CELL INJURY AND ADAPTATIONS

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Outlines

- Introduction
- Cellular adaptation
- Causes of Cell Injury
- Morphologic Alterations in Cell Injury
- Necrosis
- Apoptosis
- Mechanism of cell injury
- Intracellular Accumulations

Introduction

- The intracellular milieu of cells is normally tightly regulated and it remains fairly constant, a state referred to as **homeostasis**.
- **Adaptation** is a reversible changes in number ,size or functions of cells in response to changes in their environment to preserve viability and function of the cell .
- **Cell injury** is a sequence of event that follows if the limits of adaptive responses are exceeded or if cells are exposed to harmful external stress .

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- Cell injury is **reversible** up to a certain point, but if the stimulus persists or is severe enough from the beginning, the cell suffers **irreversible injury** and ultimately undergoes cell death.
- **Cell death**, the end result of progressive cell injury, is one of the most crucial events in the evolution of disease in any tissue or organ.
- **Necrosis** and **apoptosis** are the two principal mechanisms of cell death.

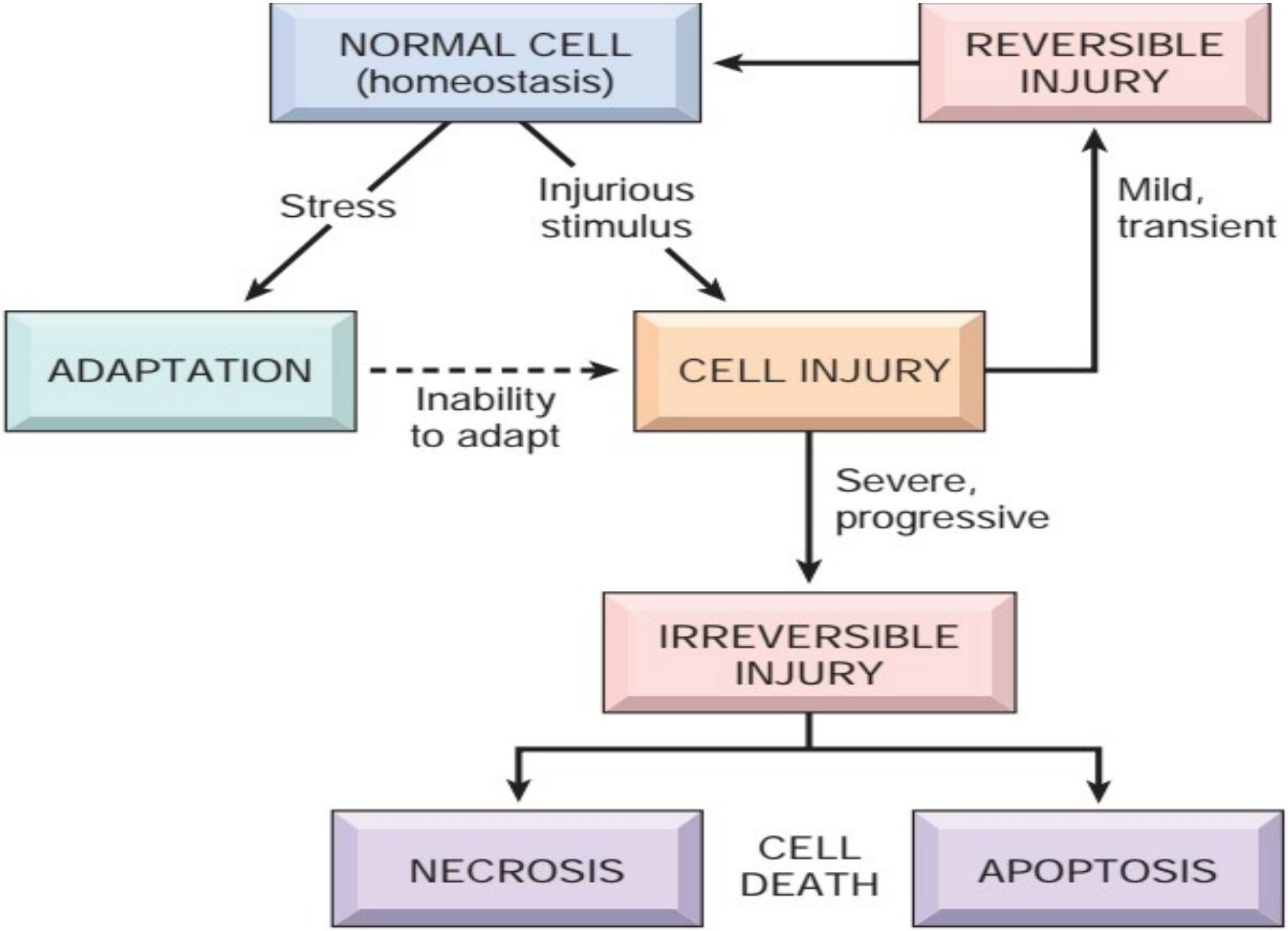
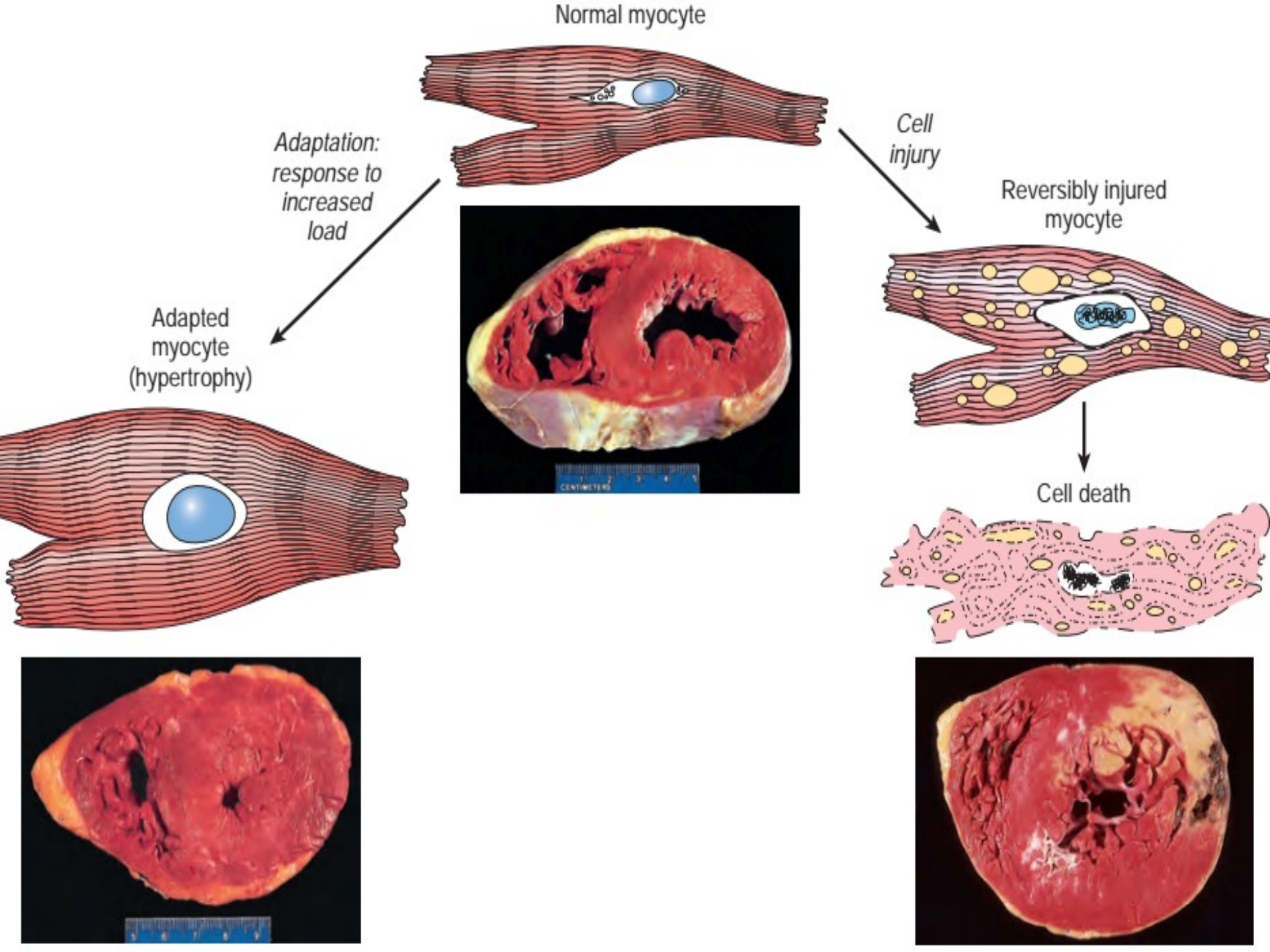


Figure 2-1 Stages of the cellular response to stress and injurious stimuli.

