Cell Injury and Cell Death

Lecture: 3 & 4

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General Pathology Grade 4

Lecture Outline:

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

Objectives:

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

CELL INJURY

Cell injury leads to the biochemical alterations & morphological abnormalities and are divided into the following -

- **Reversible cell injury**
- **Irreversible cell injury**

CELL INJURY

Reversible cell injury

- **Morphologic changes are reversible if the damaging stimulus is removed**

Irreversible cell injury

- **When damaging stimulus continues, irreversible cell injury occurs at which time the cell cannot recover**
- **Irreversibly injured cells invariably undergo morphologic changes that are recognized as cell death which are of two types i.e. Necrosis & Apoptosis**

CELL INJURY

- **Causes of cell injury**
  - **Oxygen deprivation**
  - **Physical injury**
  - **Chemical injury**
  - **Infectious agents**
  - **Immunological mechanism**
  - **Nutritional deficiency**
  - **Genetic causes**

CELL INJURY

Causes of cell injury

- **Oxygen deprivation (hypoxia)**–affects aerobic respiration and therefore ability to generate adenosine triphosphate (ATP).
- This important and common cause of cell injury and death occurs as a result of:

a) Ischemia – obstruction to arterial flow & venous drainage

- compromise of both oxygen supply & also of metabolic substrate e.g. Glucose

b) Loss of Oxygen carrying capacity of blood as in anemia or poisoning leading to hypoxia

CELL INJURY

Causes of cell injury

Physical agents –

- **Mechanical trauma**
- **Extremes of temperature e.g. Burns & Deep cold**
- **Sudden changes in atmospheric pressure**
- **Radiation**
- **Electric shock**

CELL INJURY

Causes of cell injury

Chemical agents & Drugs

- Simple chemicals such as Glucose or salt in hypertonic concentrations may cause cell injury by deranging electrolyte homeostasis of cell
- High concentration of Oxygen
- Poisons such as Arsenic cyanide or Mercuric salts
- Environmental & air pollutants, insecticides & herbicides
- Industrial & occupational hazards such as CO & Asbestos

CELL INJURY

Causes of cell injury

Infectious agents

Viruses, Rickettsia, bacteria, fungi & parasites

Immunologic reactions

- **Anaphylactic reactions to a foreign protein or a drug**
- **Reactions to endogenous self antigen – Autoimmune disease**

CELL INJURY

Causes of cell injury

Genetic derangements

Genetic defects causing enzyme defects as in inborn errors of metabolism arising from enzymatic abnormalities

Nutritional imbalances

- Protein-calorie deficiencies
- Deficiencies of specific vitamins
- Excess of lipids predispose to atherosclerosis

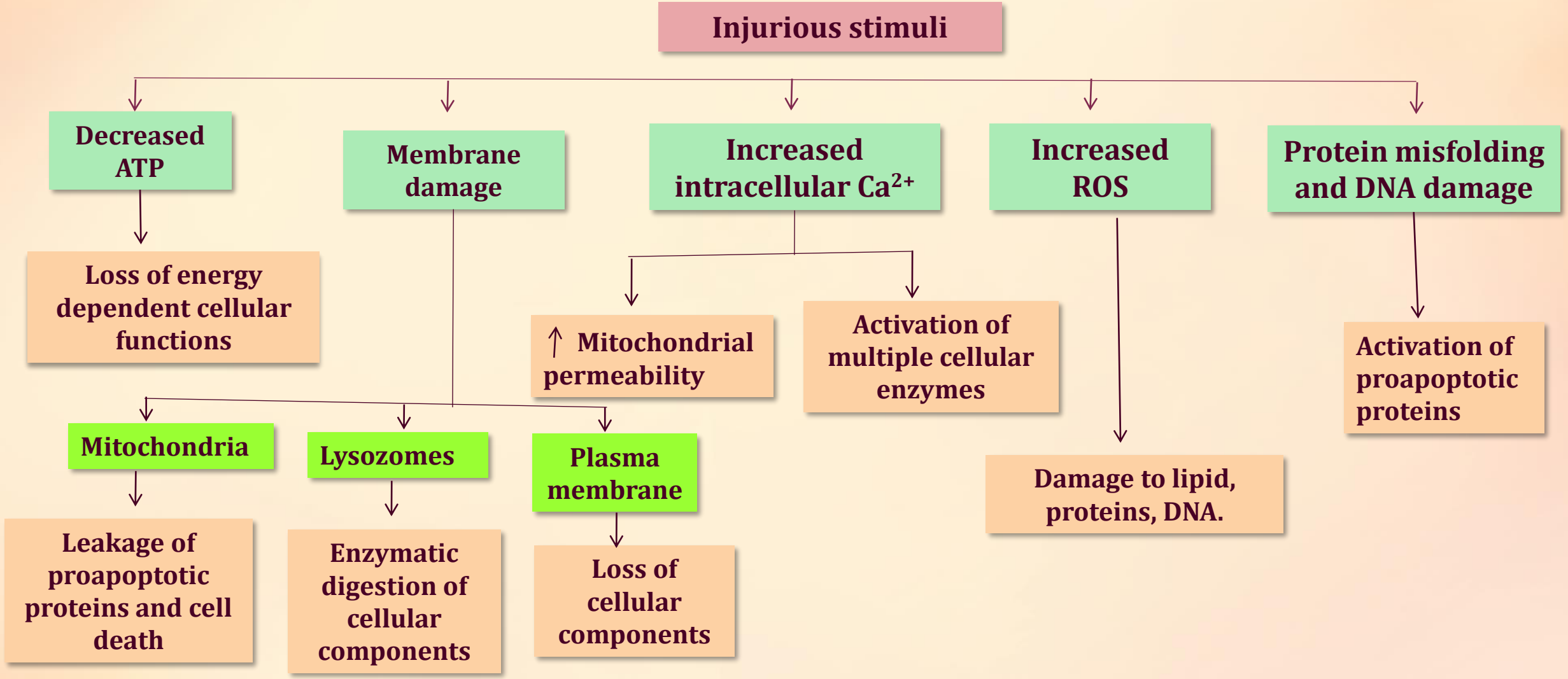
CELL INJURY

Mechanism of cell injury

- **The cellular response to injurious stimuli depends on –**
  - **Type of injury**
  - **Its duration**
  - **Severity**
- **The consequences of cell injury depend on the type , state, & adaptability of the injured cell**

CELL INJURY

Mechanism of cell injury



CELL INJURY
Mechanism of cell injury

Depletion of ATP

ATP is normally produced in two ways in mammalian cells i.e

- **By oxidative phosphorylation of Adenosine diphosphate in a reaction that results in reduction of oxygen by electron transfer system of mitochondria**
- **In glycolytic pathway which can generate ATP in the absence of oxygen using glucose derived either from body fluids or from the hydrolysis of glycogen**

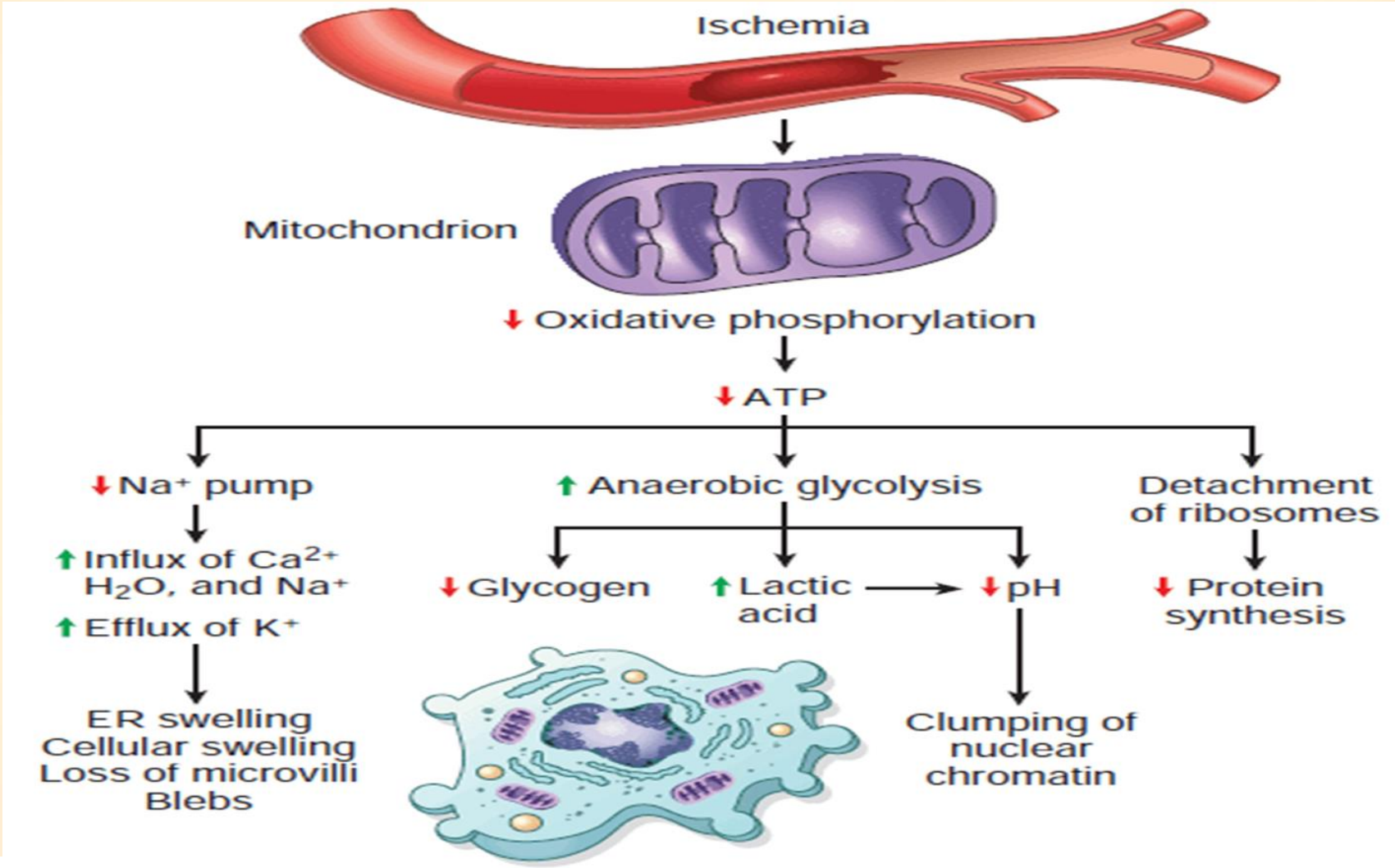
CELL INJURY

Mechanism of cell injury

ATP is required for many synthetic & degradative processes which include

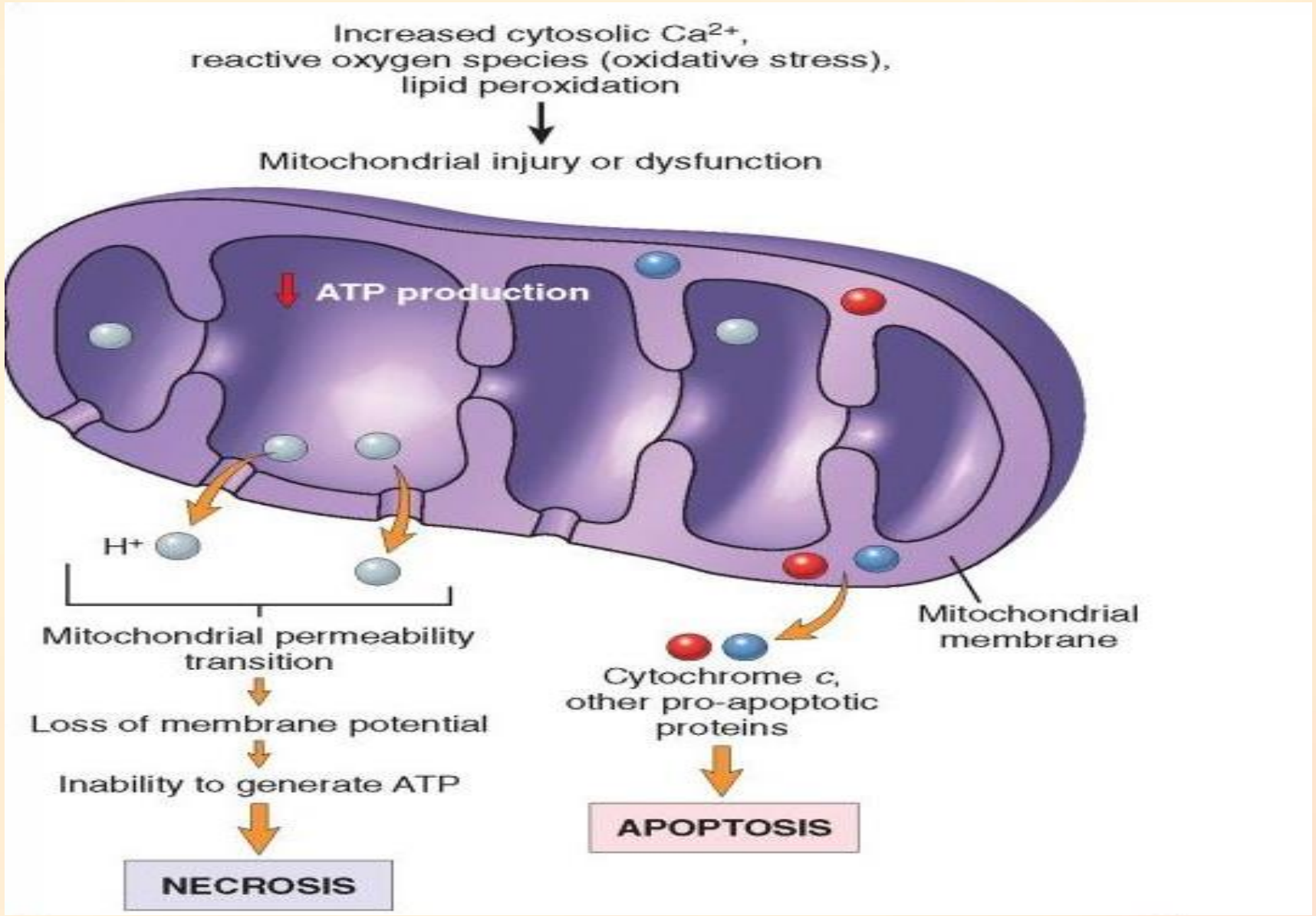
- **membrane transport**
- **Protein synthesis**
- **Lipogenesis**
- **Deacylation – reacylation reactions necessary for phospholipid turnover**

EFFECTS OF DEPLETION OF ATP

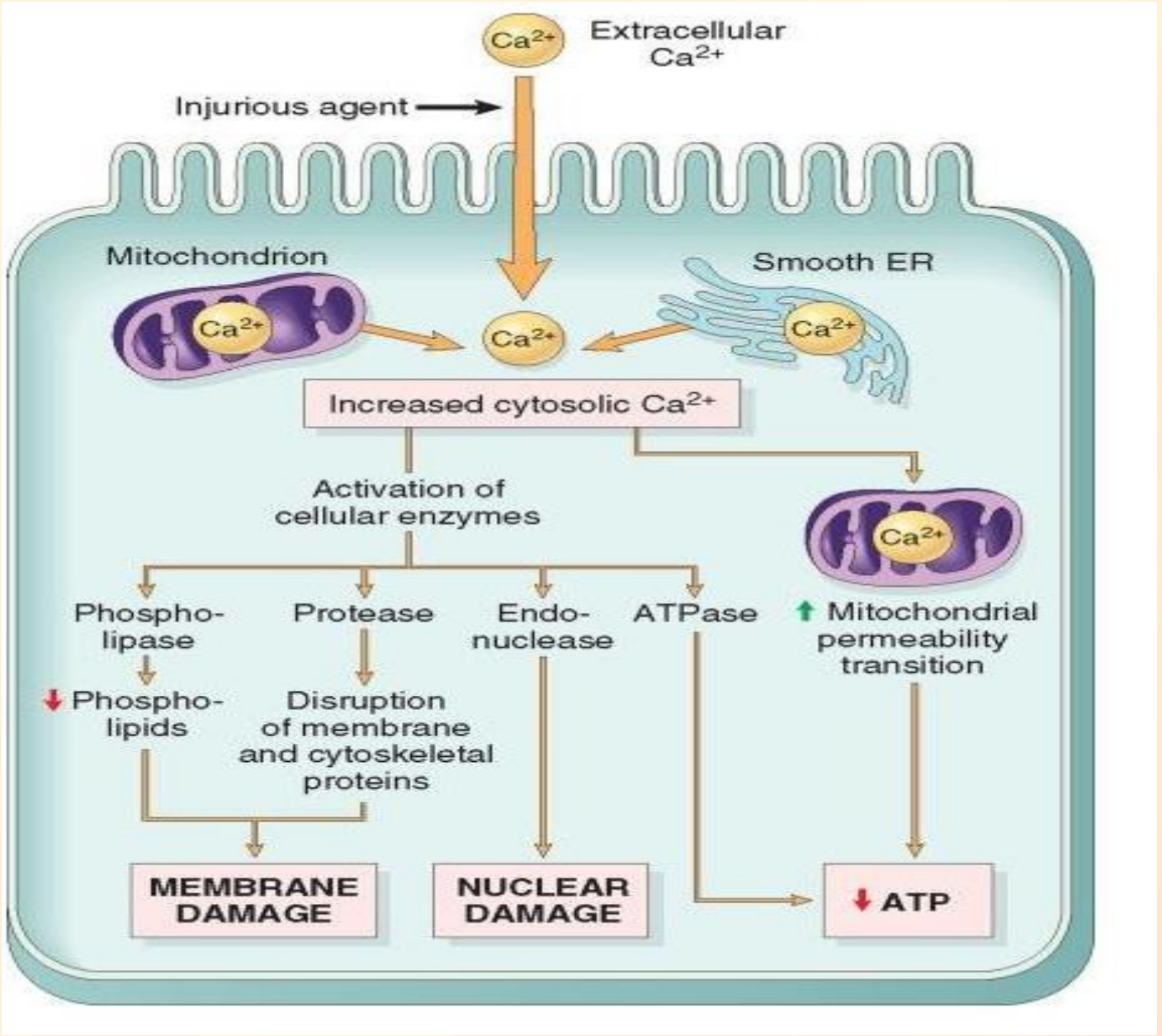


Functional and morphologic consequences of decreased intracellular adenosine triphosphate *(ATP)* in ischemic cell injury. The morphologic changes shown here are indicative of reversible cell injury. Further depletion of ATP results in cell death, typically by necrosis. *ER*, Endoplasmic reticulum.

