - Coagulation necrosis,
  - Colliquative necrosis,
  - Infarct
  - Sequestration
  - Gangrene.

# Coagulation necrosis

- **Coagulation (dry) necrosis is characterized by the predominance of dead tissue coagulation, dehydration, compression.**
- **It is found in tissues with a high content of protein and low water content.**
- **Necrotic tissues are dry, dense, gray-yellow in color.**

# Coagulation necrosis subtypes

## ■ **Caseous (cheesy) necrosis:**

- Foci of necrosis dry, whitish, friable;
- Developed in tuberculosis, syphilis.

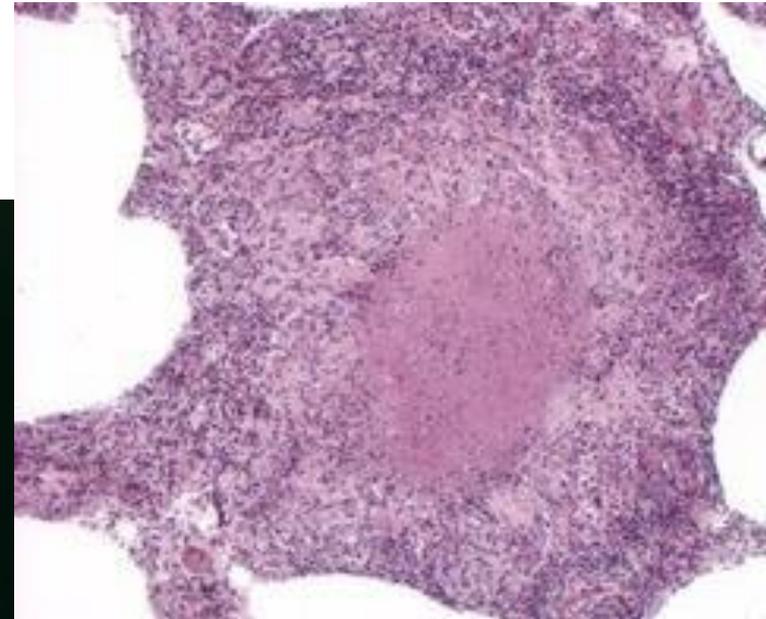
## ■ **Fibrinoid necrosis:**

- Necrotic masses are impregnated with plasma proteins, fibrinogen (interstitial tissue, the vascular walls);
- Occurs in the immunopathological processes, allergic and rheumatic diseases.

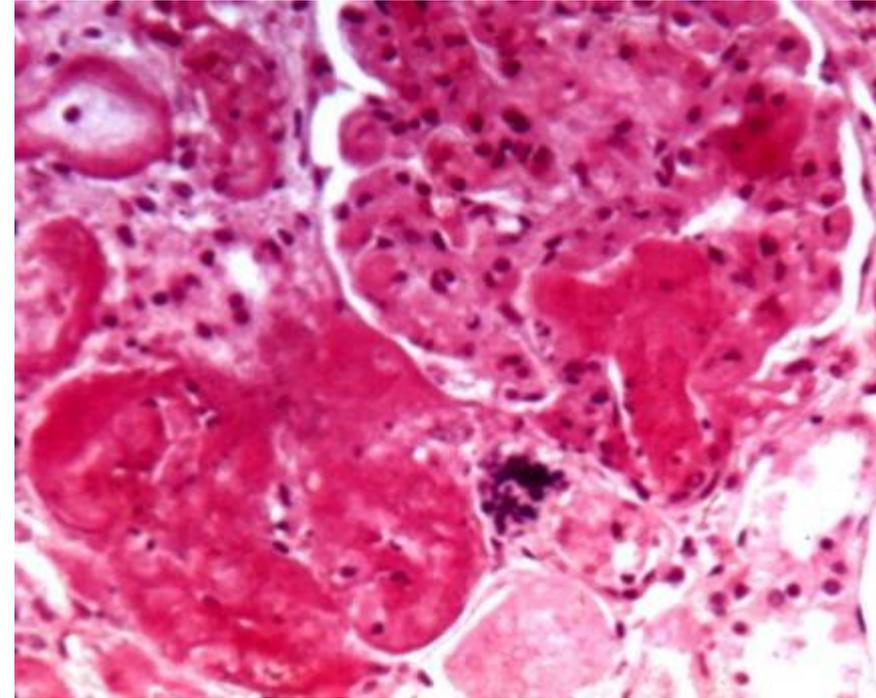
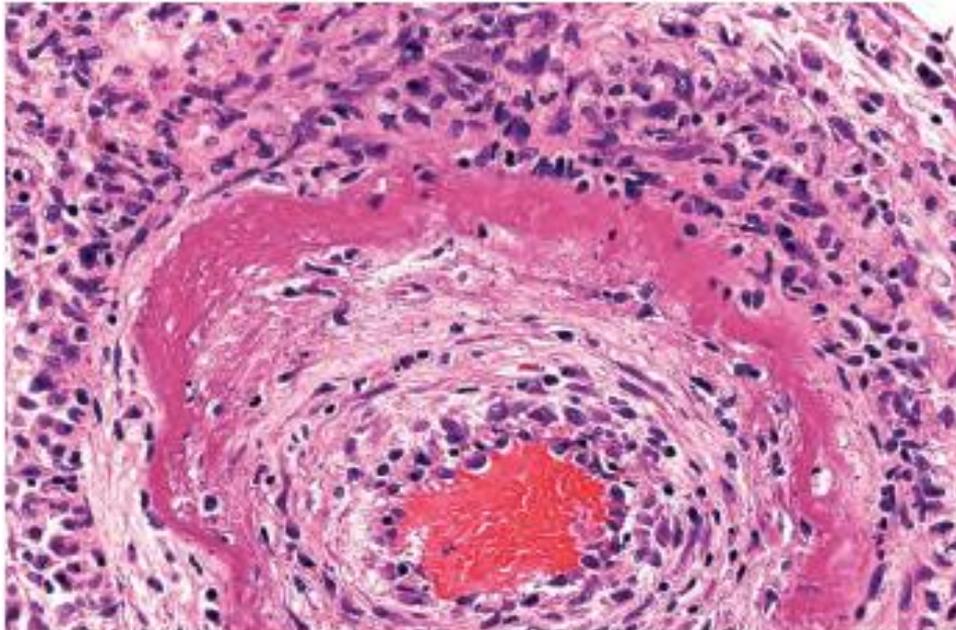
## ■ **Waxy (Zenker's) necrosis:**

- Occurs in skeletal muscle, more direct and oblique muscles of the abdomen and thigh adductor muscle;
- Develops in acute infectious diseases (typhoid, typhus), and trauma.