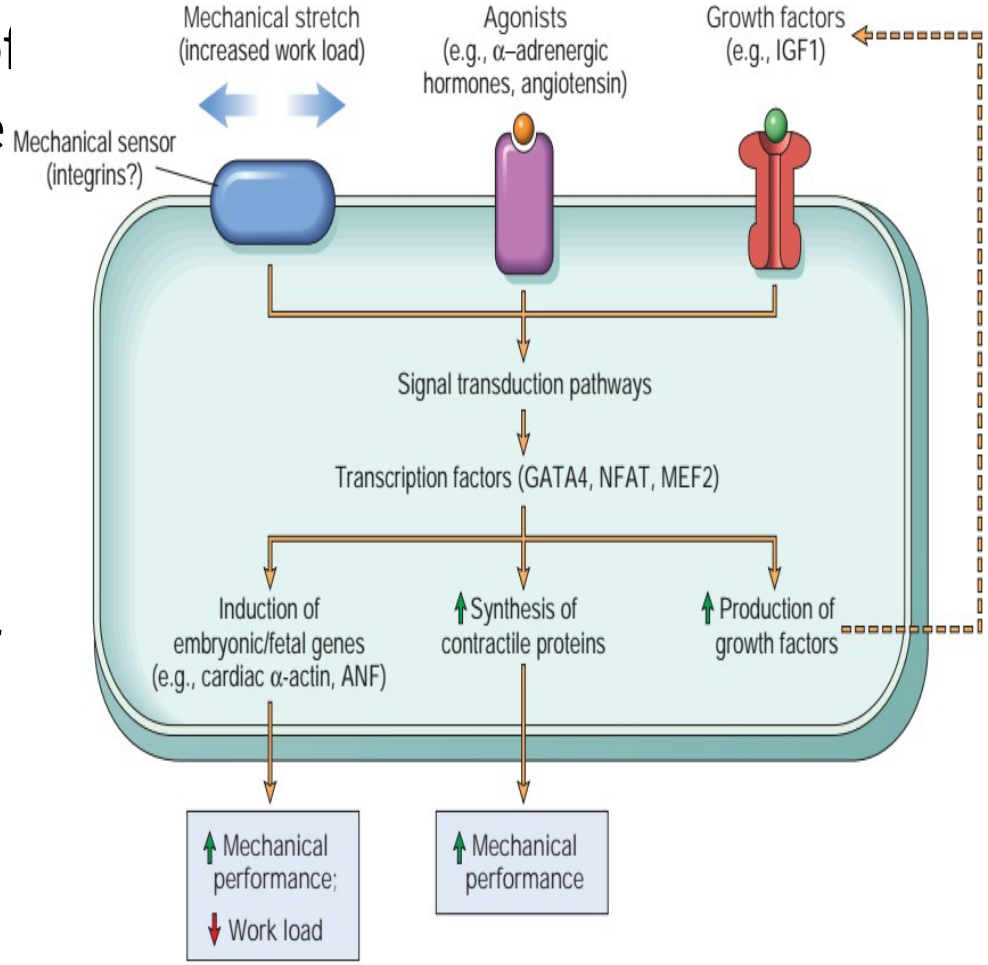

Normal myocyte
Adaptation: response to increased load
Cell injury
Adapted myocyte (hypertrophy)
Reversibly injured myocyte
Cell death

Cellular adaptations to stress

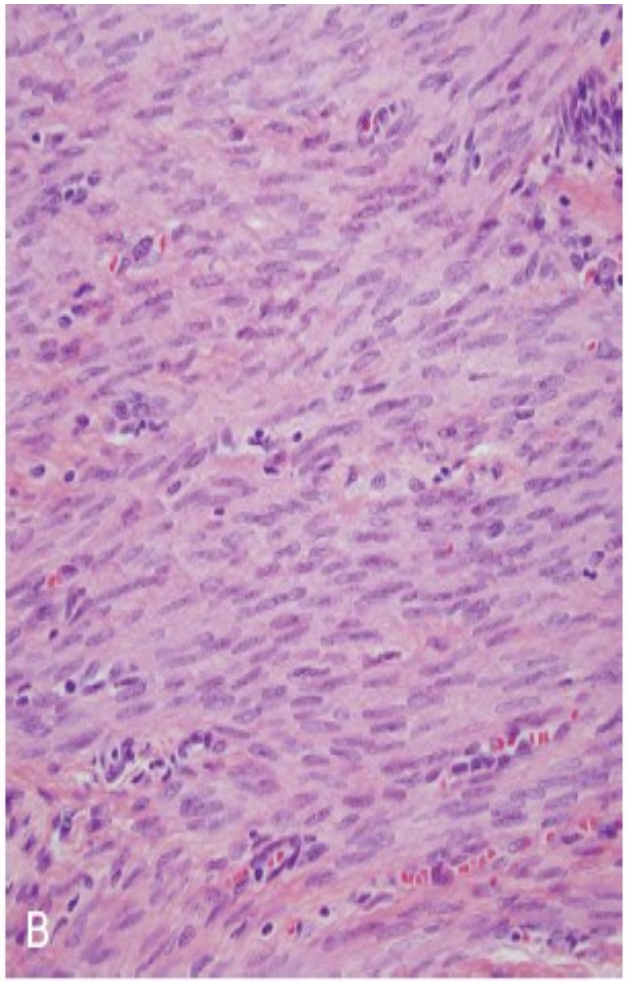
- **Adaptation** could be physiologic or pathologic.
- There are different forms of adaptations .
  - ✓ Hypertrophy
  - ✓ Hyperplasia
  - ✓ Atrophy
  - ✓ Metaplasia