MITOCHONDRIAL DAMAGE



THE ROLE OF INCREASED CALCIUM IN CELL INJURY



CELL INJURY

Free radical injury

- Cells have defense system to prevent this injury
- An imbalance between free radical generating & radical scavenging systems results in " oxidative stress"
- Free radicals are chemical species that have a single unpaired electron in an outer orbit. Energy created by this unstable configuration is released through reactions with adjacent molecules , such as proteins, lipids, carbohydrates in membranes & nucleic acid
- Free radicals initiate autocatalytic reactions whereby molecules with which they react are themselves converted into free radicals to propagate the chain of damage

CELL INJURY

Mechanism of cell injury

Free radicals are generated by –

The reduction – oxidation reactions

- **Cells generate energy by reducing molecular oxygen to water**
- **During this process , small amount of partially reduced reactive oxygen forms are produced in which different numbers of electrons have been transferred from O_2.**

CELL INJURY

Mechanism of cell injury

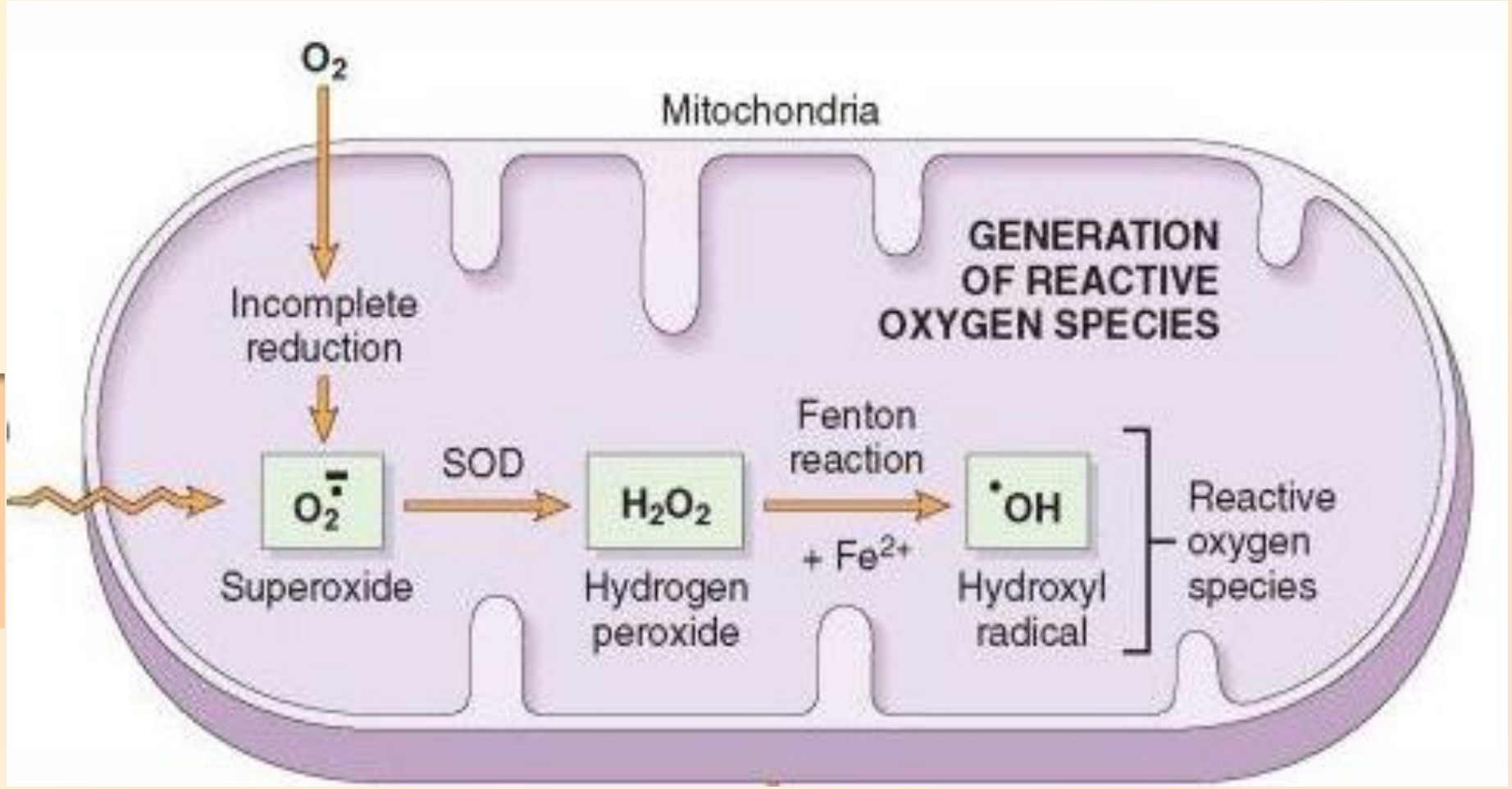
Free radicals are generated by

- **The reduction – oxidation reactions that occurs during normal metabolic process**
- **Absorption of radiant energy (UV rays , x-rays)- ionizing radiation can hydrolyze water into ·OH and hydrogen free radicals**
- **Rapid bursts of ROS in the leukocytes during inflammation**
- **Enzymatic metabolism of exogenous chemicals and drugs generate free radicals e.g. – CCl_3 from CCl_4**
- **Transition metals such as iron and copper donate or accept free electrons during intracellular reactions and catalyze free radical formation**

CELL INJURY

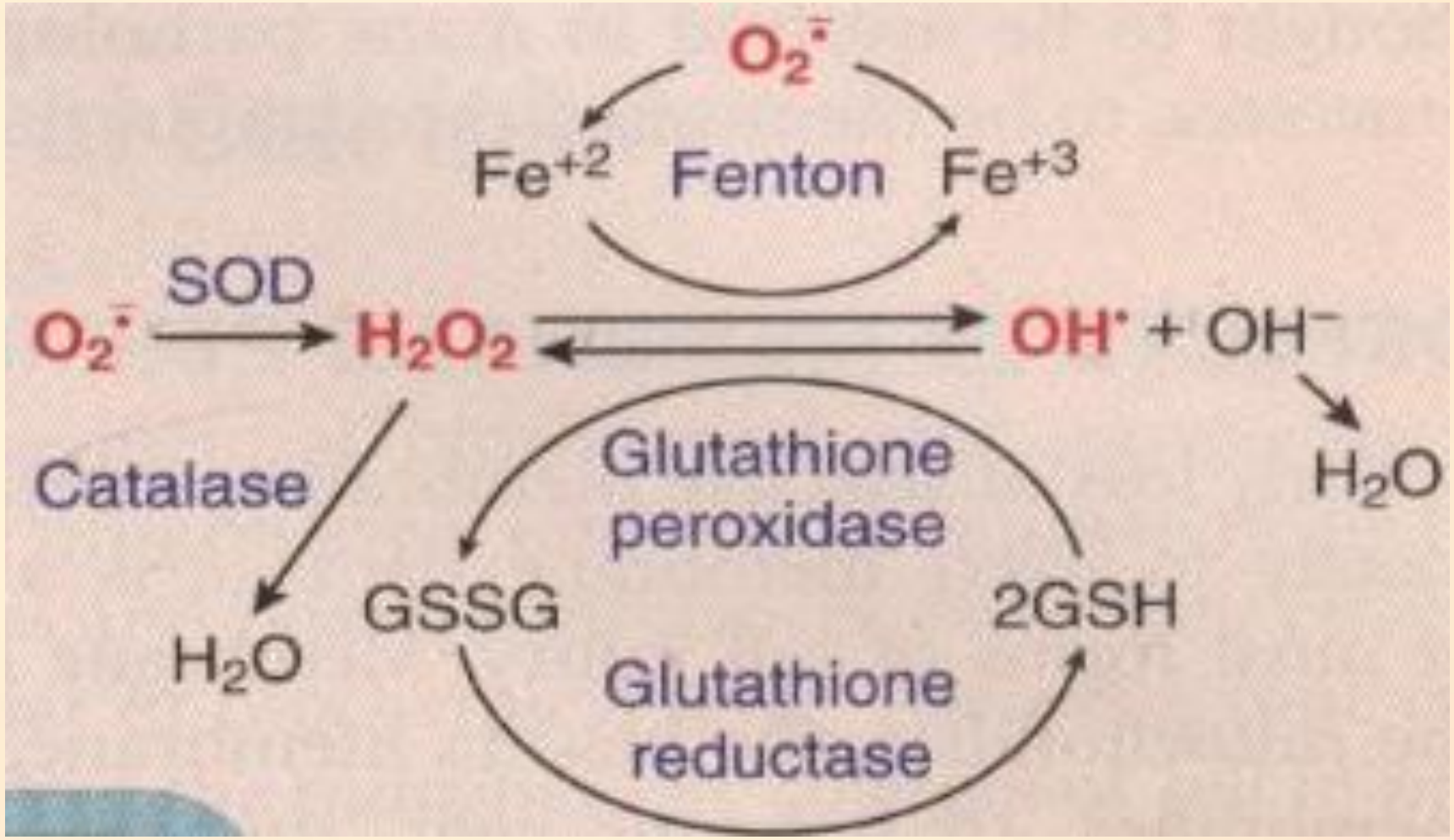
Mechanism of cell injury

- ***Inflammation***
- ***Radiation***
- ***Chemicals***
- ***Reperfusion injury***



CELL INJURY

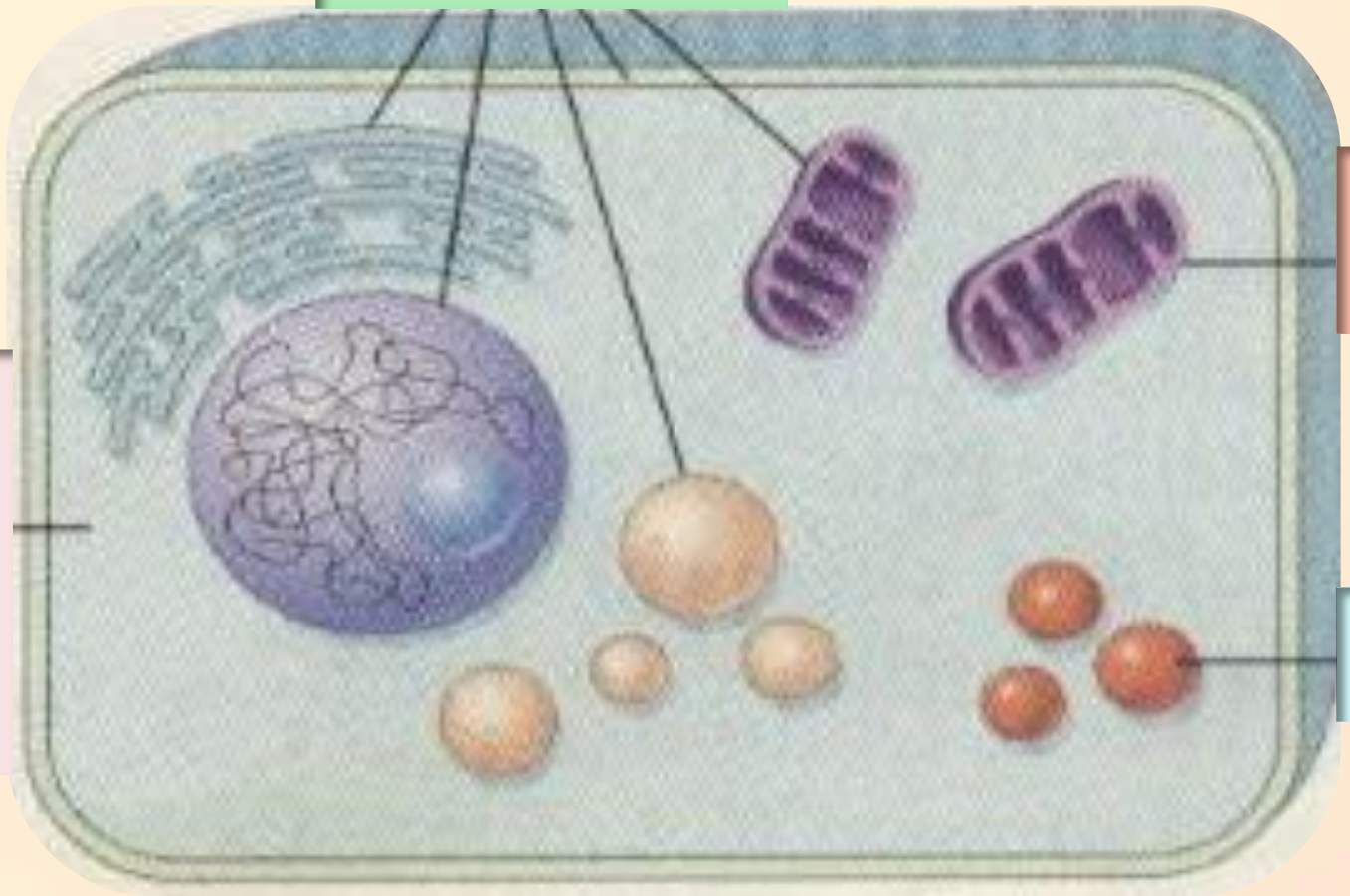
Neutralization of free radicals



CELL INJURY

Neutralization of free radicals

All membranes
- ***Vitamins E and A***
- ***β- carotene***



Mitochondria
- ***SOD***
- ***Glutathione peroxidase***

Cytosol
- ***SOD***
- ***Vitamin C***
- ***Glutathione peroxidase***
- ***Ferritin***
- ***Ceruloplasmin***

Peroxisomes
- ***Catalase***

CELL INJURY

Mechanism of cell injury

Effects of these reactive species are-

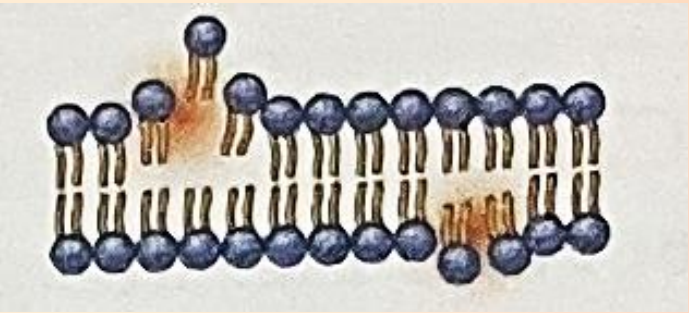
- **Lipid peroxidation of membrane**
- **Oxidative modification of proteins**
- **Lesions in DNA**

CELL INJURY

Mechanism of cell injury

Effects of these reactive species are-

Lipid peroxidation of membrane –



- **Double bonds in unsaturated fatty acids of membrane lipids are attacked by oxygen derived free radicals, particularly by OH.**
- **This produces peroxides which initiates the autocatalytic reaction**

CELL INJURY

Mechanism of cell injury

Effects of these reactive species are-

Oxidative modification of proteins-

- **Free radicals promote oxidation of amino acid residue side chains, formation of protein-protein cross linkages (e.g. disulfide bonds) & oxidation of protein back bone ⟶ protein fragmentation**

- **Oxidative modification of proteins damage the active sites of enzymes, disrupt the conformation of structural proteins and enhance proteosomal degradation of unfolded and misfolded proteins**

CELL INJURY

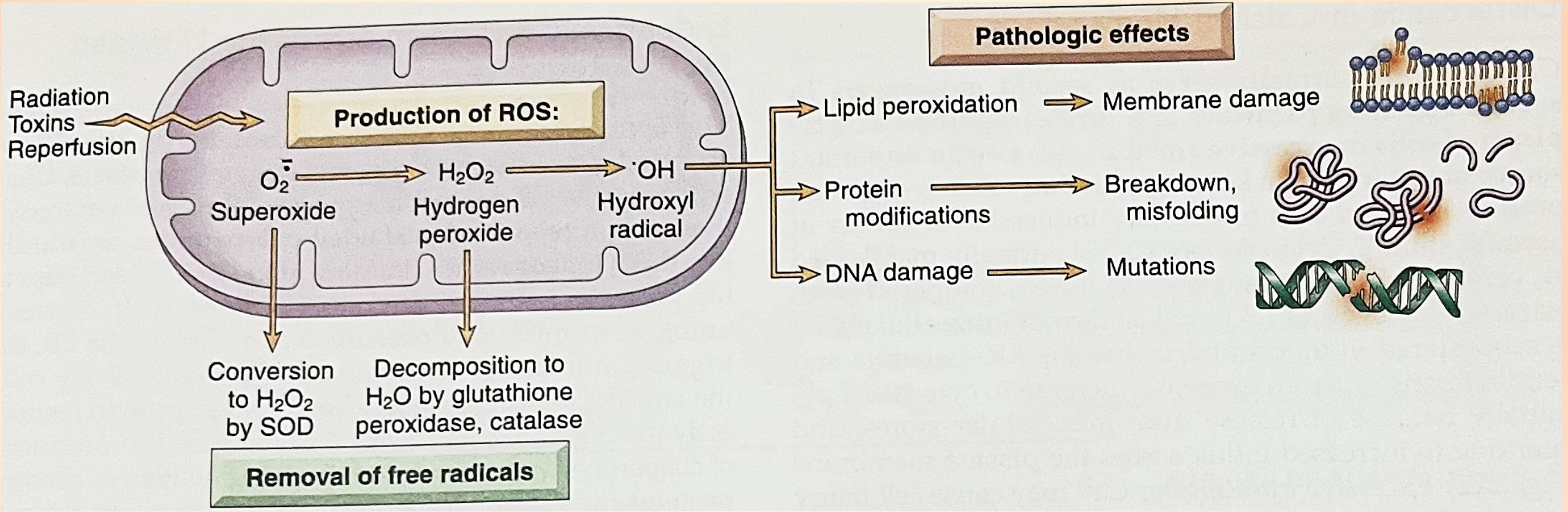
Mechanism of cell injury

Effects of these reactive species are-

Lesions in DNA –

- **Free radicals cause single and double stranded breaks in DNA, cross – linking of DNA strands and formation of adducts**
- **Oxidative DNA damage has been implicated in cell ageing & in malignant transformation**

FREE RADICAL INJURY



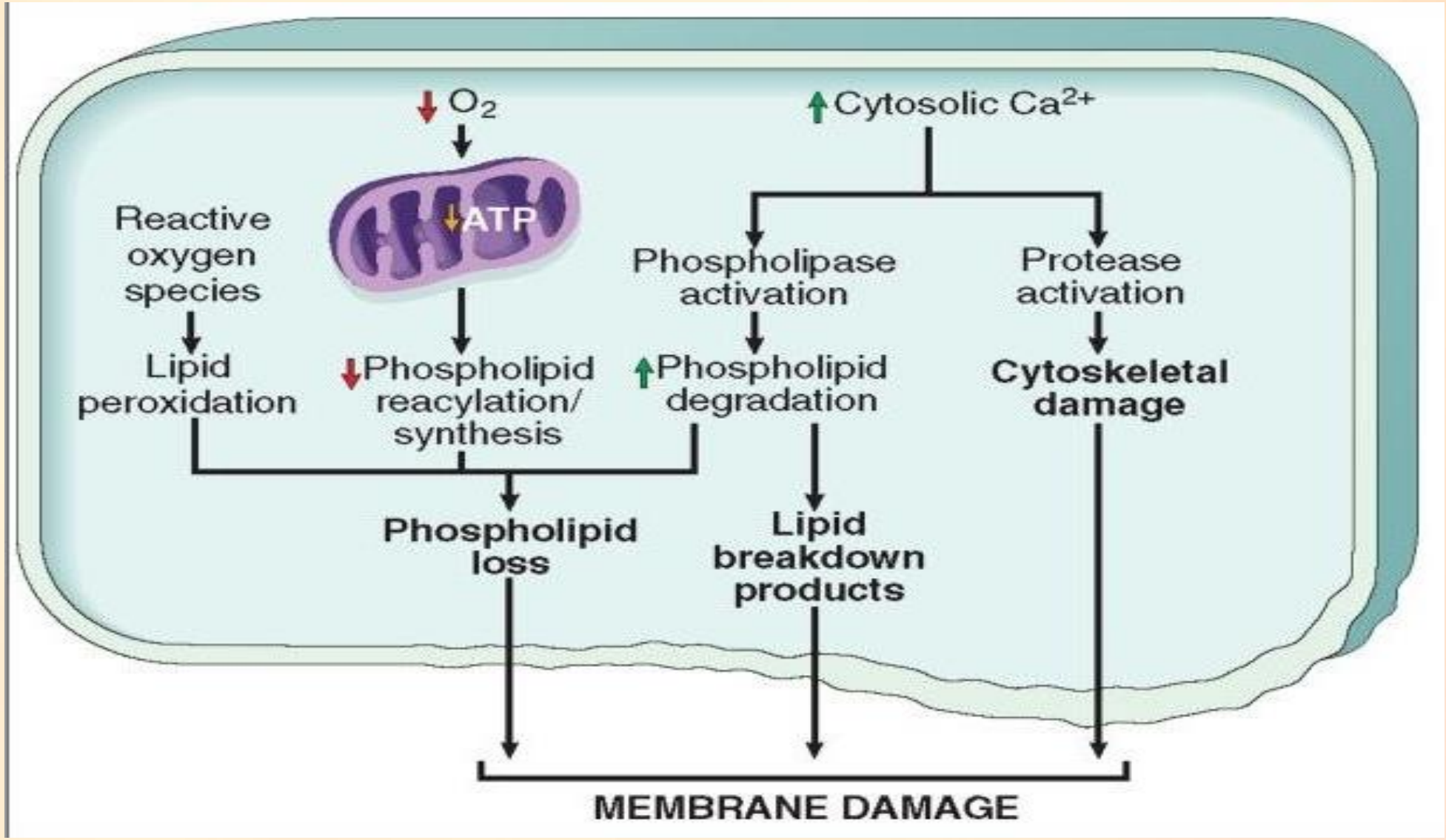
CELL INJURY

Defects in membrane permeability

- **Early loss of selective membrane permeability leading ultimately to overt membrane damage is a consistent feature of most forms of cell injury**
- **Membrane damage may effect mitochondria, plasma membrane, & other cellular membranes**