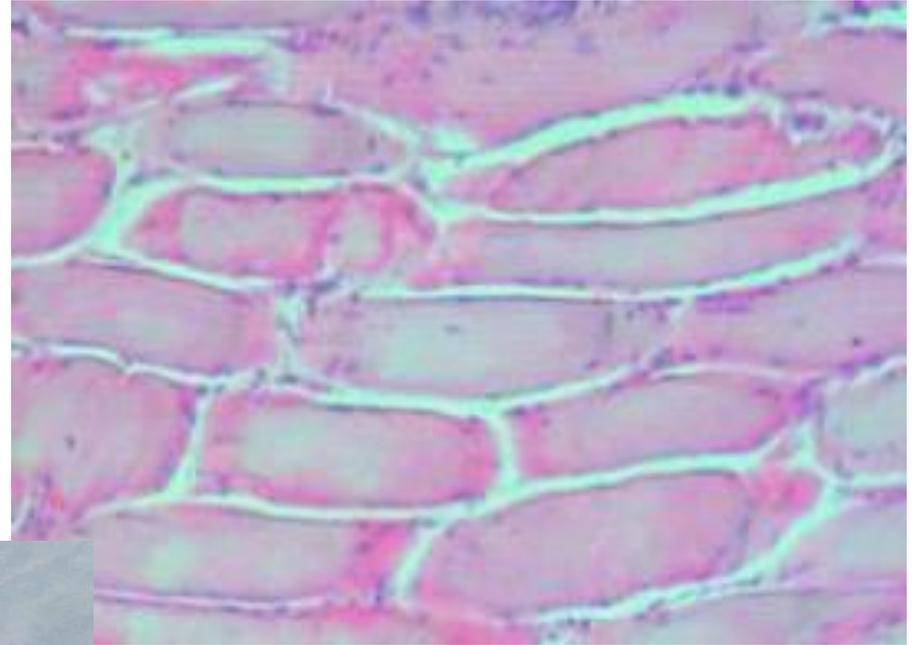
# Caseous necrosis



# Fibrinoid necrosis



# Zenker's necrosis

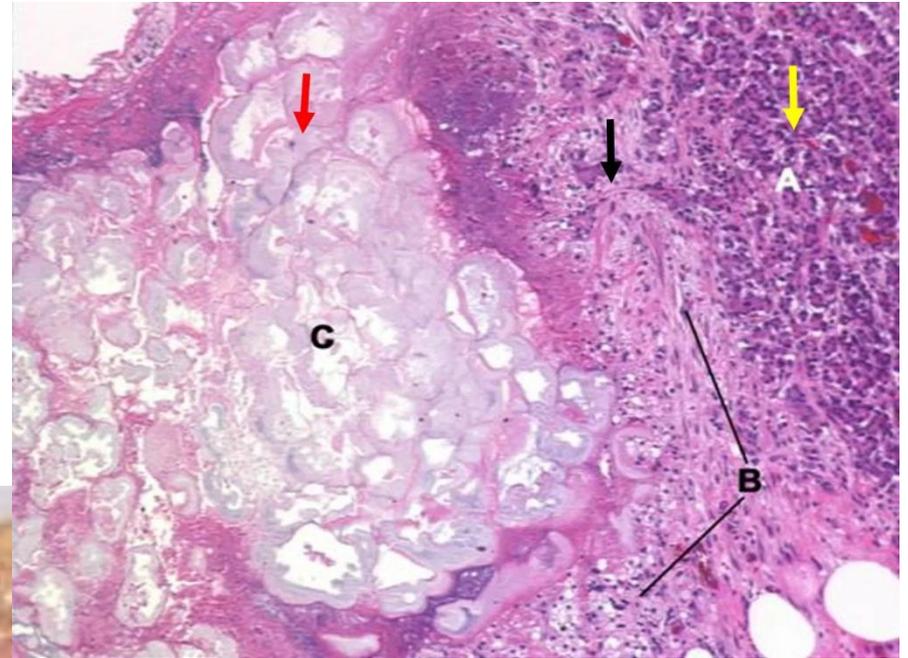


# Coagulation necrosis subtypes

## ■ Fatty necrosis:

- It occurs in two forms: a traumatic and enzymatic.
- Traumatic fatty necrosis - in damaged fatty tissue.
- Enzymatic fatty necrosis - occurs in acute pancreatitis: enzymes from the damaged glandular cells induce lipolysis, the resulting fatty acids are transformed into soaps (calcium salts).

# Fatty necrosis



# Colliquative necrosis

- **Colliquative (wet) necrosis is characterized by melting of necrotic tissue, its hydration.**
- **It is found in tissues with high water content.**
- **An example is the gray softening (ischemic necrosis) of brain:**
  - **Focus has flabby consistency, irregular shape, gray-colored.**
- **At the end of the wet necrosis, as a rule, it forms a cyst.**

# Colliquative necrosis



# Infarct

- **Infarct - necrosis that occurs in violation of circulation, i.e., vascular (ischemic) necrosis.**
- **Develops as a result of thrombosis, embolism, prolonged spasm of the arteries (i.e., causes of ischemia) or a functional overload of organ in low blood supply (applies only to myocardial infarction).**

# Morphology of infarct

- **The shape is determined by myocardial angioarchitectonics of affected organ and can be:**
  - The wedge (triangular) shape
    - Characteristic for the organs with the magistral type of vascular branching and underdeveloped collaterals (spleen, kidney, lung).
  - irregular shape
    - There is a loose blood supply type and abundance of anastomoses (myocardium, brain).
- **By type of heart attack can be:**
  - White (ischemic)
  - White with hemorrhagic rim
  - Red (hemorrhagic).