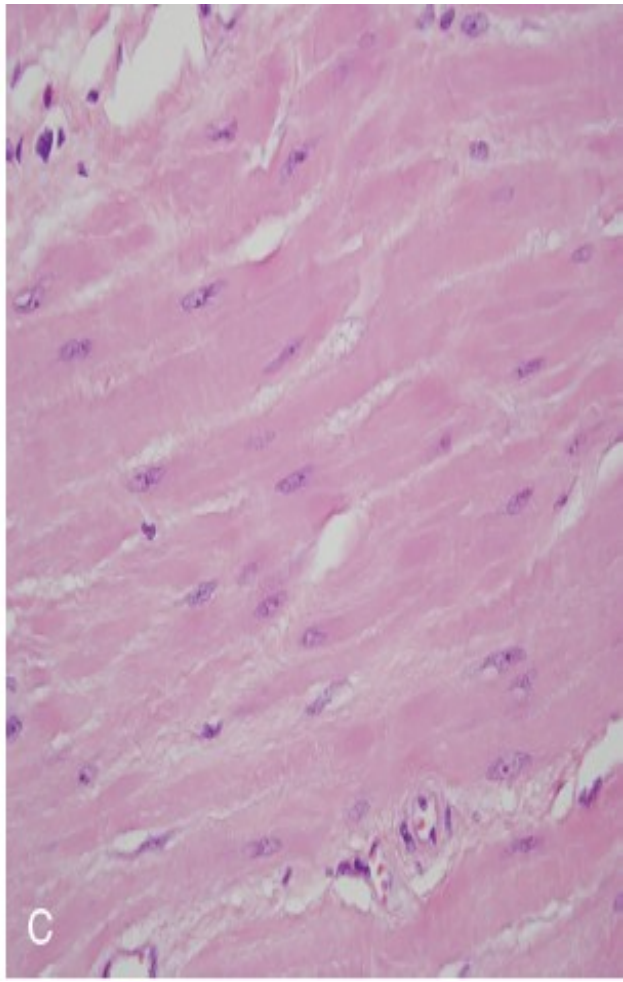
1 . Hypertrophy

- It is an increase in the size of cells resulting in an increase in the size of organ .
- It occurs when cells have limited capacity to divide .
- Hypertrophy caused by increased functional demand or growth factor or hormonal stimulation
- **Physiologic hypertrophy**
- **Pathologic hypertrophy**





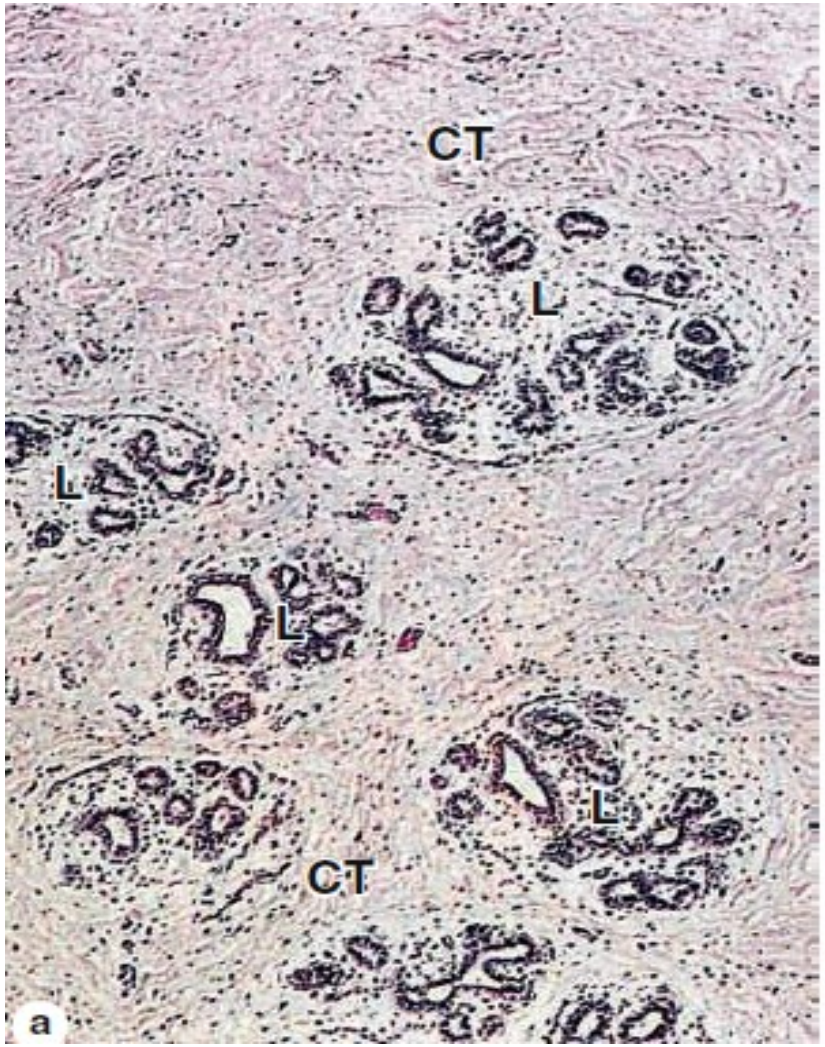


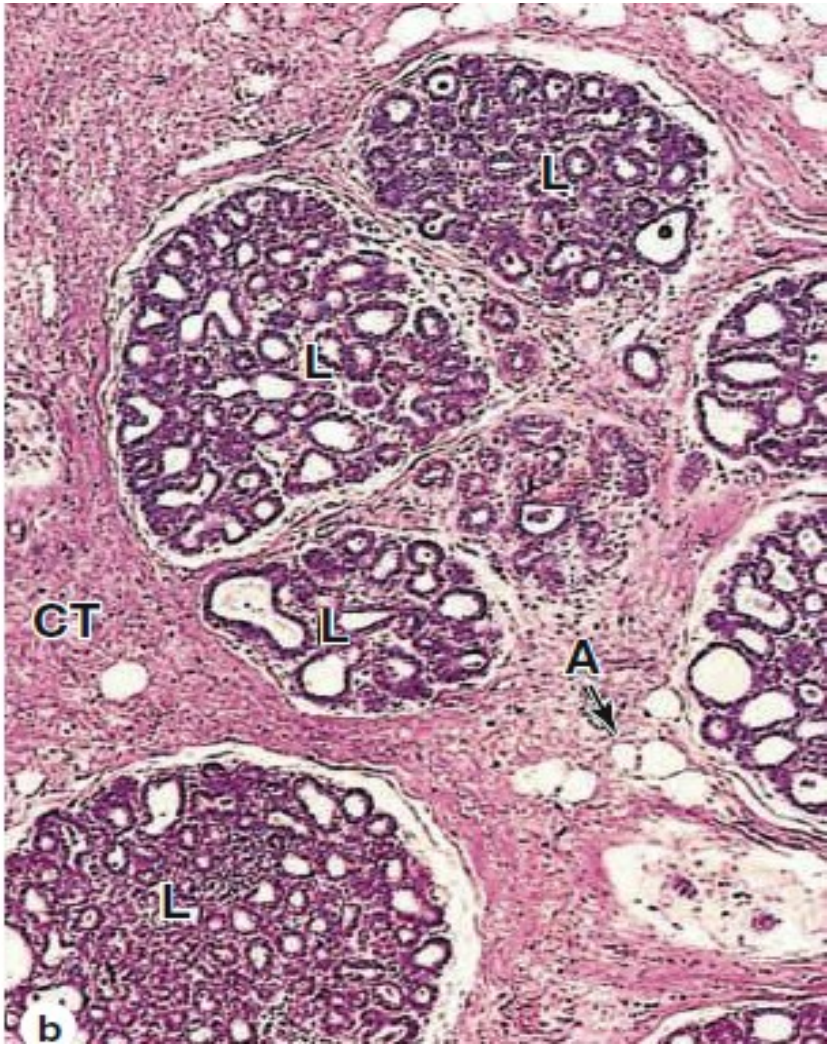


Photomicrograph of myometrium before and during pregnancy

2 . Hyperplasia

- **Hyperplasia** –refers to increase in cell number .
- It occurs in cells which are capable of replication **Mechanism**: by stimulation of growth factor and hormone .
- **Physiologic**-occurs on breast during puberty and pregnancy and compensatory hyperplasia after liver resection .
- **Pathologic** –usually due to excess hormone and growth factor stimulation ,e.g BPH and HPV
- It can provide fertile soil for malignancy

