Cell Adaptation, Cell Injury and Cell Death

pathology

LEC 2

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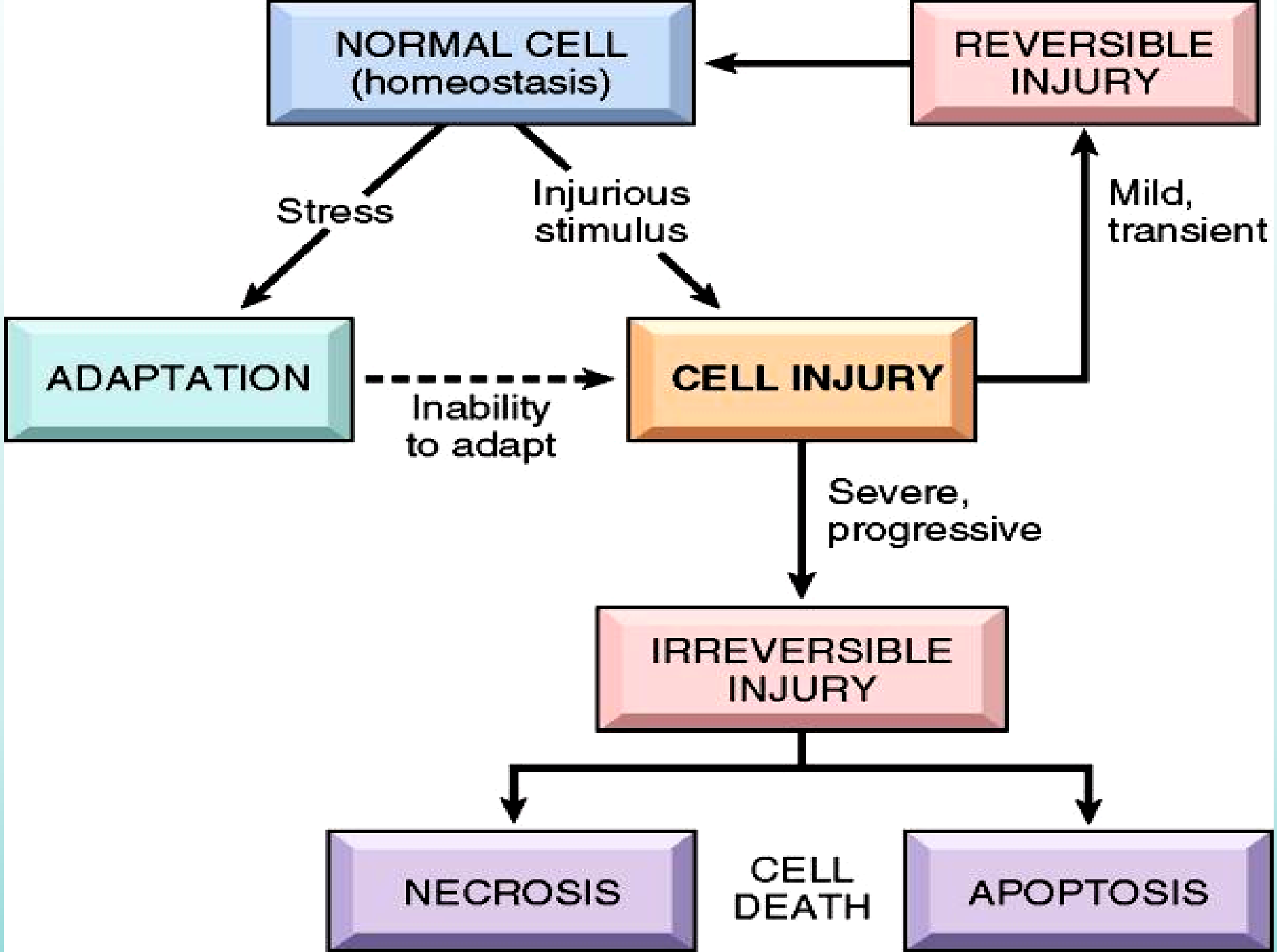

NORMAL CELL
(homeostasis)
REVERSIBLE
INJURY
Stress
Injurious
stimulus
Mild,
transient
ADAPTATION
Inability
to adapt
CELL INJURY
Severe,
progressive
IRREVERSIBLE
INJURY
NECROSIS
CELL
DEATH
APOPTOSIS

Cell injury is either

- **Reversible Cell injury(Degeneration)**
- the cells return back to their stable baseline state after removal the cause of cell injury.
- **Irreversible Cell injury** cells CANNOT return to their baseline state after removal the cause of cell injury. This is called **Cell death**

Causes of Cell Injury:

1- Hypoxia (O_2 Deprivation)

- This is **the common cause** of cell injury & cell death.
- It means the interference with **aerobic respiration** of cells
- Hypoxia should be differentiate from **ischemia** which means **loss of blood supply**
- So, it means that any case of ischemia associated with hypoxia, while not any case of hypoxia associated with ischemia
- **Causes of Hypoxia (O_2 Deprivation).**
  - **Ischemia** (decrease O_2 supply)
  - **Anemia** (decrease O_2 carrying capacity of blood)
  - **Co poisoning** (displace O_2 from Hb)

Ischemic & Hypoxic injury:

- Ischemia is the most common type of cell injury in the clinical medicine.
- Ischemia injured tissues faster than does hypoxia , WHY??
- because ischemia cease both the aerobic & anaerobic generation of energy while hypoxia will cease only the aerobic pathway)

2- **Physical agents**, including trauma, heat, cold, radiation, and electric shock .

3- **Chemical agents and drugs**, including therapeutic drugs, poisons, environmental pollutants, alcohol and narcotics.

4- **Infectious agents**, including viruses, bacteria, fungi, and parasites.

5- **Immunologic reactions** ,including **autoimmune diseases** and cell injury following **responses to infection** and **hypersensitivity reaction** to some drugs.

6- Genetic derangements, such as **chromosomal alterations** and specific gene **mutations**

7- **Nutritional imbalances**, including protein–calorie deficiency or lack of specific vitamins, as well as nutritional excesses.

8- **Aging** Can result in diminished ability of cells to response to exogenous stimuli & injury& eventually cell death.

Four intracellular systems are particularly vulnerable for cell injury

a. **Cell membrane**

b. Protein synthesis

c. ATP production by mitochondria

d. **DNA**

Mechanisns of Cell injury(Reversible)

1) ATP deprivation.

2) Generation of Free Radicals.

3) Loss of Ca^{+2} homeostasis.

4) Defect in plasma membrane permeability.

5) Mitochondrial damage.

Mechanisns of Cell injury(Reversible)

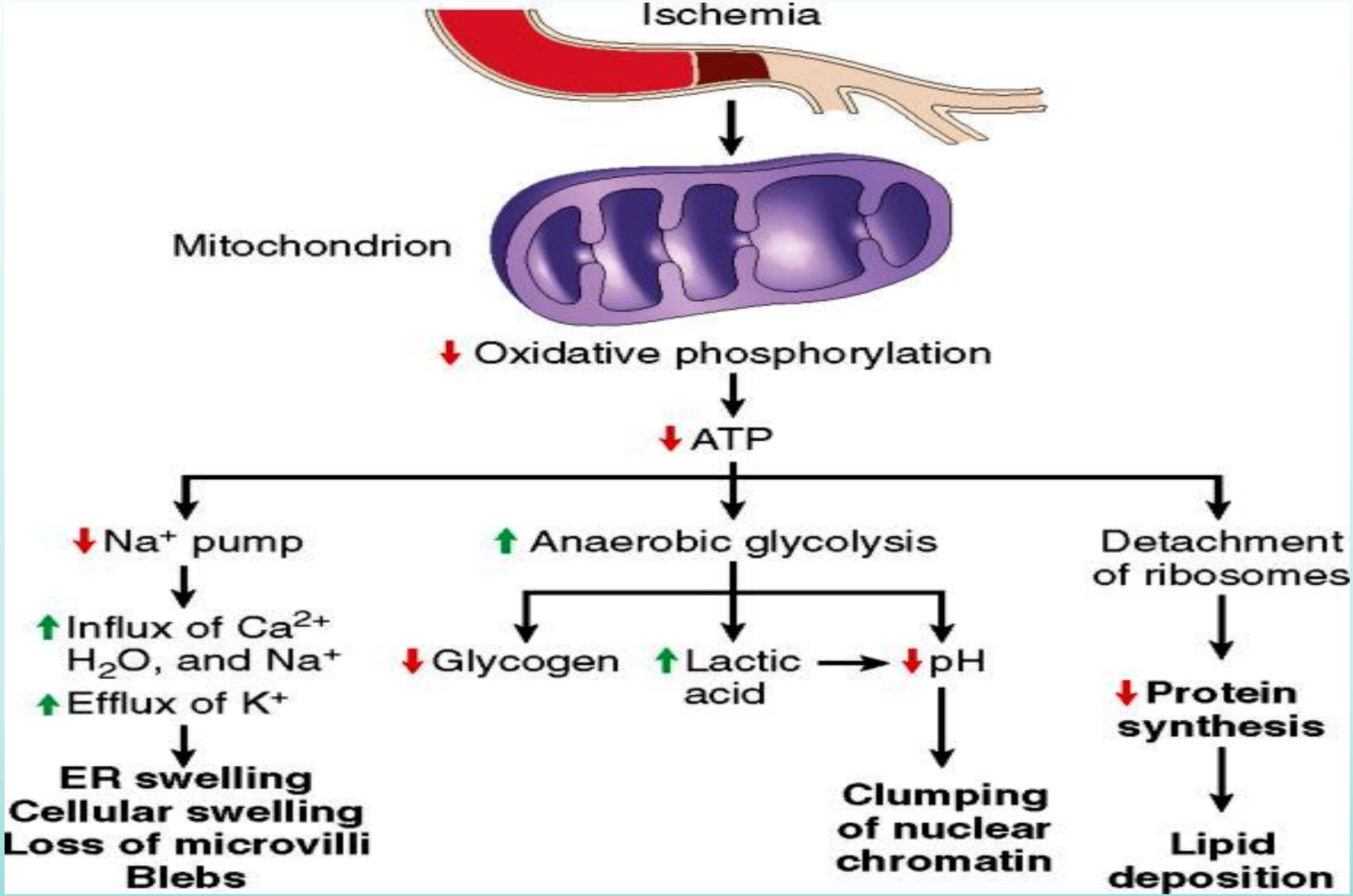
1) ATP deprivation:

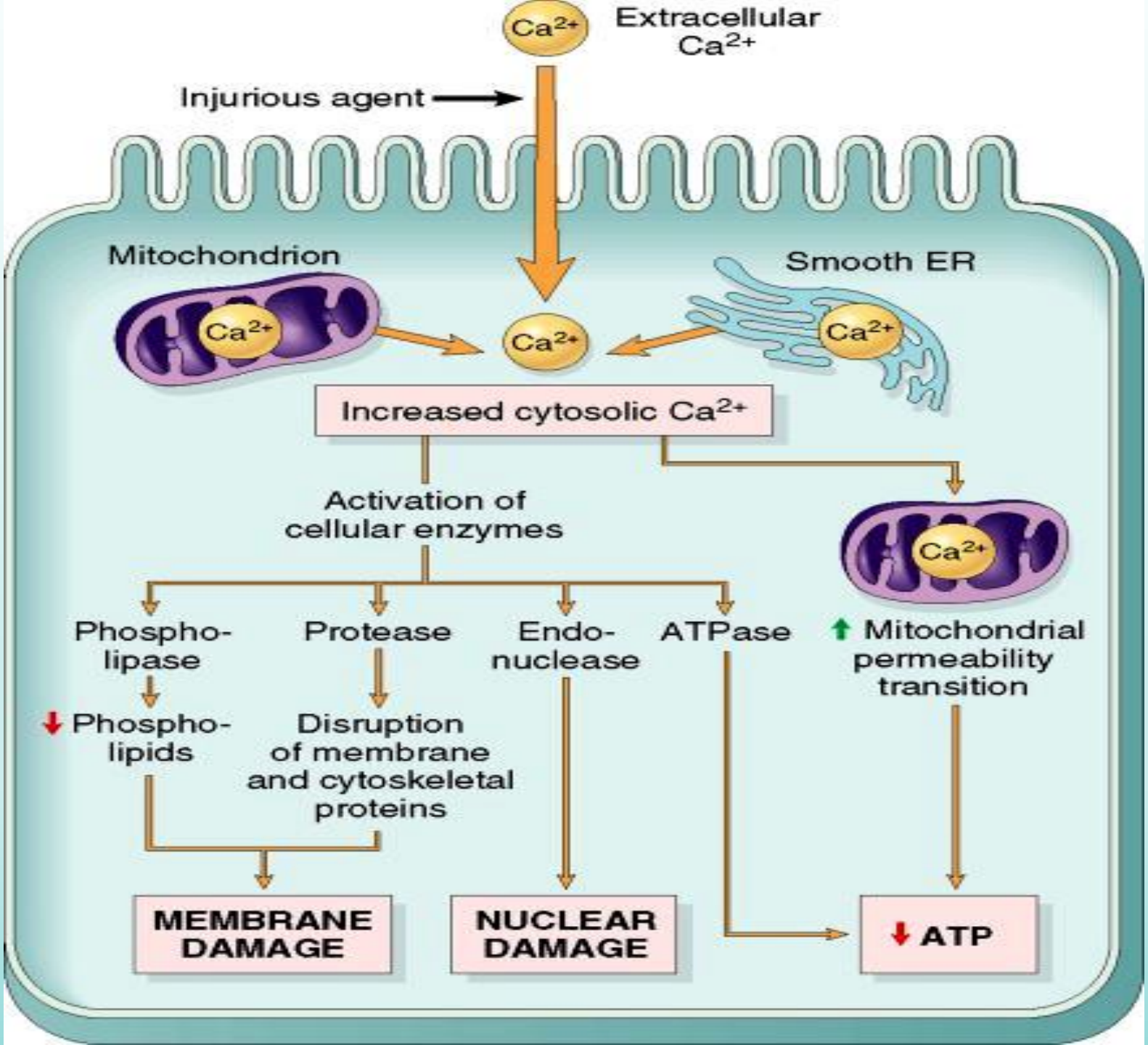
- ATP is important virtually in every processes in the cell like (protein synthesis, cellular osmolarity & transport processes)
- ATP production is either by **aerobic** cellular respiration (mitochondria) & **anaerobic** glycolysis.
- Loss of ATP results in rapid shutdown of most critical homeostatic pathways.

- The activity of plasma membrane ATP-dependent **sodium pumps** is reduced, resulting in intracellular **accumulation of sodium** and **efflux of potassium**.
- The net gain of solute is accompanied by iso-osmotic **gain of water**, causing **cell swelling** and dilation of the ER.
-
- • There is a compensatory increase in anaerobic glycolysis in an attempt to maintain the cell's energy sources. As a consequence, intracellular **glycogen stores are rapidly depleted**, and **lactic acid accumulates**, leading to **decreased intracellular pH** and **decreased activity** of many cellular **enzymes**.

2) **Loss of Ca^{+2} homeostasis**.

- **Normally,** the extra cellular concentration of Ca^{+2} is higher than the cytosolic free Ca^{+2} (this is maintain by ATP dependent transport)
- Also the Ca^{+2} normally is **stored intracellular** at **mitochondria & endoplasmic reticulum.**
- **In the cell injury** (ischemia, toxins) allow a net influx of extracellular Ca^{+2} across the cell membrane, follow by release of Ca^{+2} from intracellular stores & this result in increased cytosolic Ca^{+2},that will mediate cell injury by **activation of many enzymes** which include:
- ***Phosphlipases.*** cause cell membrane damage.
- ***Proteases.*** catabolizing the structural & membrane proteins.
- ***ATPase.*** accelerating ATP depletion.
- ***Endonuclease***. fragmented the genetic material.


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
Clumping of nuclear chromatin
Detachment of ribosomes
↓ Protein synthesis
Lipid deposition

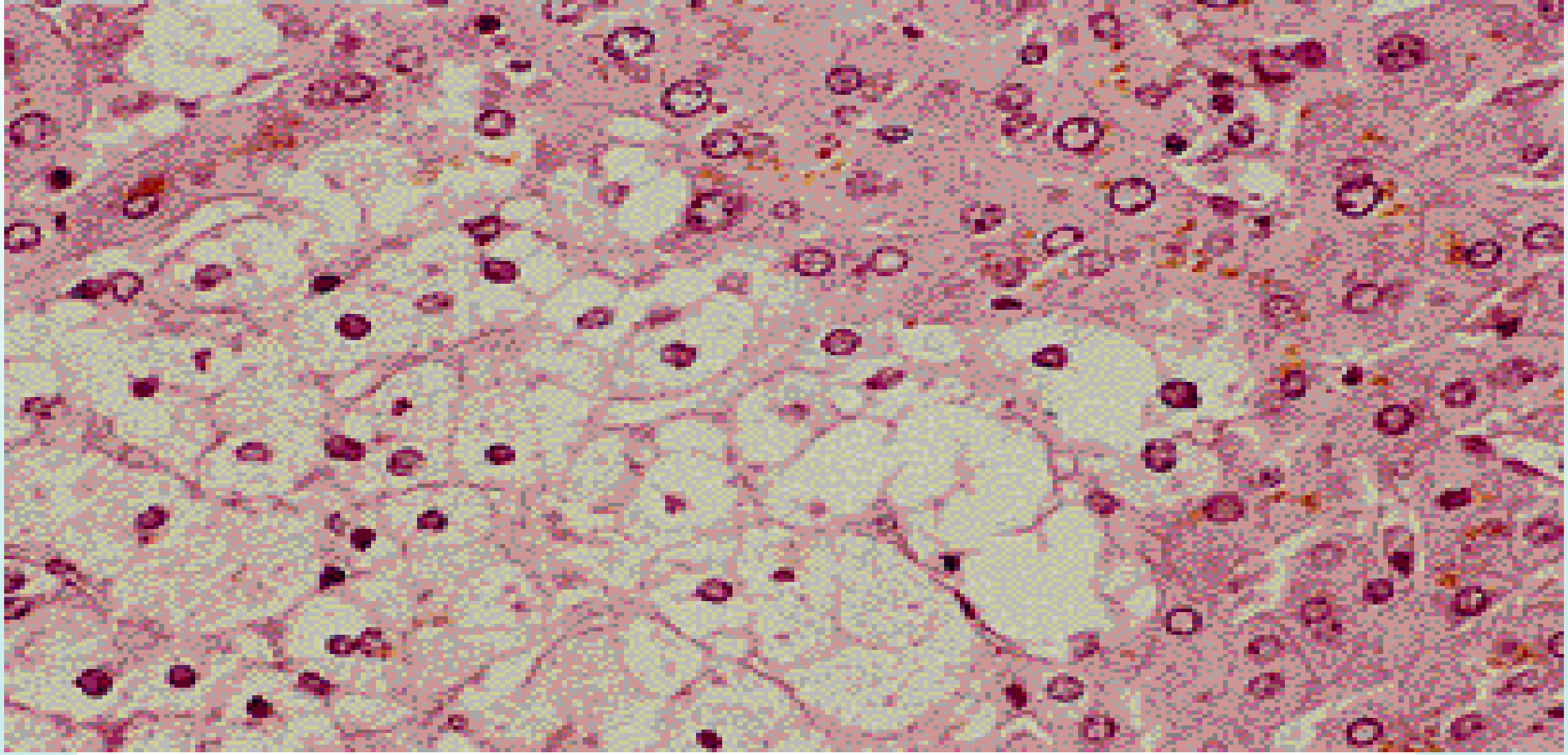

Ca2+
Extracellular Ca2+
Injurious agent
Mitochondrion
Ca2+
Smooth ER
Ca2+
Ca2+
Increased cytosolic Ca2+
Activation of cellular enzymes
Ca2+
Phospho-lipase
Protease
Endo-nuclease
ATPase
Mitochondrial permeability transition
Phospho-lipids
Disruption of membrane and cytoskeletal proteins
MEMBRANE DAMAGE
NUCLEAR DAMAGE
ATP

* Pathogenesis

* O_2

MORPHOLOGY OF REVERSIBLE CELL INJURY

- Two patterns of morphologic changes are characteristic for reversible cell injury; include **Cellular swelling & Fatty change.**
- **Cellular Swelling:**
- Is the **first manifestation** of almost forms of injury to cells, occur due to ***incapability of cells to maintain ionic & fluid homeostasis.***
- It is more apparent at the level of whole organ (Gross) than at cellular level (light microscope).
- Cellular swelling also called **Hydropic change(degeneration), vacuolar degeneration**.
- **Gross:** Increased weight, increased pallor of the organ.
- **Mic:** Small, clear vesicles within the cytoplasm (distended endoplasmic reticulum)

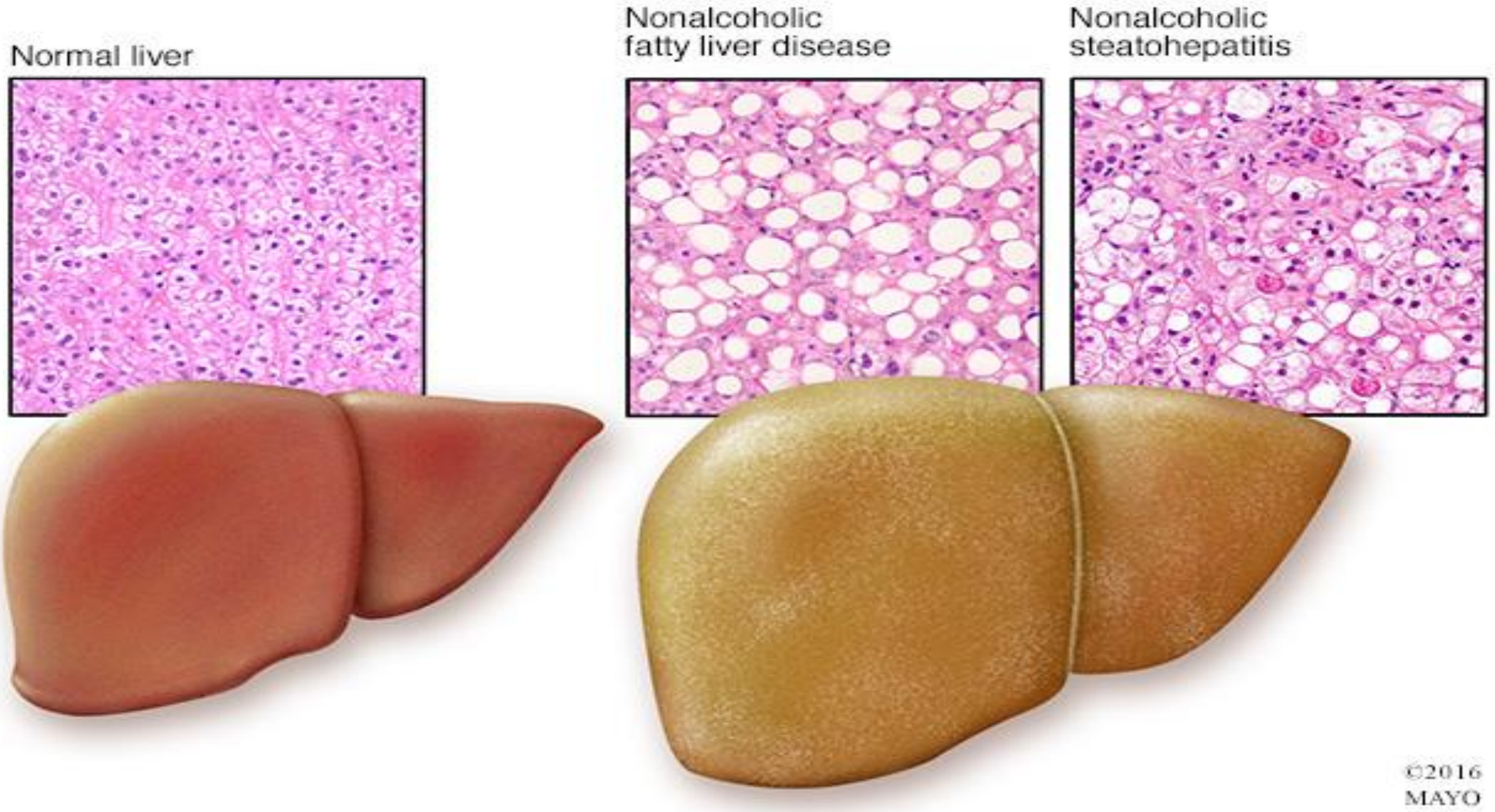


Cellular swelling (hydropic change)

The affected hepatocytes are distended by accumulated water that imparts cytoplasmic pallor.