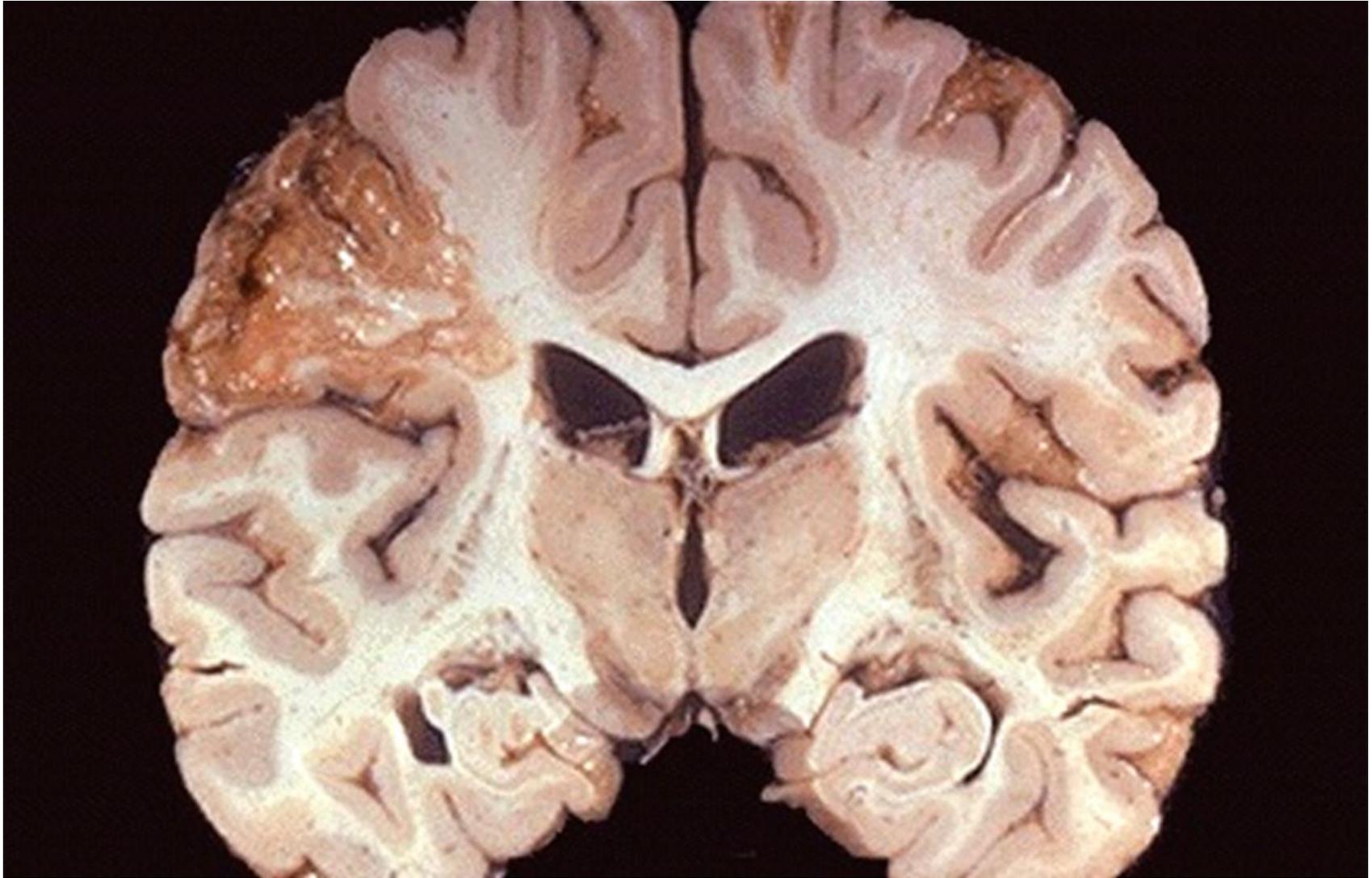
# White (ischemic) infarct

- There is usually in areas of insufficient collateral circulation, which eliminates the blood flow to the area of necrosis.
- Most often it occurs in the brain and spleen.

# Brain infarction

- **It occurs in atherosclerosis and hypertension.**
- **Immediate causes - thrombosis, thromboembolism.**
- **Macroscopic features:**
  - Focus of irregular shape,
  - Flabby consistency,
  - Grayish color.

# Brain infarction



# Spleen infarction

- **The most common cause - thromboembolism.**
- **Macroscopic features:**
  - The focus of the triangular shape,
  - The basis turned to the capsule,
  - White color
  - Rather dry, solid consistency,
  - Drinks off the capsule,
  - Capsule in the infarcted area is rough, covered with fibrinous deposits.

# Spleen infarction



# White infarct with red rim

- It occurs after the spasm of blood vessels at the periphery of infarction is being replaced by their paretic dilatation and development of diapedetic hemorrhage.
- Often it occurs in the myocardium, the kidneys.