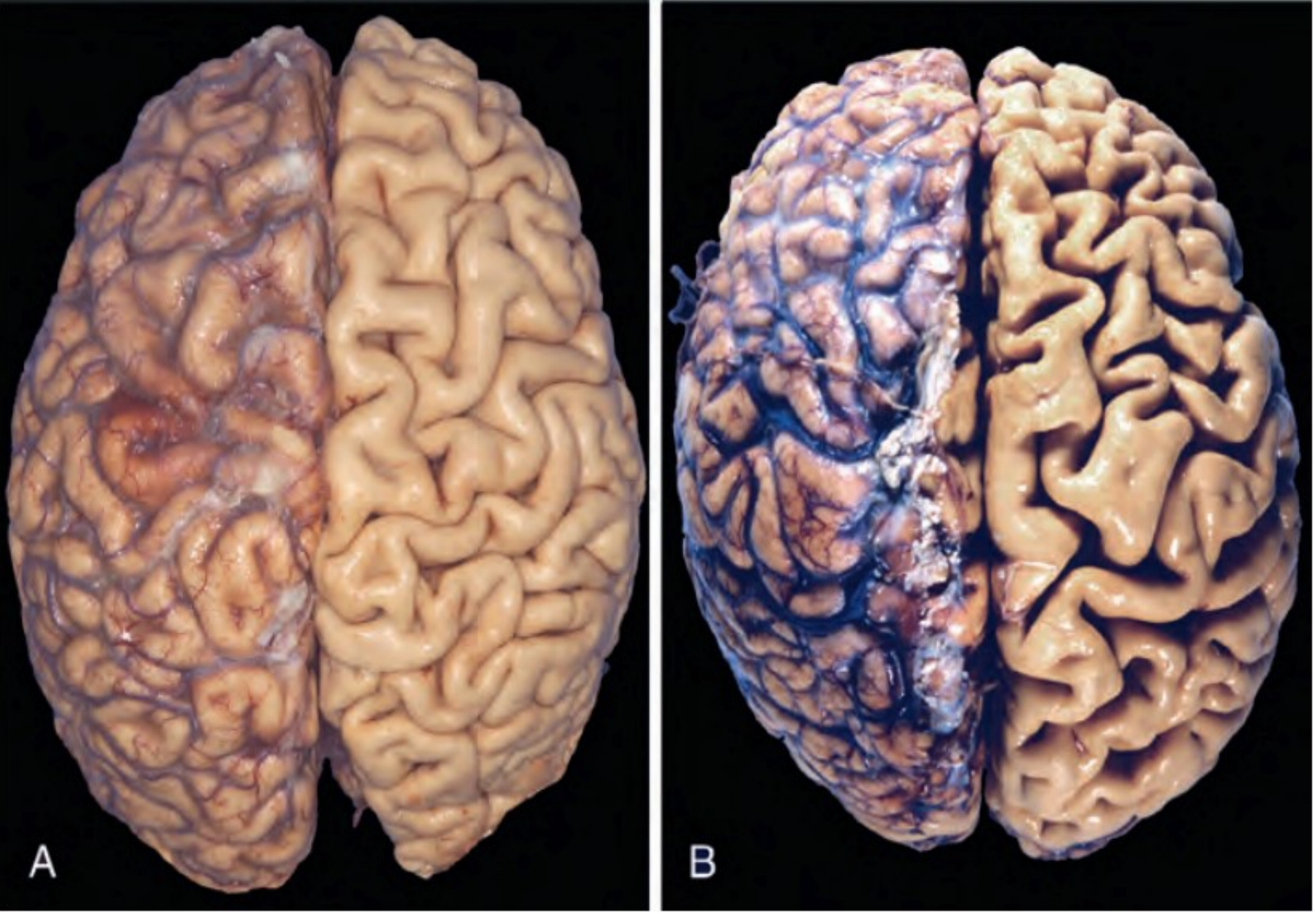




NON PREGNANT AND PREGNANT BREAST HISTOLOGY

3 . Atrophy

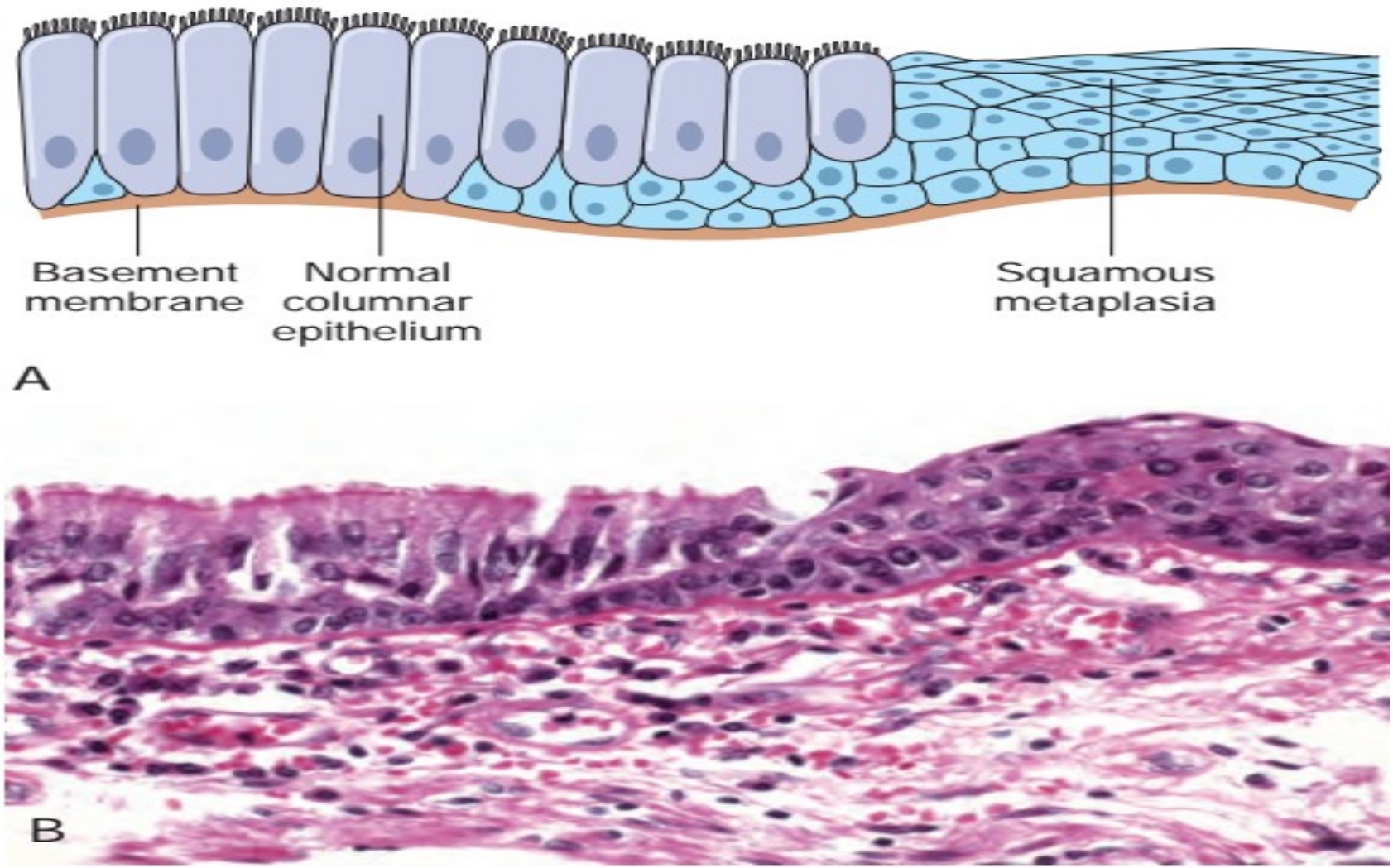
- **Atrophy** is shrinkage in size of cells by the loss of cell substance .
- **Mechanism:** decrease protein synthesis due to reduced metabolic activity and degradation of cellular protein
- **Physiologic-** common during menopause due to loss of hormonal stimulation .
- **Pathologic** –several causes, include decreased work load ,blood supply, innervation ,nutrition and endocrine stimulation and pressure over surrounding tissue by tumors.