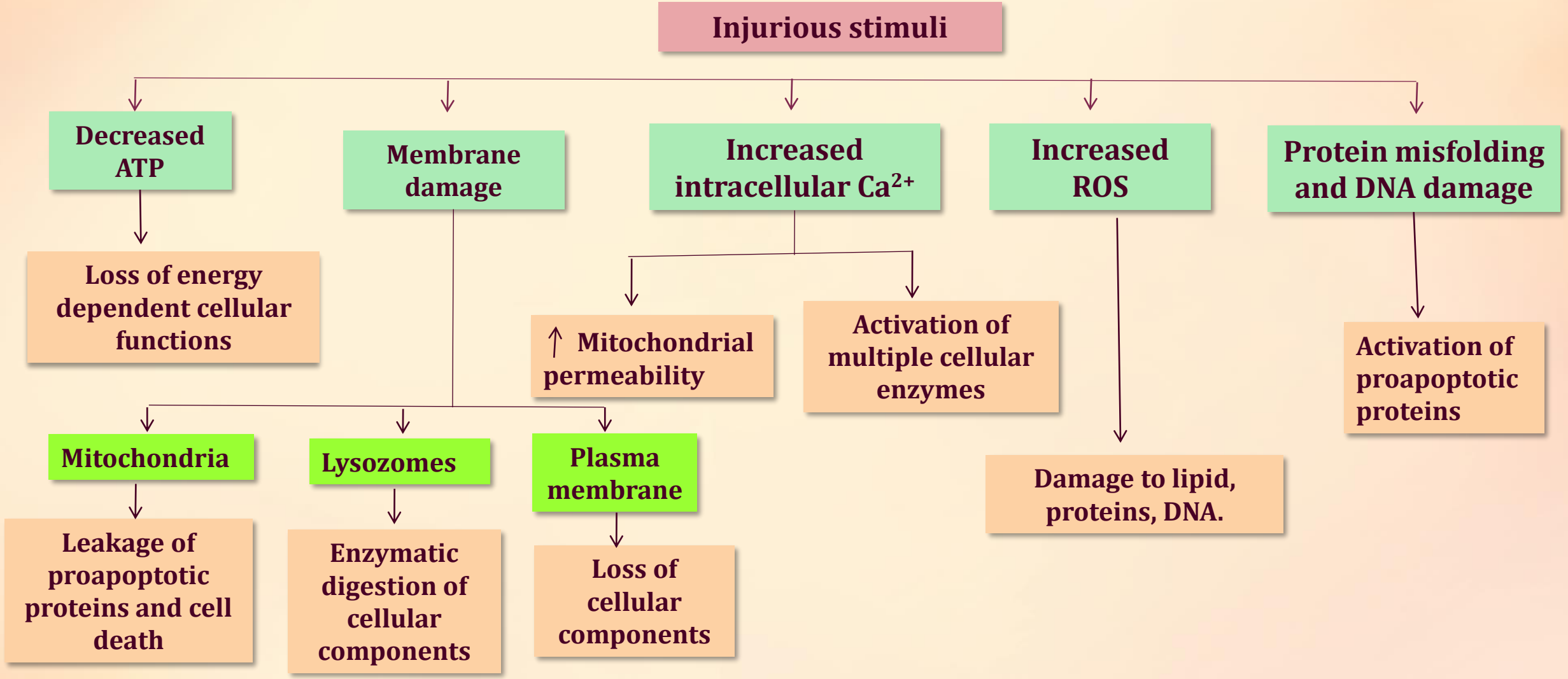
CELL INJURY

Mechanism of cell injury



CELL INJURY

Mechanism of cell injury



Morphology of Cell Injury and Necrosis

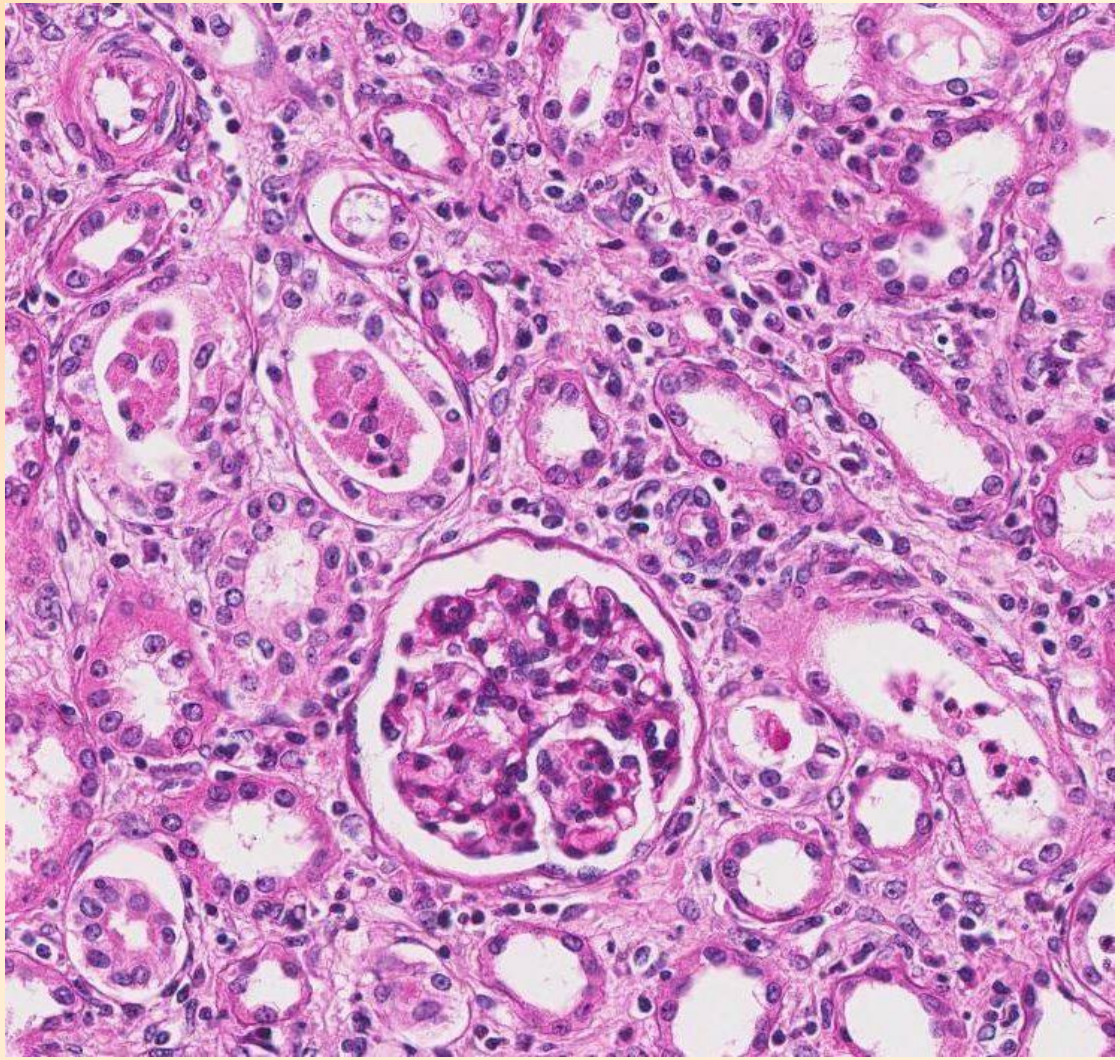
◦ Reversible Injury:

◦ Cell Swelling:

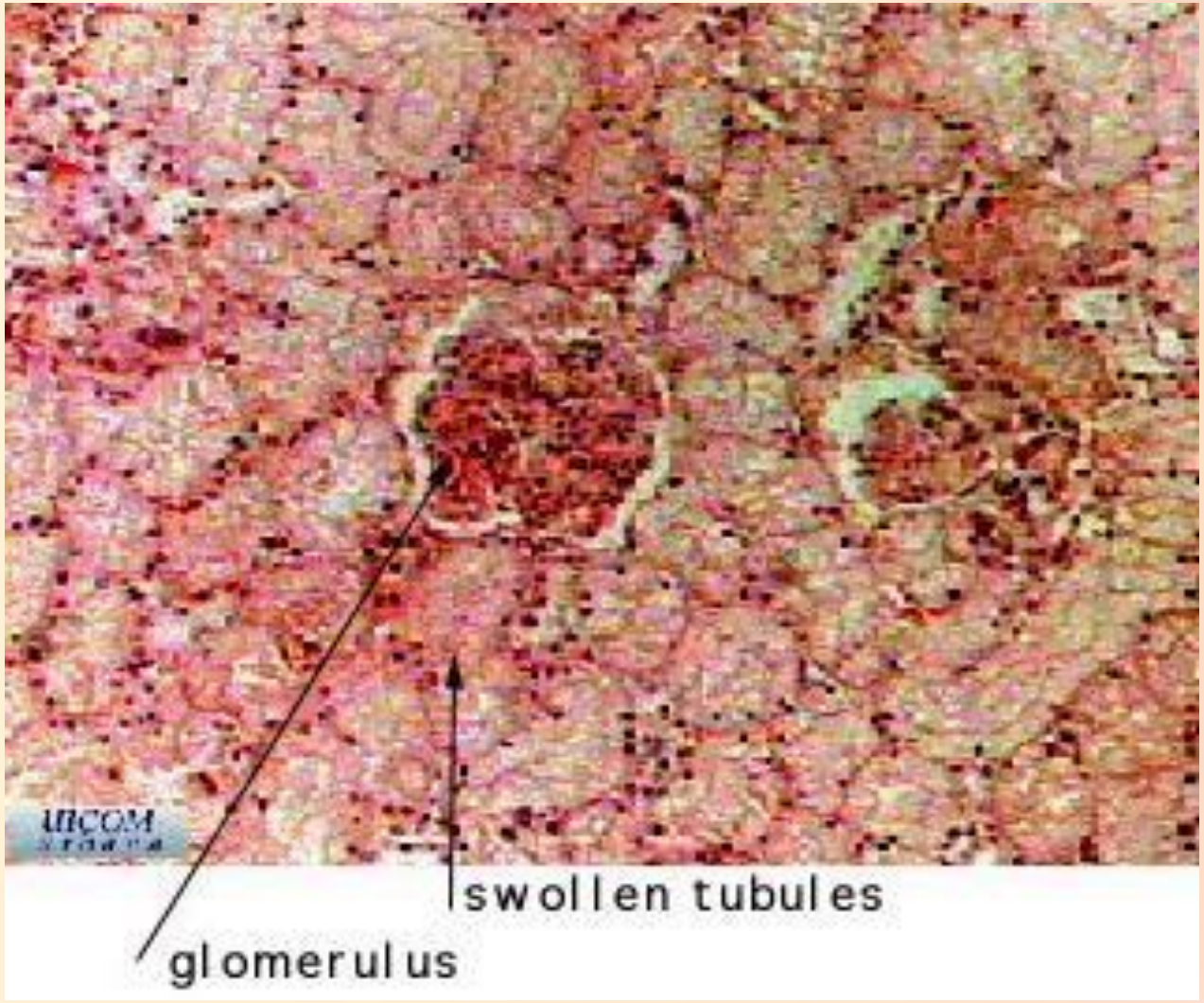
appears whenever cells cannot maintain ionic and fluid homeostasis it is difficult to appreciate with the light microscope;

- **it may be more apparent at the level of the whole organ. it causes some pallor, and increases the 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

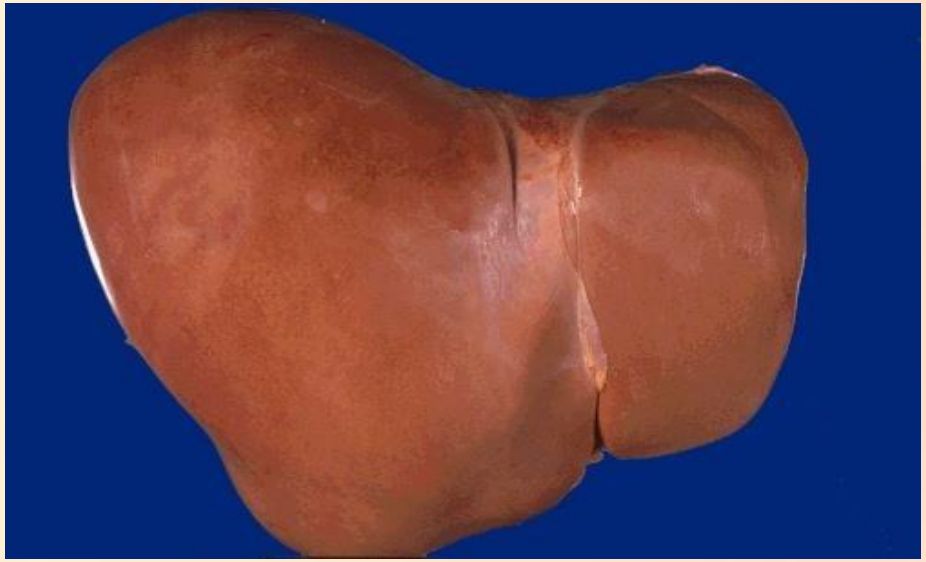


Hydropic swelling of renal tubules

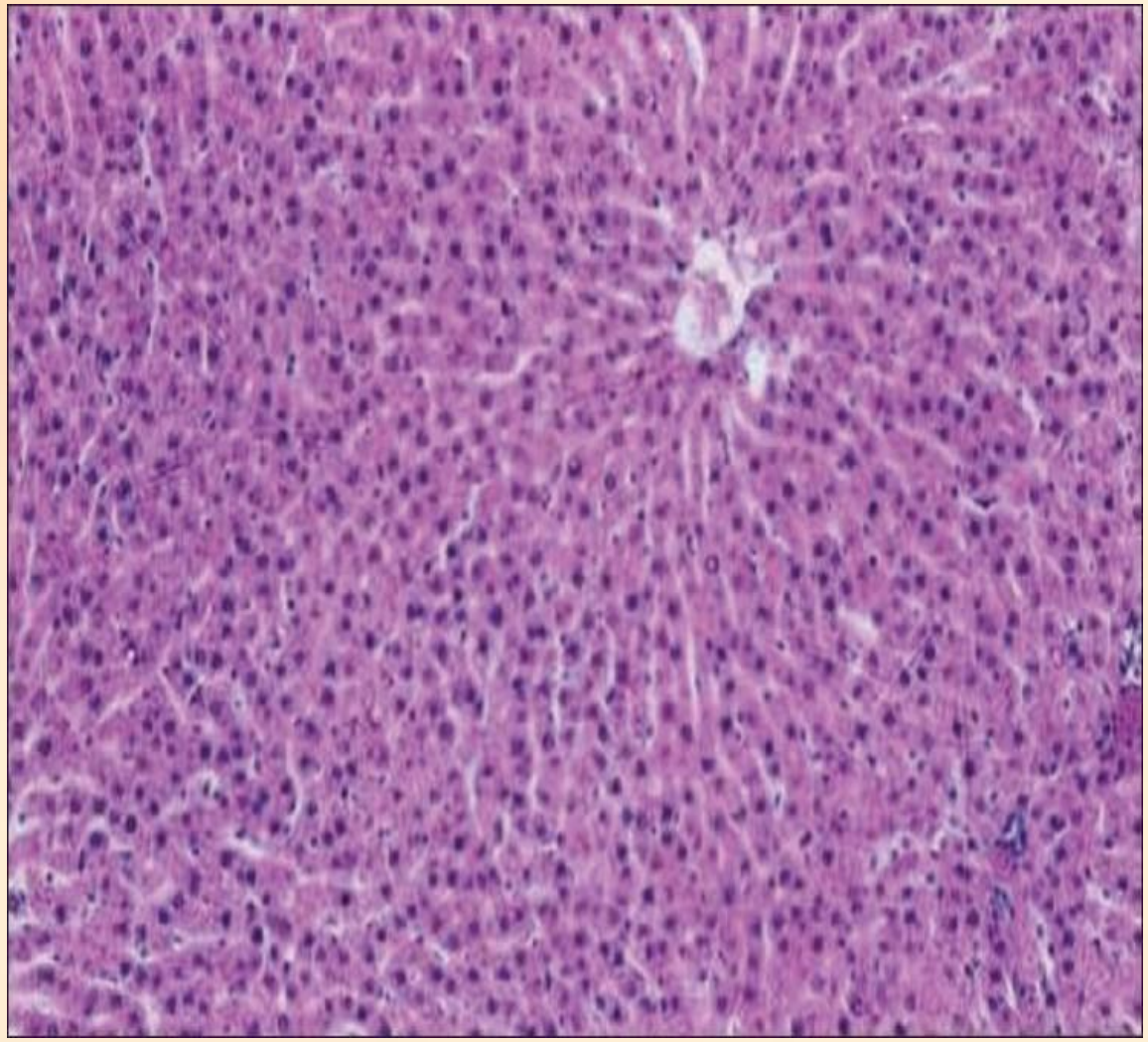
Fatty change:

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.