# Myocardial infarction

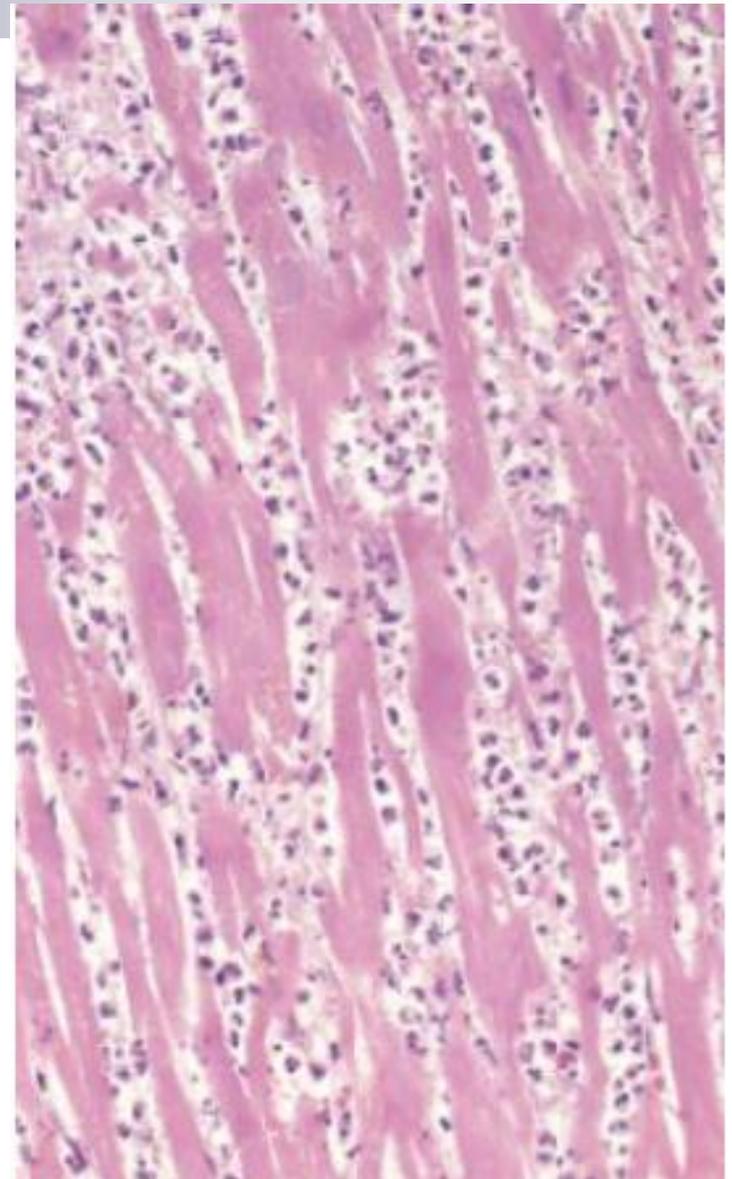
## ■ **Macroscopic picture:**

- The focus of irregular shape in the left ventricular wall or the interventricular septum,
- Flabby consistency,
- Yellowish-white, surrounded by a red rim.

## ■ **Microscopic:**

- In the area of necrosis - cardiomyocytes enucleated (karyolysis), with the collapse of cytoplasm (plasmorrhaxis);
- On the periphery of necrosis - vascular congestion, infiltration of leucocytes (demarcation inflammation);
- The remaining areas of the myocardium - degenerative changes of cardiomyocytes.

# Myocardial infarction



# Renal infarction

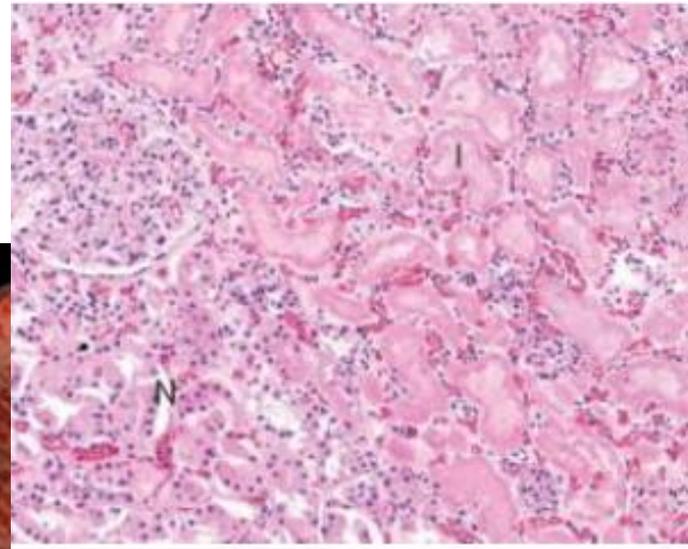
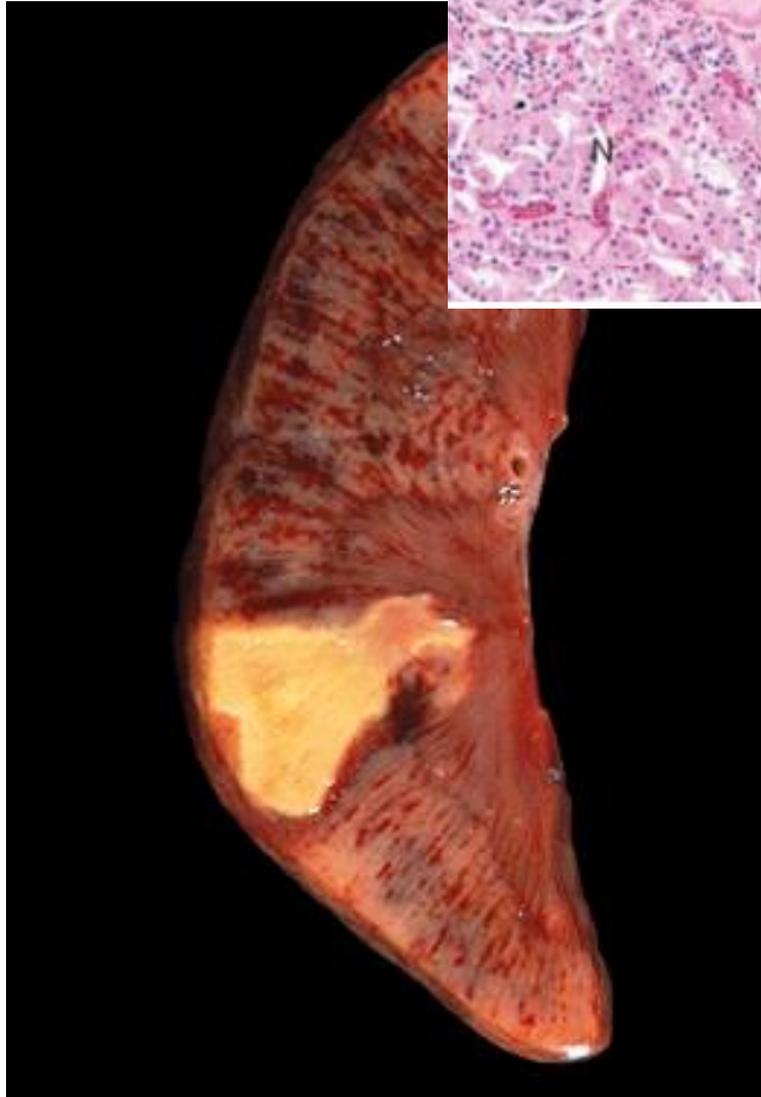
## ■ **Macroscopic picture:**

