Cell Injury and Cell Death

Lecture: 4

Dr. Payman Anwar Rashid

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Faculty of Applied Science
Physiotherapy Department

Fall Semester
Systemic Pathology
Second Grade

Lecture Outline:

- Reversible & Irreversible injury.
- Mechanisms of cell injury.
- Morphology of Cell Injury and Necrosis.
- Apoptosis: Definition & Causes

Objectives:

1. To define reversible & irreversible injury
2. To understand mechanisms of cell injury
3. To explain morphology of cell injury and necrosis.
4. To define apoptosis & its causes

- **Reversible injury:**

means pathologic cell changes that can be restored to normalcy if the stimulus is removed or if the cause of injury is mild.

- **Irreversible injury:**

occurs when the stressors exceed the capacity of the cell to adapt and indicate permanent pathologic changes that cause cell death.

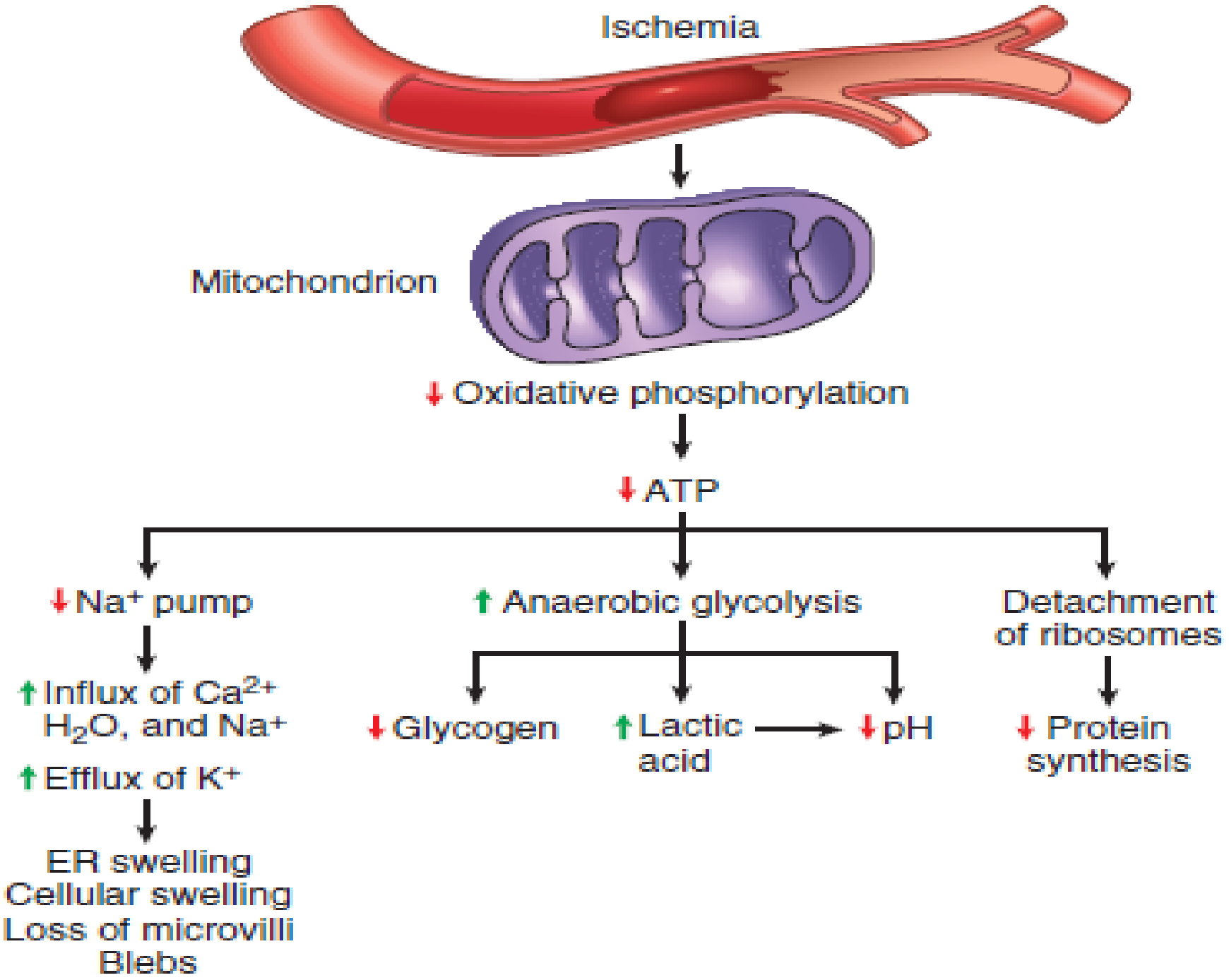
Mechanisms of cell injury

The biochemical mechanisms responsible for cell injury are complex but may be organized around a few relevant principles:

- **Responses to injurious stimuli depend on the type of injury its duration, and its severity.**
- **The consequences of injury depend on the type, state, and adaptability of the injured cell.**

Cell injury results from abnormalities in one or more of five essential cellular components:

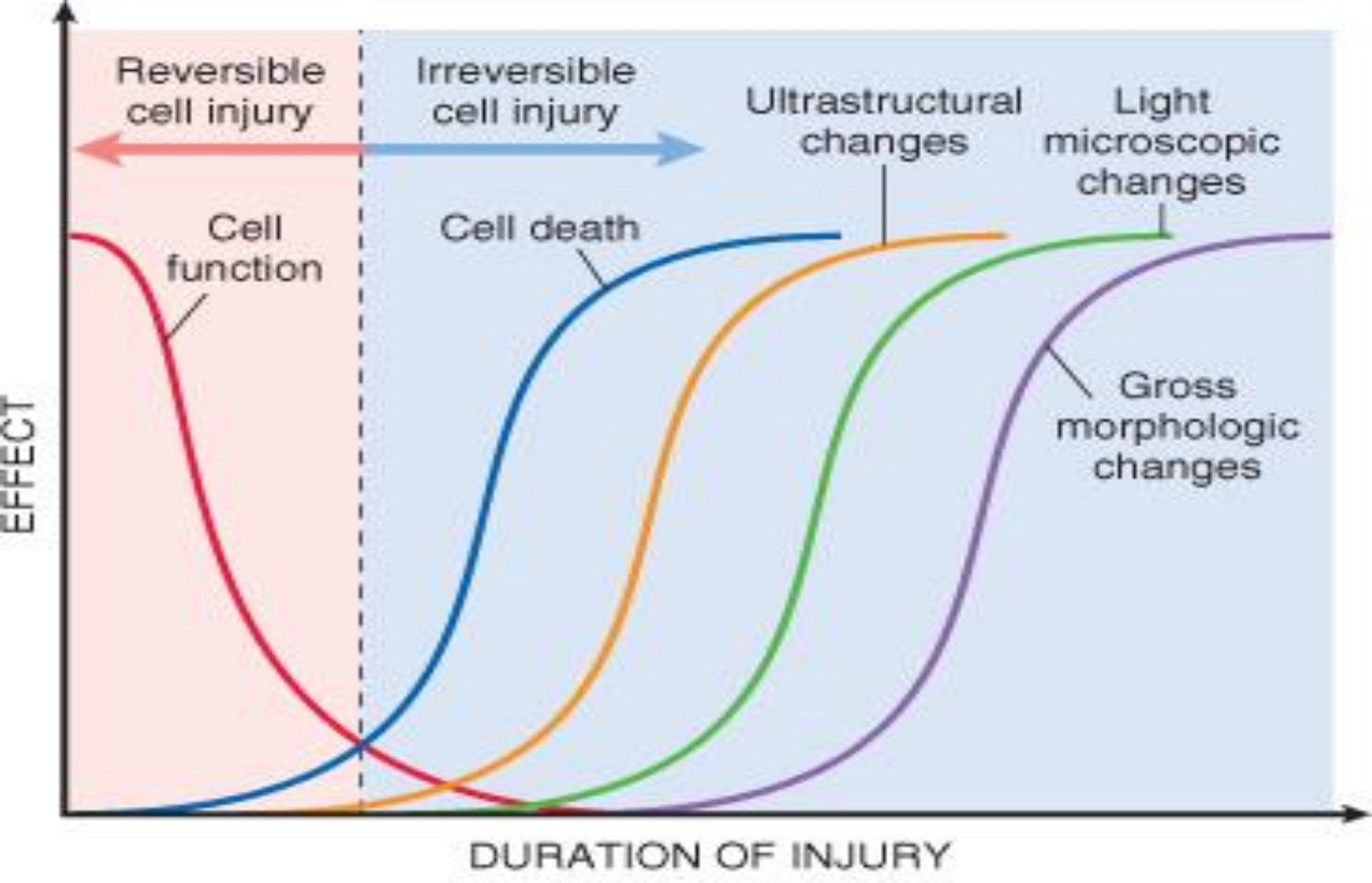
- 1. Aerobic respiration, involving mitochondrial oxidative phosphorelation and ATP production.
- 2. Maintenance of cell membrane integrity, critical for cell and organellar ionic and osmotic homeostasis.
- 3. Protein synthesis.
- 4. Intracellular cytoskeleton.
- 5. Integrity of the genetic apparatus.