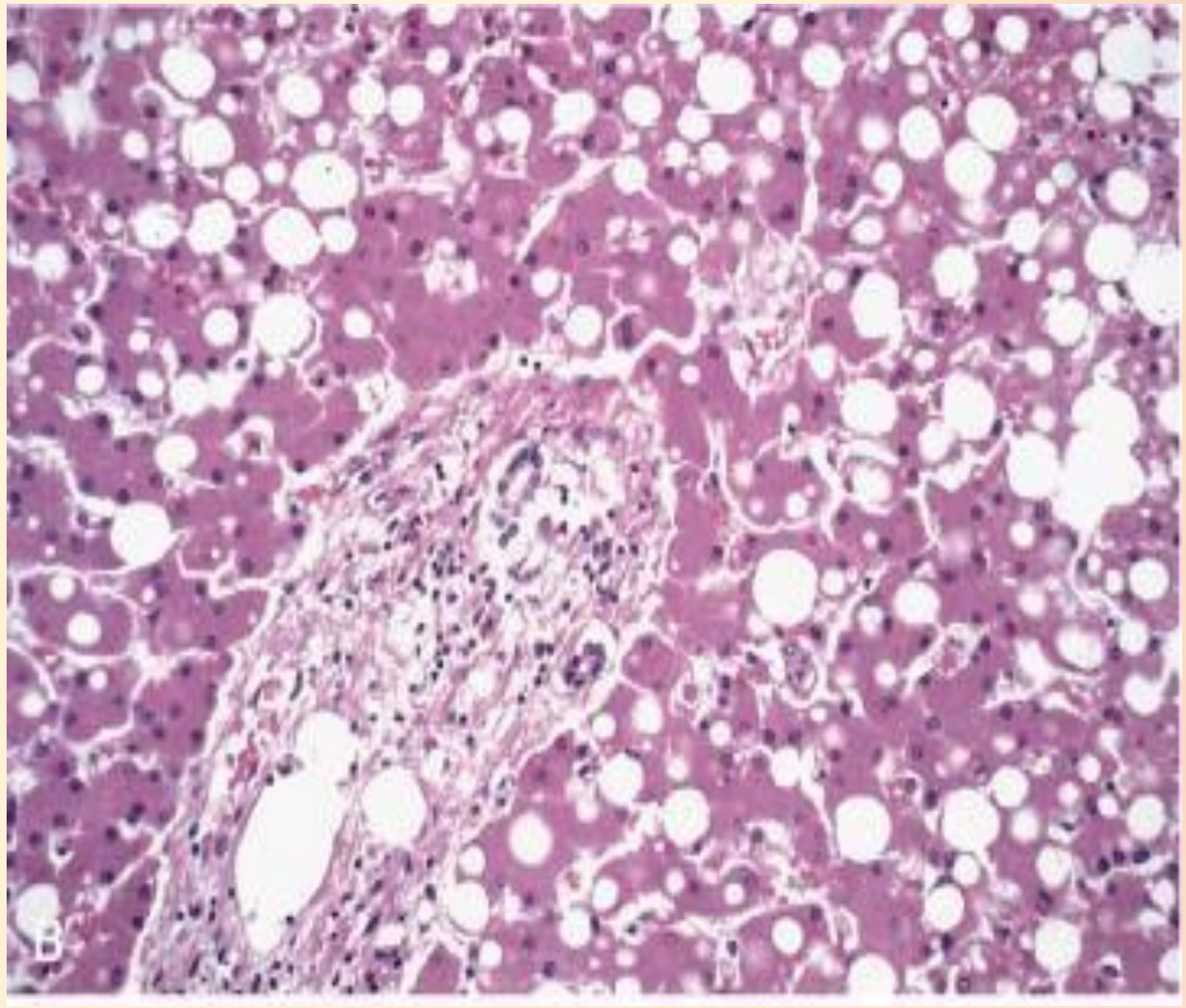
Fatty change of liver



Normal liver



Normal liver histology



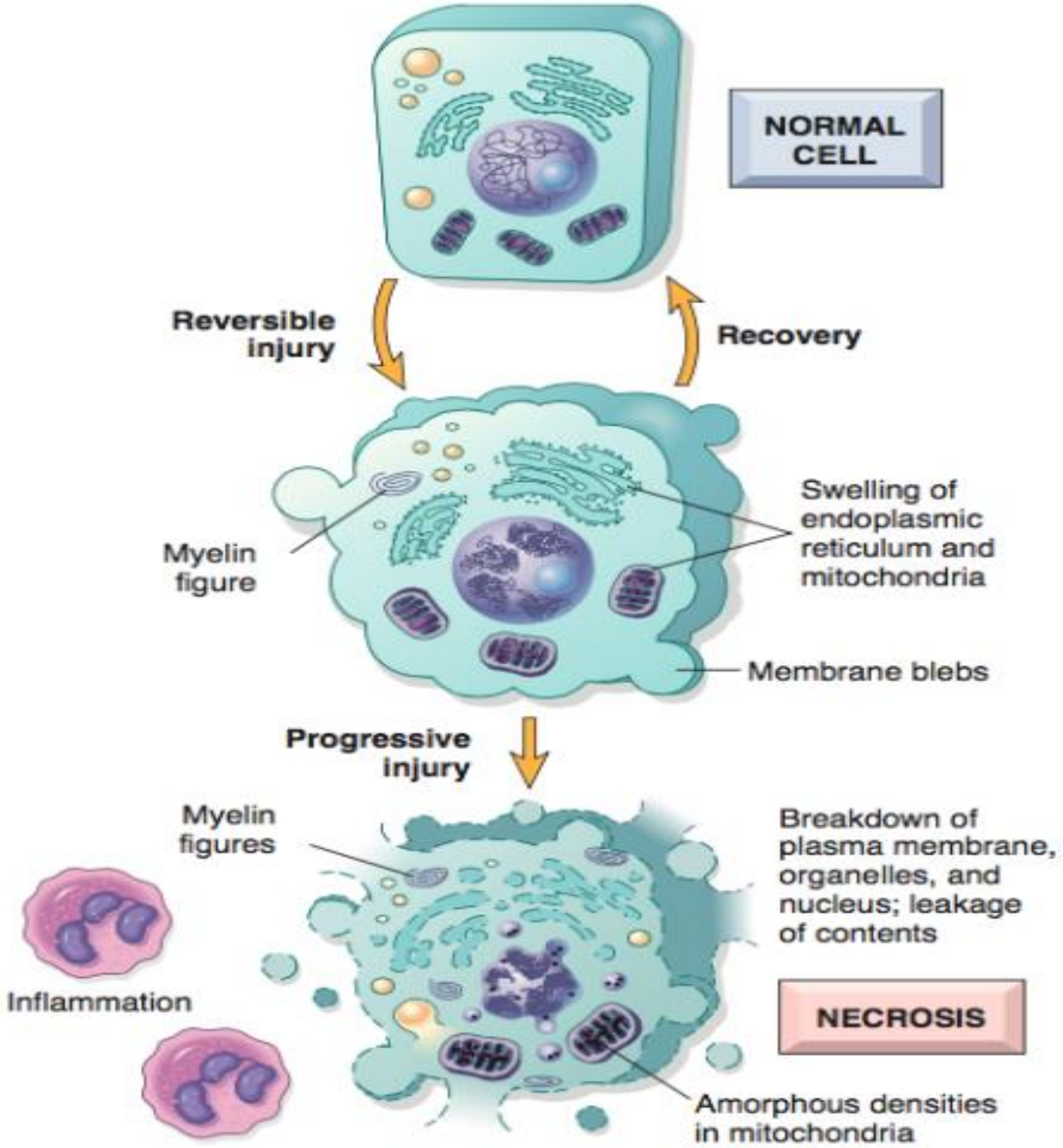
Microscopical appearance of fatty change of liver

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 CELL
Reversible injury
Recovery
Myelin figure
Swelling of endoplasmic reticulum and mitochondria
Membrane blebs
Progressive injury
Myelin figures
Breakdown of plasma membrane, organelles, and nucleus; leakage of contents
Inflammation
NECROSIS
Amorphous densities in mitochondria

NECROSIS

- The morphologic appearance of necrosis is the result of denaturation of intracellular proteins & enzymatic digestion of the cell
- The enzymes are derived from either lysosomes of the dead cells themselves (Autolysis) or from the lysosomes of the immigrant leukocytes (heterolysis)

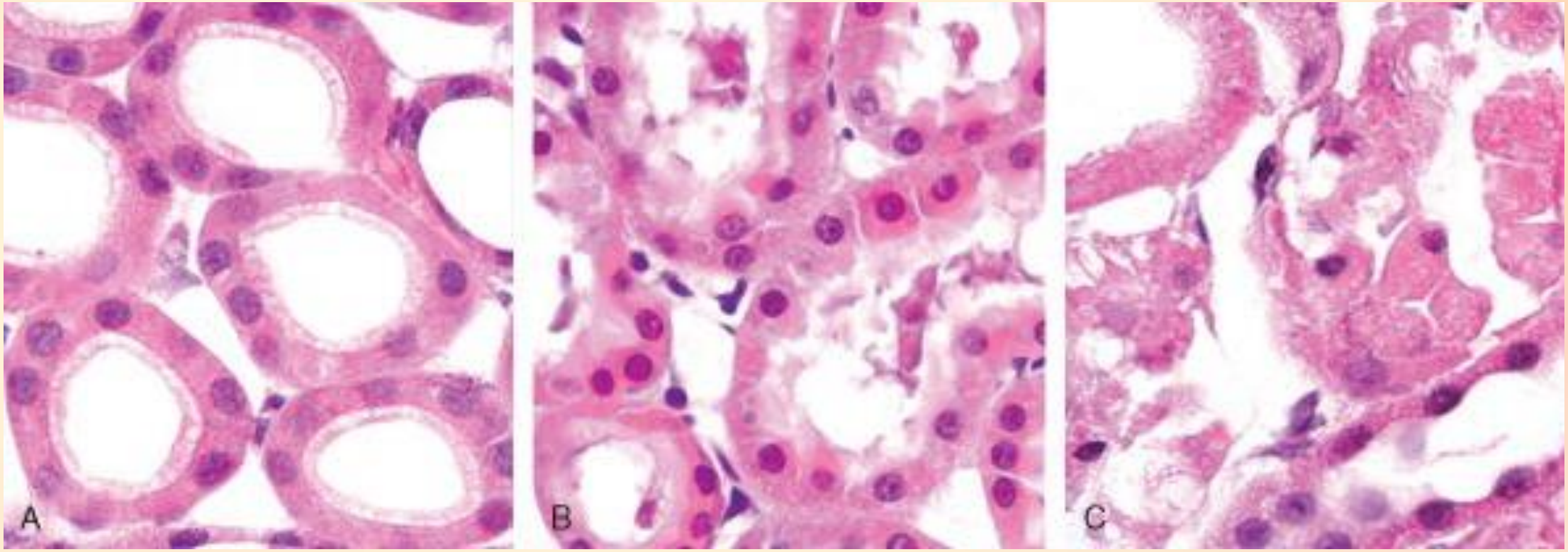
NECROSIS

Microscopic appearance

Cytoplasmic changes

- **Increased eosinophilia – Due to denatured proteins and loss of cytoplasmic RNA**
- **Glassy homogenous appearance – loss of glycogen particles**
- **Moth eaten appearance of cytoplasm – enzymatic digestion of cytoplasmic organelles**
- **Whorled phospholipid masses derived from damaged cell membranes – myelin figures**
- **Calcifications – fatty acids derived from phospholipid masses**

NECROSIS



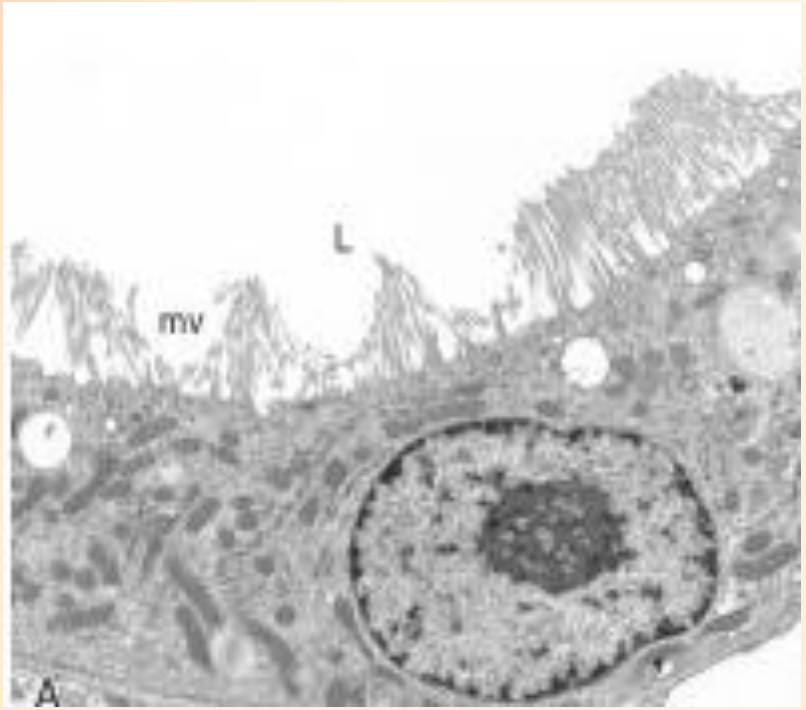
NECROSIS

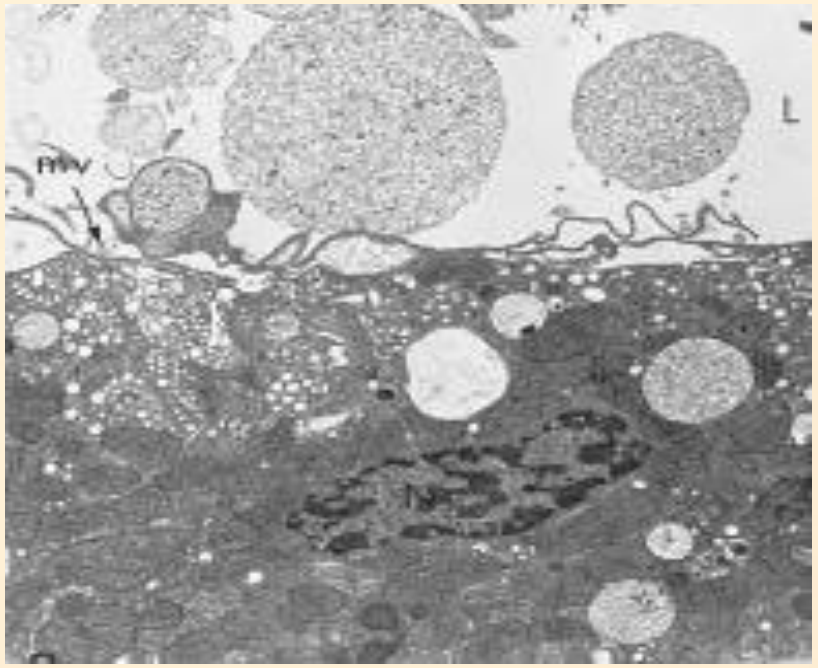
Electron microscopic findings

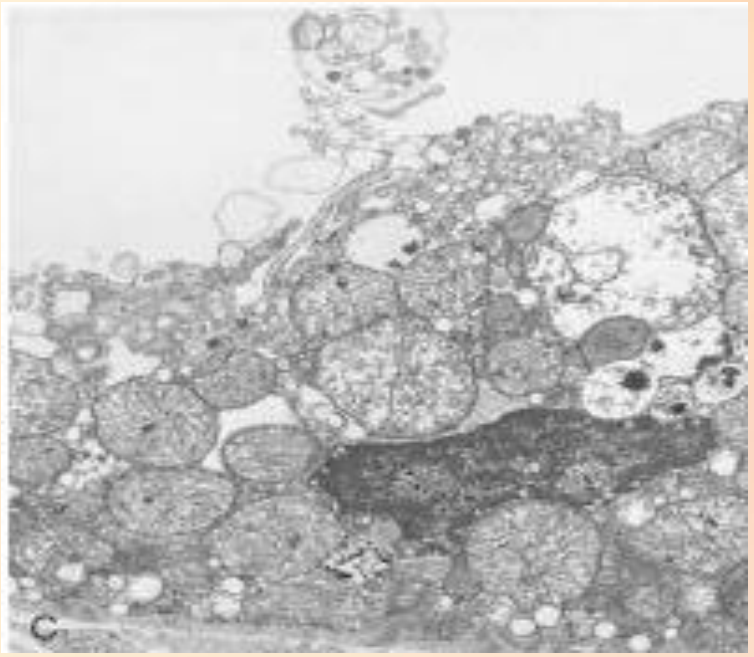
Necrotic cells are characterized by

- Discontinuities in plasma and organellar membrane
- Swollen mitochondria with large amorphous densities
- Intracytoplasmic myelin figures
- Aggregates of fluffy material representing denatured proteins

ELECTRON MICROSCOPIC FINDINGS

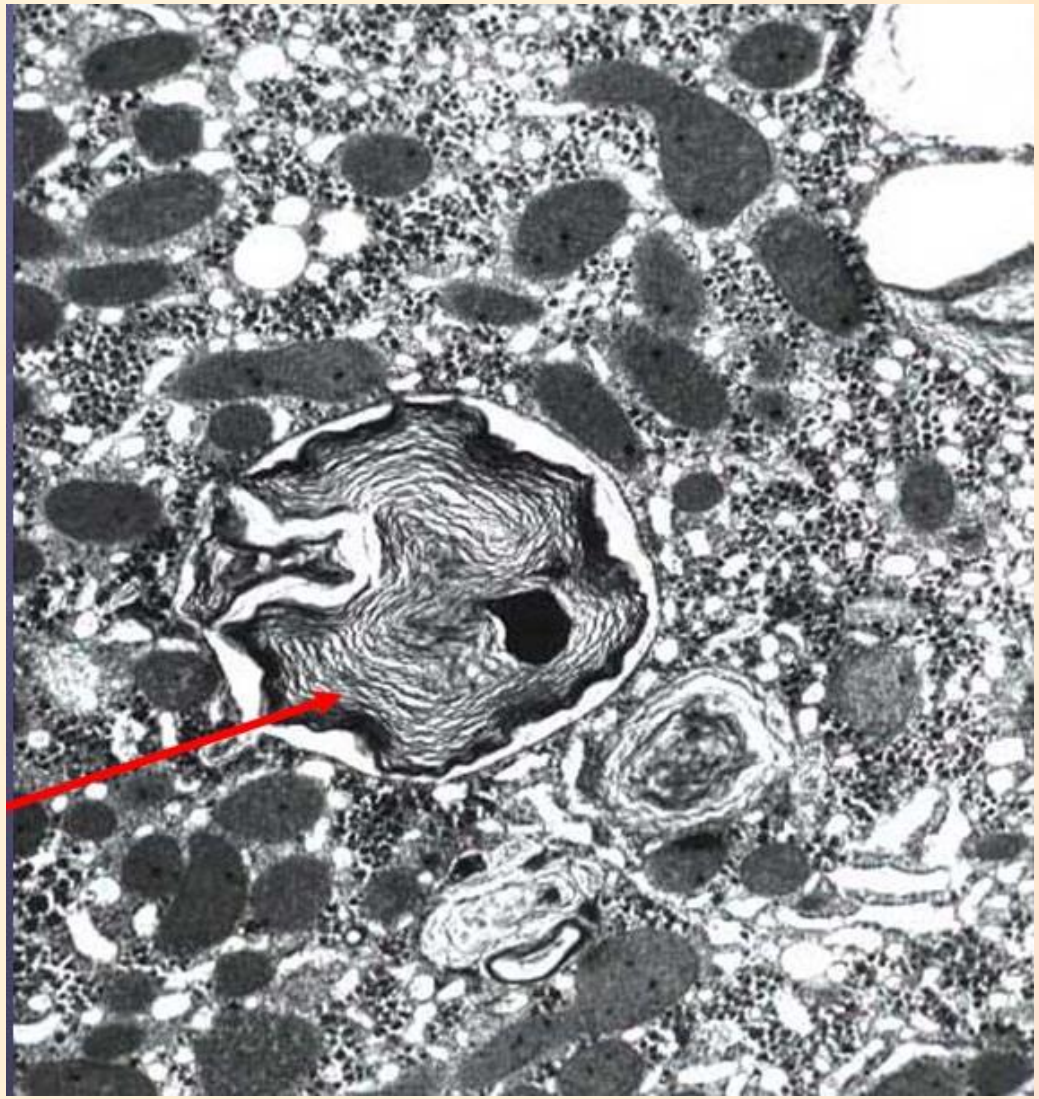






ELECTRON MICROSCOPIC FINDINGS

MYELIN FIGURES



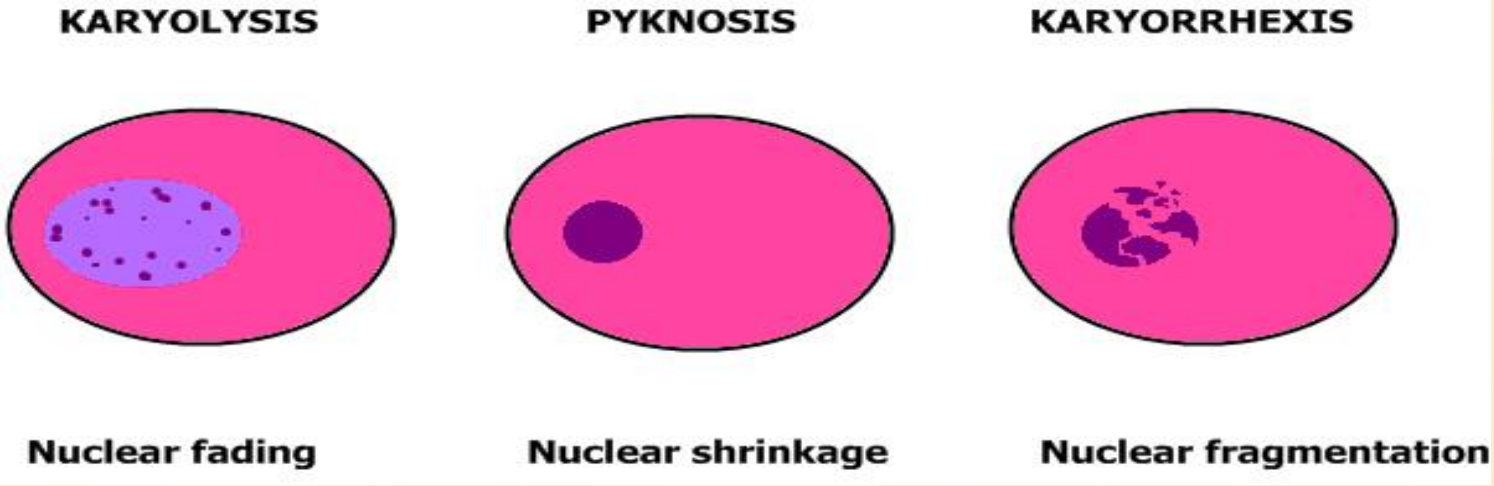
NECROSIS

Microscopic appearance

Nuclear changes

Due to non-specific break down of DNA , 3 patterns are identified

- **Karyolysis – fading of basophilia of chromatin due to enzymatic degradation of DNA by endonucleases**
- **Pyknosis – nuclear shrinkage & increased basophilia**
- **Karyorrhexis – pyknotic nucleus undergoes fragmentation**