- Triangular shaped,
- The basis turned to the capsule,
- Surrounded by dark red rim.

## ■ **Microscopically:**

- In the area of necrosis – only the contours of the glomeruli and tubules, absent nucleus in the cells (karyolysis), sometimes lysed cytoplasm - pink structureless masses (necrotized detritus).
- On the periphery - vascular congestion, hemorrhage, infiltration of neutrophils (demarcation inflammation);
- The preserved renal tissue - degenerative changes in the tubular epithelium.

# Renal infarction



# Red (hemorrhagic) infarction

- Occurs usually in venous stasis, with great importance of angioarchitectonics of organ.
- Most often it occurs in the lungs in thrombosis or thromboembolism of pulmonary artery branches in the conditions of venous plethora.
- Mechanism: in a stagnant plethora and closed branches of the pulmonary artery by thrombus or embolus blood from the bronchial artery anastomoses rushes through the anastomoses under the influence of high pressure into the area of necrosis, thus there is a rupture of capillaries and blood infiltration of dead tissue (by erythrocytes).

# Hemorrhagic lung infarction

## ■ **Macroscopic picture:**

- Focus triangular, base faces the capsule,
- Dark red
- Dense texture,
- On the pleura in area of infarct - fibrinous deposits.

## ■ **Microscopic:**

- In the area of necrosis - the rupture of alveolar septae, no nuclei in septal cells and alveolar epithelium, infiltration by red blood cells,
- The area of demarcation inflammation - leukocyte accumulation;
- The preserved lung tissue - emphysema

# Hemorrhagic lung infarction



# Infarction stages

## ■ 1. Necrotic stage:

- It is characterized by the above mentioned changes.

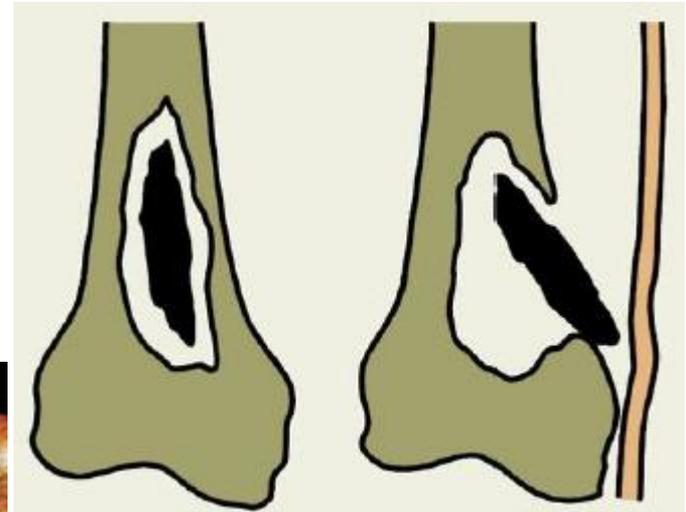
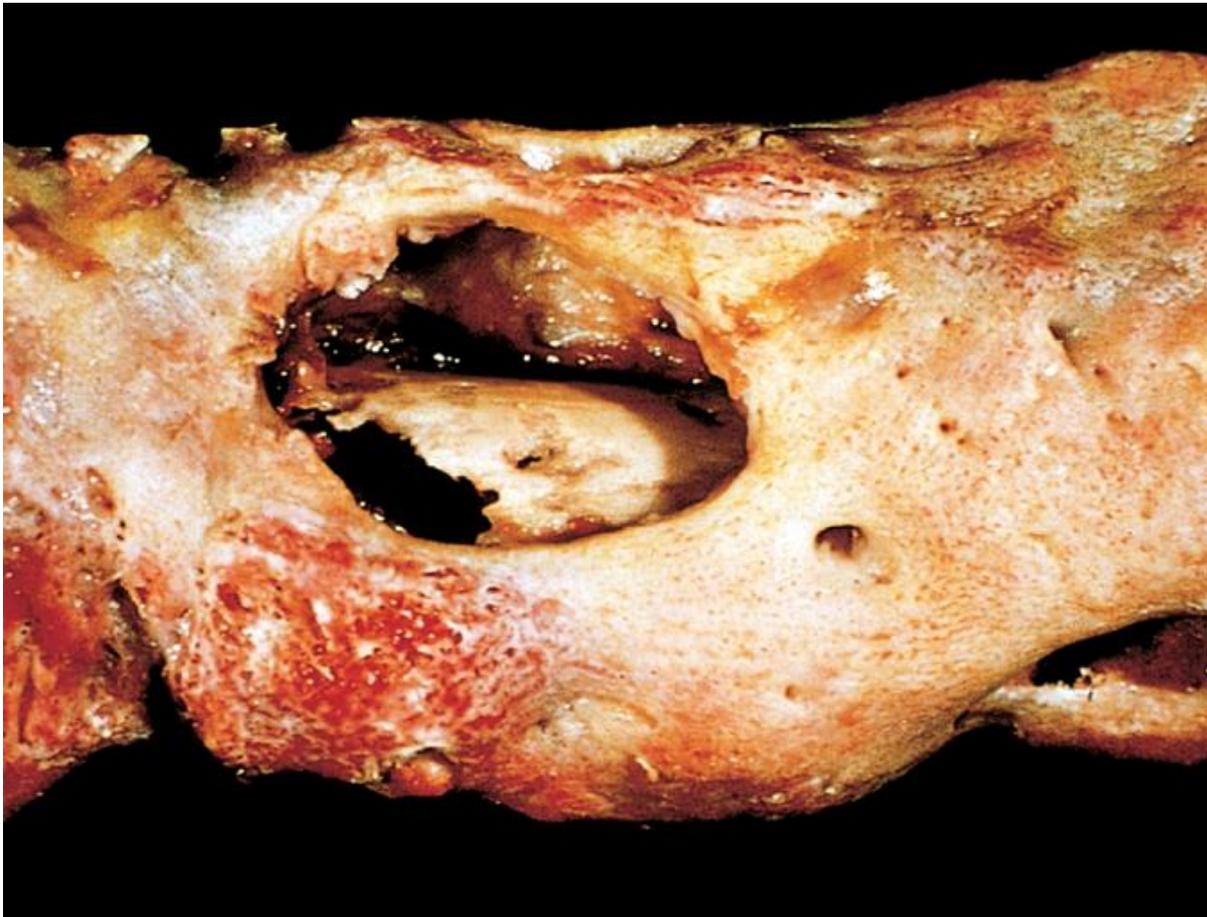
## ■ 2. Organization stage:

- In the area of demarcation inflammation appears young connective (granulation) tissue that gradually replaces necrosis
- Ripening, leads to the formation of scar in place of infarction.

# Sequestration

- **Sequestration - focus of dead tissue, which is not subjected to autolysis, not replaced by connective tissue and lies freely among the living tissue.**
- **As a rule, is accompanied by the development of purulent inflammation with the formation of fistula tracts, through which fragments of sequestration may go out.**
- **It occurs mainly in the bones (osteomyelitis).**

# Sequestration



# Gangrene

- **Gangrene - death of tissues that are in contact with the environment and having a black color due to the formation of iron sulfide.**
- **There are three morphological varieties of gangrene:**
  - Dry gangrene,
  - Wet gangrene,
  - Bedsore.

# Dry gangrene

- Accompanied by mummification of tissue, well-defined demarcation inflammation area.
- Often it occurs in the lower extremities atherosclerosis, frostbite and burns, Raynaud's disease.
- Gangrene of the foot (the macroscopic picture):
  - Necrotic tissue reduced in volume,
  - Dry,
  - Black color,
  - Pronounced demarcation zone.

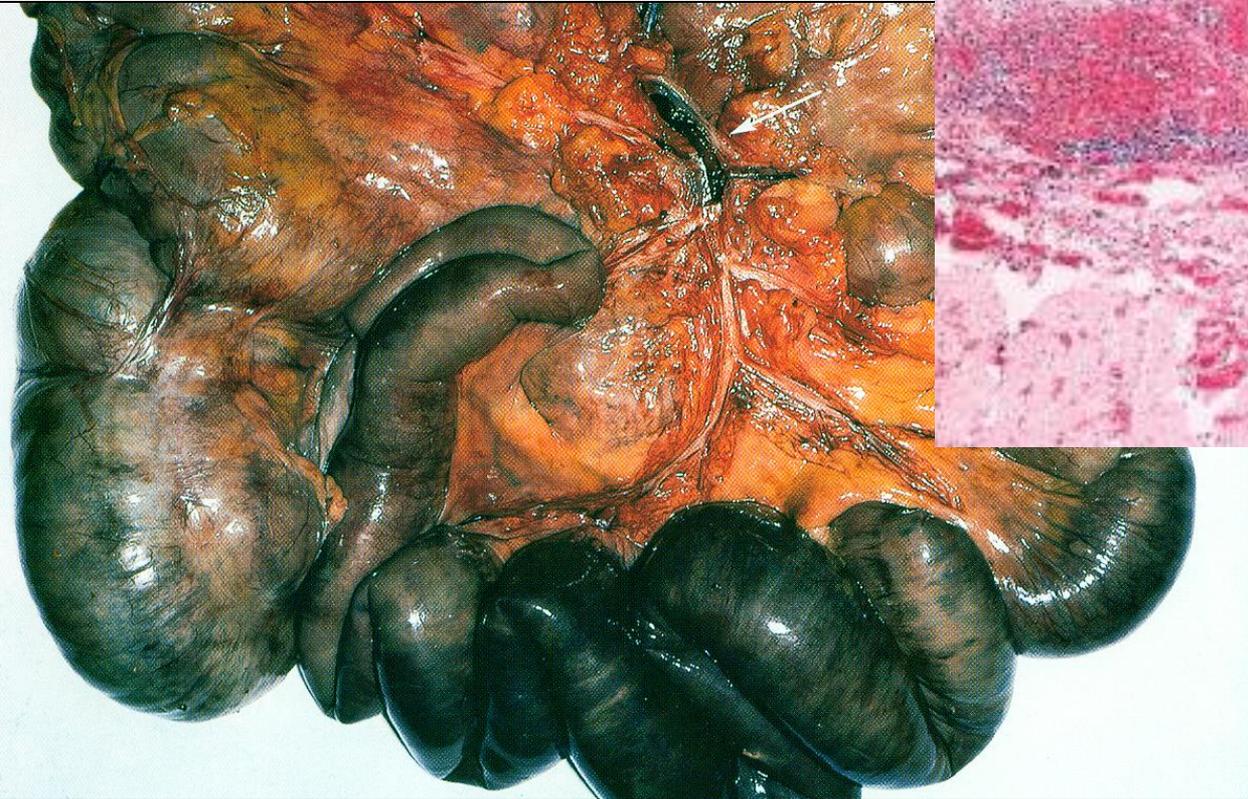
# Foot gangrene



# Wet gangrene

- **Develops in tissues with accession of putrefactive flora.**
- **Tissue swells, becomes edematous, the demarcation zone is not defined.**
- **It occurs in the intestine, lung, uterus, limbs.**
- **In weakened by measles children wet gangrene may develop in the skin of the cheeks, the perineum and called noma.**
- **gangrene of the intestine (the macroscopic picture):**
  - thickened bowel loop,
  - swelling
  - Flabby consistency,
  - Black-red
  - Serous membrane dull, covered with fibrin.