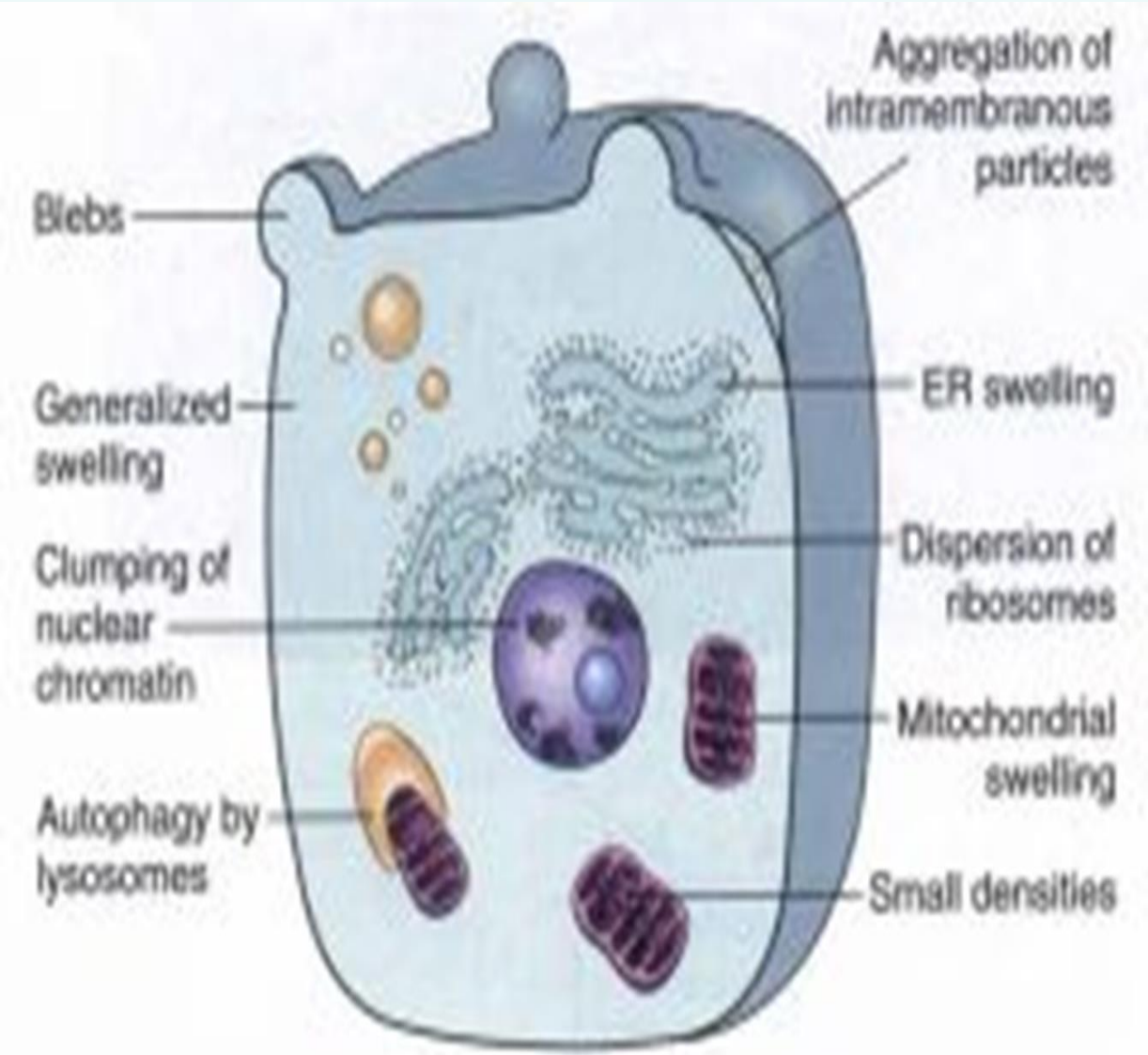
Fatty change(degeneration):

- **Causes:** hypoxic, toxic or metabolic injury.
- **Site**: Mainly occur in cells participating in fat metabolism e.g hepatocytes & myocardial cells.
- **microscopically** :lipid vacuoles in the cytoplasm of the cells.

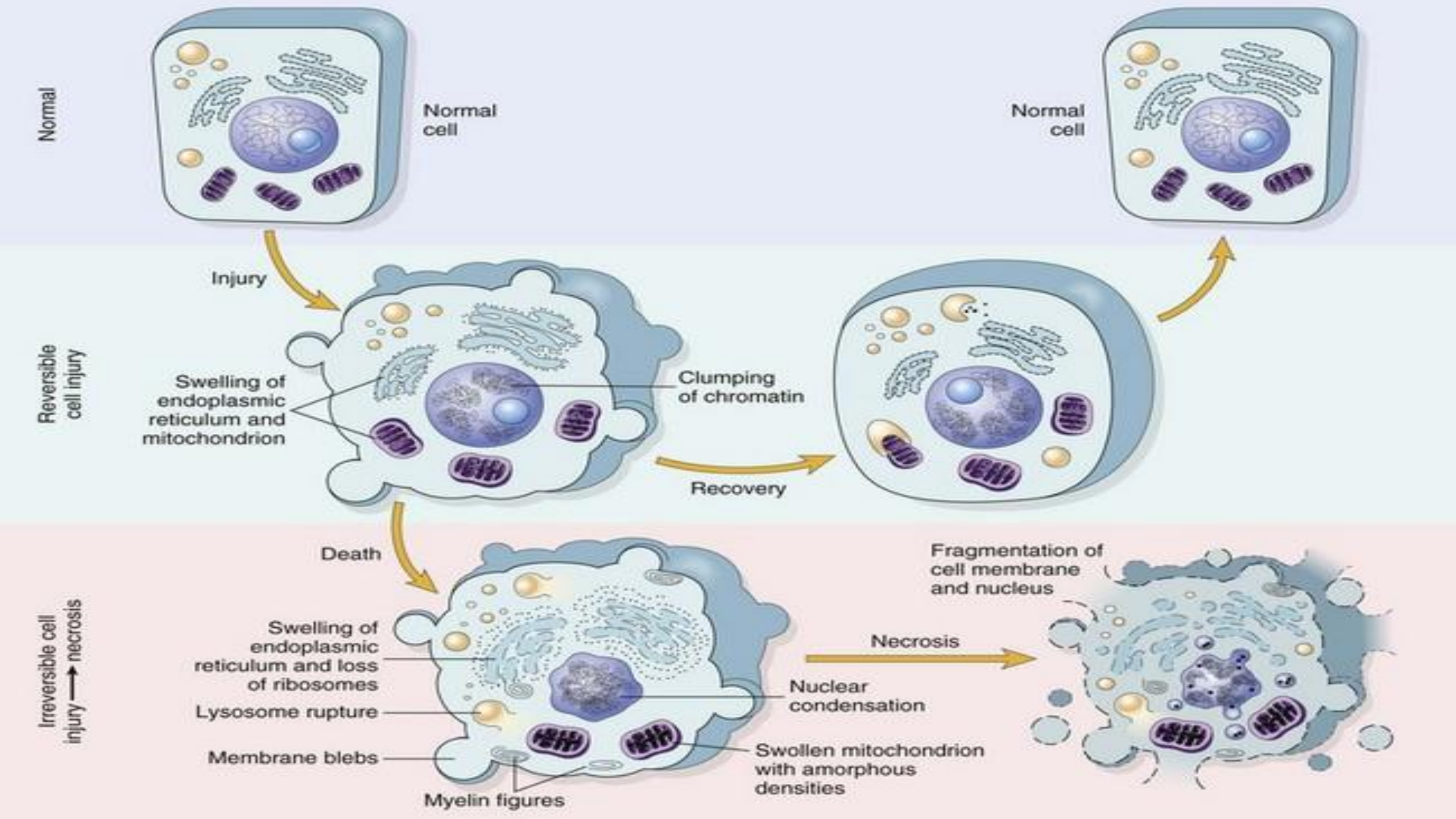


Ultrastructural(EM) features of Reversible injury:

- **mitochondrial swelling** &presence of amorphous Ca rich **small densities** cause decrease in mitochondrial function.
- Increase **membrane permeability cause generalized cellular swelling**.
- **Loss of microvili.**
- Formation of cell **surface blebs.**
- Swelling of **endoplasmic reticulum with dispersion of ribosomes**.
- **Clumping of nuclear chromatin**.
- If oxygen restores, the cell return back to normal



B. Reversible injury


Normal
Normal cell
Normal cell
Injury
Reversible cell injury
Swelling of endoplasmic reticulum and mitochondrion
Clumping of chromatin
Recovery
Death
Irreversible cell injury → necrosis
Swelling of endoplasmic reticulum and loss of ribosomes
Lysosome rupture
Membrane blebs
Myelin figures
Nuclear condensation
Swollen mitochondrion with amorphous densities
Necrosis
Fragmentation of cell membrane and nucleus

Ischemia / Reperfusion injury.

- is the tissue damage caused when blood supply returns to tissue (re- perfusion) after a period of ischemia or lack of oxygen (anoxia or hypoxia).

Ischemia / Reperfusion injury.

- Restoration of blood flow in reversibly injured cells but still viable can promote recovery but it may also **paradoxically exacerbate the injury** result in further injury of the cells or even cause cell death.
- by following mechanisms.
- **1- Oxidative stress**. Re oxygenation increase generation of reactive oxygen and nitrogen species *as a result of incomplete reduction of oxygen by damaged mitochondria and/or* ***cellular antioxidant defense mechanisms may be compromised by ischemia,*** **favoring the accumulation of free radicals.**
- **2-Increase intracellular Ca+2** due to influx of calcium resulting from cell membrane damage
- **3- inflammation:** production of **free radicals** by the inflammatory cells at the perfusion area.
- **4-Activation of the complement system**

Free Radicals induced cell injury:

Free radicals are **chemical species with a single unpaired electron in outer orbital.**

In such chemical state are extremely unstable & readily react with inorganic & organic chemicals.

They initiate autocatalytic reactions, molecules that react with free radicles are in turn converted into free radicles.

Sources of Free Radicals

1- Redox reactions (reduction – oxidation reaction)

- This reaction normally occurs in the mitochondria.
- During this reaction small amount of toxic intermediate species are formed include (*superoxide* $O_2^{\cdot -}$ *&* $OH^{\cdot}$*)*

2-Nitric Oxide (NO).

- Nitric oxide is normally synthesized by a variety of cell types which then act as free radicals by itself or by conversion to highly reactive nitrite species.