NECROSIS

Types of necrosis

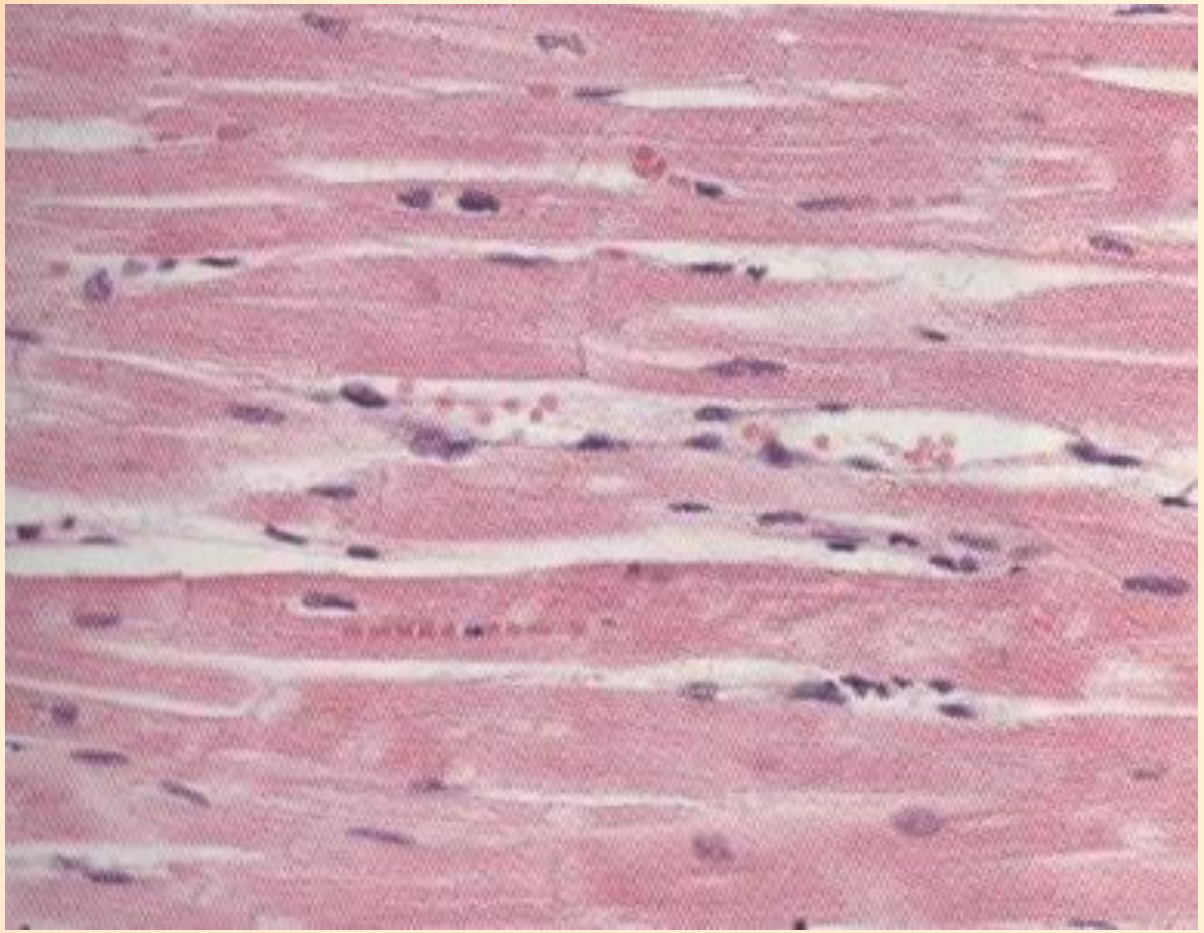
- Coagulative necrosis
- Liquefactive necrosis
- Caseous necrosis
- Fat necrosis
- Fibrinoid necrosis

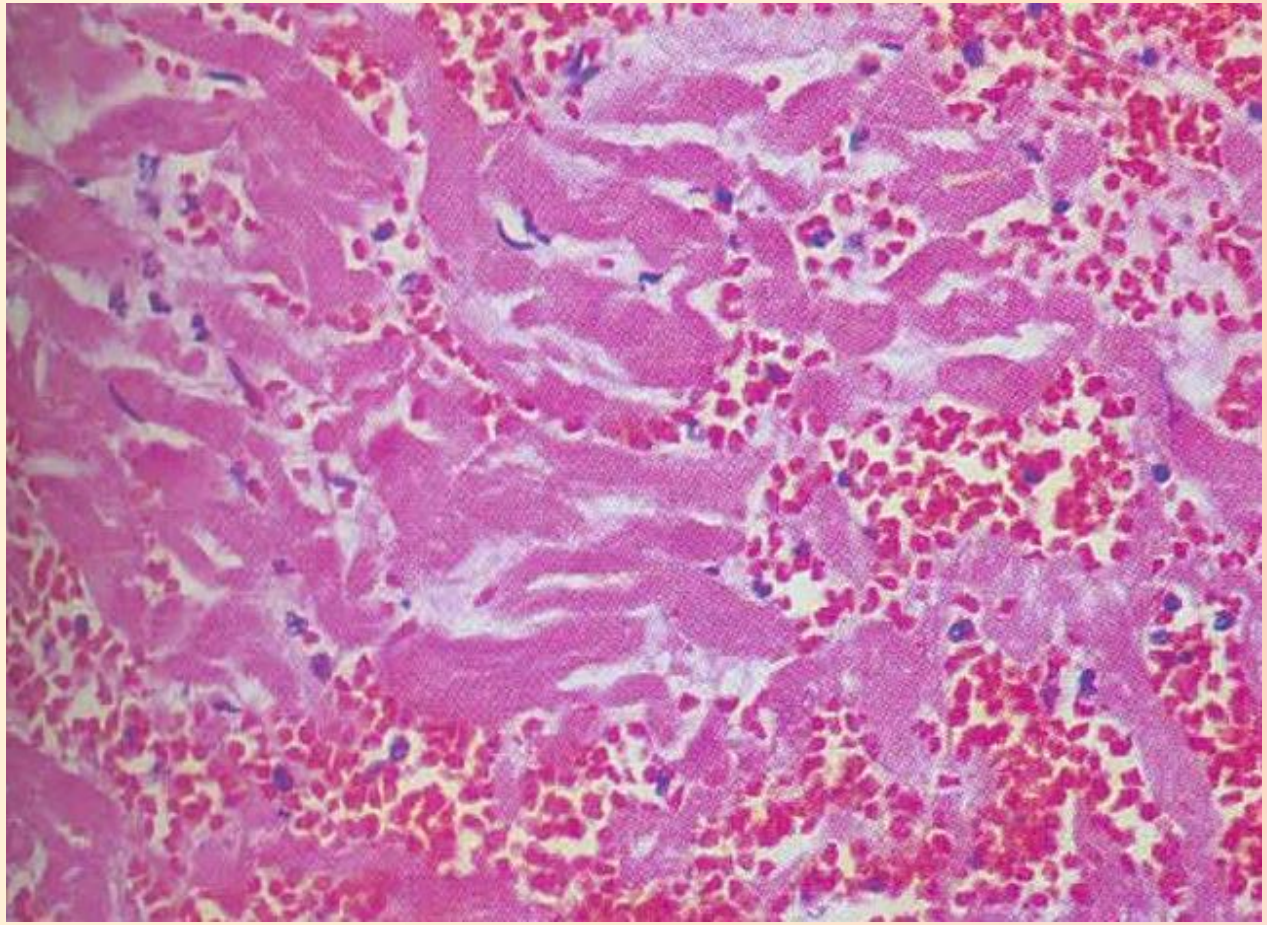
NECROSIS

COAGULATIVE NECROSIS

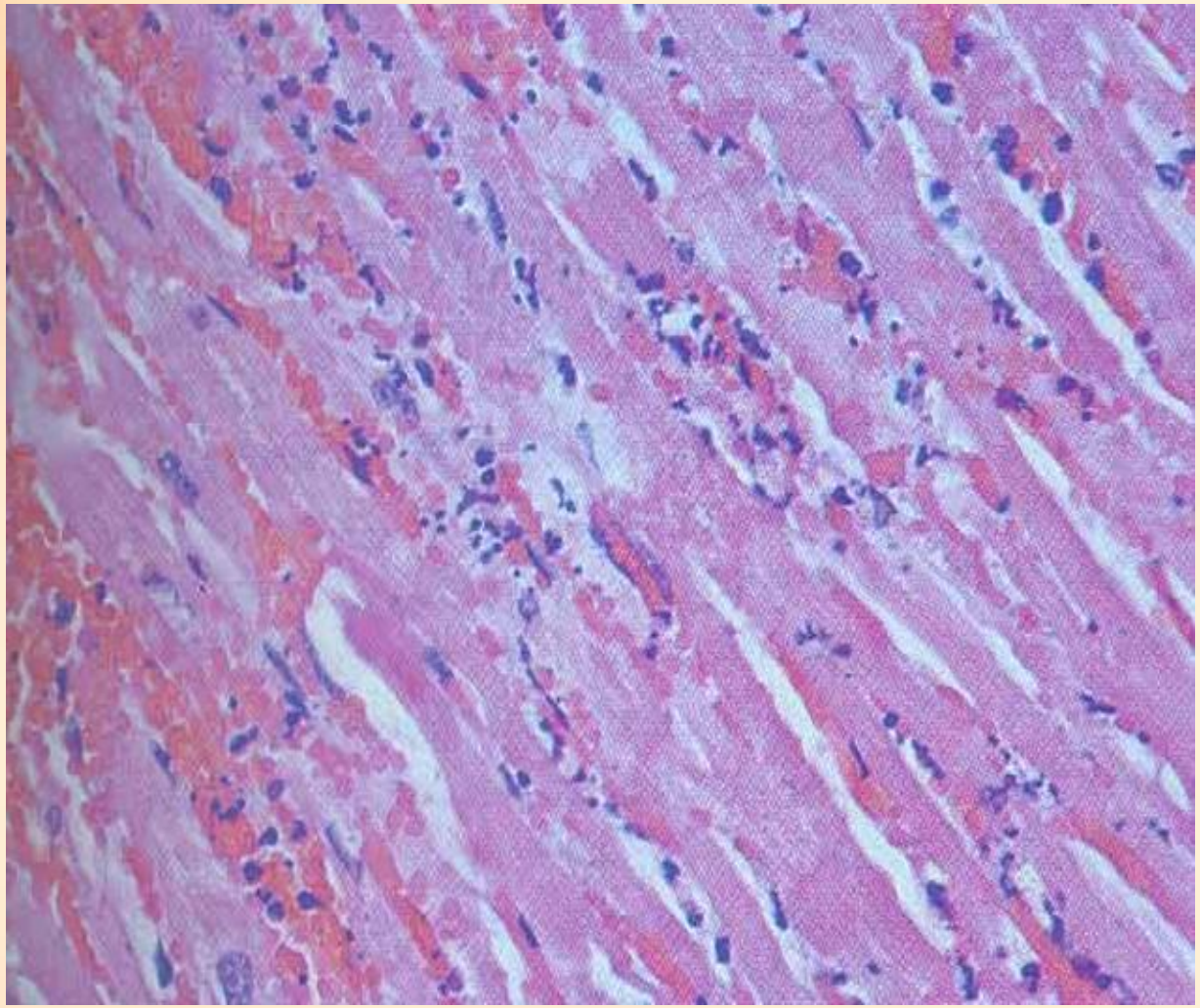
- There is preservation of basic outline of the cell
- The increasing intracellular acidosis denatures not only structural proteins but also the enzymes & so blocks the proteolysis of the cell
- E.g. Myocardial infarct
- This is characteristic of hypoxic death of cells in all tissues except the brain