Ischemia
Mitochondrion
↓ Oxidative phosphorylation
↓ ATP
↓ Na+ pump
↑ Influx of Ca2+ H2O, and Na+
↑ Efflux of K+
ER swelling
Cellular swelling
Loss of microvilli
Blebs
↑ Anaerobic glycolysis
↓ Glycogen
↑ Lactic acid
↓ pH
Detachment of ribosomes
↓ Protein synthesis

Morphology of Cell Injury and Necrosis

- Injury leads to loss of cell function long before damage is morphologically recognizable. Morphologic changes become apparent only some time after a critical biochemical system within the cell has been deranged; the interval between injury and morphologic change depends on the method of detection.

However, once developed, reversible injury and irreversible injury both have characteristic features.



Timing of biochemical & morphologic changes in cell injury

Reversible Injury:

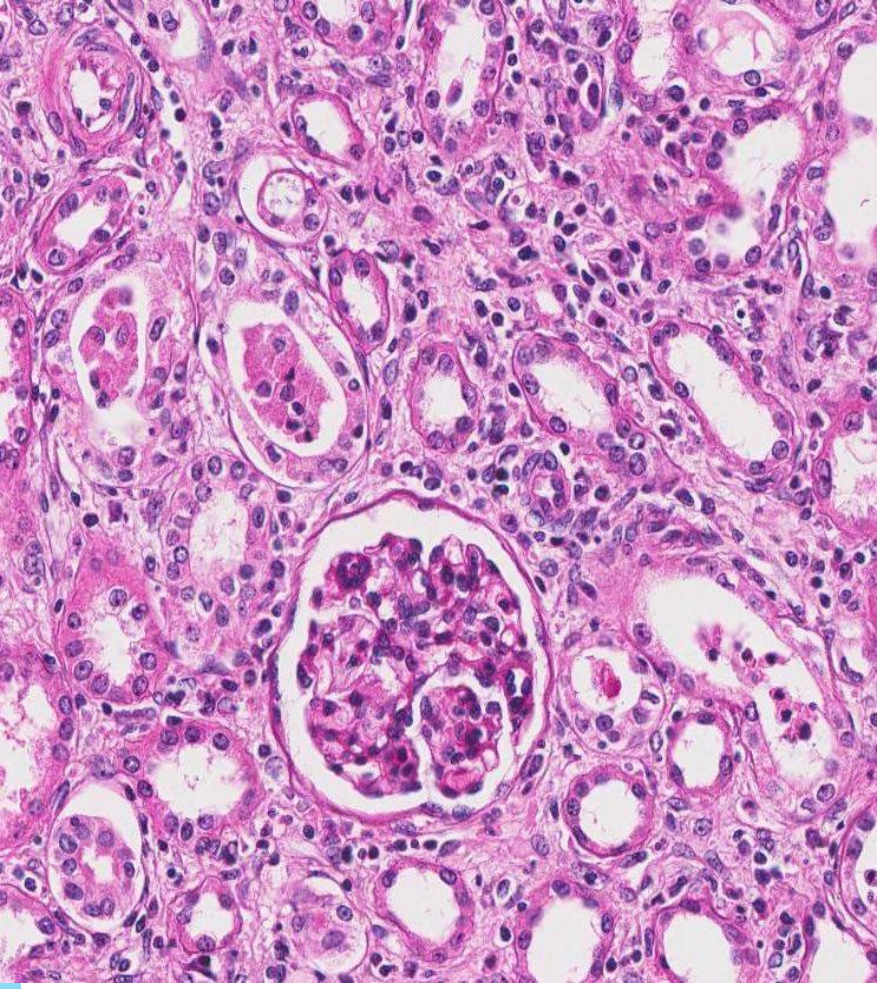
Cell Swelling:

appears whenever cells cannot maintain ionic and fluid homeostasis (largely due to loss of activity in plasma membrane energy-dependent ion pumps).

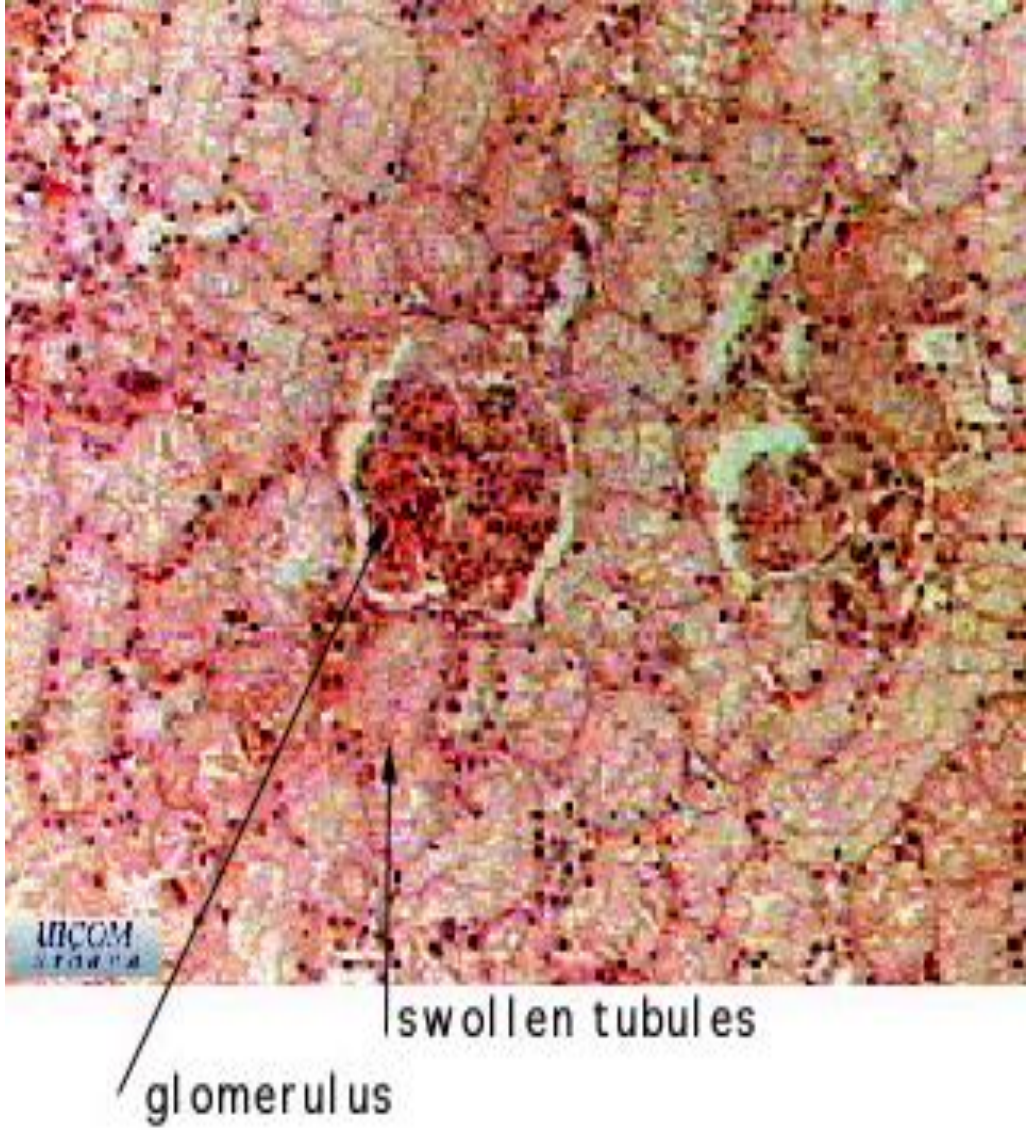
- is difficult to appreciate with the light microscope;
- it may be more apparent at the level of the whole organ. it causes some pallor, and increase in weight of the organ.
- Microscopically, may reveal small, clear vacuoles within the cytoplasm.

This pattern of nonlethal injury is called ***hydropic change***

Swelling of cells is reversible.