3- Absorption of radiant energy (U.V light, X-ray), these radiation can hydrolyze the water into $OH^{\cdot}$ & hydrogen free radicals ($H^{\cdot}$).

4- During Enzymatic Metabolism of exogenous chemicals like CCL_4.

- 5-Free radicals can generate as a part of routine cellular activities like **respiration process, defence mechanisms.**

Mechanisms of Cell Injury by (FREE RADICALS)

- *Free radicals* can injured the cells *by the following mechanisms.*

1- Lipid Peroxidation.

2- DNA Fragmentation.

3- Cross – Linkage of Proteins.

Inactivation of Free Radicals:

- Inactivation of free radicals can achieve by the following mechanisms.
- 1-spontenous decay

2- Enhancement the rate of spontaneous decay of free radicals by **SuperOxide Dismutase (SOD)** which is present in many cell types of body $(_{SOD})2O_2^{\cdot -} + 2H \longrightarrow H_2O_2 + O_2$

2- Glutathione (GSH) Peroxide, which catalyzing the free radicals by the following equation

- $2OH^{\cdot -} + 2GSH \longrightarrow H_2O_2 + GSSG$ (glutathione homodimer)

3- Catalase, which direct the degradation of hydrogen superoxide as the following equation

- $2H_2O_2 \longrightarrow 2H_2O + O_2$

4- Endogenous or Exogenous antioxidants (Vitamins A, E,C), these act either by block the formation of free radicals or removed them as they are formed.

5- Plasma Transporting proteins e.g. *Transferrin*, *Ceruloplasmin*, free iron and copper can catalyze the formation of reactive oxygen species (ROS).

Under normal circumstances, reactivity of these metals is minimized by their **binding to storage and transport proteins** (e.g., **transferrin, ferritin, and ceruloplasmin)** which prevents these metals from participating in reactions that generate reactive oxygen species (ROS).

Reversible Changes

- REDUCED oxidative phosphorylation
- ATP depletion
- Cellular “SWELLING”

Irreversible changes

- Irreversible Mitochondrial damage.
- Irreversible membrane defects.
- Lysosomal digestion.

REVERSIBLE = INJURY

IRREVERSIBLE = DEATH

Some Injuries can lead to death if prolonged and/or sever enough

Irreversible Cell injury (Necrosis)

- **Persistent or excessive injury** causes cells pass into **irreversible cell injury.**

Two important events indicate that the cells reach(point of no return) or reach cell death or irreversible cell injury, these include:

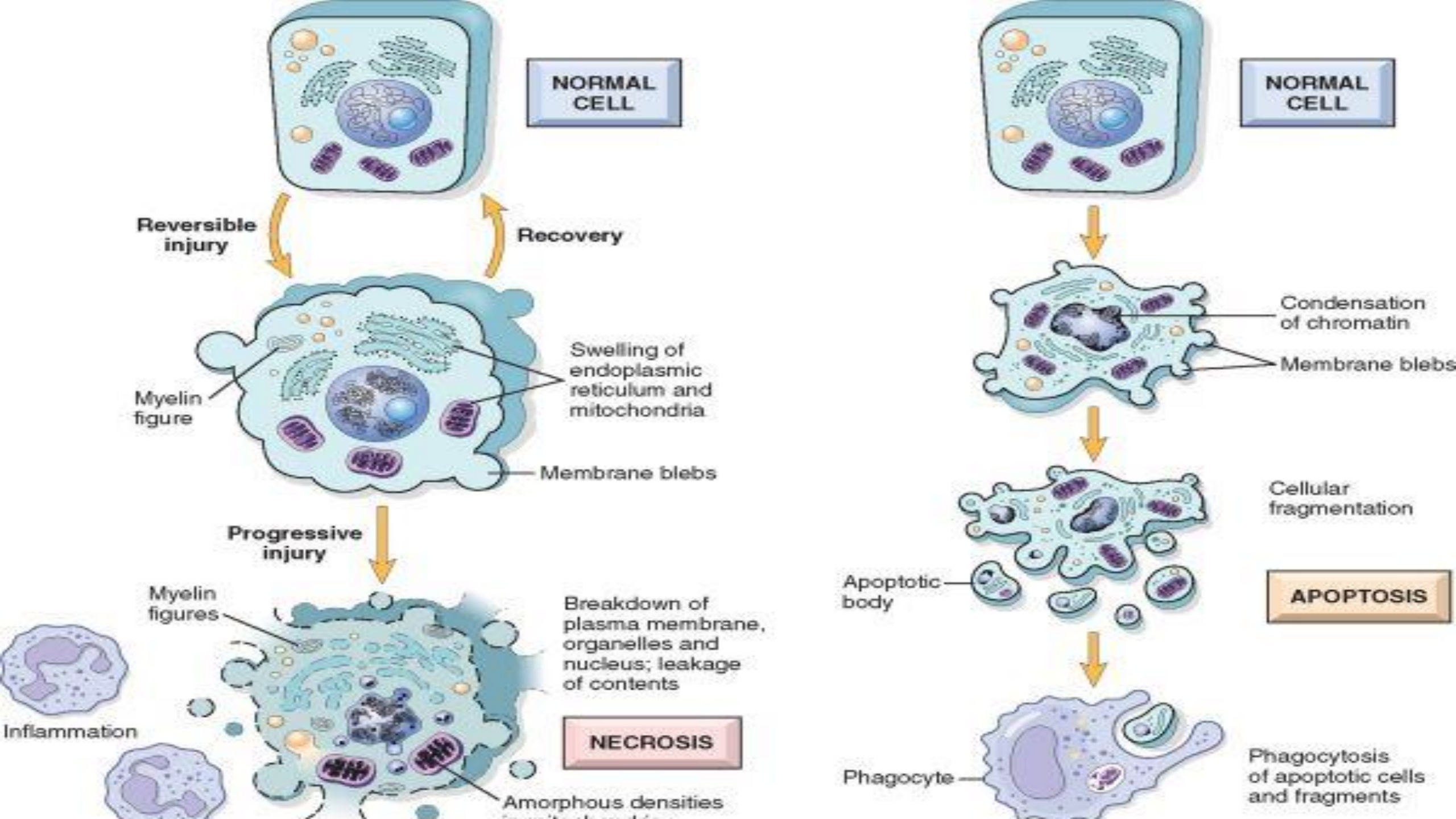
- **Irreversible Mitochondrial damage (lack of ATP production)**
- **Profound damage & disturbances in cell membrane function (this is the central factor in development of irreversible cell injury).**

Clinical correlation

- Leakage of intracellular proteins through the damaged cell membrane and ultimately into the **circulation** provides a means of detecting tissue-specific cellular injury and necrosis **using blood serum samples**.
- **for example: Cardiac muscle :**enzyme **creatine kinase and troponin**;
- **liver hepatocytes contain transaminases.**
- Irreversible injury and cell death in these tissues are reflected in increased levels of such proteins in the blood, and **measurement of these biomarkers is used clinically to assess damage to these tissues**.

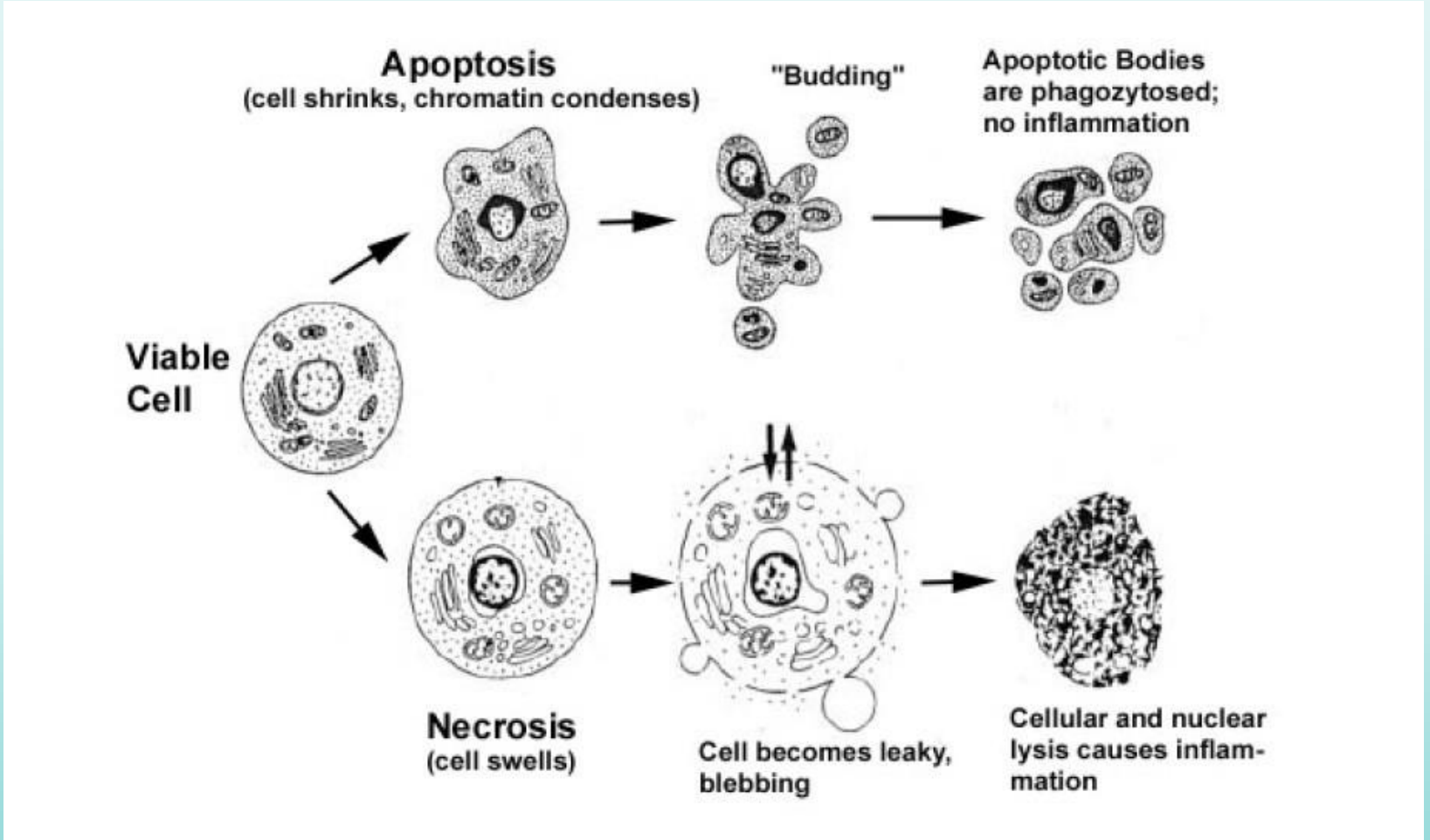
CELL DEATH

- **APOPTOSIS (programmed cell death) cell suicide**
- **NECROSIS (death due to "causes")homicide**


NORMAL CELL
Reversible injury
Recovery
Swelling of endoplasmic reticulum and mitochondria
Myelin figure
Membrane blebs
Progressive injury
Myelin figures
Breakdown of plasma membrane, organelles and nucleus; leakage of contents
Inflammation
NECROSIS
Amorphous densities
NORMAL CELL
Condensation of chromatin
Membrane blebs
Cellular fragmentation
Apoptotic body
APOPTOSIS
Phagocyte
Phagocytosis of apoptotic cells and fragments

Cell death mechanisms

- Death by suicide
- Death by injury



Necrosis

sequence of morphologic changes that follow cell death in living tissue.

The morphologic appearance of necrosis is the **result of two essentially concurrent processes**

- **Enzymatic digestion of the cell** (sources of these enzymes are either from the dead cells themselves or from lysosomes of invading inflammatory cells)
- **Denaturation of proteins**.