Brain atrophy

4 . Metaplasia

- **Metaplasia** is a change in which one cell type replaced by another cell type .
- Occurs due to reprograming of stem cell to differentiate along a new path rather than transdifferentiation
- These type of adaptation enables the cells to withstand particular stressful environment .
- E.g metaplasia of respiratory epithelium to squamous cells



Bronchial Metaplasia of columnar to squamous epithelium

Causes of cell injury

- Causes of cell injury include ;

1. Hypoxia and ischemia – occlusion of blood vessel , respiratory diseases,anemia ,CO poisoning .

2.physical agents–trauma , burn , atmospheric pressure change

3.Toxins –alcohol ,poisons, drugs ,air pollutants

4.infection –viruses ,bacteria …

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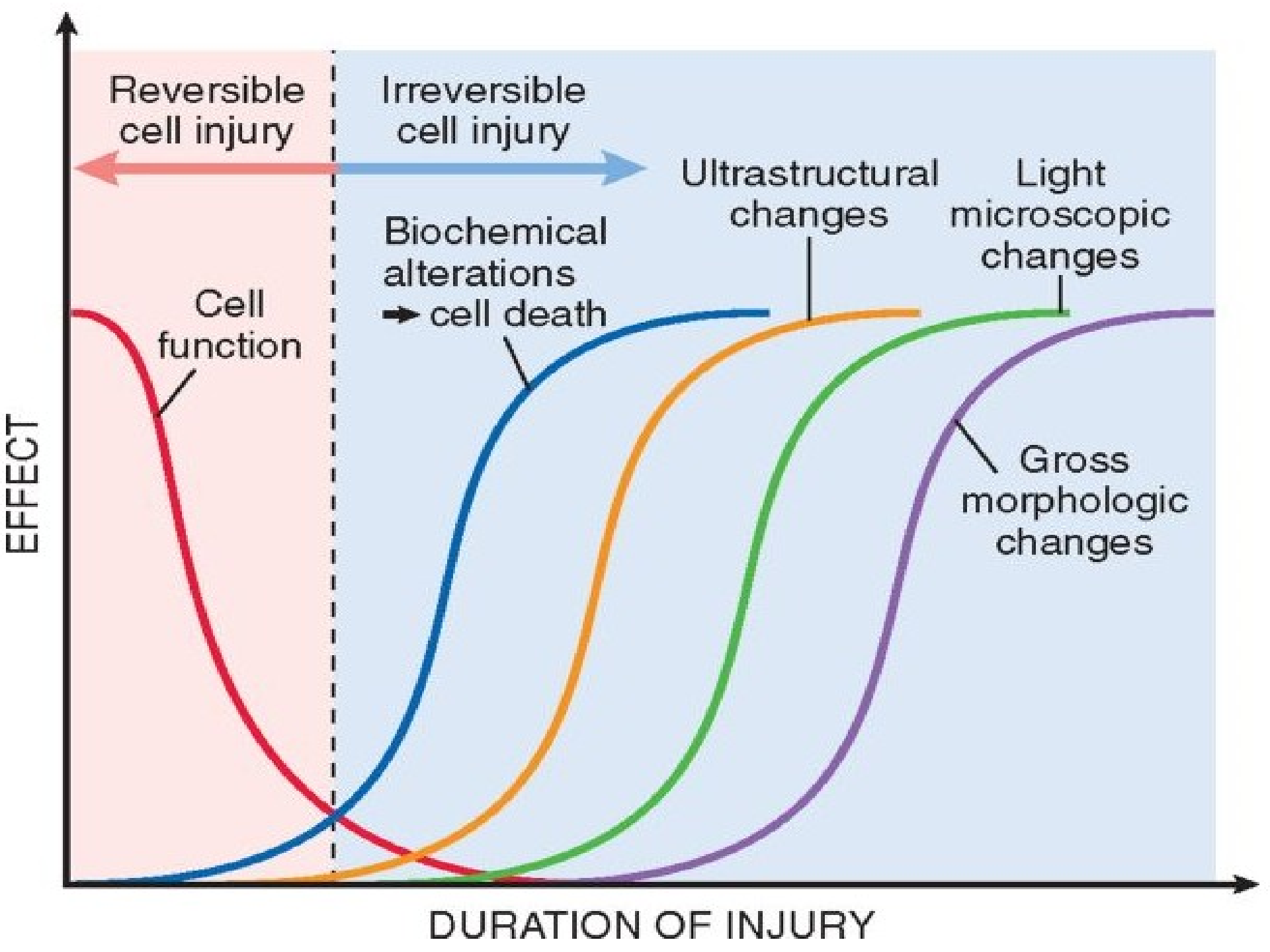
5.Immunologic reactions –autoimmunity , immune reactions