Normal Kidney histology

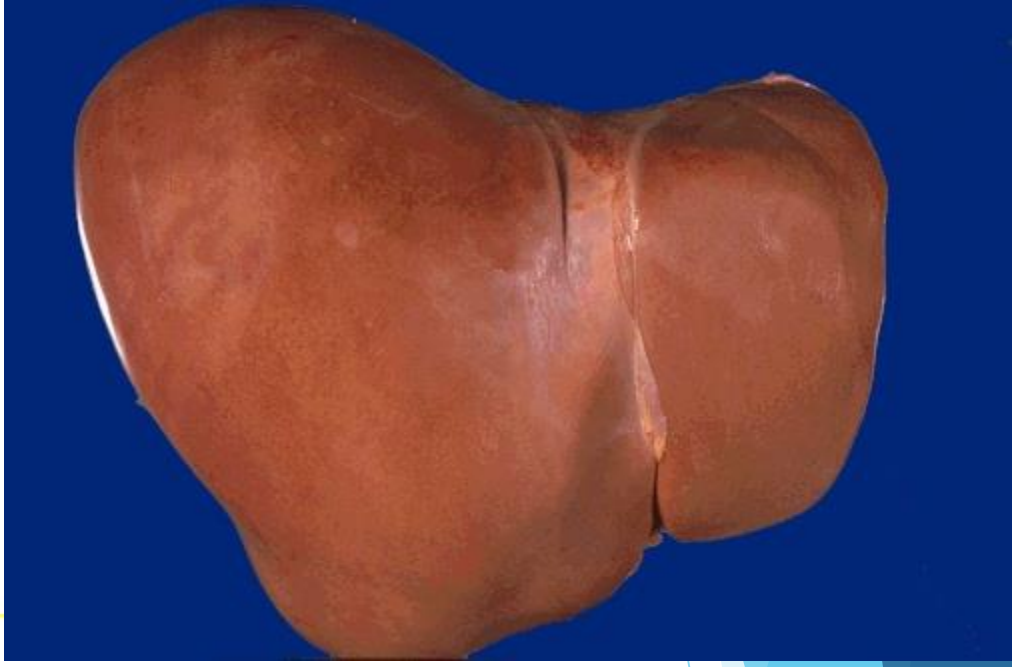


Hydropic swelling of renal tubules

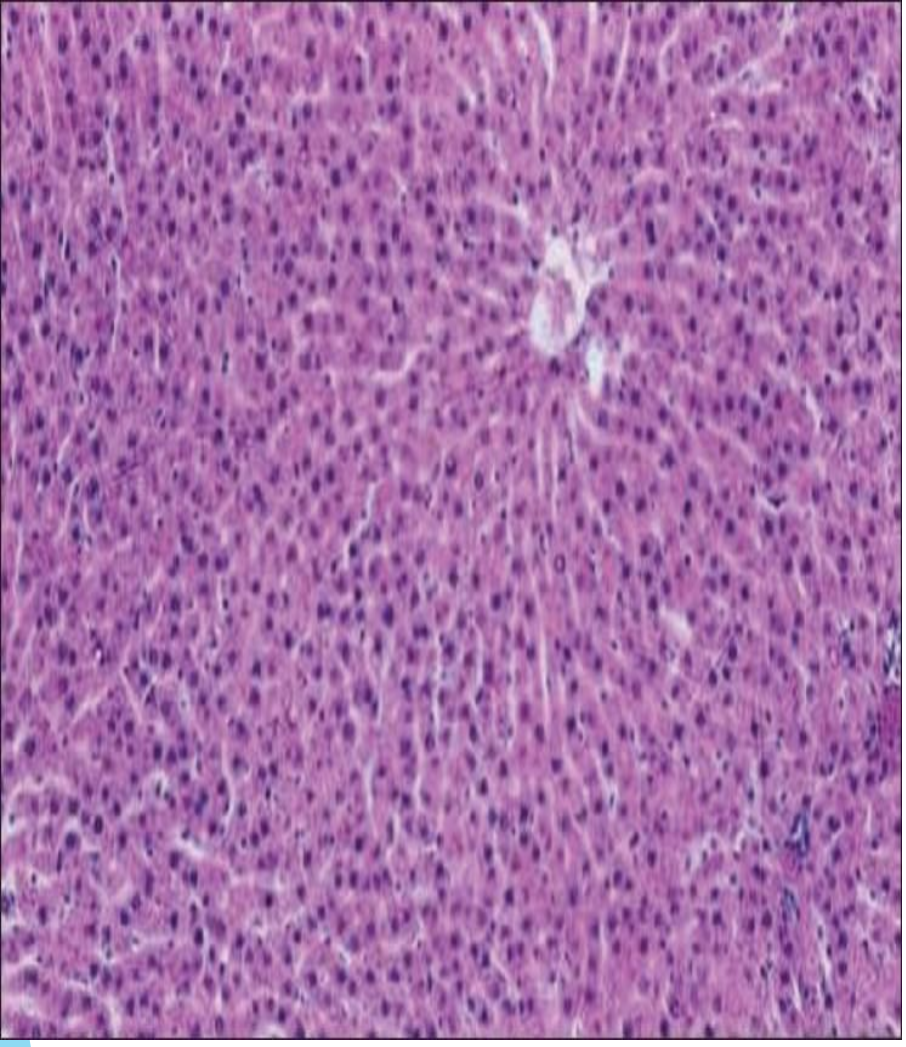
Fatty change:

is manifested by cytoplasmic lipid vacuoles principally encountered in cells involved in or dependent on fat metabolism (e.g. hepatocytes and myocardial cells), and it is also reversible.