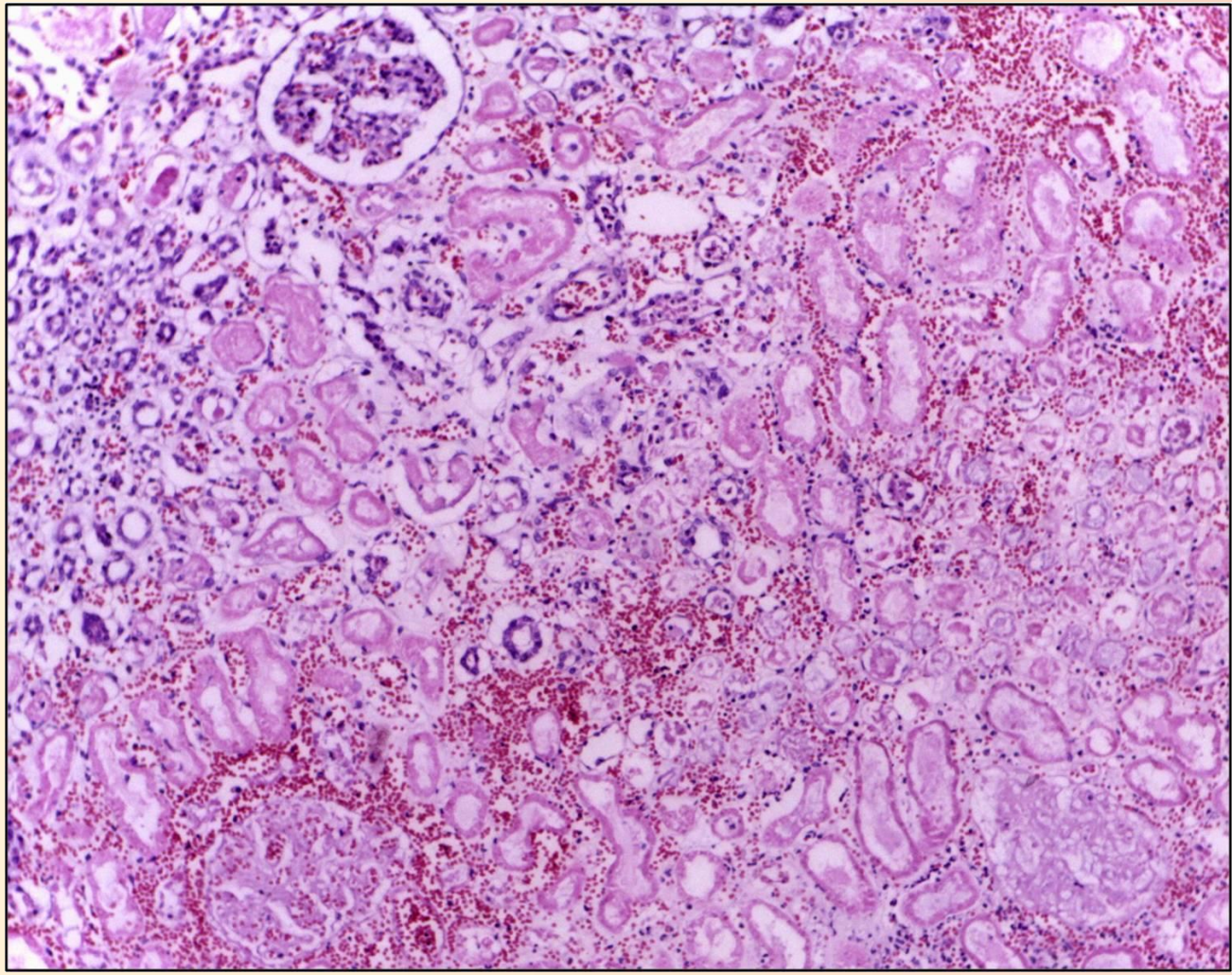
COAGULATIVE NECROSIS

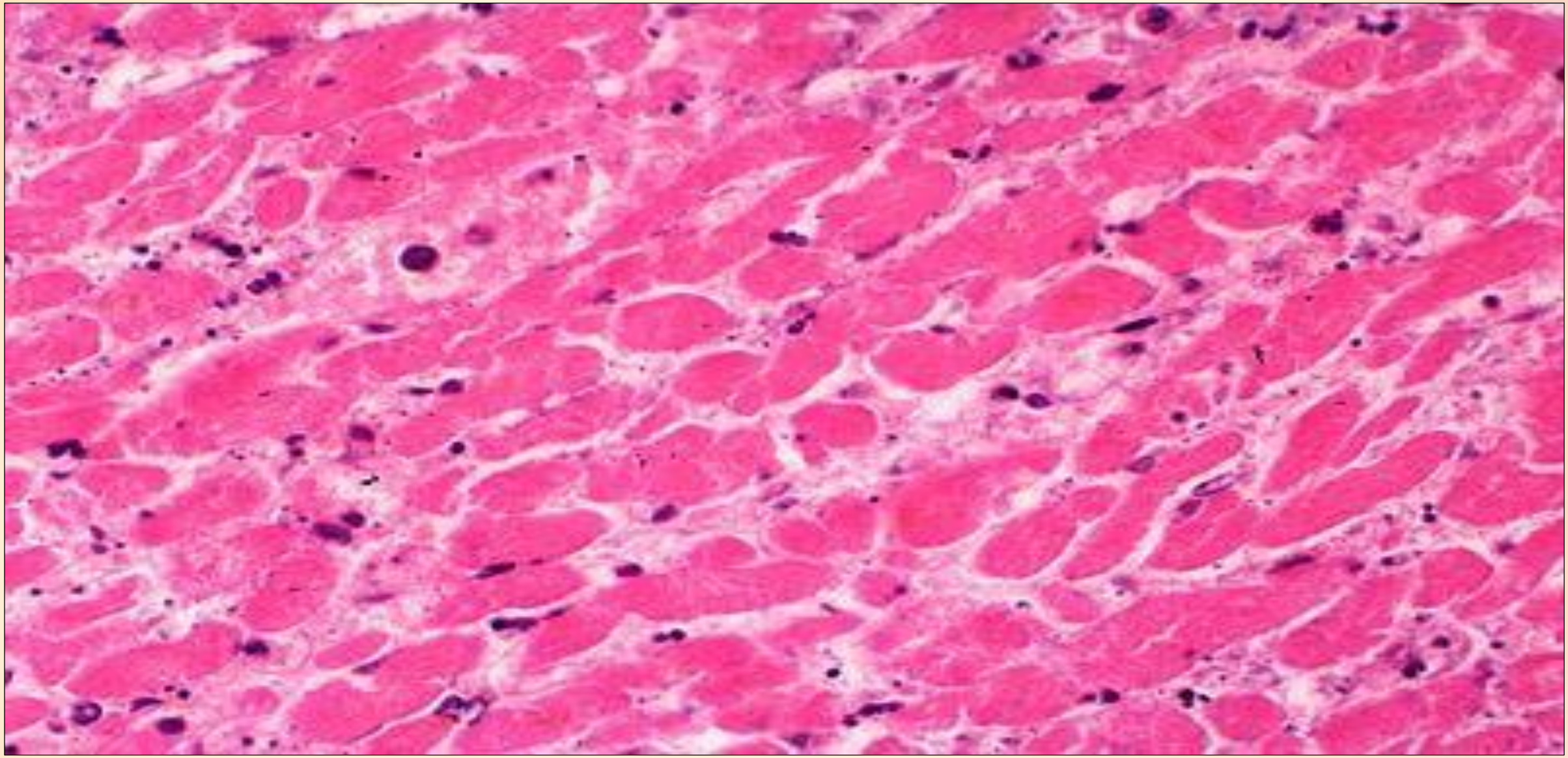




COAGULATIVE NECROSIS

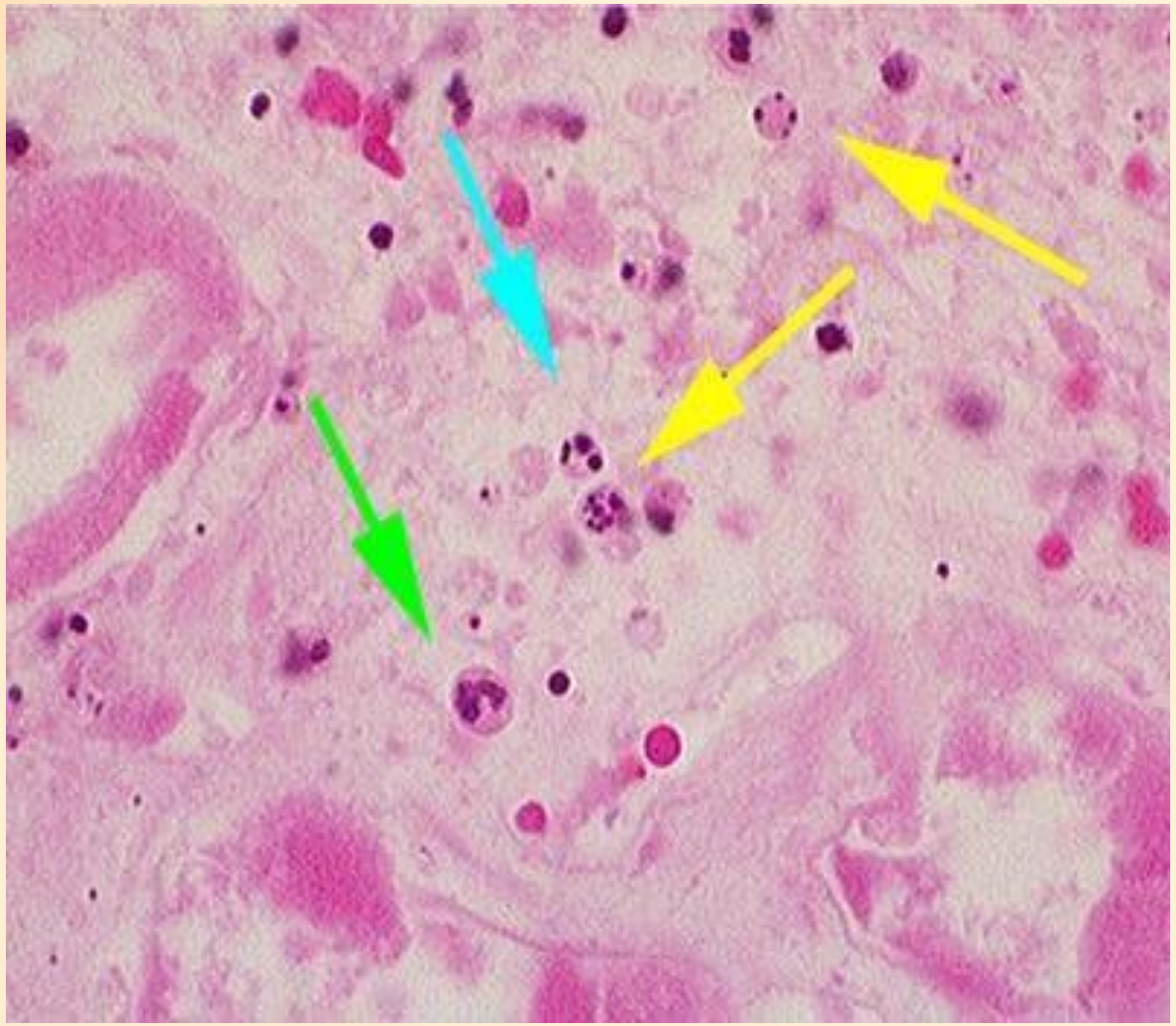


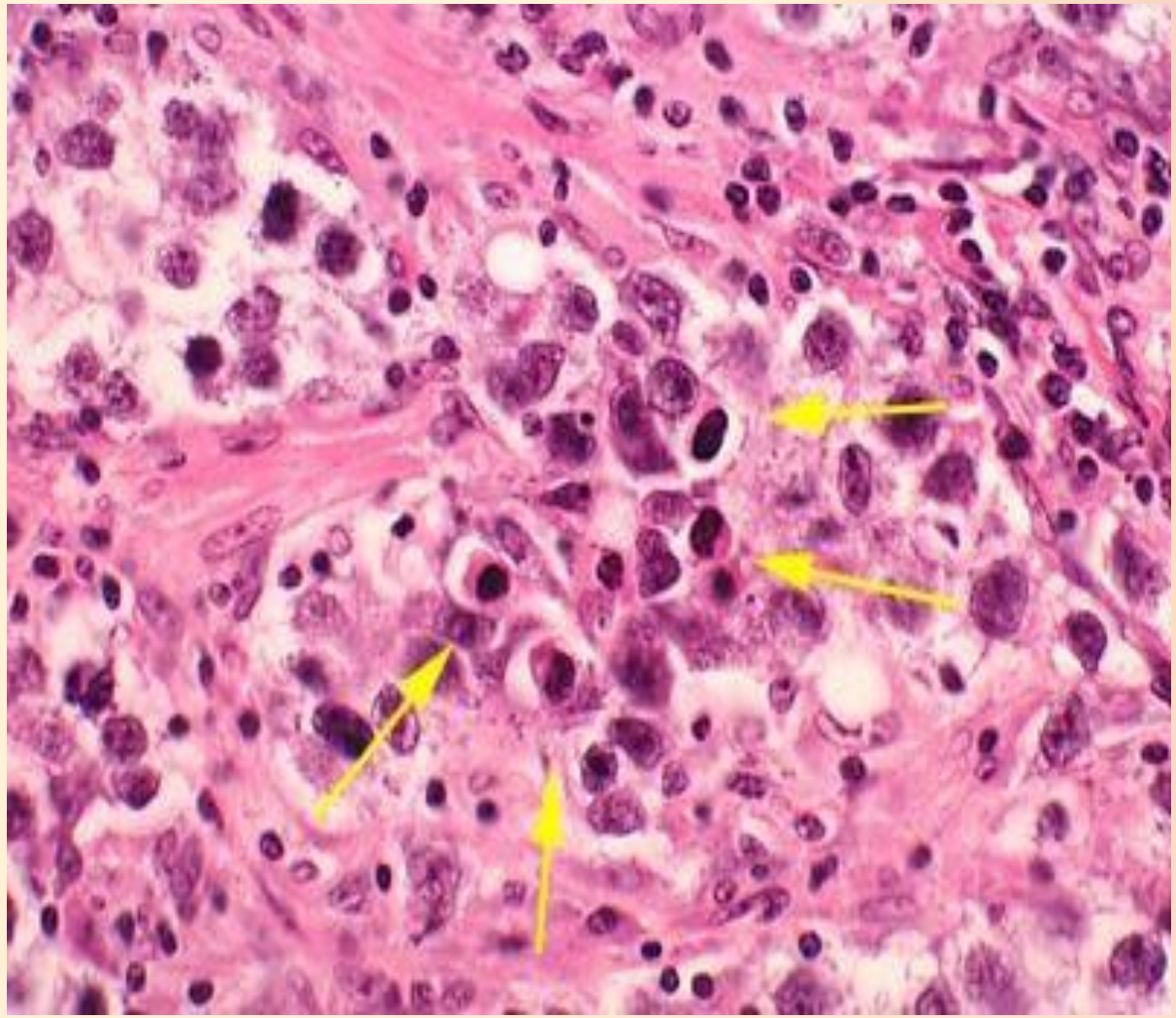




Myocardial infarction (coagulative necrosis)

Cytoplasmic eosinophilia & nuclear karyolysis





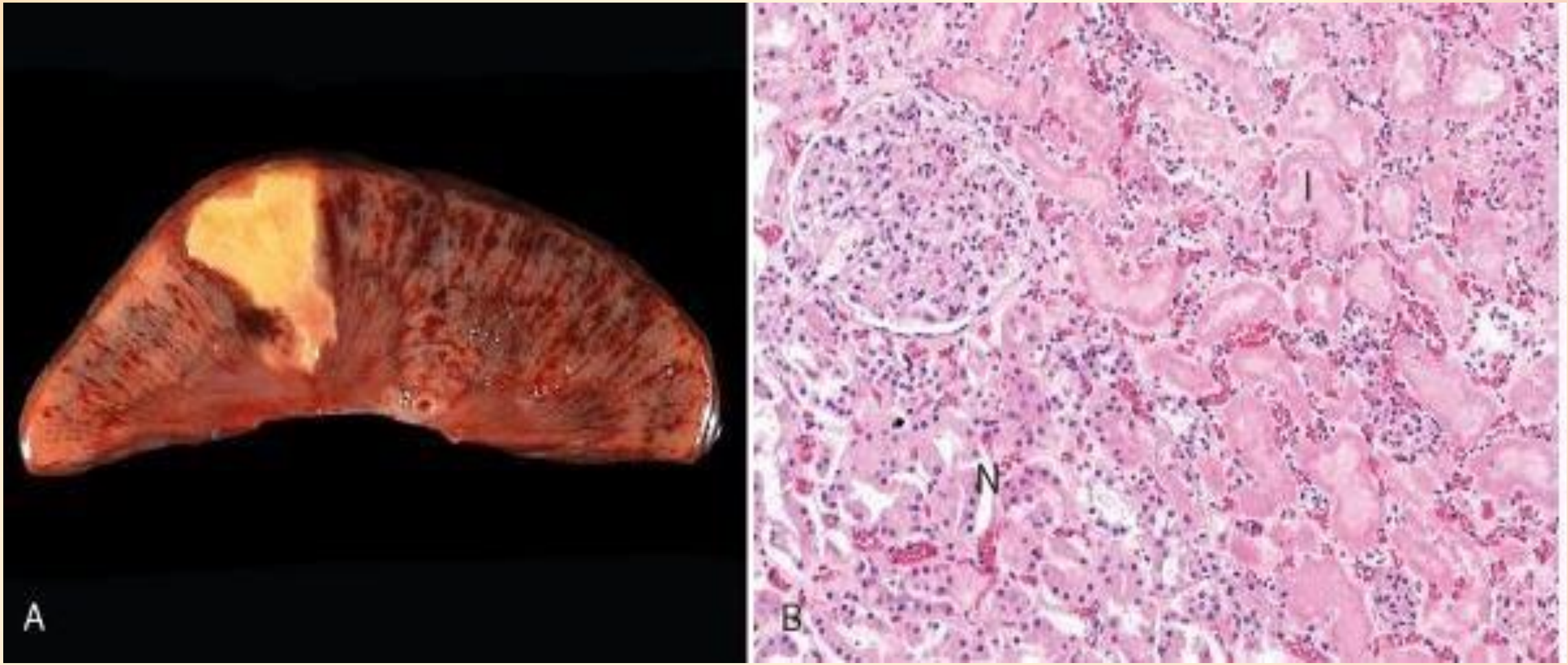
Microscopical appearance of nuclear changes in necrotic cells.

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.

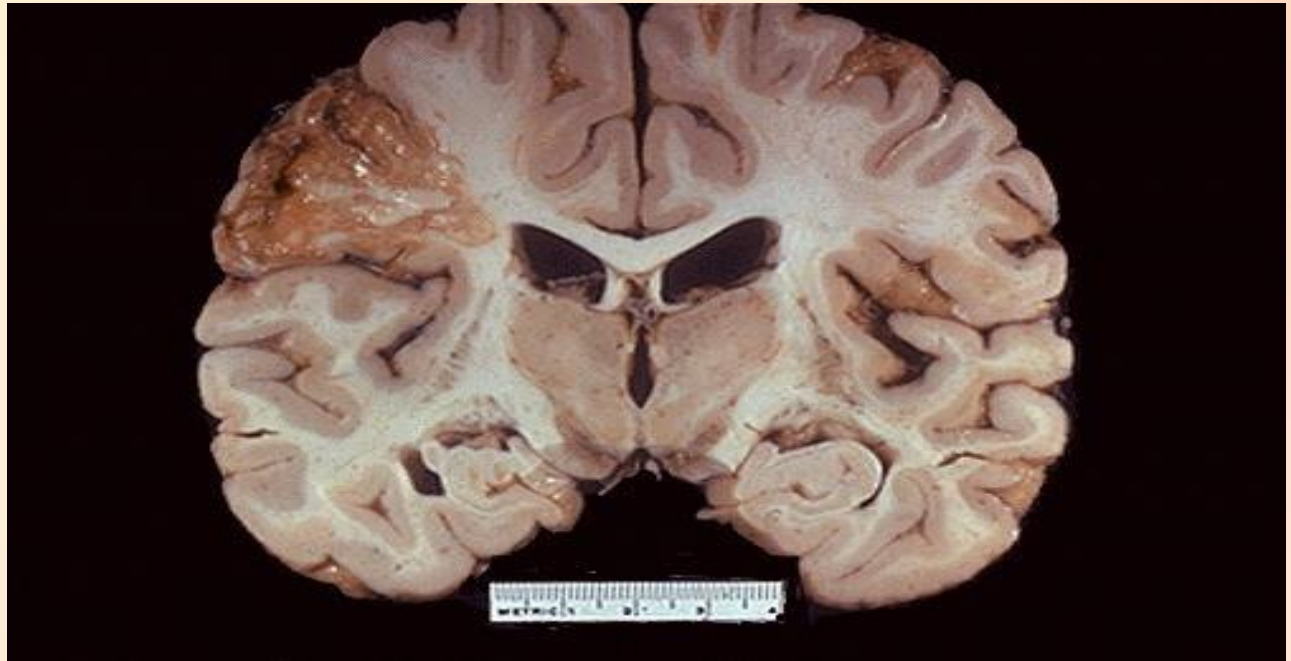


Coagulative necrosis. A, A wedge-shaped kidney infarct (yellow). B, Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I) showing preserved cellular outlines with loss of nuclei and an inflammatory infiltrate

◦ 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)

NECROSIS

LIQUEFACTIVE NECROSIS

- Is characteristic of focal bacterial, or occasional fungal infections because microbes stimulate the accumulation of inflammatory cells
- If the process is initiated by acute inflammation, the material is creamy yellow because of the presence of dead white cells & called pus
- E.g. hypoxic death in central nervous system

NECROSIS

GANGRENOUS NECROSIS

- The term is applied to a limb , usually lower leg that has lost its blood supply & has undergone coagulation necrosis.
- When bacterial infection is superimposed , coagulative necrosis is modified by the liquefactive action of the bacteria & the attracted leukocytes (wet gangrene)

GANGRENE

Types of the gangrenes

- **Dry gangrene – dead necrotised tissue remains uninfected.**
- **Wet gangrene -necrotic tissue becomes infected.**
- **Gas gangrene – Wet gangrene infected by one of the gas forming Clostridia**

DRY GANGRENE

- Gangrene begins in distal part of limb due to ischemia
- Causes-
  - Atherosclerosis of arteries supplying limb
  - Thromboangitis obliterans
  - Raynauds disease
  - Trauma
  - Ergot poisoning
- Due to ischemia tissues undergoes infarction and line of separation is formed between the necrotic tissue and healthy tissue
- At the margins of necrotic tissue, granulation tissue develops

DRY GANGRENE

Morphology

- Grossly the affected part is dry shrunken and dark in color resembling the mummified foot.
- Black color is due to release of hemoglobin from the hemolysed RBC's which are acted upon by the hydrogen disulfide produced by bacteria which results in the formation of black iron sulphide
- Gradually the gangrenous tissue falls from the healthy tissue at the line of separation.
- Because of the risk of infection it should be surgically separated

WET GANGRENE

Wet gangrene typically occurs in the organs with venous blockage or both venous and arterial blockage

- Diabetic foot –High glucose content in the necrosed tissue favours bacterial growth
- Bed sores –In bed ridden patients at the pressure on the sites like sacrum, buttocks and heel
- Also in organs like bowel (due to strangulated hernia, volvulus or intusscesception) lung, mouth, cervix and vulva

WET GANGRENE

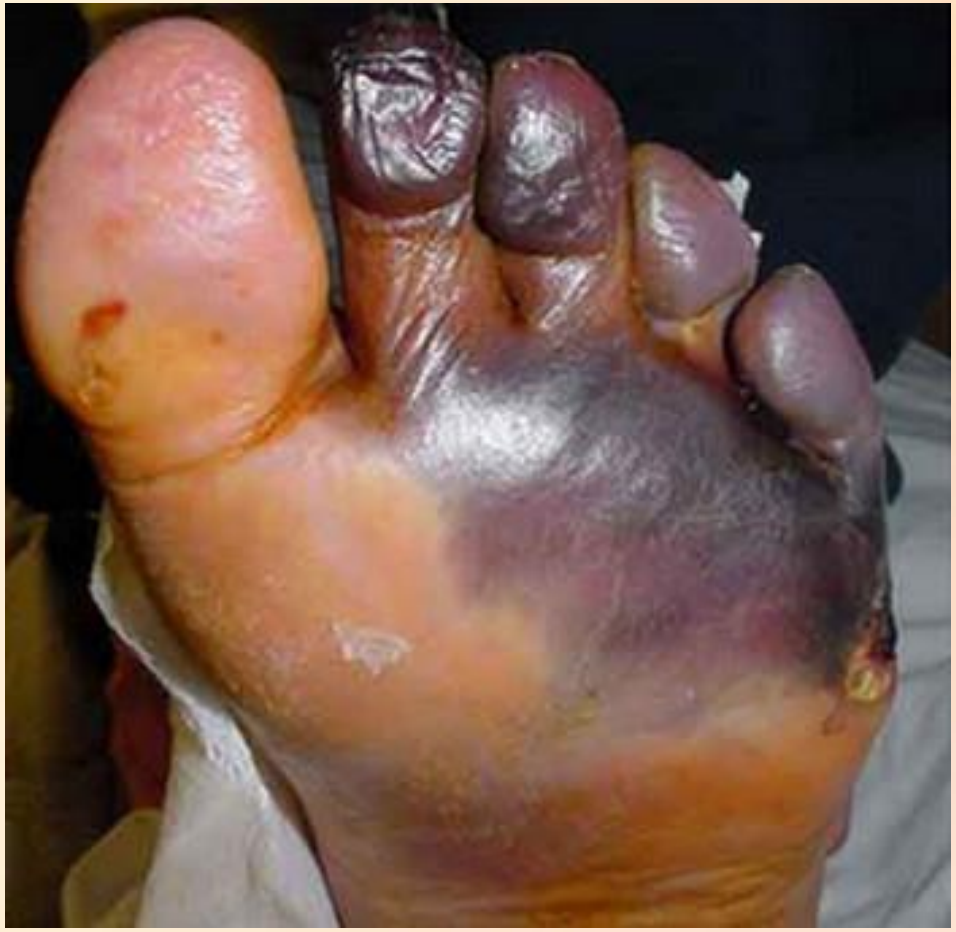
Morphologic features:

- **Grossly the affected part is black, rotten, and soft and pulpy**
- **The affected part is dark due to same reason as in dry gangrene**
- **Microscopically the tissue shows coagulative necrosis with extensive areas of hemorrhage**
- **Line of demarcation between variable and necrosed tissue is absent**

GANGRENOUS NECROSIS

	Dry gangrene	Wet gangrene
Site	Lower limbs	More common in bowel
Mechanism	Arterial occlusion	More commonly venous occlusion, less often arterial occlusion
Macroscopy	Organ is dry, shrunken and black	Moist, soft swollen and dark
Line of demarcation	Present between gangrenous and healthy part	No line of demarcation
Presence of bacteria	Bacteria fail to survive	Numerous bacteria is present
Prognosis	General better due to little septicemia	Generally poor due to profound toxemia

GANGRENOUS NECROSIS



Wet gangrene
(liquefactive necrosis)

Dry gangrene
(coagulative necrosis)

Gas gangrene

- It is wet gangrene infected by one of the gas forming Clostridia (Gram positive anaerobic bacteria)
- Gas forming Clostridia enters the tissue through a contaminated wound or as a complication of operation on colon which normally contains Clostridia
- Clostridia rapidly spreads through tissues especially in muscles and cause extensive necrosis and massive edema