Morphology of Necrosis:

1- Cytoplasmic Changes. Include

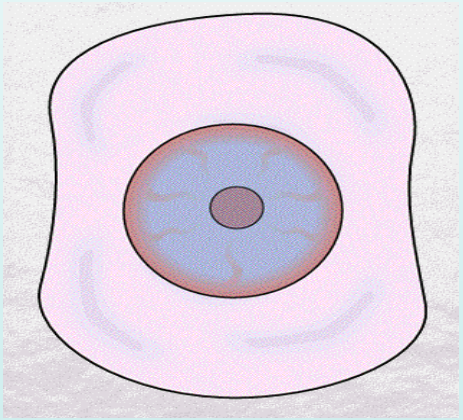
- **Increased eosinophilia** (due to increased binding of eosin to denaturated intracytoplasmic proteins).
- The cells become more **glassy homogenous appearance** than the normal cell (due to loss glycogen particles).
- The **cytoplasm becomes vacuolated** (due to degradation of organelles by lysosomal enzymes).
- Finally the **cells become calcified**.

2- Nuclear Changes. Include **one the following three patterns:**

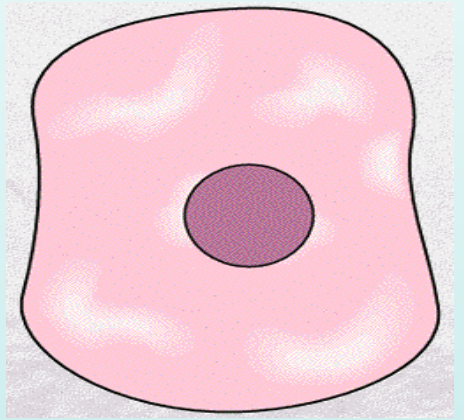
- **Pyknosis** (nuclear shrinkage & condensation due to DNA condenses into small shrunken mass).

- **Karyorrhexis** (**Fragmentation** of chromatin)
- **Karyolysis** (breakdown of DNA by DNAase)
- the nucleus is completely disappear within 1 to 2 days.