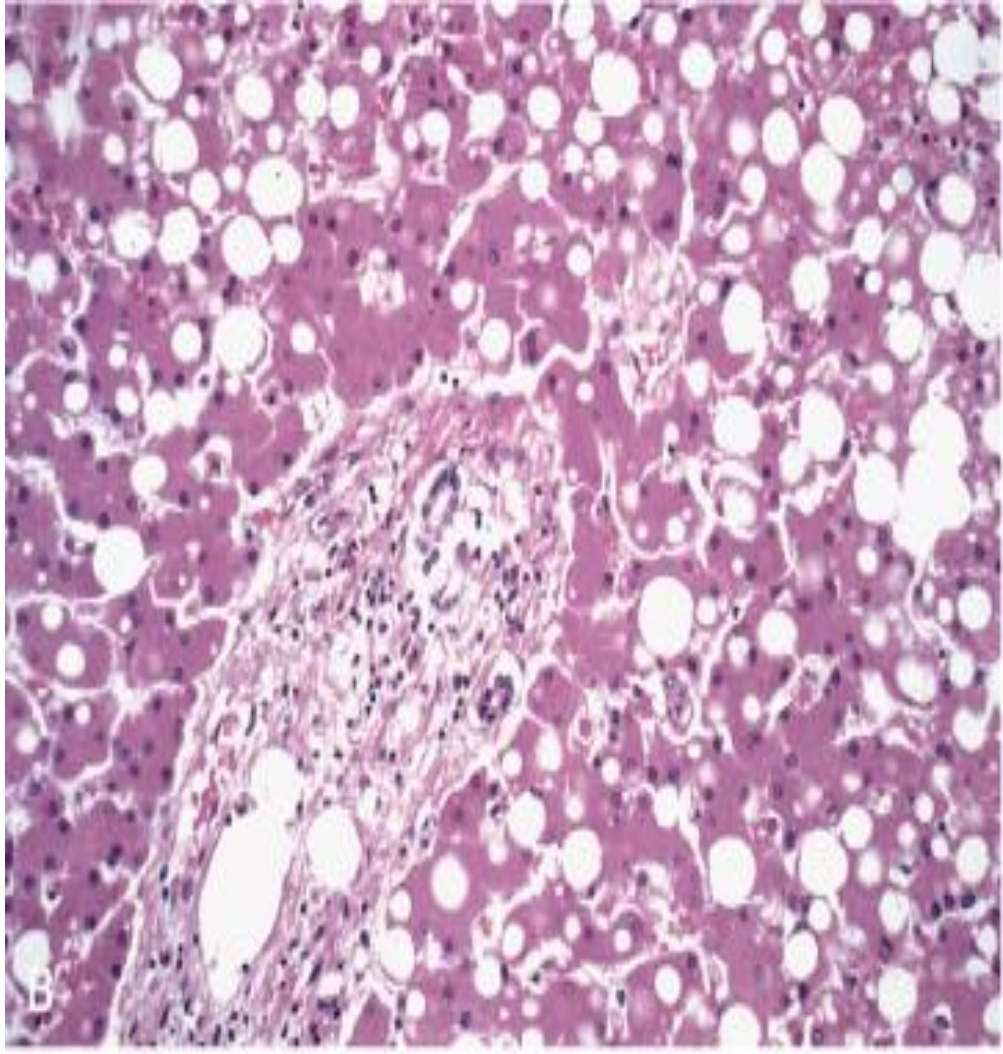
Normal liver



Fatty change of liver



Normal liver histology



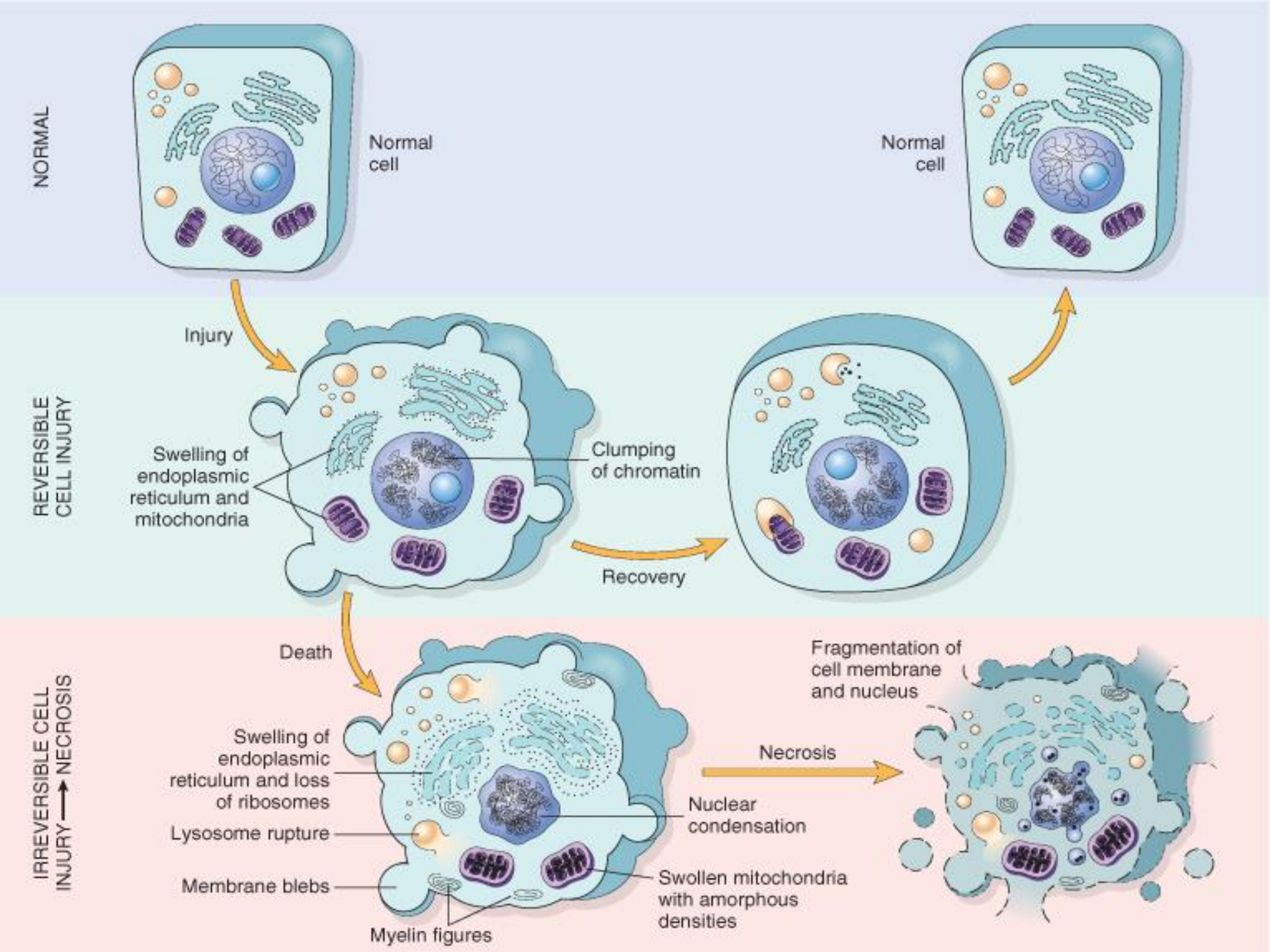
Microscopical appearance of fatty change of liver

Necrosis:

- Is the sum of the morphologic changes that follow cell death in living tissue or organs.

Two processes underlie the basic morphologic changes:

- 1. Denaturation of protein.
- 2. Enzymatic digestion of organelles and other cytosolic components.

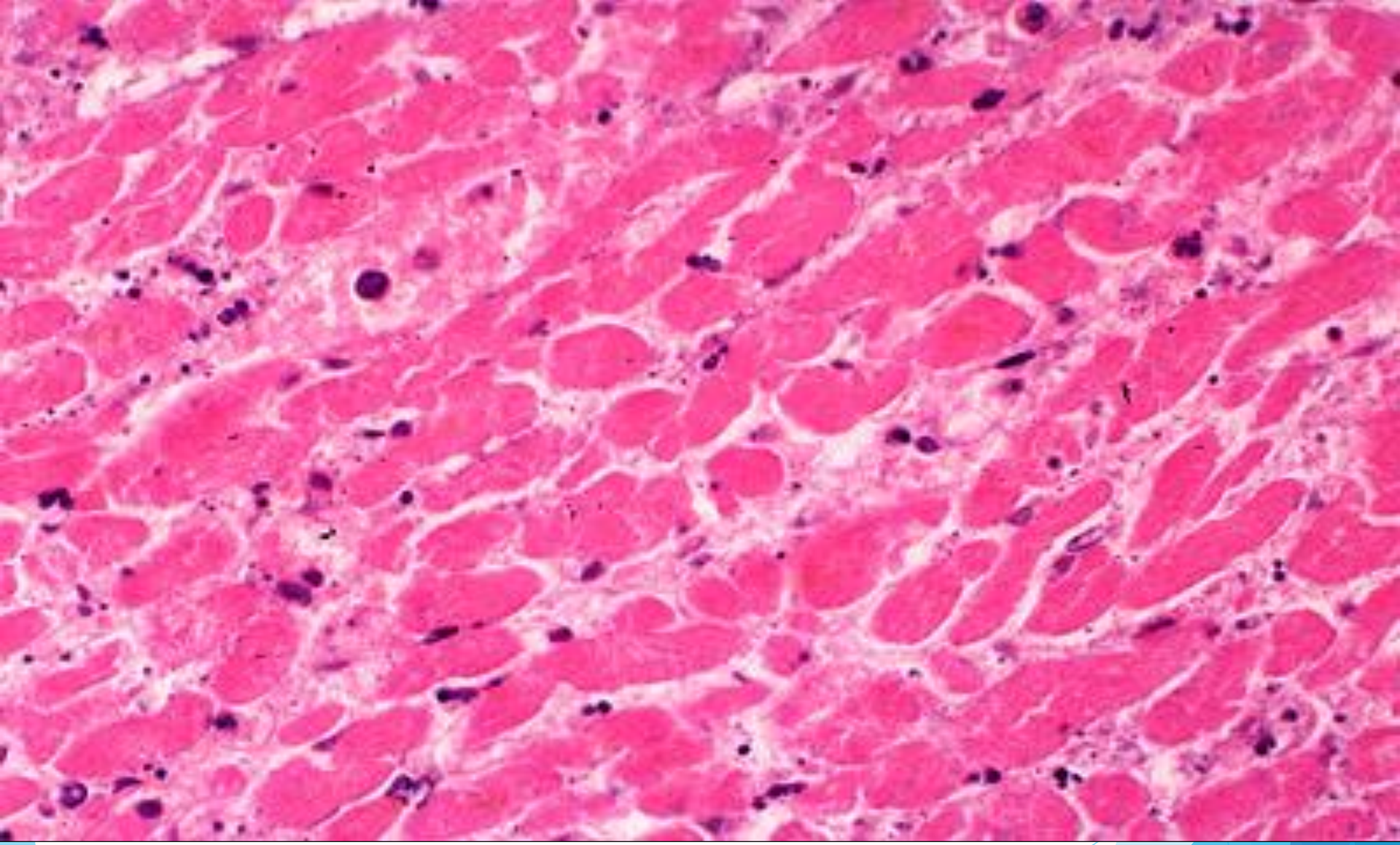

NORMAL
Normal cell
Normal cell
REVERSIBLE CELL INJURY
Injury
Swelling of endoplasmic reticulum and mitochondria
Clumping of chromatin
Recovery
IRREVERSIBLE CELL INJURY → NECROSIS
Death
Swelling of endoplasmic reticulum and loss of ribosomes
Lysosome rupture
Membrane blebs
Myelin figures
Nuclear condensation
Swollen mitochondria with amorphous densities
Necrosis
Fragmentation of cell membrane and nucleus

- There are several distinctive features:
- Necrotic cells are more eosinophilic (pink) than viable cells by standard hematoxylin and eosin (H&E) staining.

They appear glassy owing to glycogen loss and may be vacuolated; cell membrane are fragmented.