6.genetic abnormalities– down syndrome ,sickle cell anemia

7.nutritional imbalance –malnutrition or over nutrition

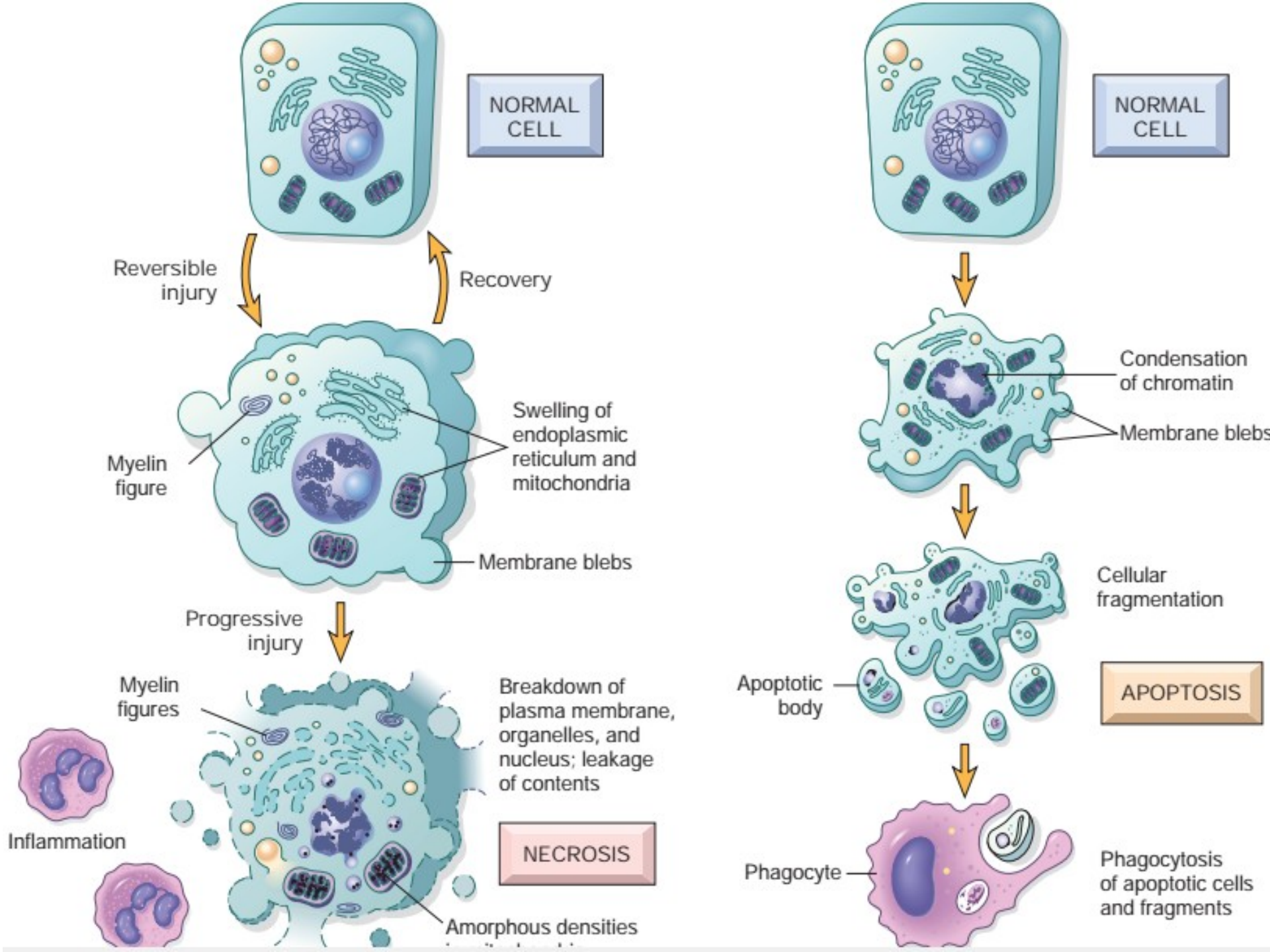
Morphologic alterations in cell injury

- All stresses and noxious influences exert their effects first at the molecular or biochemical level.
- There is a time lag between the stress and the morphologic changes of cell injury or death
- It may take considerably longer (hours to days) before changes can be seen by light microscopy or on gross examination.


Reversible cell injury
Irreversible cell injury
Ultrastructural changes
Light microscopic changes
Biochemical alterations → cell death
Cell function
Gross morphologic changes
EFFECT
DURATION OF INJURY

Reversible cell injury

- Is the stage of cell injury at which the deranged function and morphology of cell can return to normal If the stimulus is removed .
- **Morphologic changes**
- ***Cellular swelling*** *due to increased permeability of plasma membrane ,microscopically clear vacuoles within cytoplasm(vacuolar degeneration)*
- ***Fatty changes*** *appearance of lipid vacuoles in the cytoplasm* .
- plasma membrane blebbing,mitochondrial swelling, clumping of chromatin,detachment of ribosomes .


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
NORMAL CELL
Condensation of chromatin
Membrane blebs
Cellular fragmentation
Apoptotic body
APOPTOSIS
Phagocyte
Phagocytosis of apoptotic cells and fragments

Necrosis

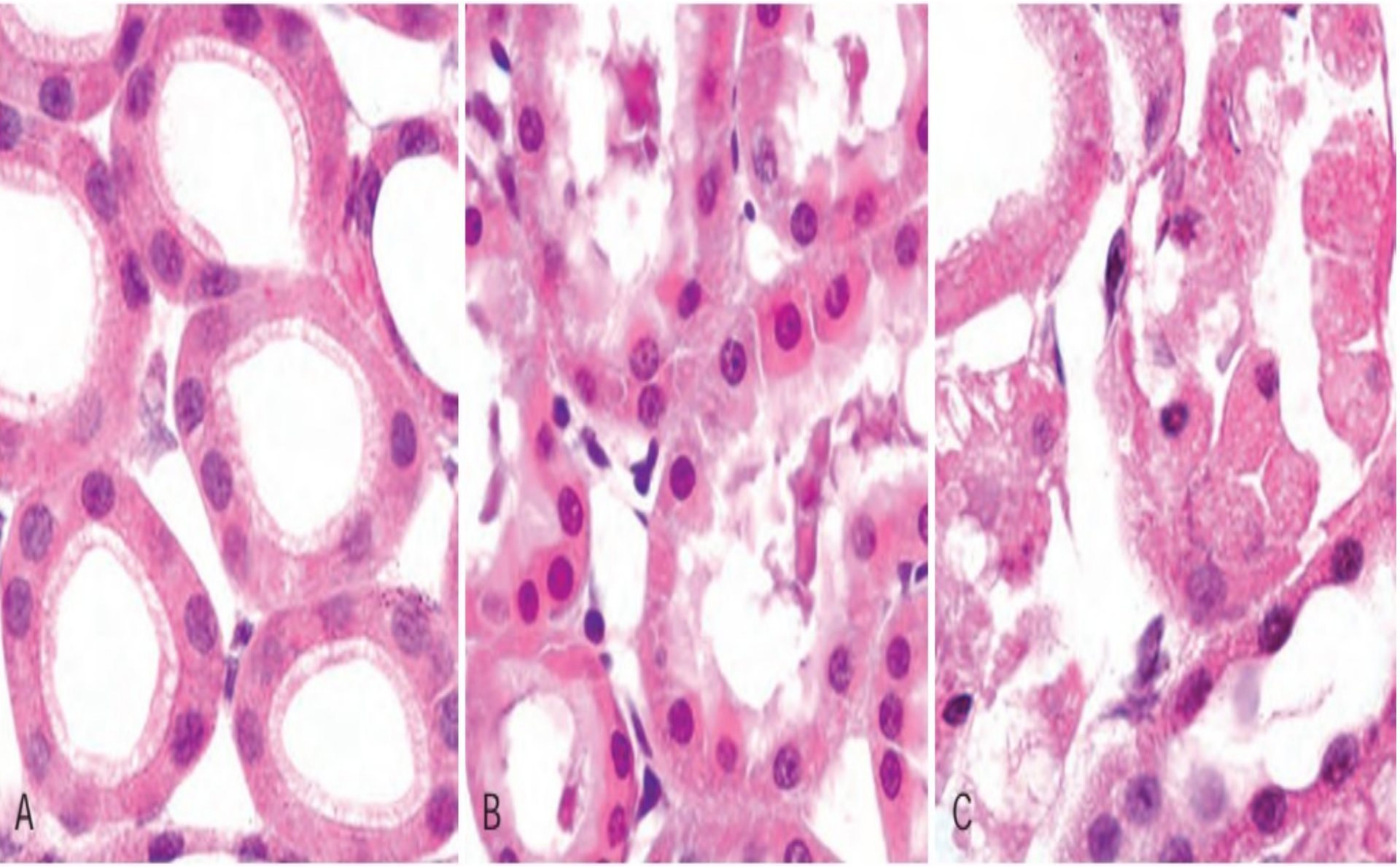
- *Is a form of cell death in which cellular membrane disrupted , cellular enzymes leak out and finally the cell is digested .*
- *It elicits inflammation*
- *Enzymes responsible for digestion are derived from lysosomes .*

Morphologic changes

- ***Cytoplasmic changes :*** Increased eosinophilia due to loss of cytoplasmic RNA and denatured cytoplasmic proteins and became vacuolated