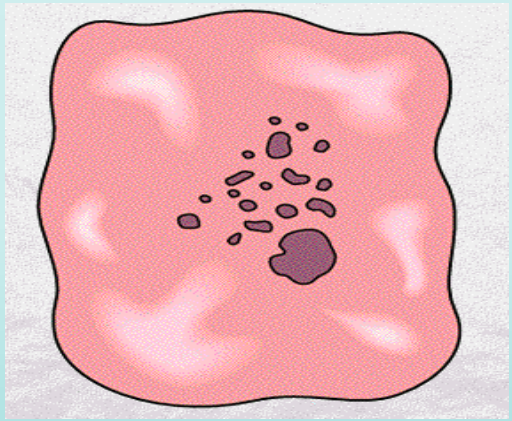
normal



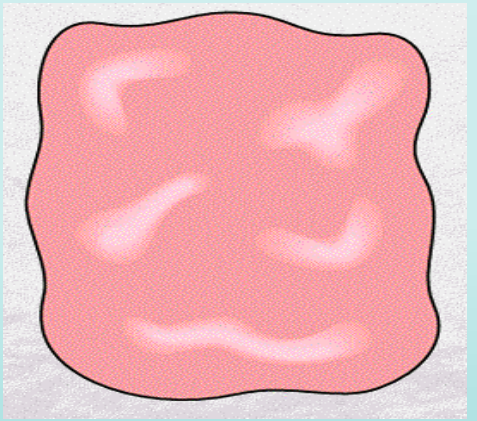
pyknosis



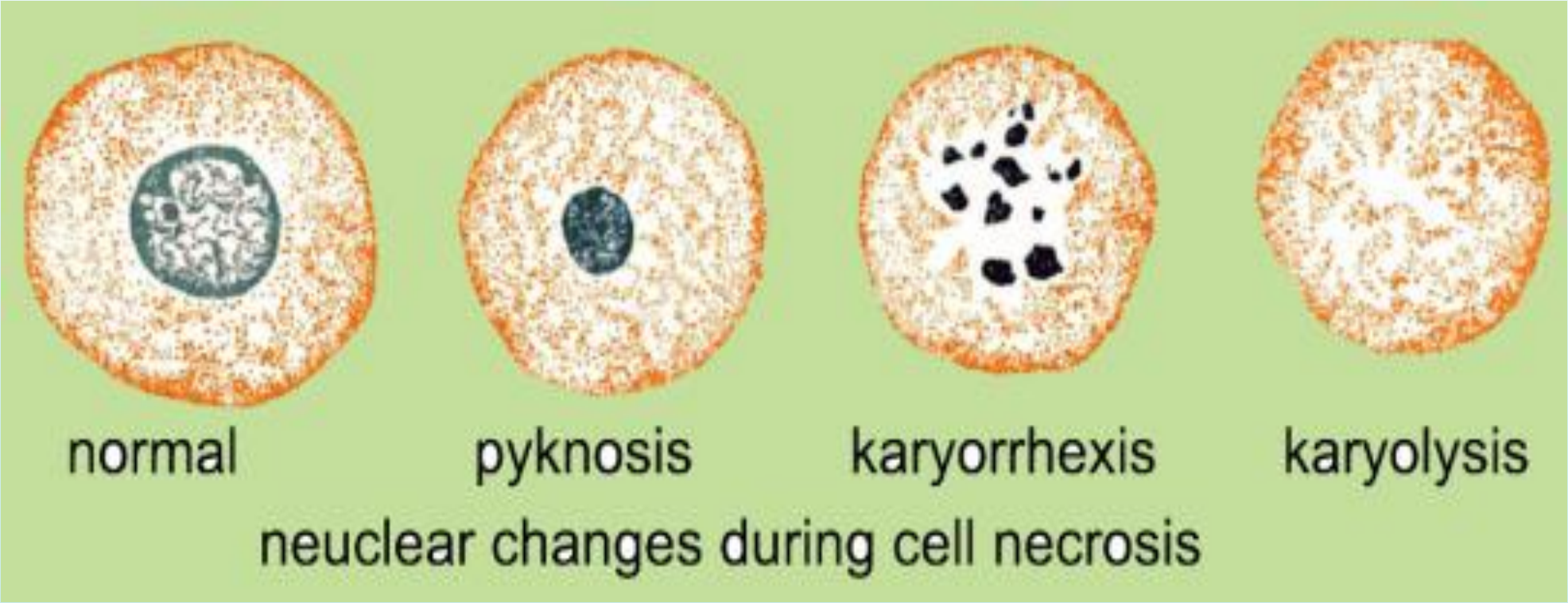
karyorrhexis



karyolysis

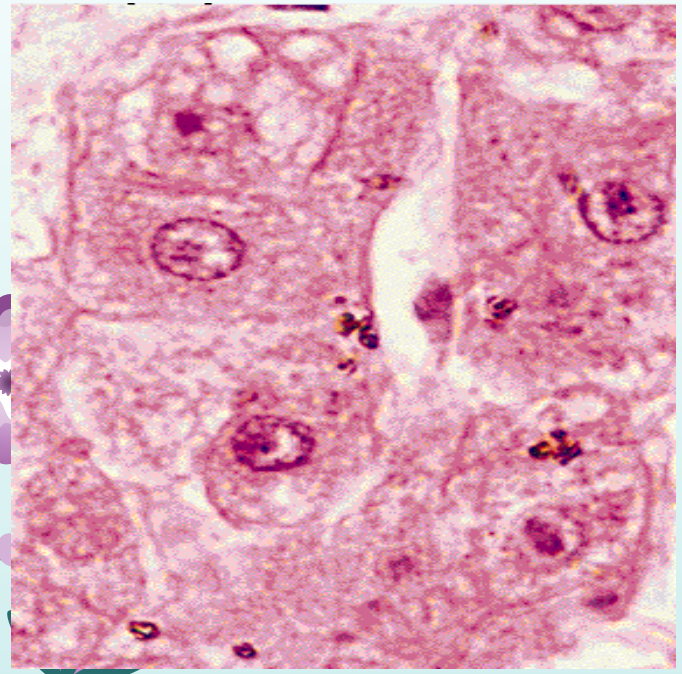


Cell necrosis: Nuclear changes



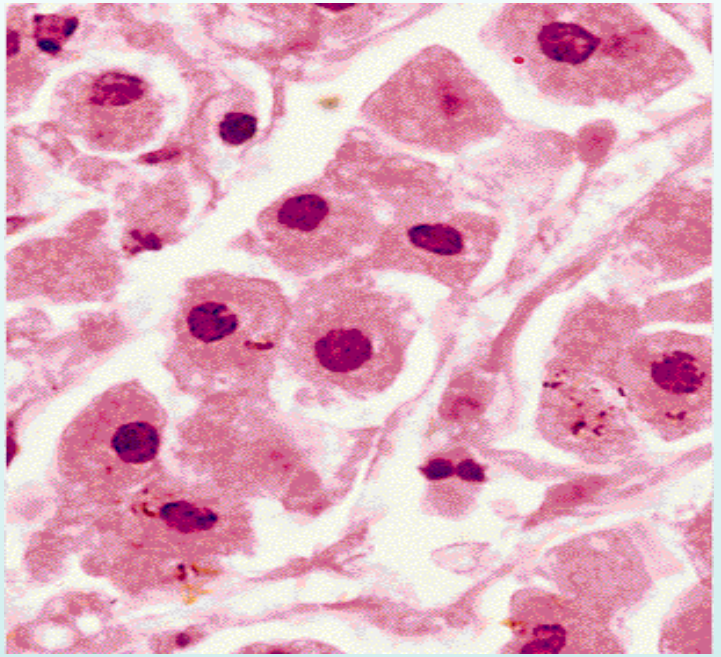
neuclear changes during cell necrosis

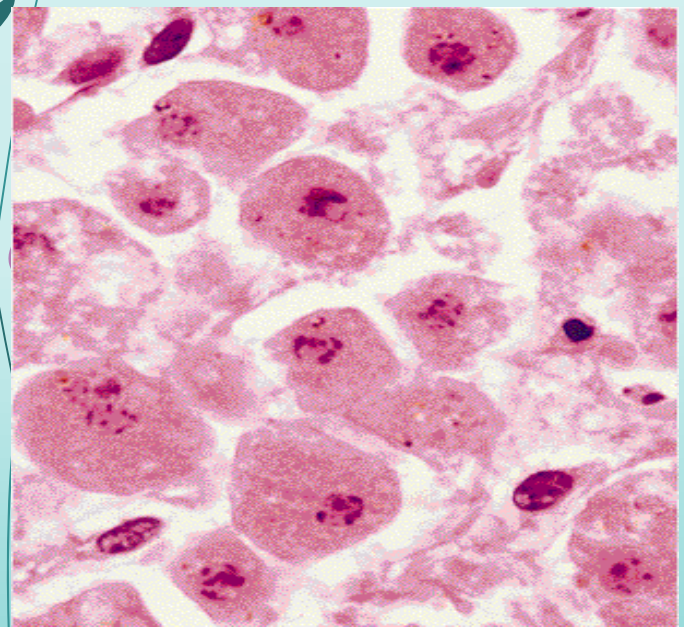
Liver cell necrosis: Nuclear changes



normal

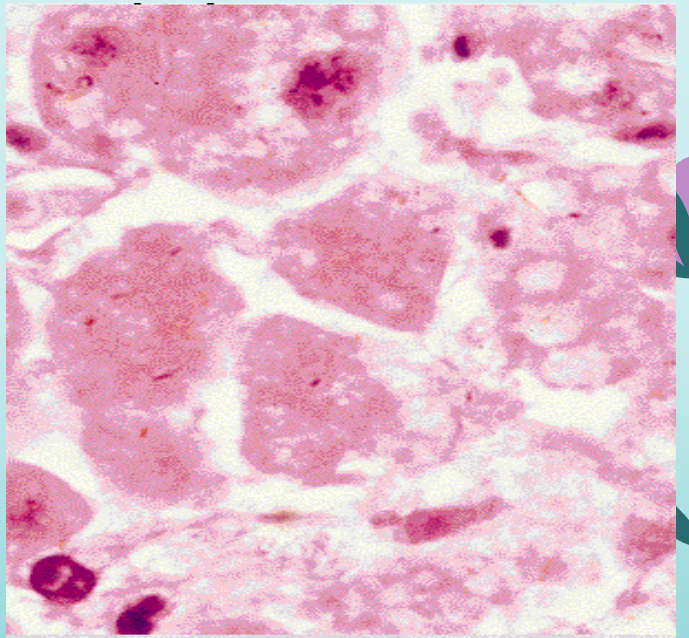
pyknosis

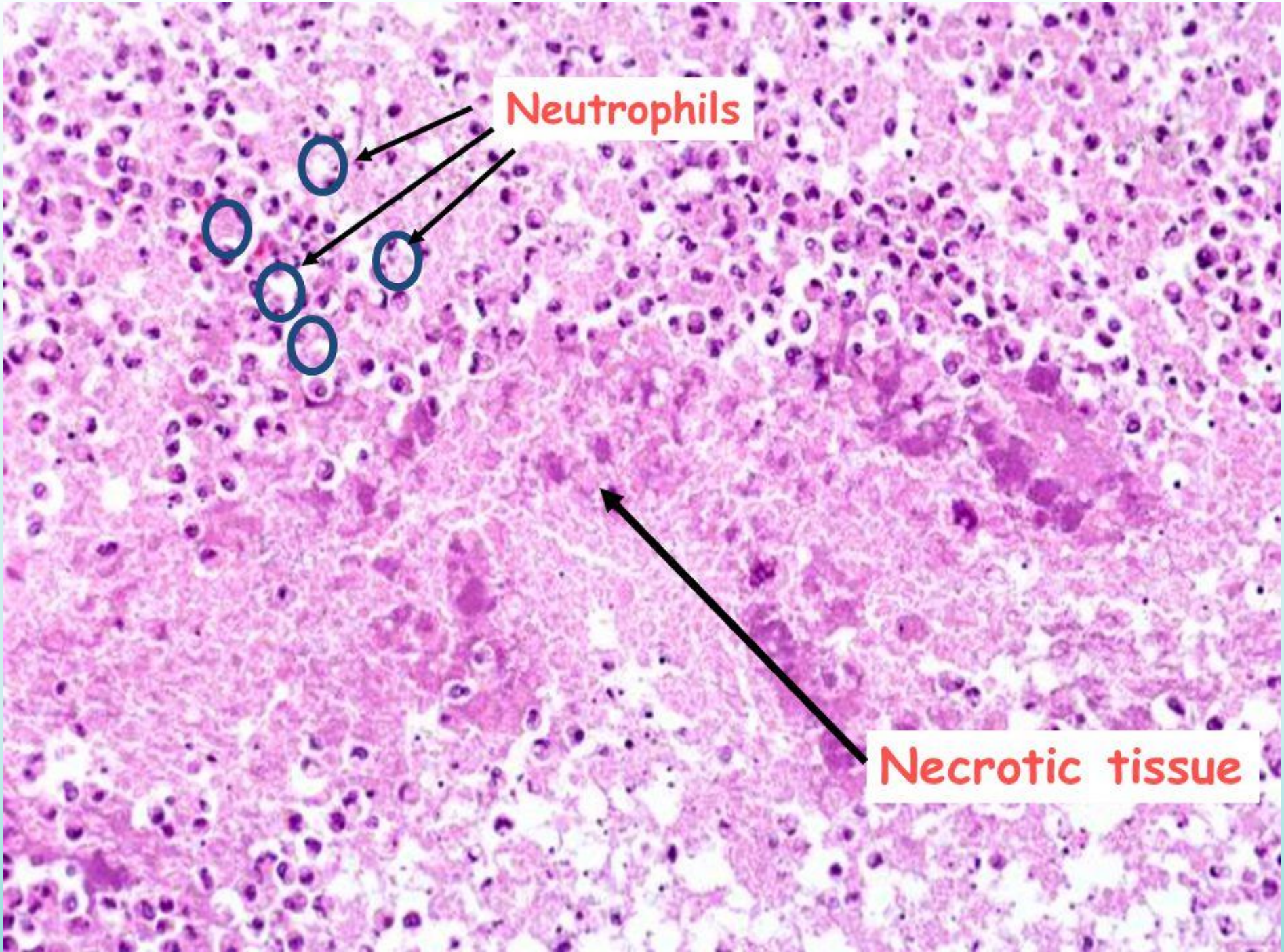




karyorrhexis

karyolysis




Neutrophils
Necrotic tissue

Types of Necrosis:

- There are many types of NECROSIS depend on whether the enzymatic digestion is predominant or denaturation of proteins, these types include :

1- Coagulative Necrosis

2-Liquifactive Necrosis:

3- Caseous Necrosis

4- Gangrenous Necrosis:

1.Dry gangrene

2. Wet gangrene

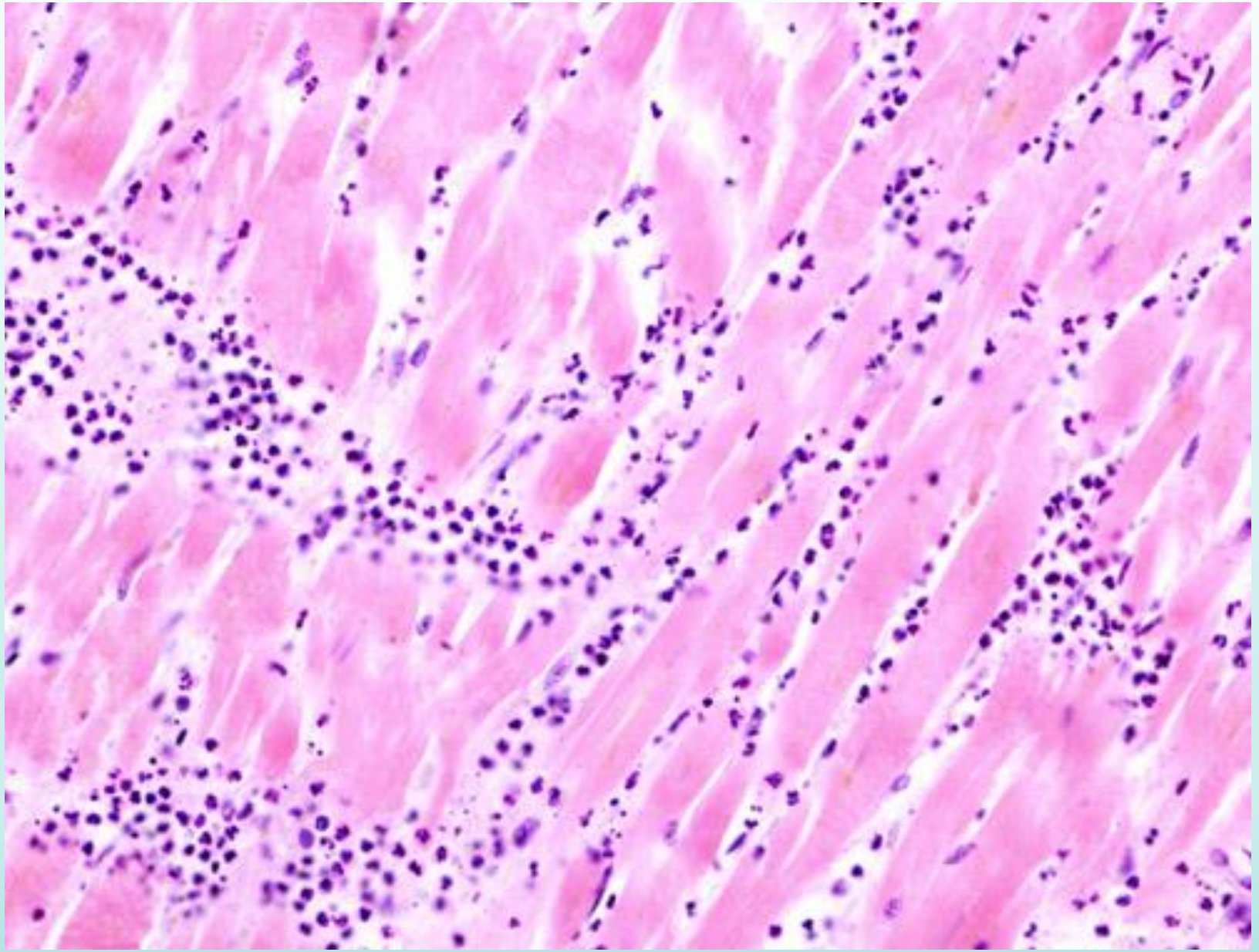
3. Gas gangrene

5- Fat Necrosis 1- Traumatic Fat Necrosis. 2. Enzymatic Fat Necrosis.