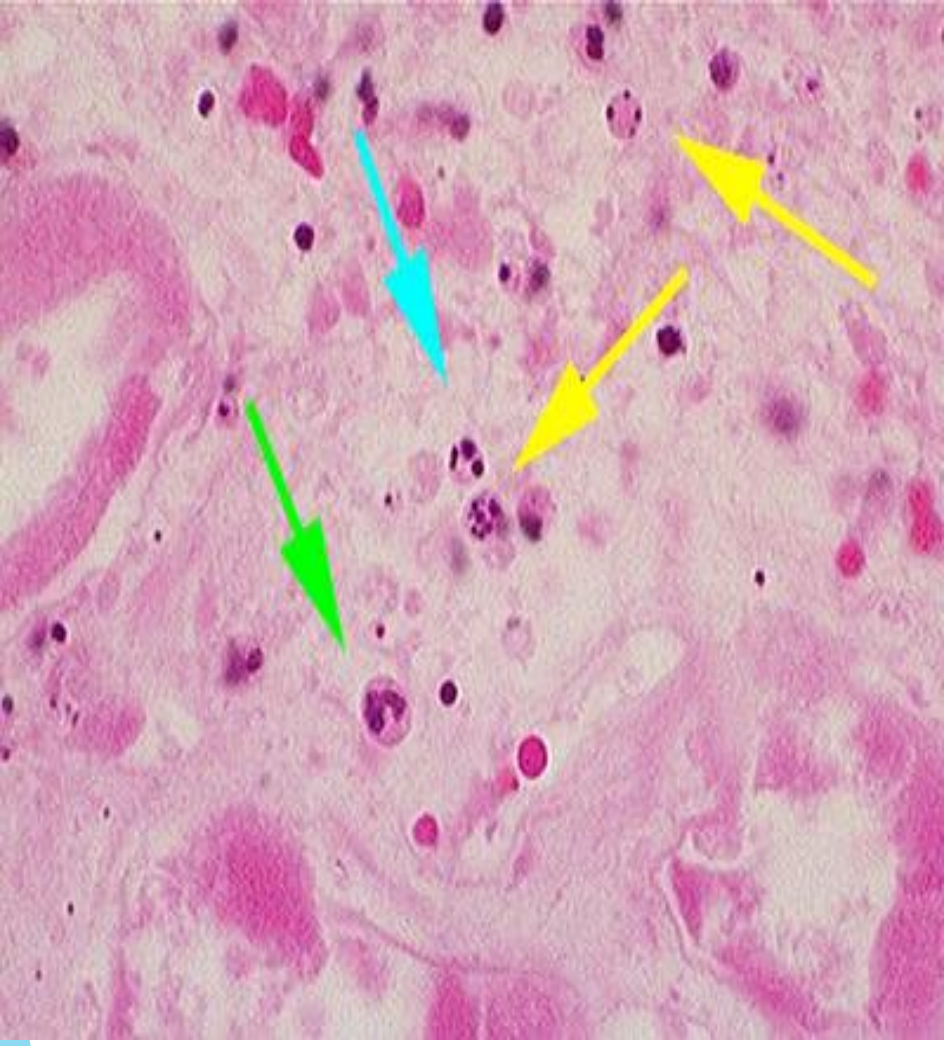
Nuclear changes include:

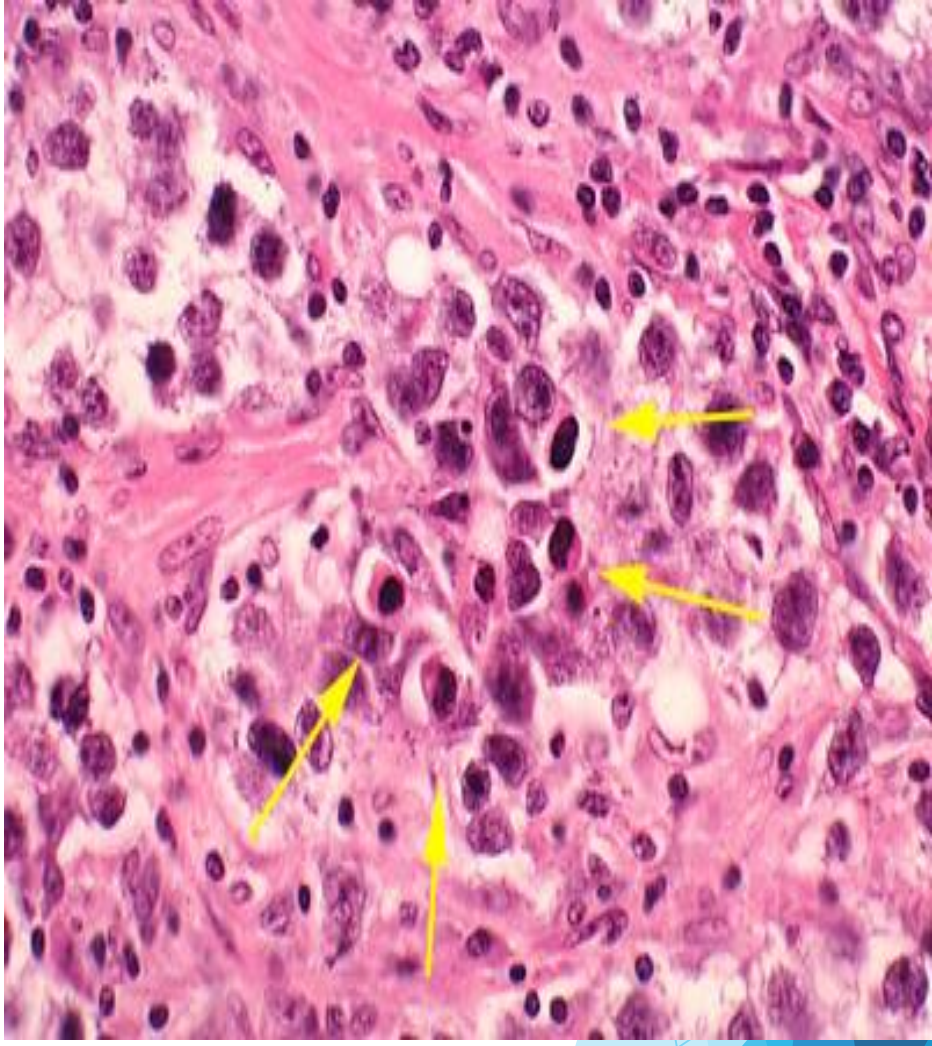
* Pyknosis (small dense nucleus).
* Karyolysis (faint, dissolved nucleus).
* Karyorrhexis (fragmented nucleus).



Myocardial infarction (coagulative necrosis)

Cytoplasmic eosinophilia & nuclear karyolysis





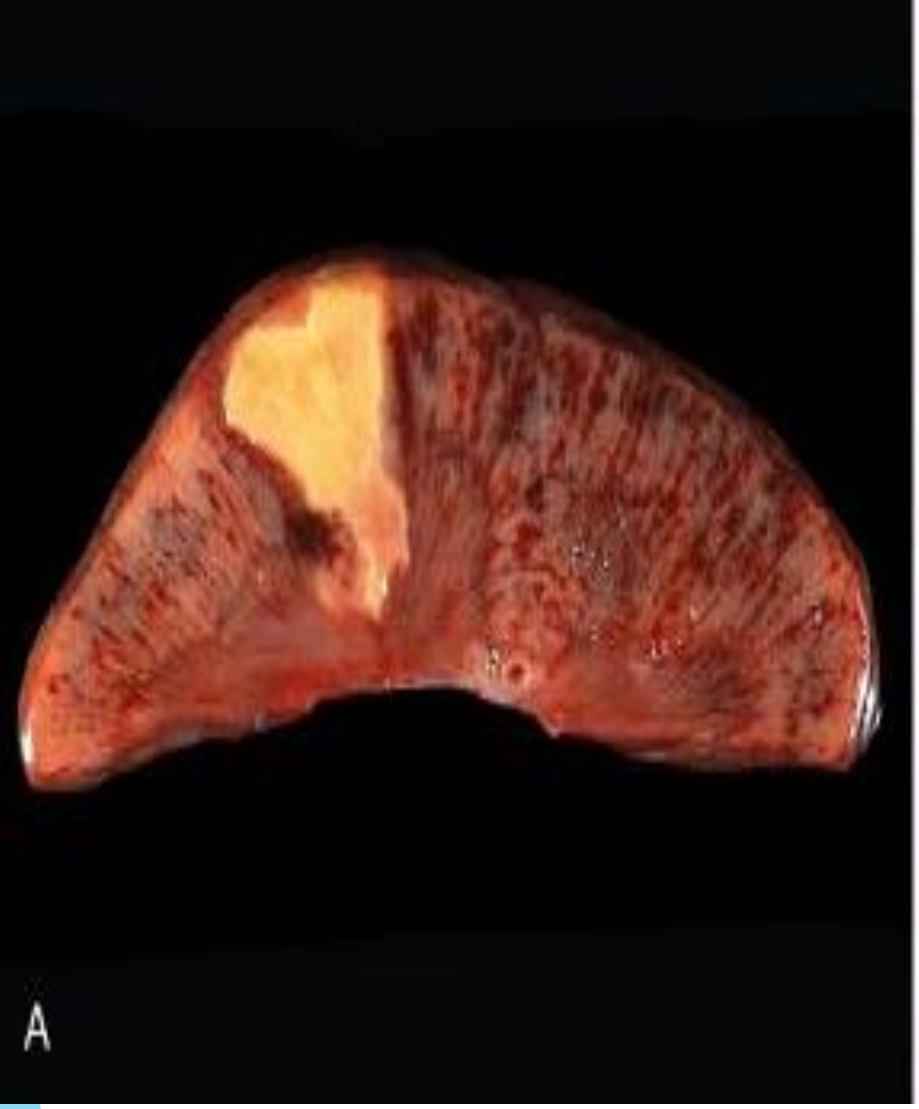
Microscopical appearance of nuclear changes in necrotic cells.