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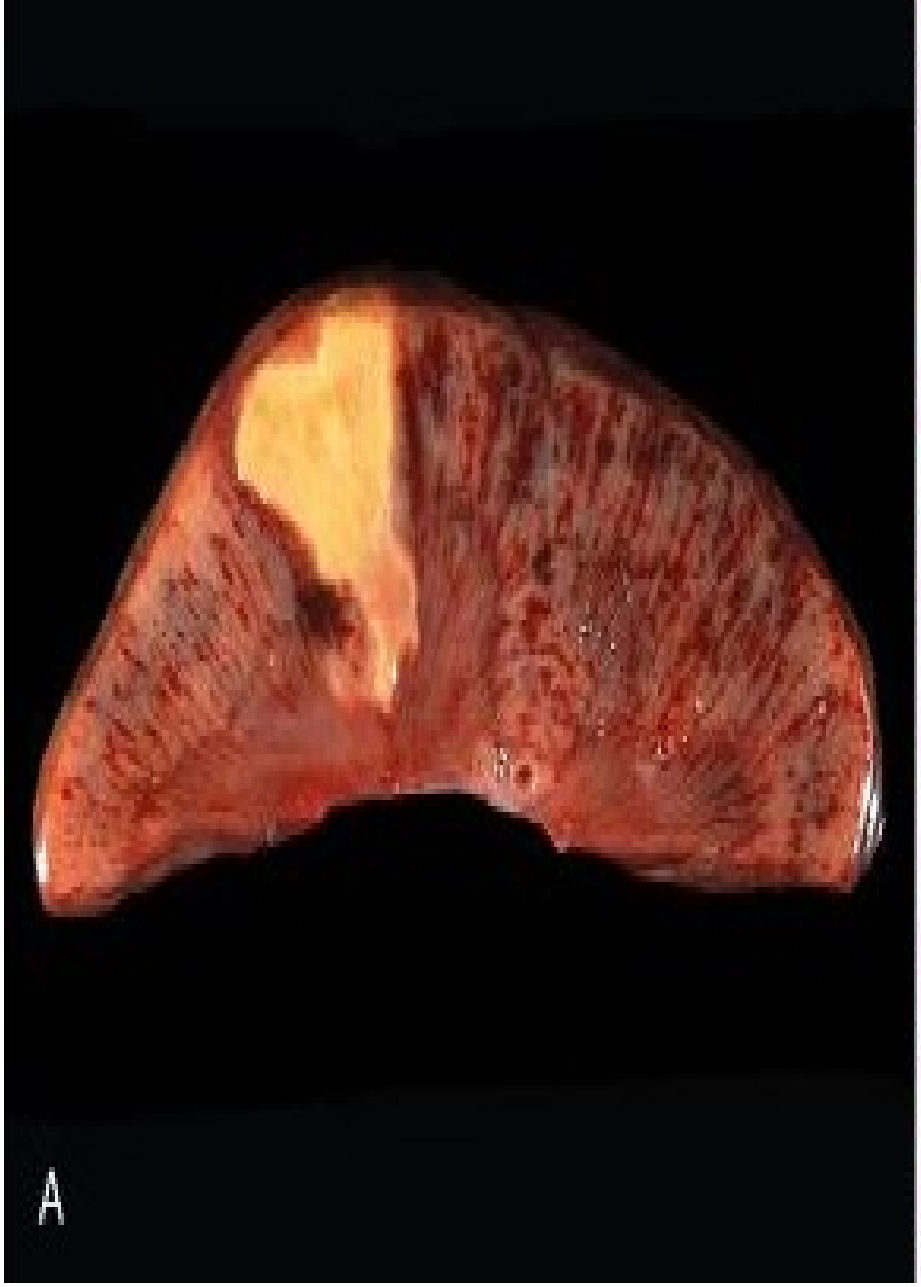
- Glassy homogenous appearance , myelin figures , marked dilation of mitochondria and disruption of lysosomes .
- **Nuclear changes**
- ✓ **Pyknosis** – nuclear shrunken basophilia mass
- ✓ **Karyorrhexis** –fragmentation of pyknotic nucleus
- ✓ **Karyolysis** –faded basophilia of chromatin due to loss of DNA by deoxyribonucleases .
- Total loss of nucleus after a day or two.

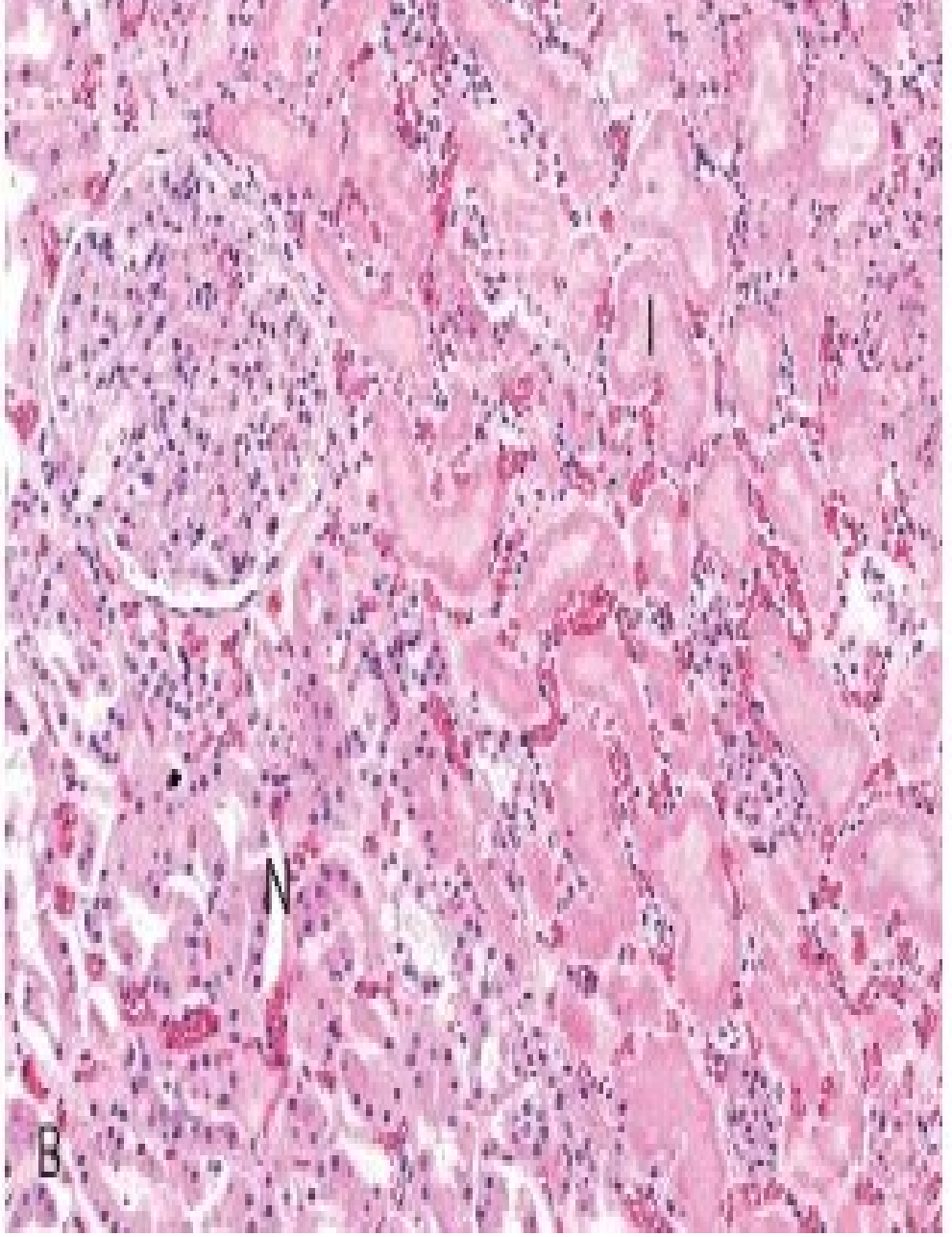


Photomicrograph showing Morphologic changes in reversible cell injury and necrosis

Patterns of tissue necrosis

- **1 . Coagulative necrosis** *is characteristic of infarcts(area of necrosis caused by ischemia) in all solid organs except brain* . Underlying tissue architecture is preserved for some days .
- *Dead* cells are digested by leukocytes .
- Microscopically eosinophilic anucleated cells may be found .