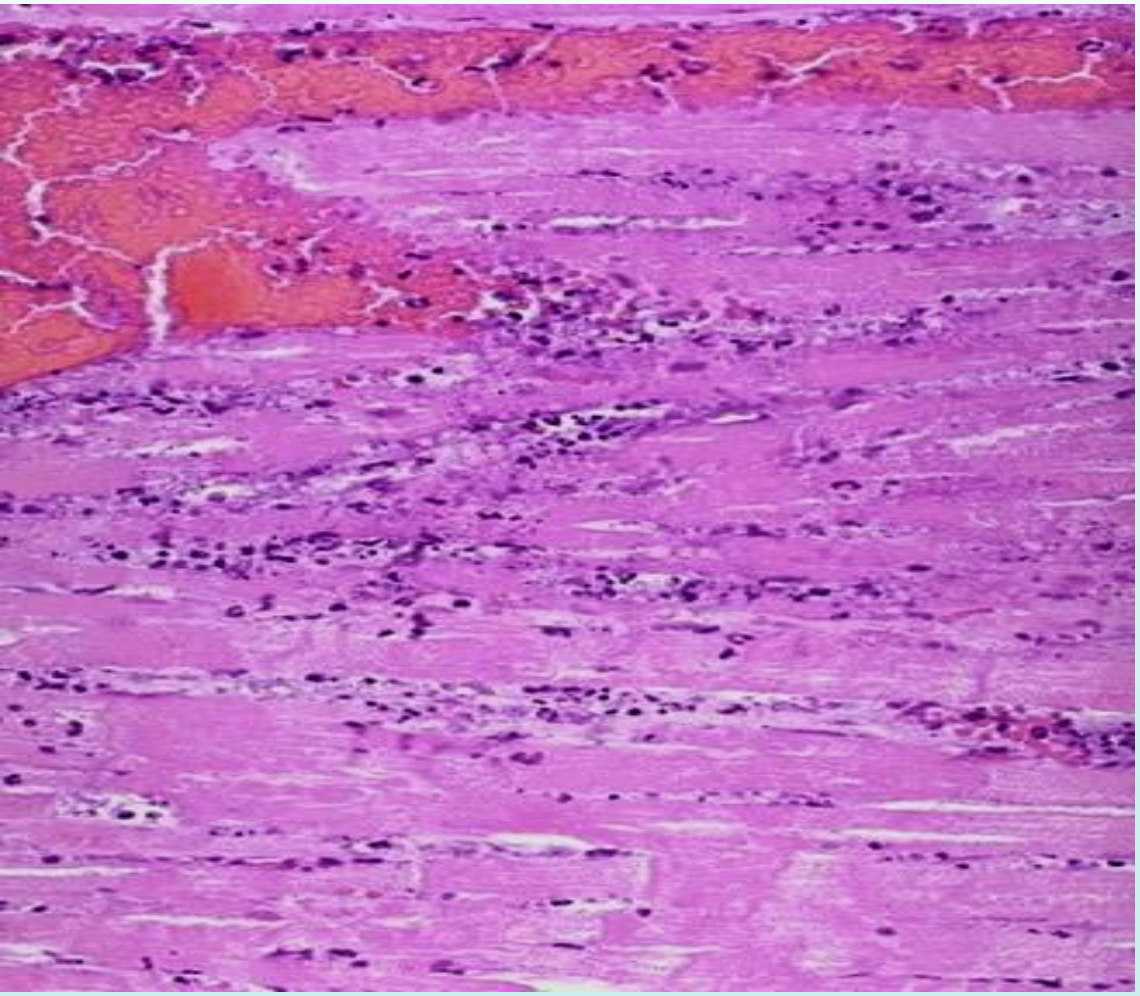
6-Fibrinoid necrosis

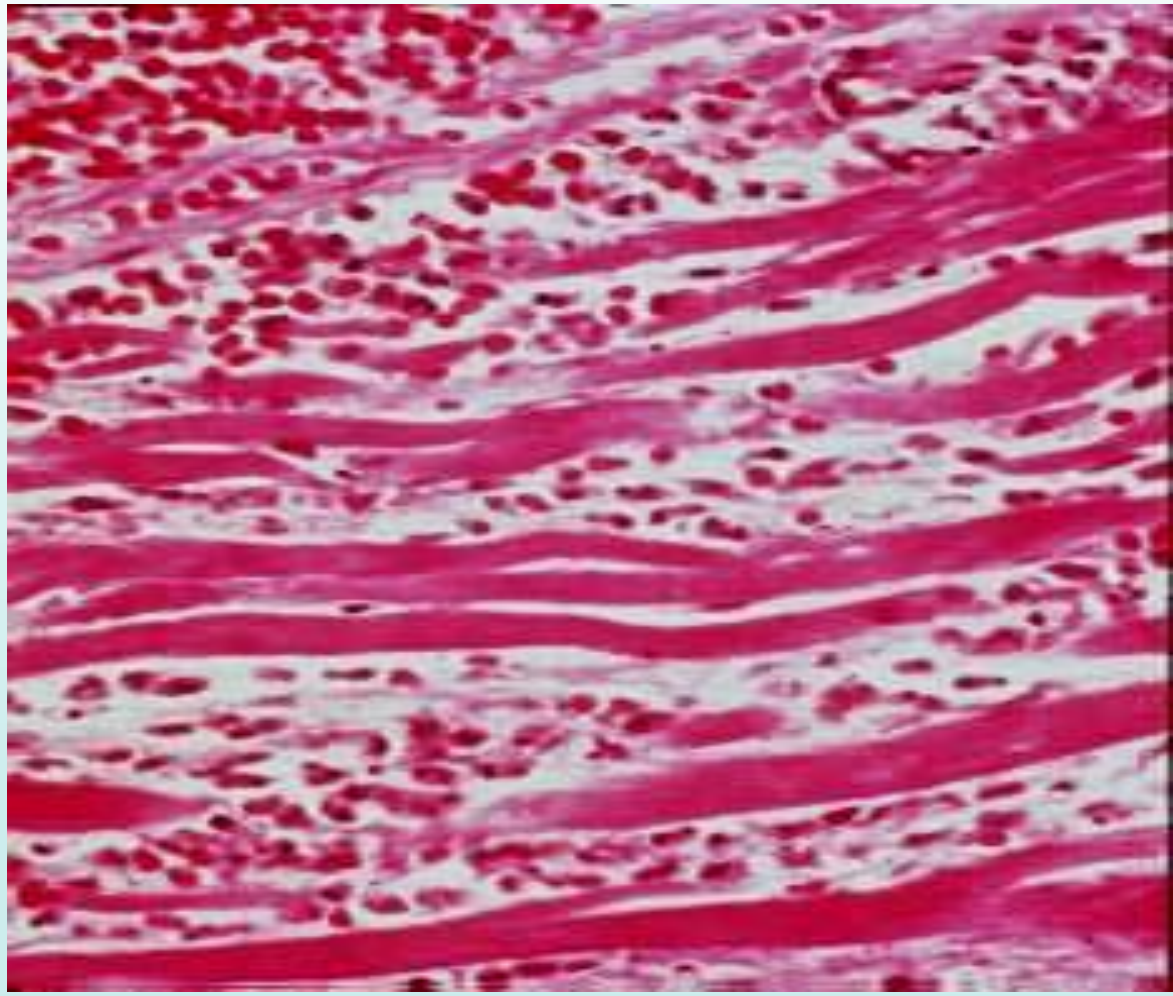
1- Coagulative Necrosis:

- It is characteristics for of Hypoxic cell death in all tissues except the brain.
- The myocardial infarction is an excellent example for this type of necrosis
- In the coagulative necrosis, there is preservation of the general tissue architecture, with loss of cellular details (acidophilic, coagulated, anucleate cells)
- Protein Denaturation is predominant in this type of necrosis



Myocardil infarction coagulative necrosis



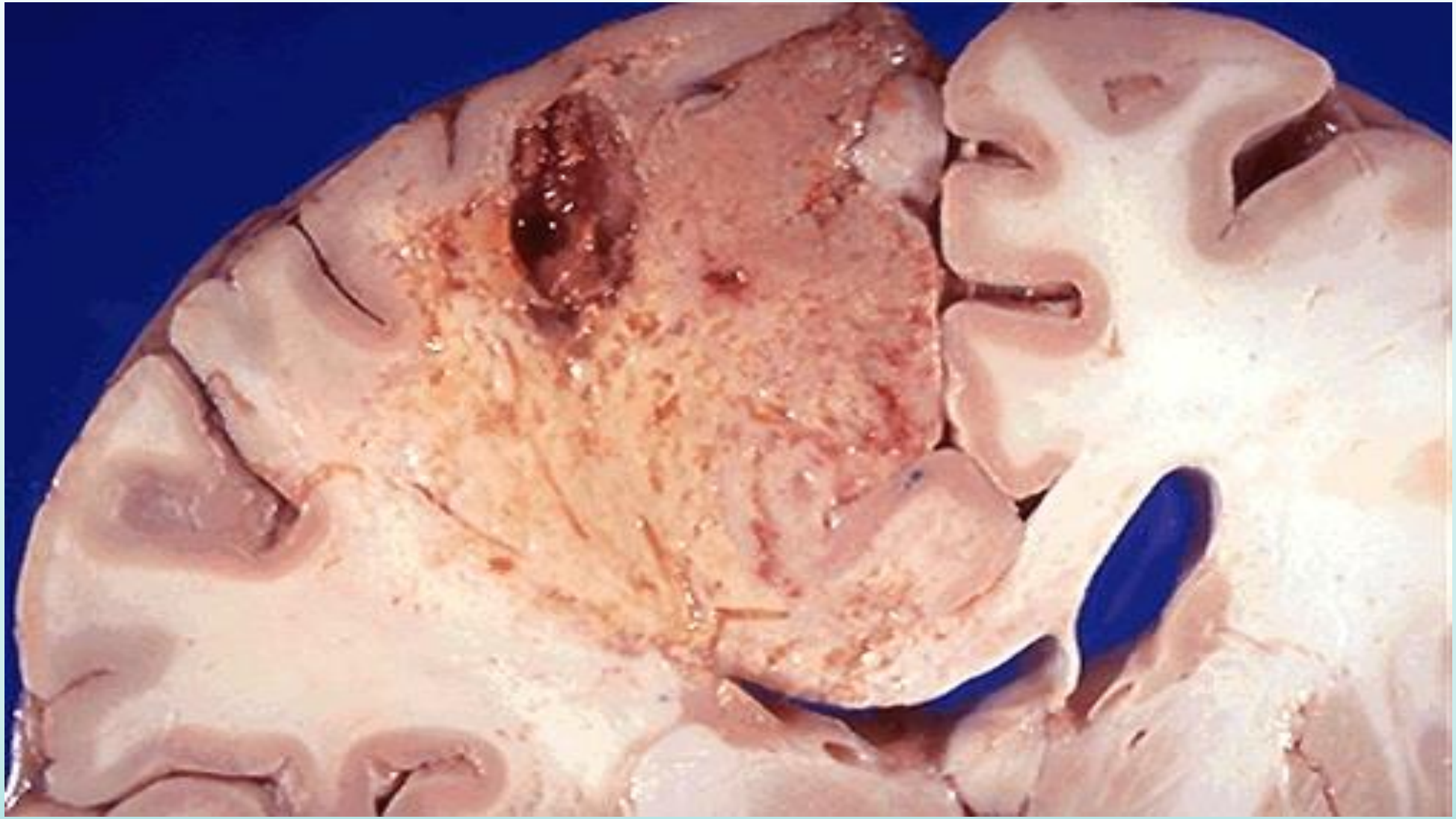


Coagulative necrosis myocardium

The necrotic myocytes are intensely eosinophilic with loss of both cross striations & nuclei. The outlines of individual fibres are still maintained. There are inflammatory cells infiltration & RBCs in-between the necrotic fibers.

2-Liquifactive Necrosis:

- 1- Suppurative infections characterized by the formation of **pus** (liquefied tissue debris and neutrophils)in some focal bacterial or, occasionally, fungal infections (due to the action of inflammatory cells)
- 2- For unclear reasons, hypoxic death of cells within the CNS often evokes liquefactive necrosis. Whatever the pathogenesis.
- Liquefaction completely digests the dead cells. The end result is transformation of the tissue into a liquid viscous mass.
- Enzymatic digestion is predominant in this type of necrosis.
- In the liquefactive necrosis, **there is loss of both tissue architecture & cellular details.**



Brain infarction

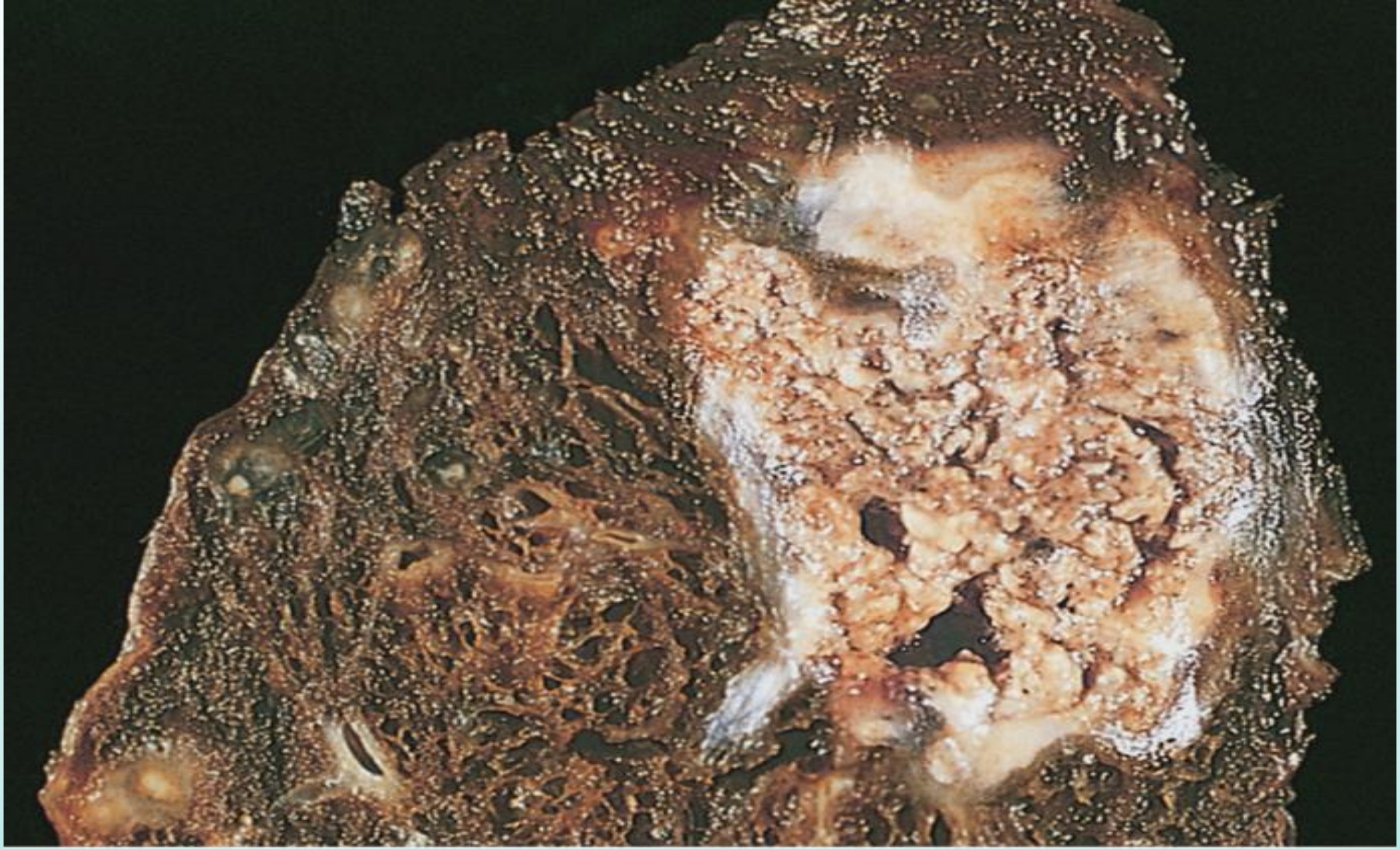
This is an example of liquefactive necrosis; the affected area is wedge-shaped, pale, soft & cystic.