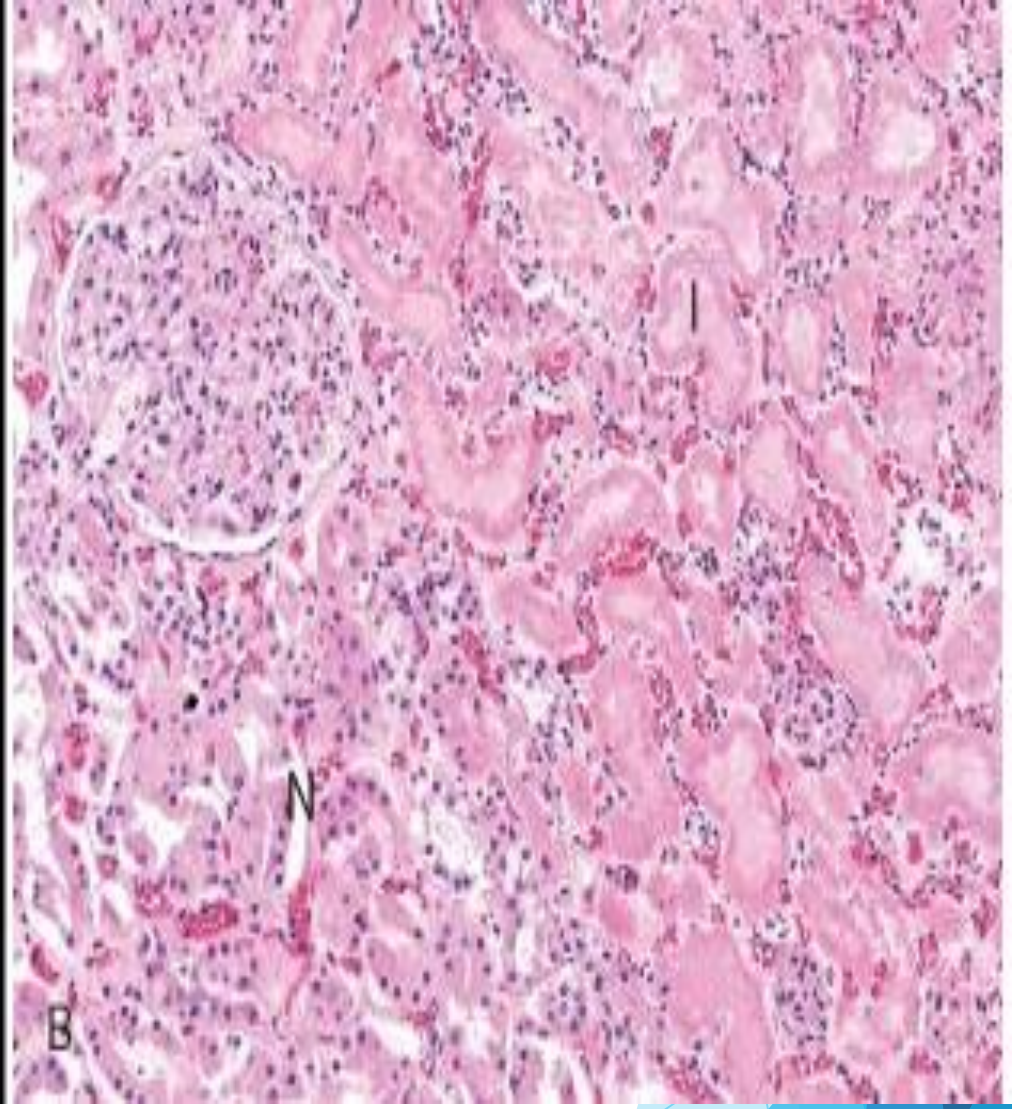
Karyrorrhexis **Pyknosis**

- **General tissue patterns of necrosis include:**
- **1. Coagulative necrosis:**

is the most common pattern predominated by protein denaturation with preservation of the cell and tissue framework.

This pattern is characteristic of hypoxic death in all tissues except the brain.



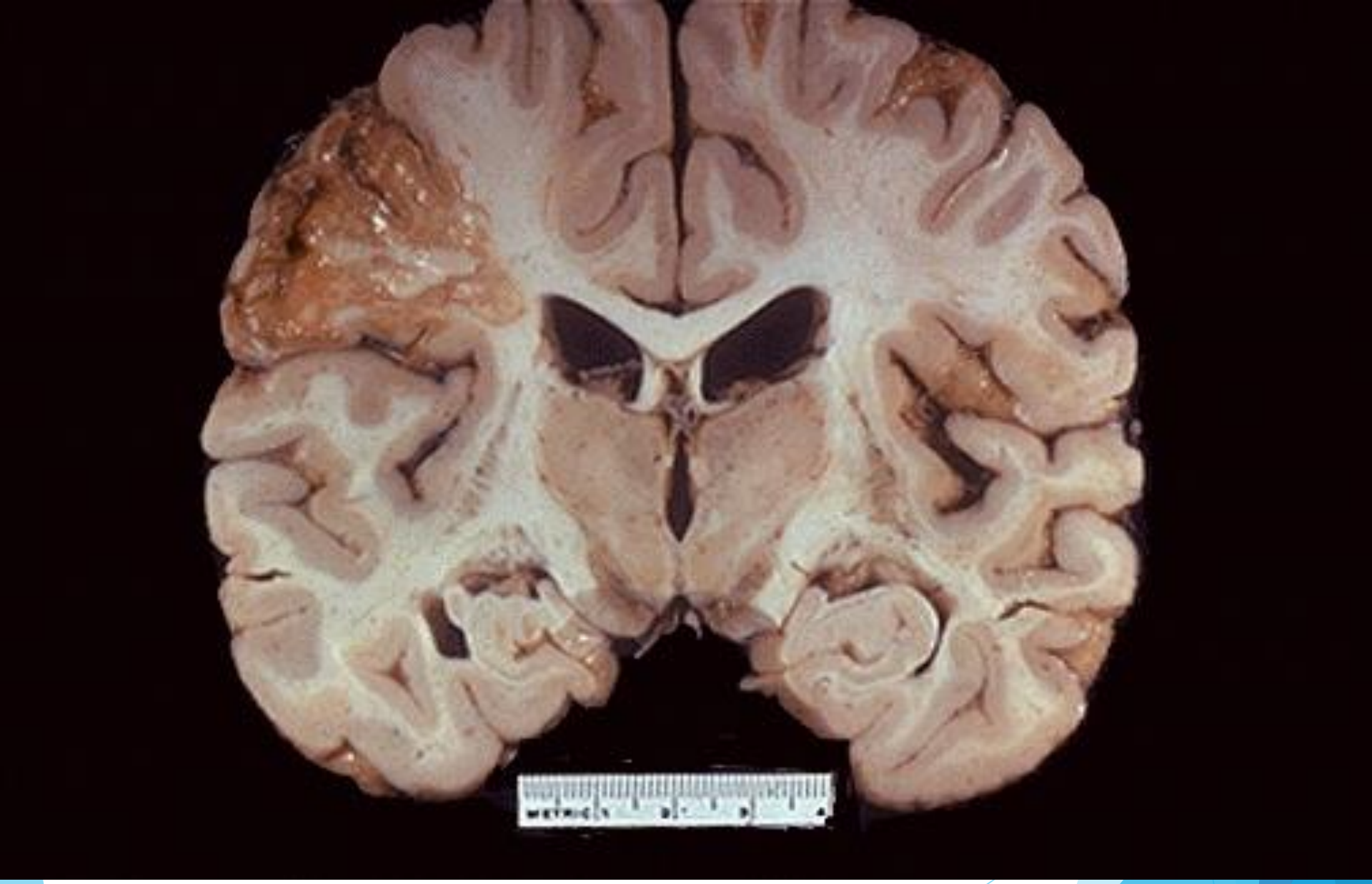


Coagulative necrosis. A, A wedge-shaped kidney infarct (yellow). B, Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I) showing preserved cellular outlines with loss of nuclei and an inflammatory infiltrate

2. Liquefactive necrosis:

occur when enzymatic digestion predominates over protein denaturation. The necrotic area is soft and filled with fluid.

This type of necrosis is most frequently seen in localized bacterial infections (abscesses) and in brain.



Cerebral infarction (Liquefactive necrosis)

3. Gangrenous necrosis:

It is usually applied to a limb, generally the lower leg, that has lost its blood supply and has undergone coagulative necrosis involving multiple tissue layers.

When bacterial infection is superimposed, coagulative necrosis is modified by the liquefactive action of the bacteria and the attracted leukocytes (so-called wet gangrene).