Gas gangrene

Morphology

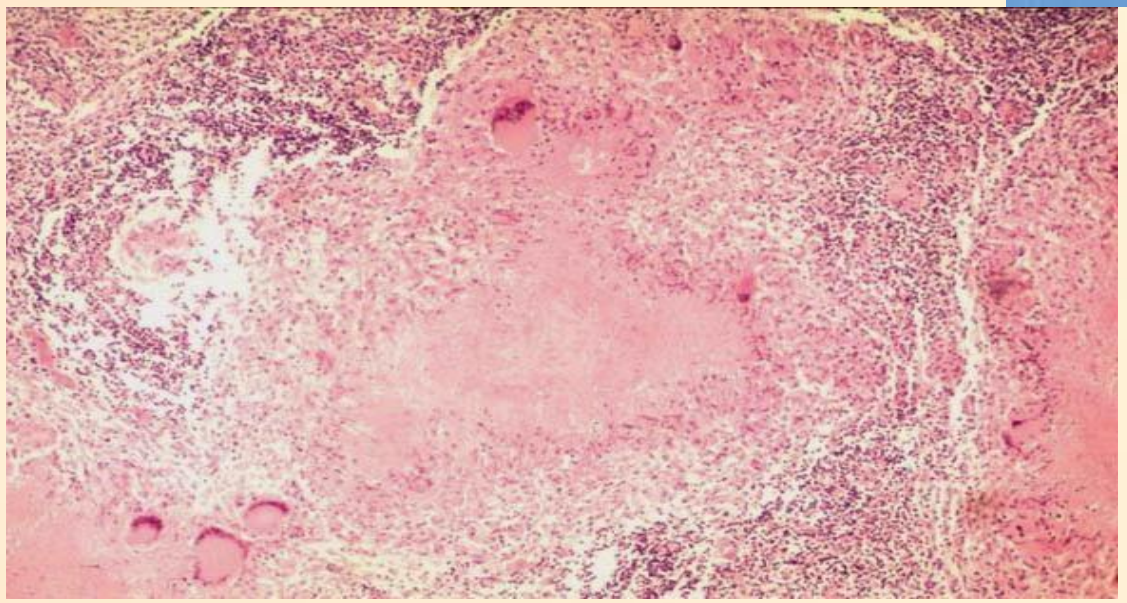
- **Gross – the affected part is edematous, swollen and has crepitations on palpation due to accumulation of gas in tissues**
- **Microscopically**
  - **Muscle fibres undergo coagulative necrosis with liquefaction**
  - **At the periphery, a zone of leukocytic infiltration, oedema and congestion are found**

NECROSIS

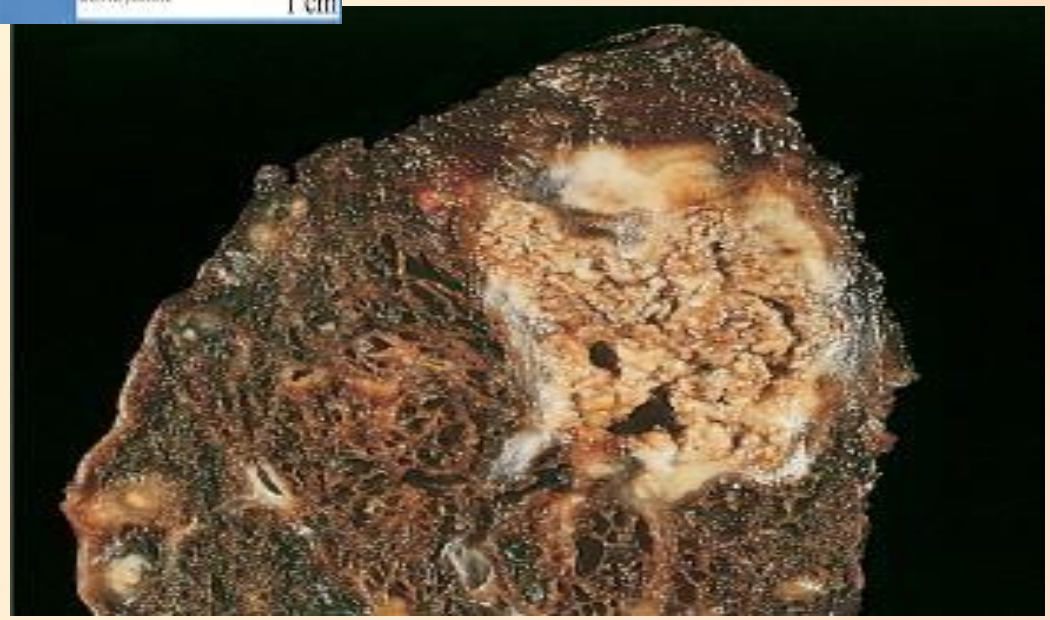
CASEOUS NECROSIS

- Distinctive form of coagulative necrosis most often encountered in tuberculous infection
- The term caseous is derived from cheesy white gross appearance of area of necrosis which is friable and white

- **Caseous necrosis:**



Caseous necrosis is surrounded by granulomatous inflammation with giant cells.



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

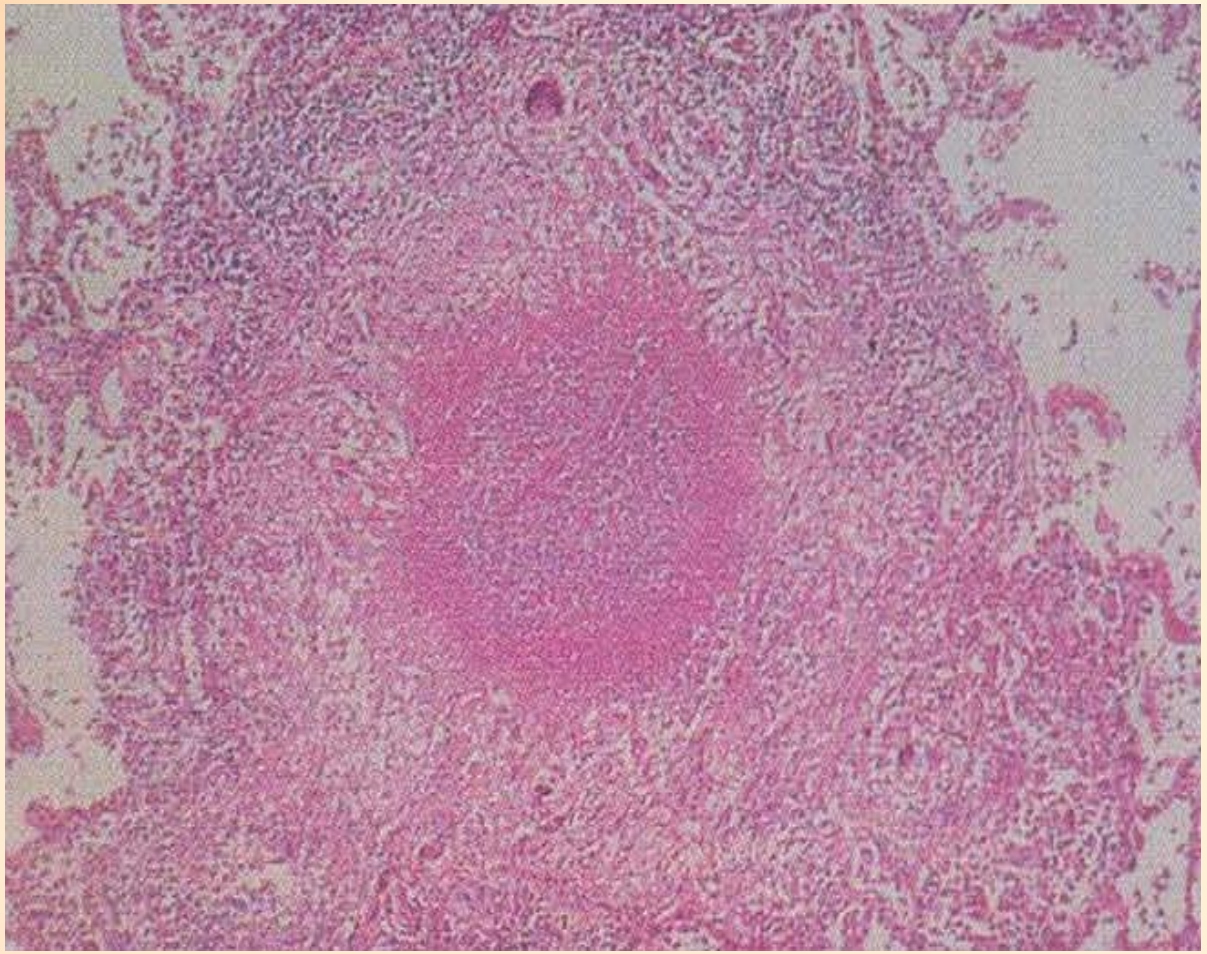
NECROSIS

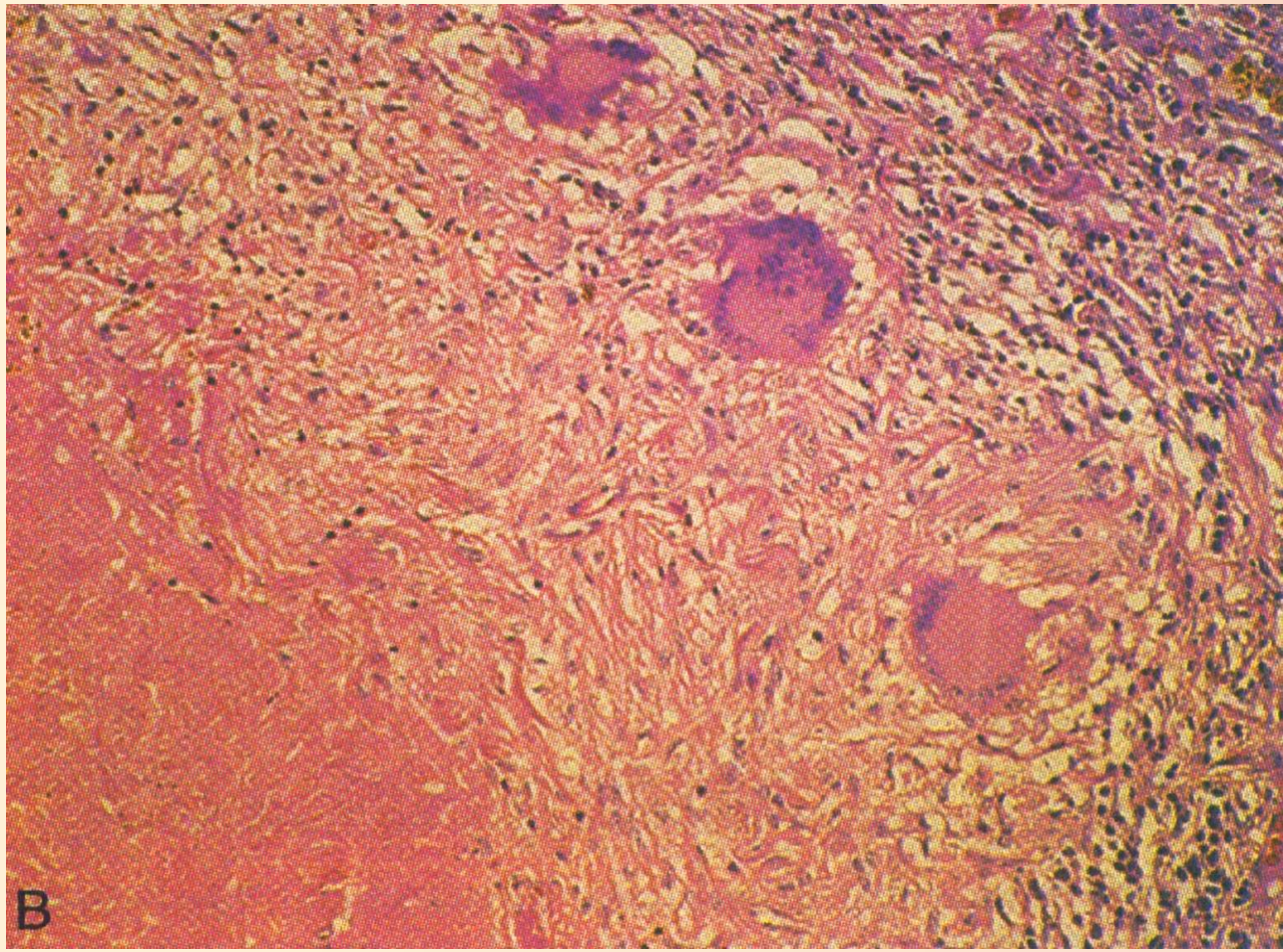
CASEOUS NECROSIS

Microscopic appearance

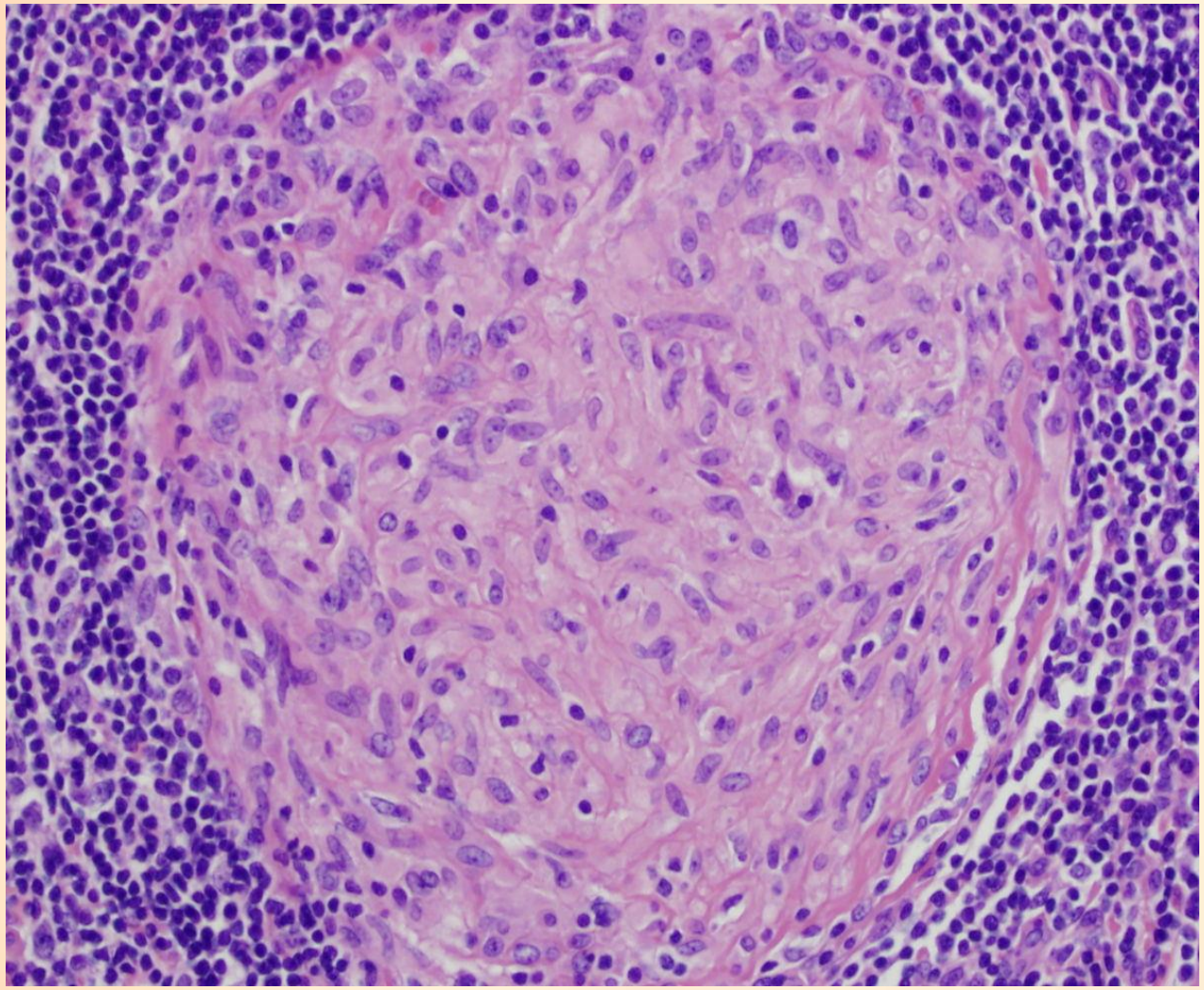
- Necrotic focus – collection of fragmented or lysed cells and amorphous granular debris enclosed with in distinctive inflammatory border – granulomatous reaction