Comparison between Coagulative & Liquifactive necrosis

	Coagulative necrosis	Liquifactive necrosis
Cause of cell injury	Hypoxia / Ischemia	Infection / hypoxia
Examples	Myocardial infarction	Hypoxic death of brain cells
Pathogenesis	Protein Denaturation	Enzymatic digestion
Morphological features	Preserve general architecture of tissue with loss of cellular details	Loss of both tissue architecture & cellular details

3- Caseous Necrosis:

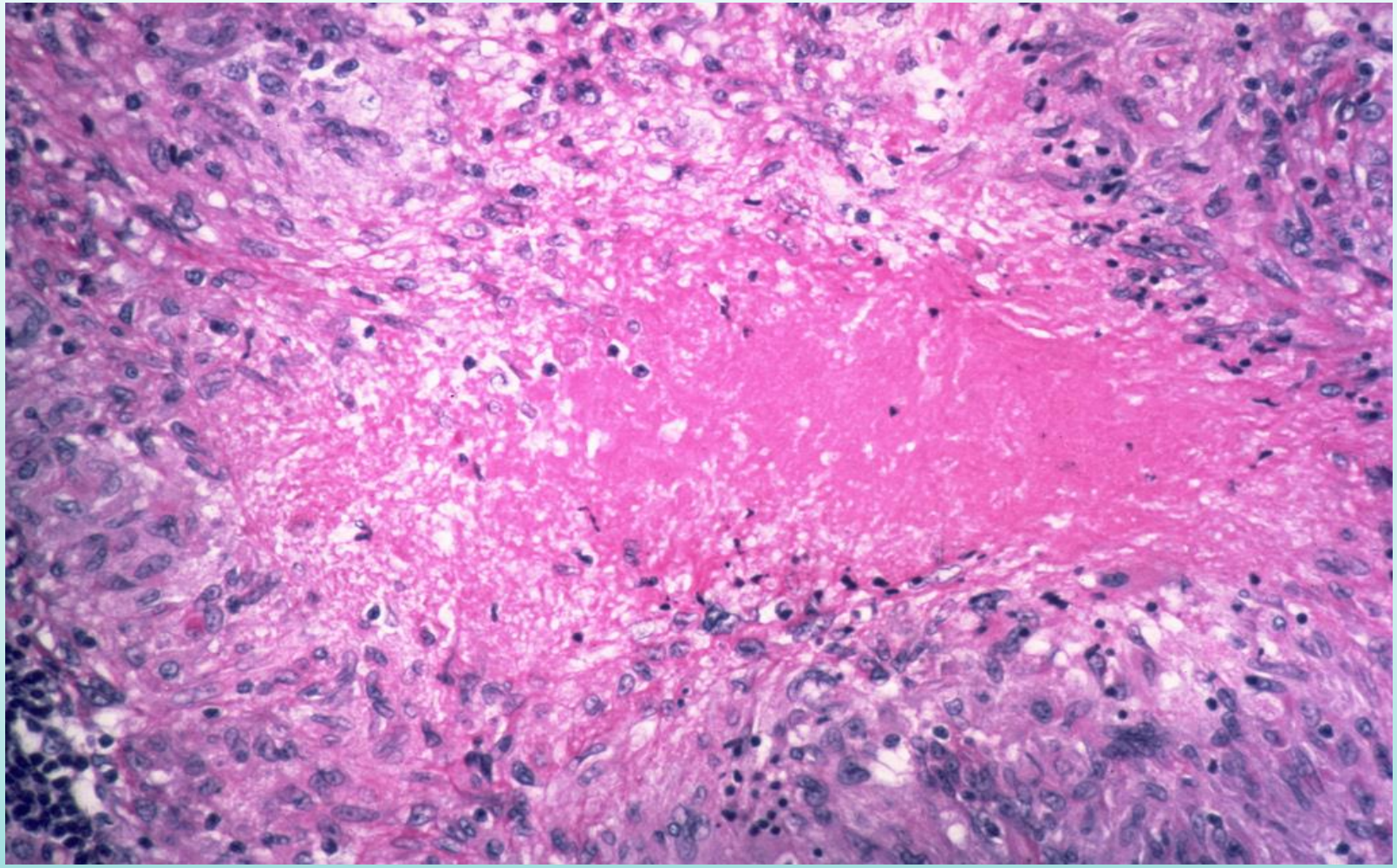
- A distinctive form of necrosis is often present in foci of tuberculous infection.
- The term caseous is derived from the cheesy white gross appearance of the area of necrosis.
- Combination of **coagulative and liquefactive necrosis**
- In this type of necrosis, both Enzymatic Digestion & Protein Denaturation are **equally predominant**.
- Unlike coagulative necrosis, the tissue architecture is completely obliterated.
- On microscopic examination, (composed of fragmented, coagulated cells and amorphous granular debris) surrounded by a characteristic lesion which is called granuloma
- Characterized by the presence of soft, dry, cheesy homogenous necrotic material but It is not liquified

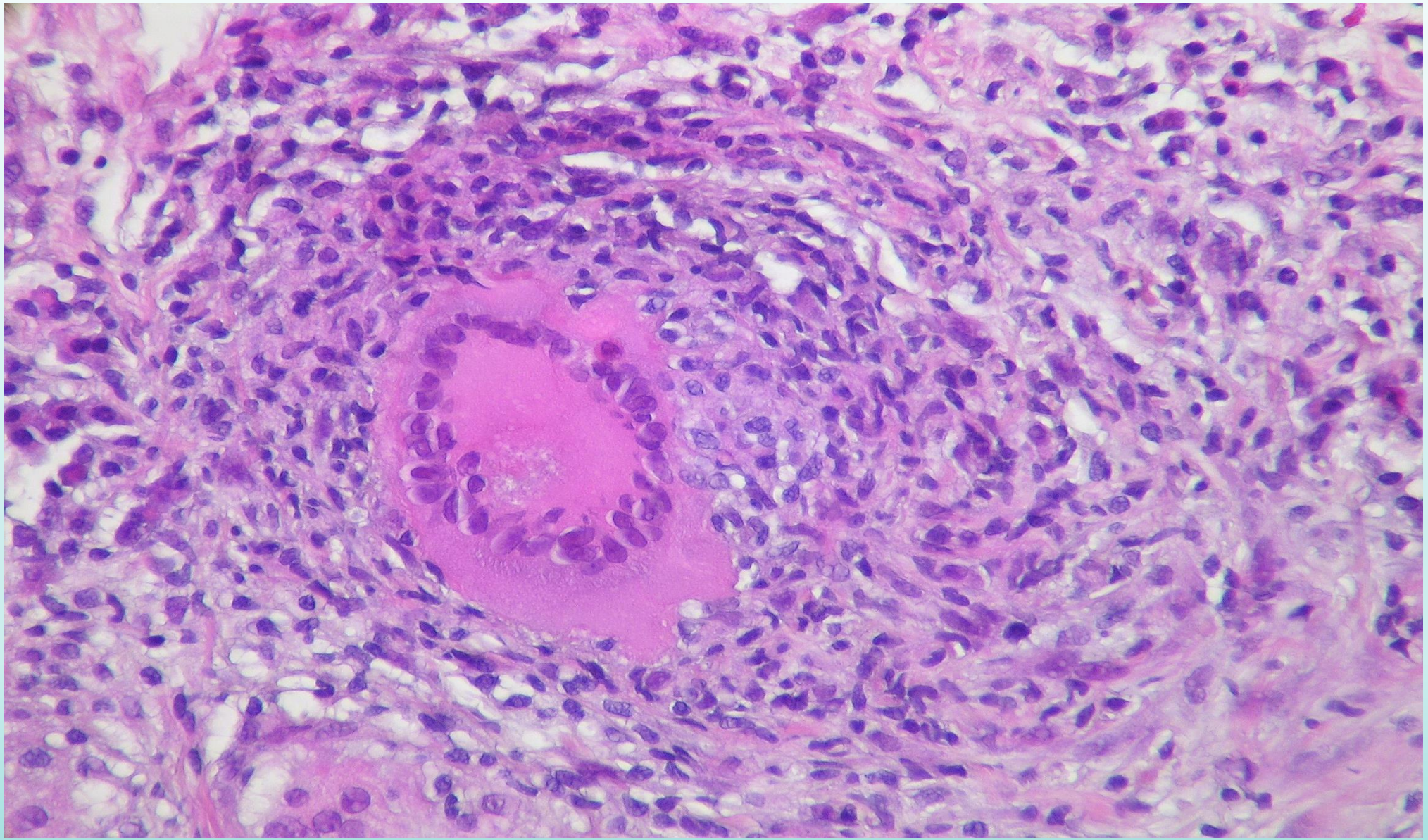


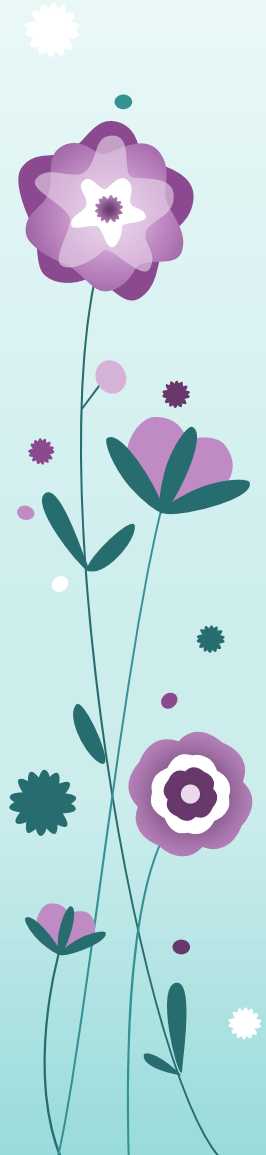
Caseous necrosis

A tuberculous lung with a large area of caseous necrosis containing yellow-white and cheesy debris.

fragmented, coagulated cells and amorphous granular debris surrounded by a characteristic lesion which is called granuloma







Thank you