Dry gangrene
(coagulative necrosis)

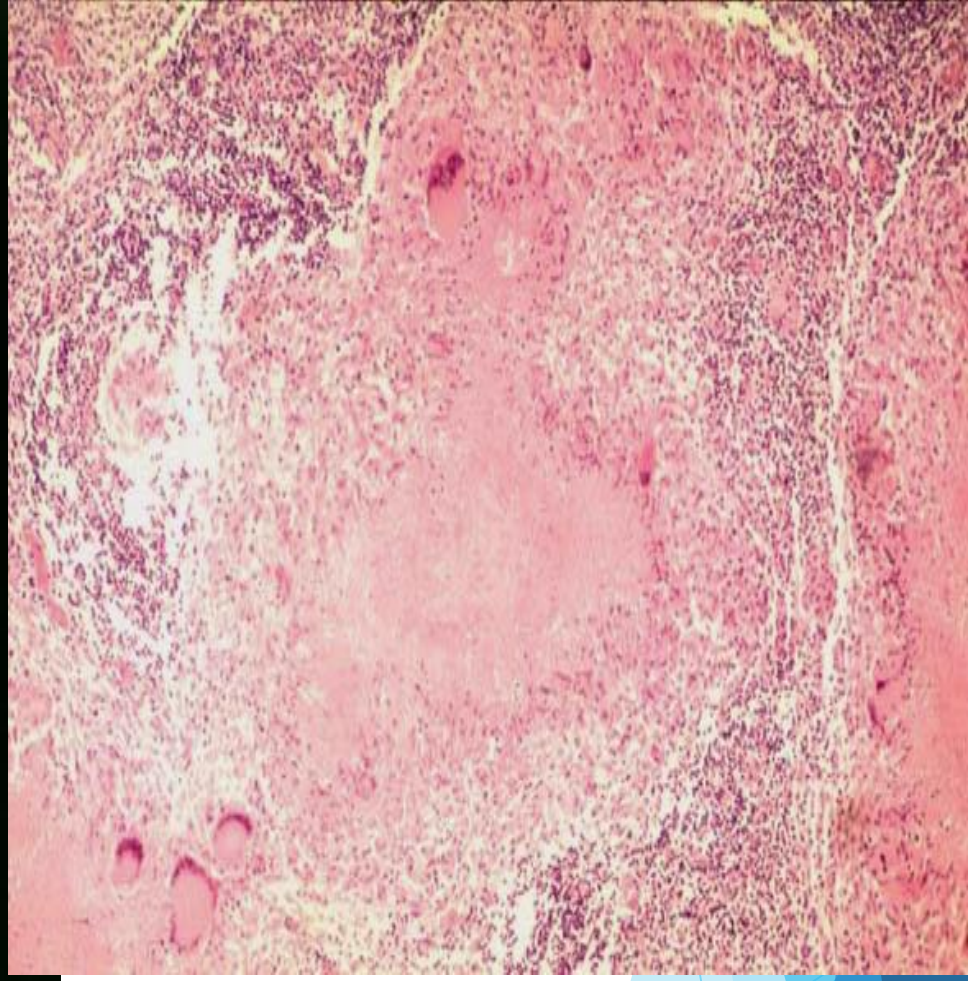
Wet gangrene
(liquefactive necrosis)

4. Caseous necrosis:

is characteristics of tuberculous lesion; it appear grossly as soft, friable, cheesy material and microscopically as amorphous eosinophilic material with cell debris.

A tuberculous lung with a large area of caseous necrosis.

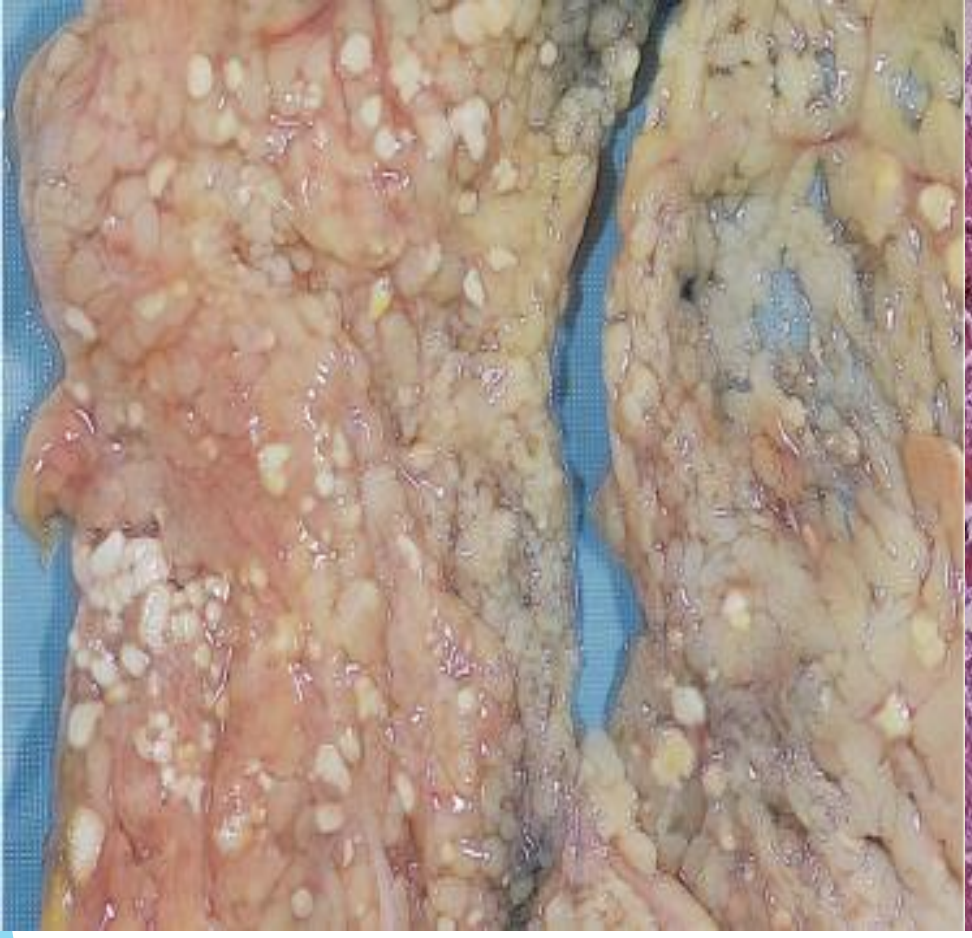
The caseous debris is yellow- white and cheesy.



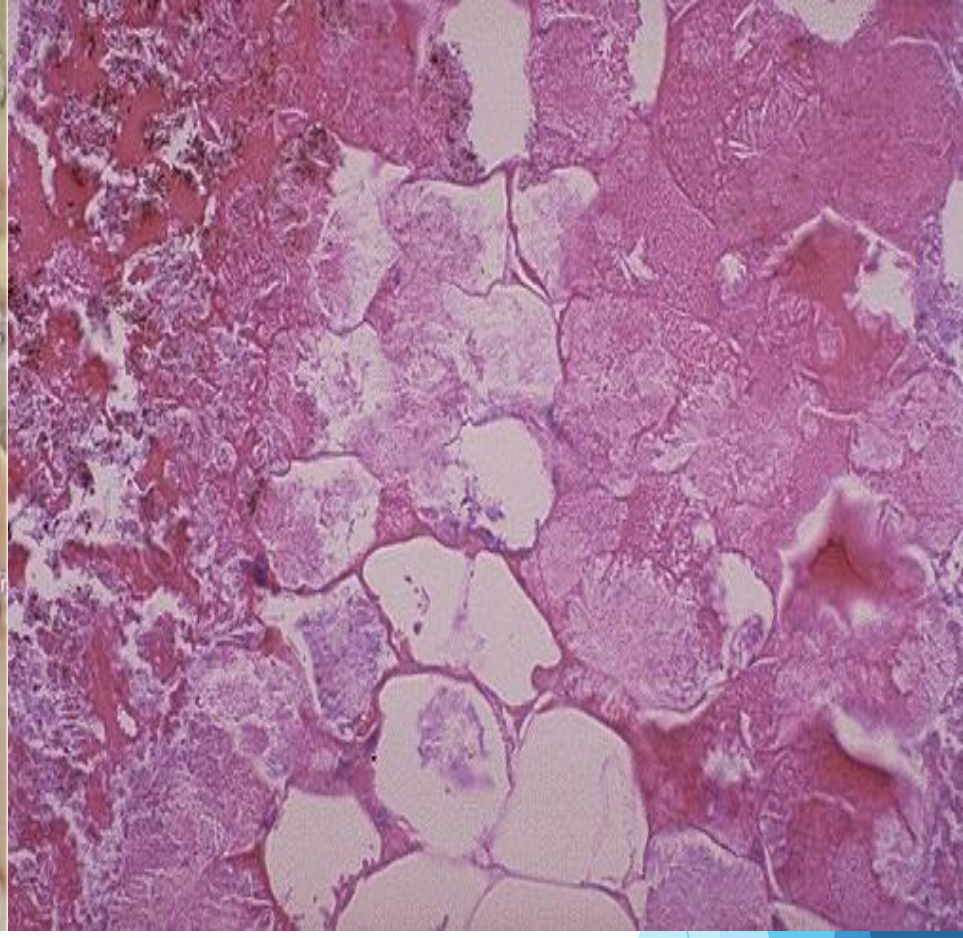
Caseous necrosis surrounded by granulomatous inflammation with giant cells.

5. Fat necrosis:

is seen in adipose tissue, grossly these are white, chalky areas (fat saponification), histologically there are vague cell outlines and calcium deposition.



Foci of Fat necrosis with saponification in the mesentery .