# Bowel gangrene



# Bedsore (decubitus)

- **Bedsore - a kind of gangrene, occurring as a result of trophoneurotic violations in debilitated bedridden patients in the areas of the body exposed to the greatest pressure.**
- **Most often, pressure ulcers are located in the tissues located in the projection of bone protruding areas: elbows, buttocks, heels, ankles, pelvis, spine.**



# Outcomes of necrosis

- **Favorable outcomes of necrosis (associated with the processes of separating and repair, spreading out from the area of demarcation inflammation):**
  - Organization or formation of scar - replacement of necrotic masses by connective tissue.
  - Encapsulation - delimitation of the necrosis site by connective tissue capsule.
  - Petrification - impregnation of necrosis area by the calcium salts (dystrophic calcification).
  - Ossification - appearance of bone tissue in the area of necrosis (very rare – Ghon's lesions).
  - cyst formation - the outcome of colliquative necrosis.
- **Unfavorable outcomes of necrosis:**
  - Purulent melting of necrotic masses,
  - Possible development of sepsis.
  - Mutilation

# Mutilation



# Apoptosis

- **The apoptosis - genetically programmed cell death in vivo.**
- **The term "apoptosis" (Greek apoptosis = defoliation) proposed in 1972**
- **Apoptosis - a form of death, in which individual cells are removed from living tissue.**
- **The main role of apoptosis in normal conditions:**
  - Establishing the necessary balance between the processes of cell proliferation and cell death,
  - That in some cases provides a stable condition of the body, in others - the growth, in the third - atrophy of tissues and organs.
- **Suppression of cell death mechanisms through apoptosis can lead to the development of tumors.**

# Apoptosis

## ■ It occurs in following conditions:

- Removing cells during embryogenesis (implantation, organogenesis, involution).
- The involution of hormone-dependent organs after reduction of the action of the corresponding hormone in adults (rejection of the endometrium during menstruation, ovarian atrophy in postmenopausal period, regression of lactating mammary glands after weaning).
- Cell death in tumors (usually during spontaneous regression, but also in actively growing tumors).
- The death of immune cells (T and B lymphocytes after cessation of the stimulating action of cytokines).
- Atrophy of parenchymal organs in the excretory tract obstruction.

# Apoptosis

## ■ It occurs in the following conditions:

- Cell death due to the action of cytotoxic T-lymphocyte responses in graft rejection and graft versus host disease.
- The cell damage under the influence of some viruses (formation of Councilman bodies in viral hepatitis B).
- Cell death under the influence of various damaging factors that can lead to high doses to necrosis (moderate thermal, radiation damage, cytotoxic anticancer drugs, hypoxia).

# Apoptosis mechanisms

- In apoptosis there is enhanced expression of genes controlling cell proliferation and differentiation - oncogenes (c-fos, c-myc, c-bcl2) and anti-oncogenes (p53).
- Activation of cellular oncogenes should lead to increased cell proliferation, but simultaneous activation of the p53 antioncogene leads to apoptosis.

# Apoptosis morphogenesis

## ■ The condensation and marginization of the chromatin:

- The most characteristic feature of apoptosis.
- It leads to the formation of clumps of bizarre shape under the nuclear membrane.
- The nucleus becomes jagged, it may be fragmented.

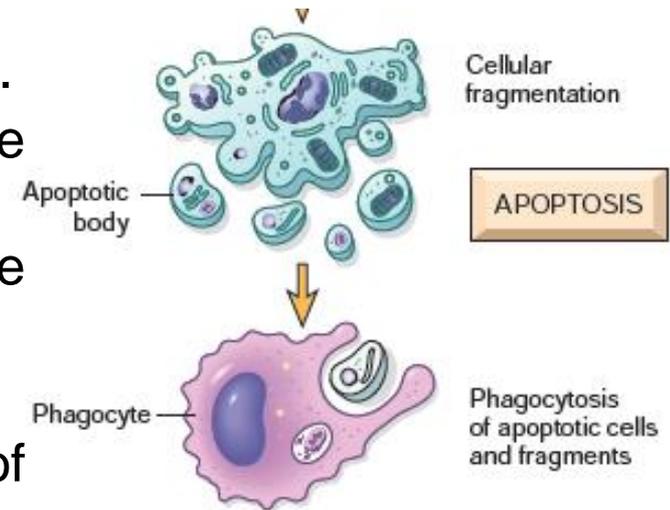
## ■ Cell shrinkage:

- It occurs as a result of condensation of intracellular organelles.