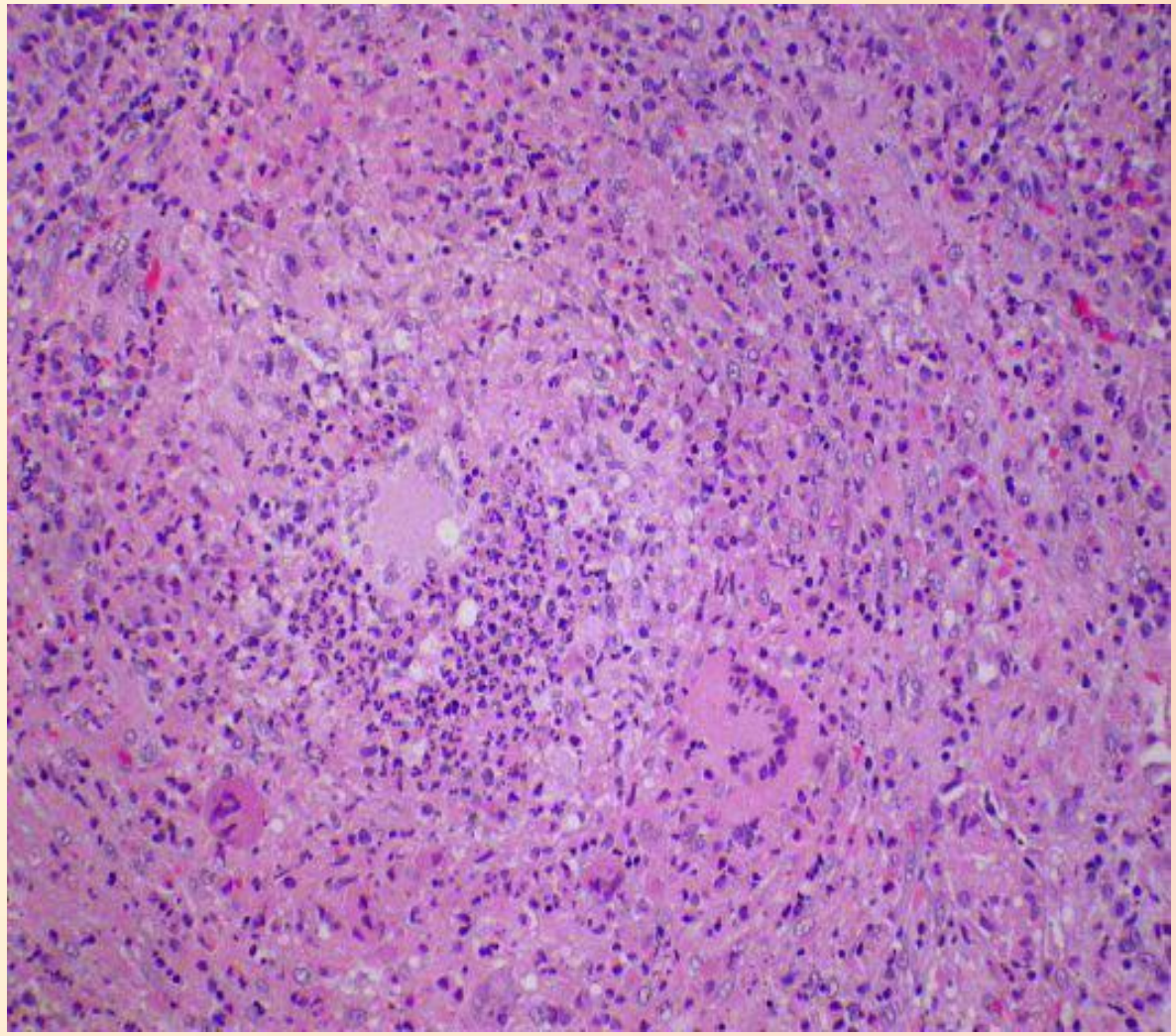
GRANULOMA FORMATION IN CASEOUS NECROSIS





GRANULOMA



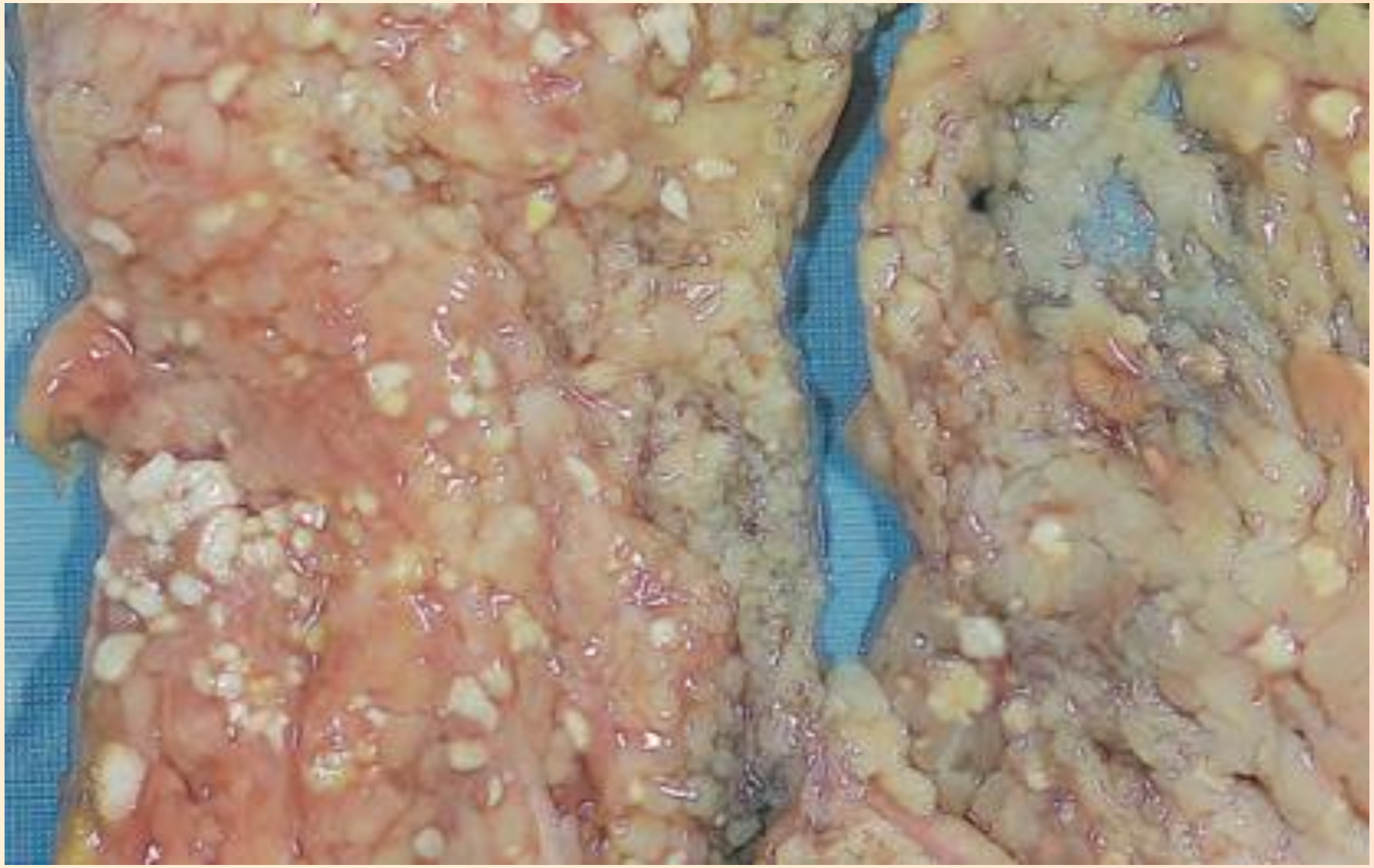


NECROSIS

FAT NECROSIS

- It is descriptive term for focal areas of fat destruction , typically occurring as a result of release of activated pancreatic lipases into the substance of pancreas & the peritoneal cavity
- The fatty acids released combine with calcium to produce grossly visible chalky white areas (fat saponification)

FAT NECROSIS



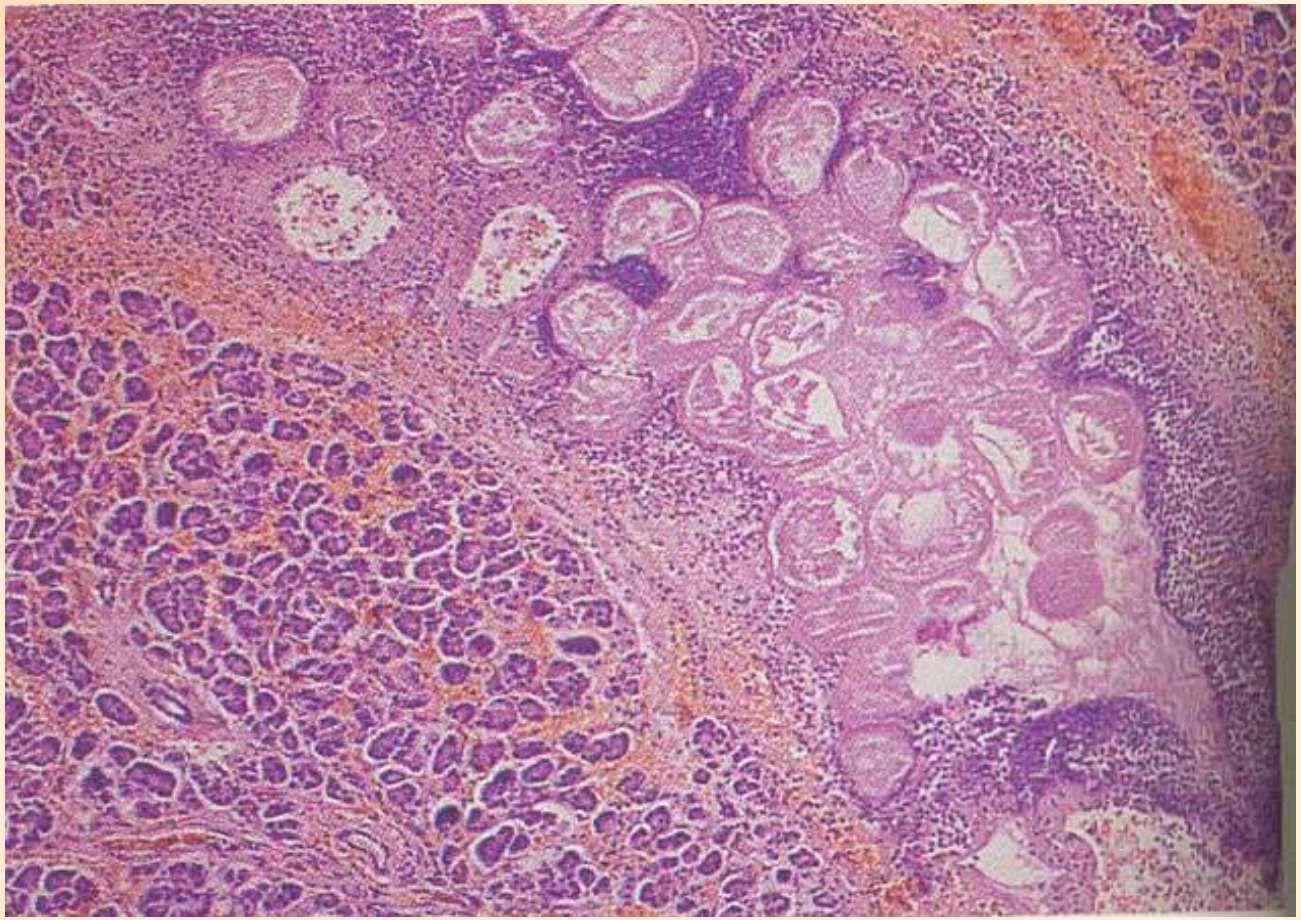
NECROSIS

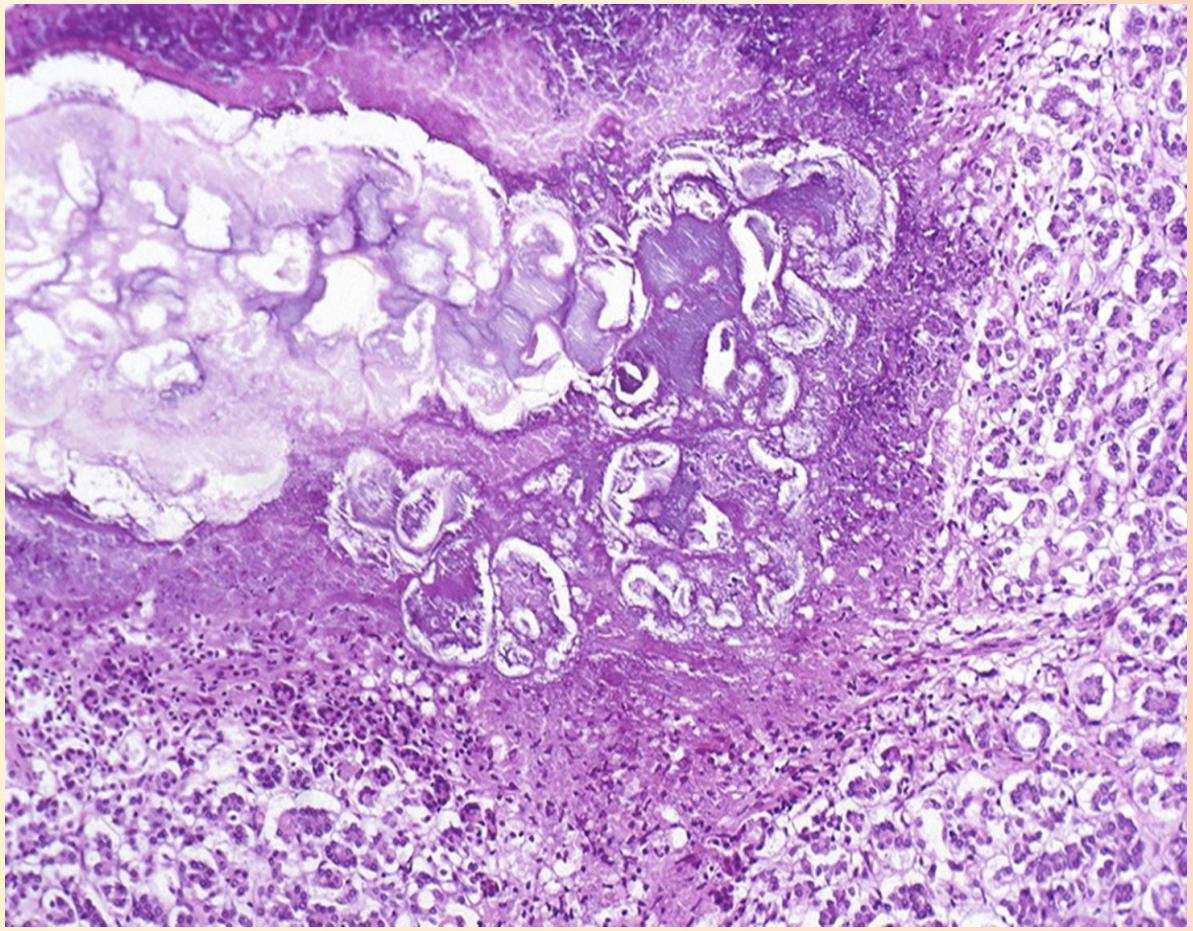
FAT NECROSIS

Microscopic appearance

- **Necrosis take the form of shadowy outlines of necrotic fat cells, with basophilic calcium deposits surrounded by an inflammatory reaction**

FAT NECROSIS



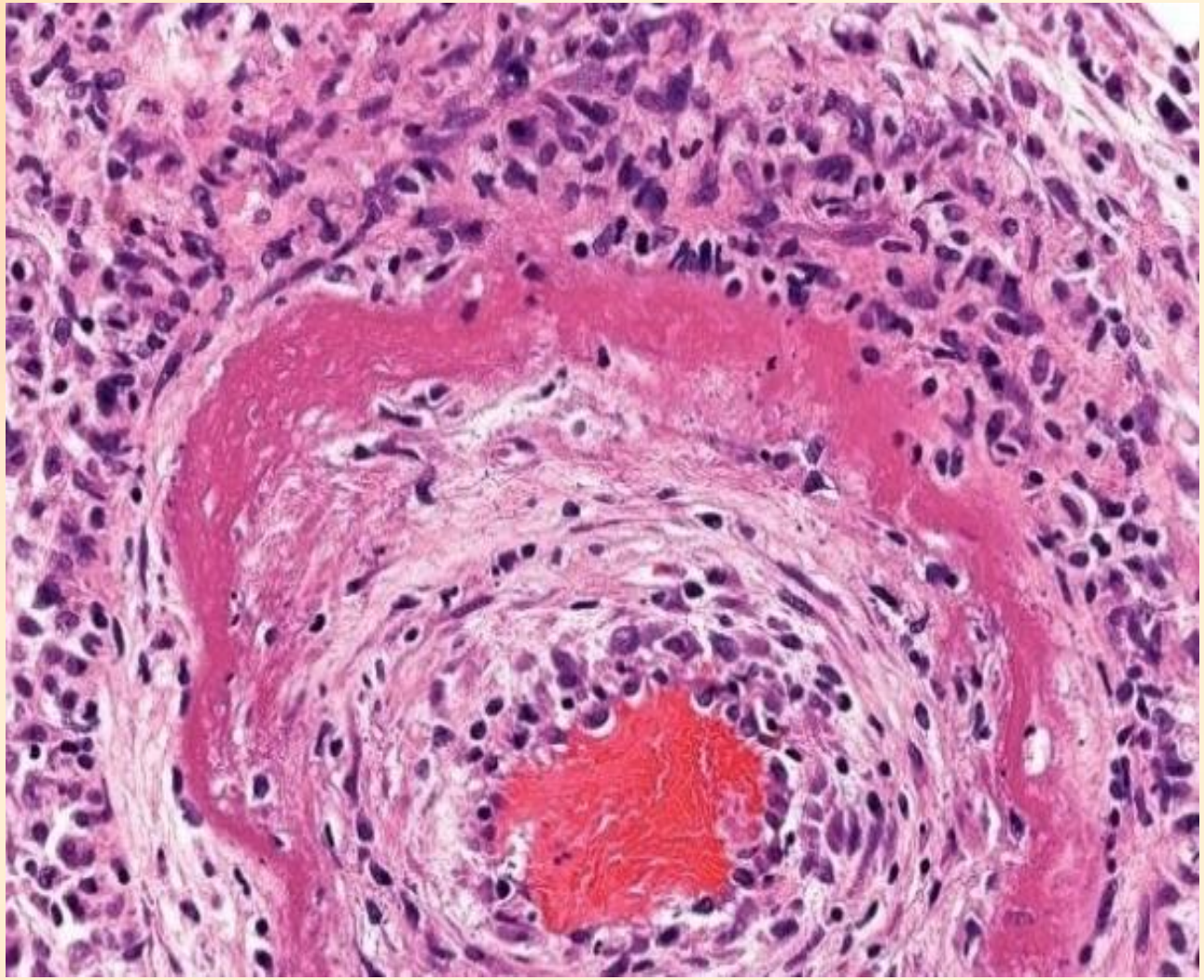


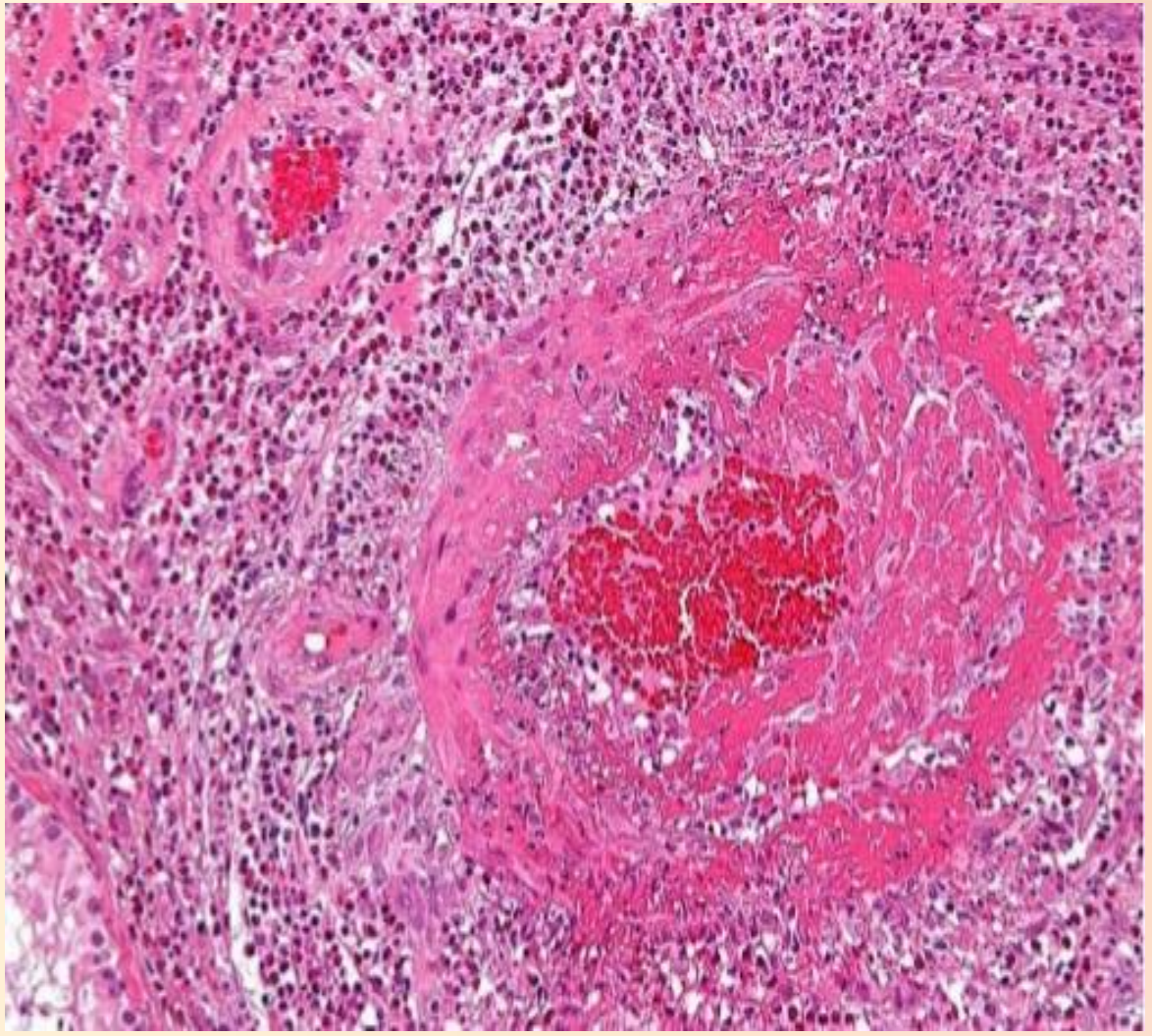
NECROSIS

FIBRINOID NECROSIS

- Special form of necrosis seen in immune reactions involving blood vessels
- Occurs when complexes of antigens and antibodies are deposited in the walls of arteries
- Along with these complexes fibrin which has leaked out of vessels give bright pink amorphous appearance called fibrinoid (Fibrin like)

FIBRINOID NECROSIS





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

Think twice before you open your mouth. What comes out of your mind & your mouth is important than what goes in

- Master Choa Kok Sui

THANK YOU