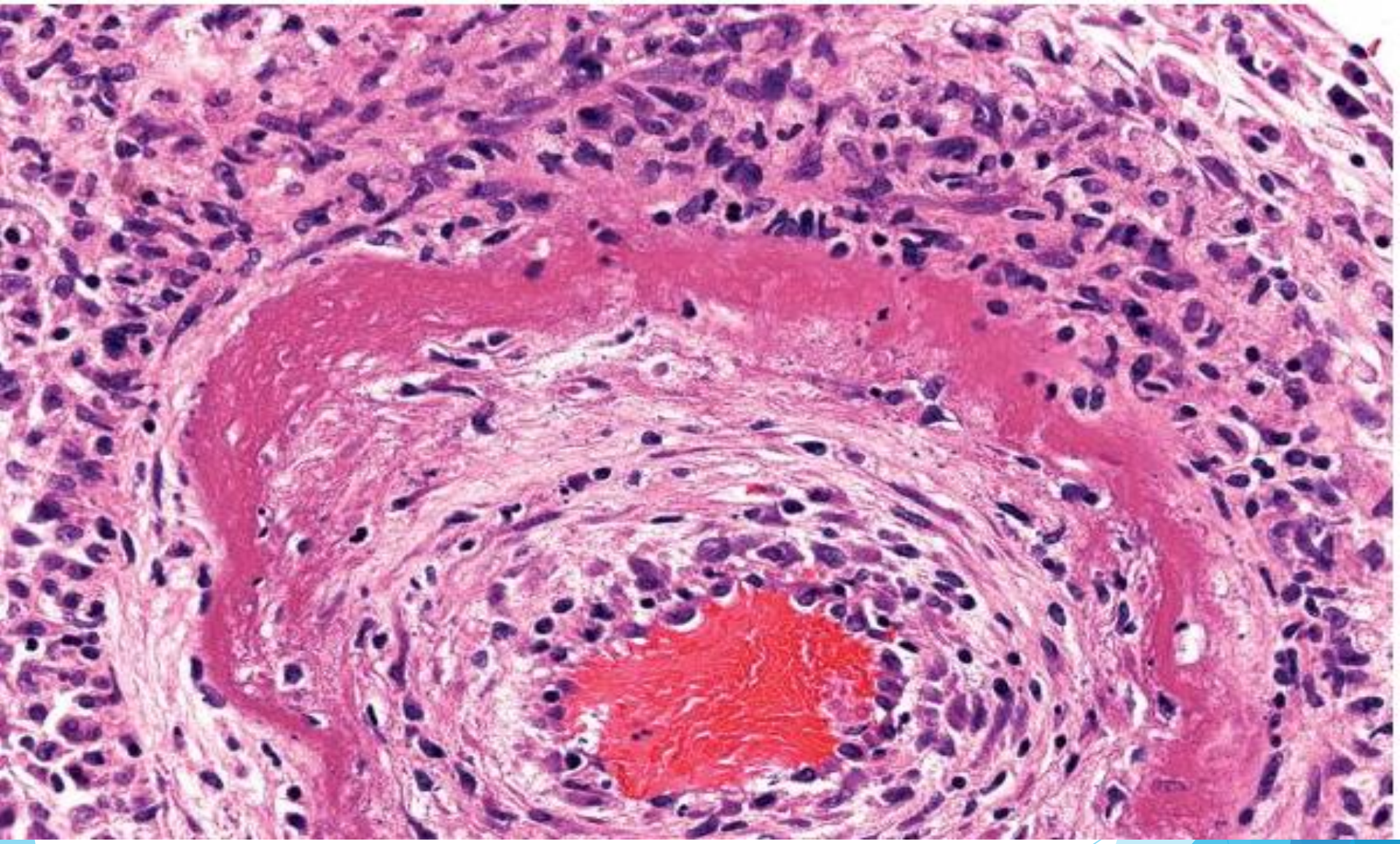
Microscopical appearance of fat necrosis

6. Fibrinoid necrosis:

is a special form of necrosis usually seen in immune reactions involving blood vessels.

Occurs when complexes of antigens and antibodies are deposited in the walls of arteries.

Deposits of these “immune complexes,” together with fibrin that has leaked out of vessels, result in a bright pink and amorphous appearance in H&E stains, called “fibrinoid” (fibrin-like)



Fibrinoid necrosis in an artery. The wall of the artery shows a circumferential bright pink area of necrosis with inflammation (neutrophils with dark nuclei).

Apoptosis:

- (programmed cell death) occurs when a cell dies through activation of a tightly regulated internal suicide program.
- The function of apoptosis is to eliminate unwanted cells selectively with minimal disturbances to surrounding cells.

The plasma membrane remains intact, but the structure is altered so the apoptotic cell becomes target for phagocytosis.

The dead cell cleared rapidly before its content leaked out therefore it does not induce inflammatory reaction in the surrounding tissue.

Apoptosis may be physiologic or pathologic.

Physiologic causes:

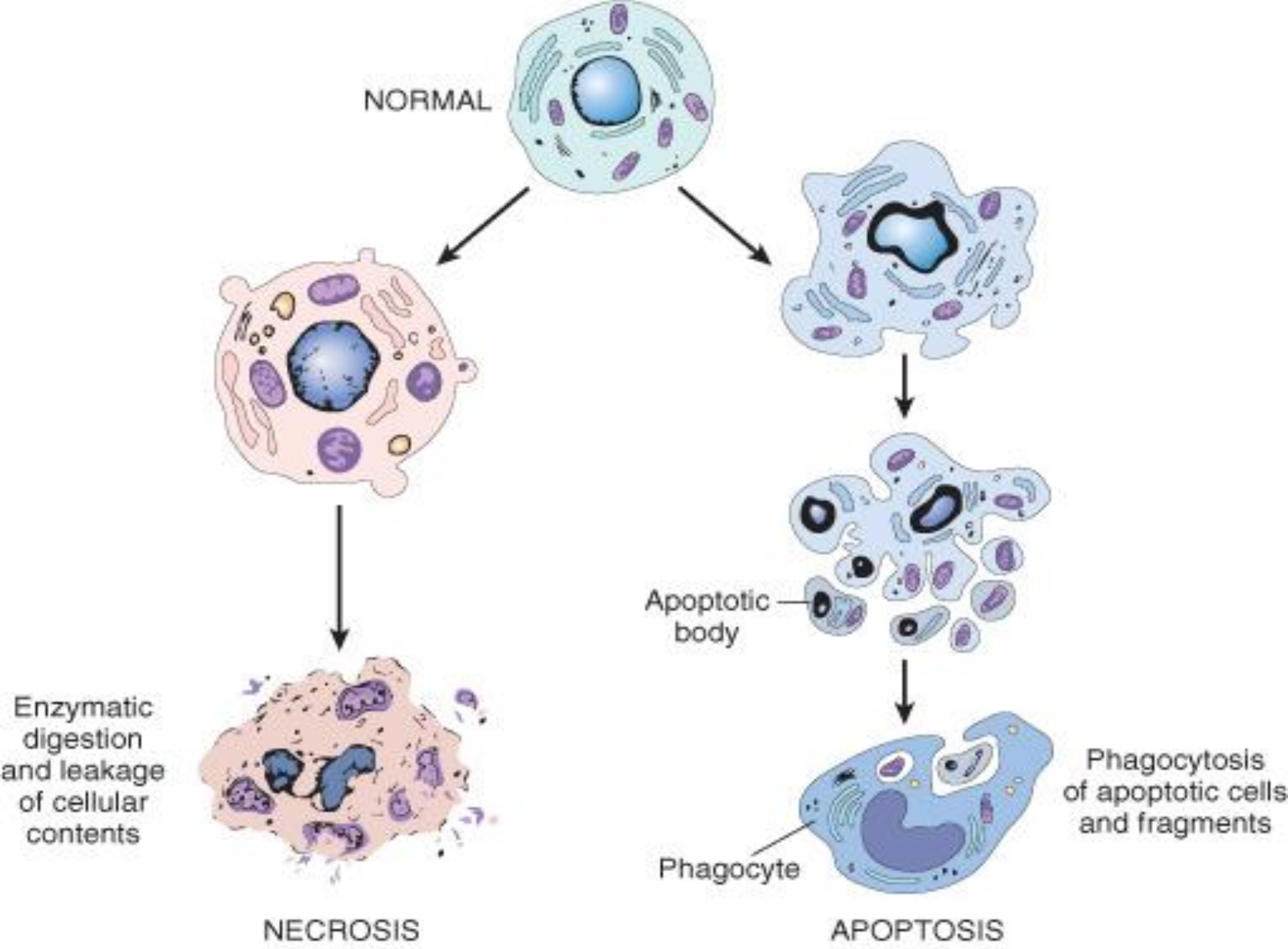
Programmed destruction of cells during embryogenesis.

Pathologic causes:

Cell death produced by variety of injurious stimuli. (e.g. radiation or cytotoxic drugs).

Morphologic features include:

1. Cell shrinkage.
2. Chromatin condensation and fragmentation.
3. Cellular blebbing and fragmentation into apoptotic bodies.
4. Phagocytosis of apoptotic bodies by adjacent healthy cells or macrophages.
5. Lack of inflammation.


NORMAL
Apoptotic body
Enzymatic digestion and leakage of cellular contents
Phagocytosis of apoptotic cells and fragments
Phagocyte
NECROSIS
APOPTOSIS

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-sized fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA and protein damage

Thank You