## ■ The formation of apoptotic bodies:

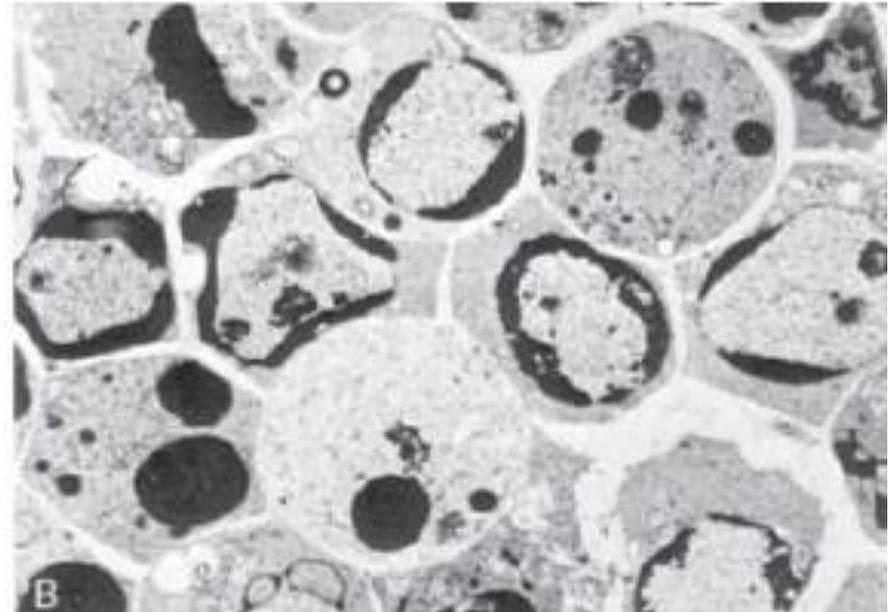
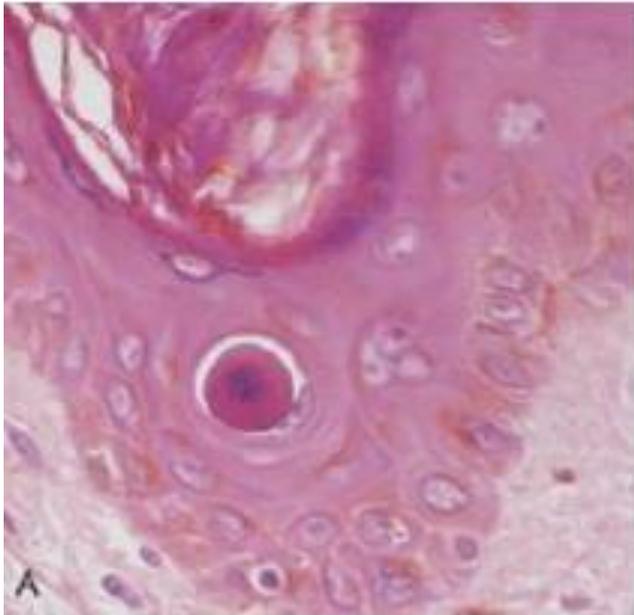
- They consist of cytoplasm fragment with densely packed organelles and the nucleus fragment (sometimes without).

## ■ Phagocytosis of apoptotic cells by surrounding parenchymal cells or macrophages.



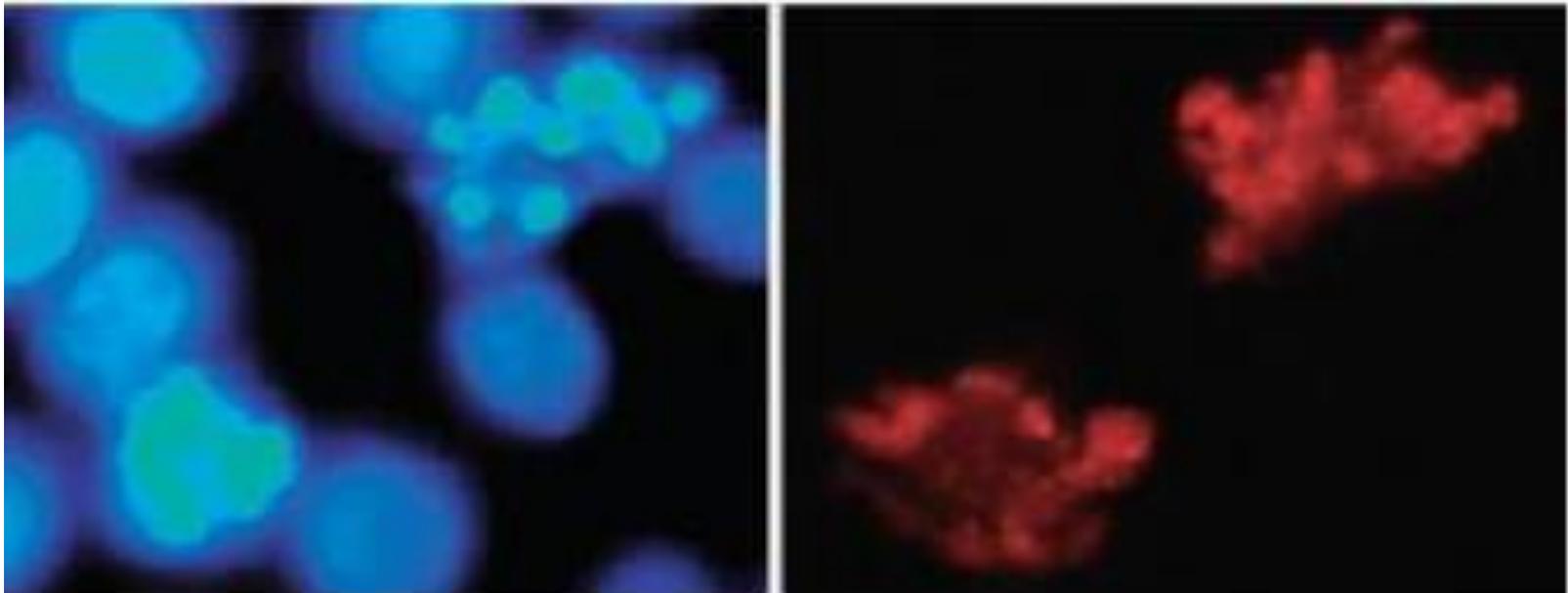
# Morphology of apoptosis

- **Histological examination reveals apoptotic bodies as follows:**
  - Round or oval particles,
  - The small size (comparable to the size of lymphocytes)
  - With intensely eosinophilic cytoplasm,
  - With dark fragments of nuclear chromatin.



# Morphology of apoptosis

- The most reliable methods of morphological verification of apoptosis are considered methods based on detection of unpaired DNA regions at the point of endonucleases cleavage: method of in situ uridine bases labels - TUNEL-test.



# Necrosis vs Apoptosis

<b>Necrosis</b>	<b>Criteria</b>	<b>Apoptosis</b>
Large	Volume	Single cells
Exogenous	Cause	Endogenous or mild exogenous
-	Energy dependence	+
+	Inflammation	-
+	Antigenicity	-



**Thanks for attention!**