Photomicrograph of edge of infarct in kidney

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- **2 . Liquefactive necrosis** –due to digestion of dead cells by leukocytes and formation of liquid viscous mass
  - Mostly occur in focal bacterial infection exception in hypoxic death of cells in CNS

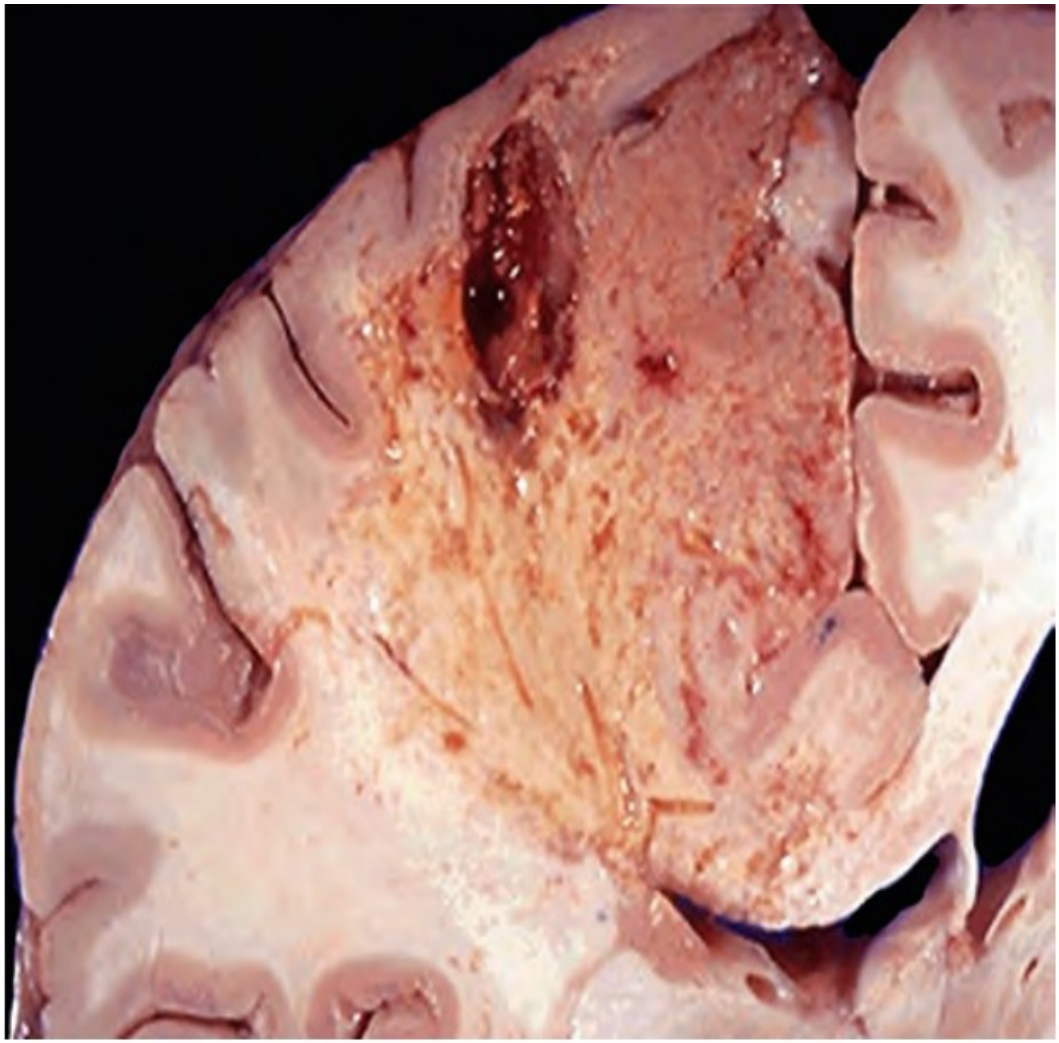
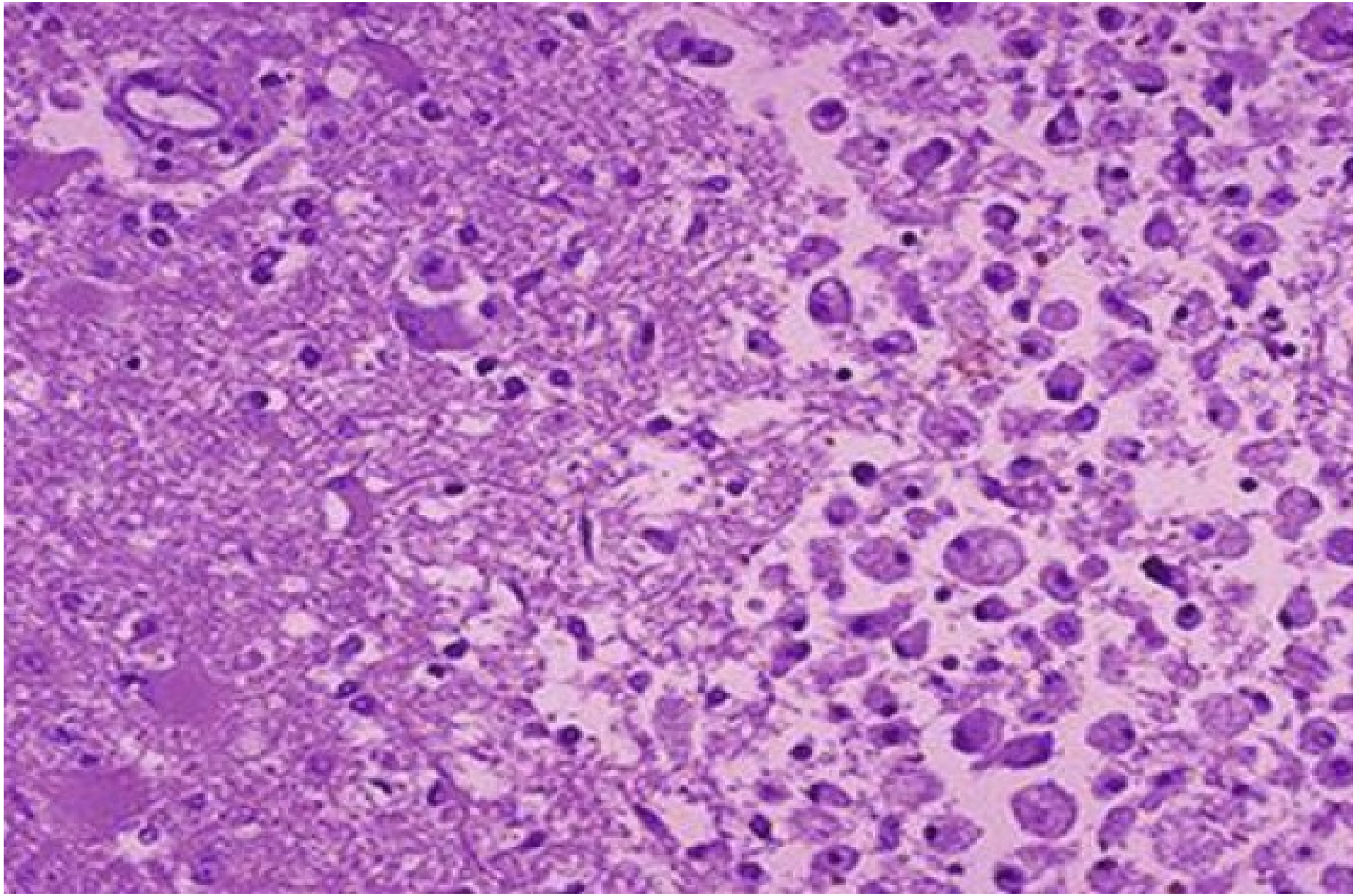


Figure 2-12 Liquefactive necrosis. An infarct in the brain, showing dissolution of the tissue.



Liquefactive necrosis of brain

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3 . Gangrenous necrosis – not specific type but its given to coagulative necrosis of the limb

- when bacteria is superimposed its called **wet gangrene**

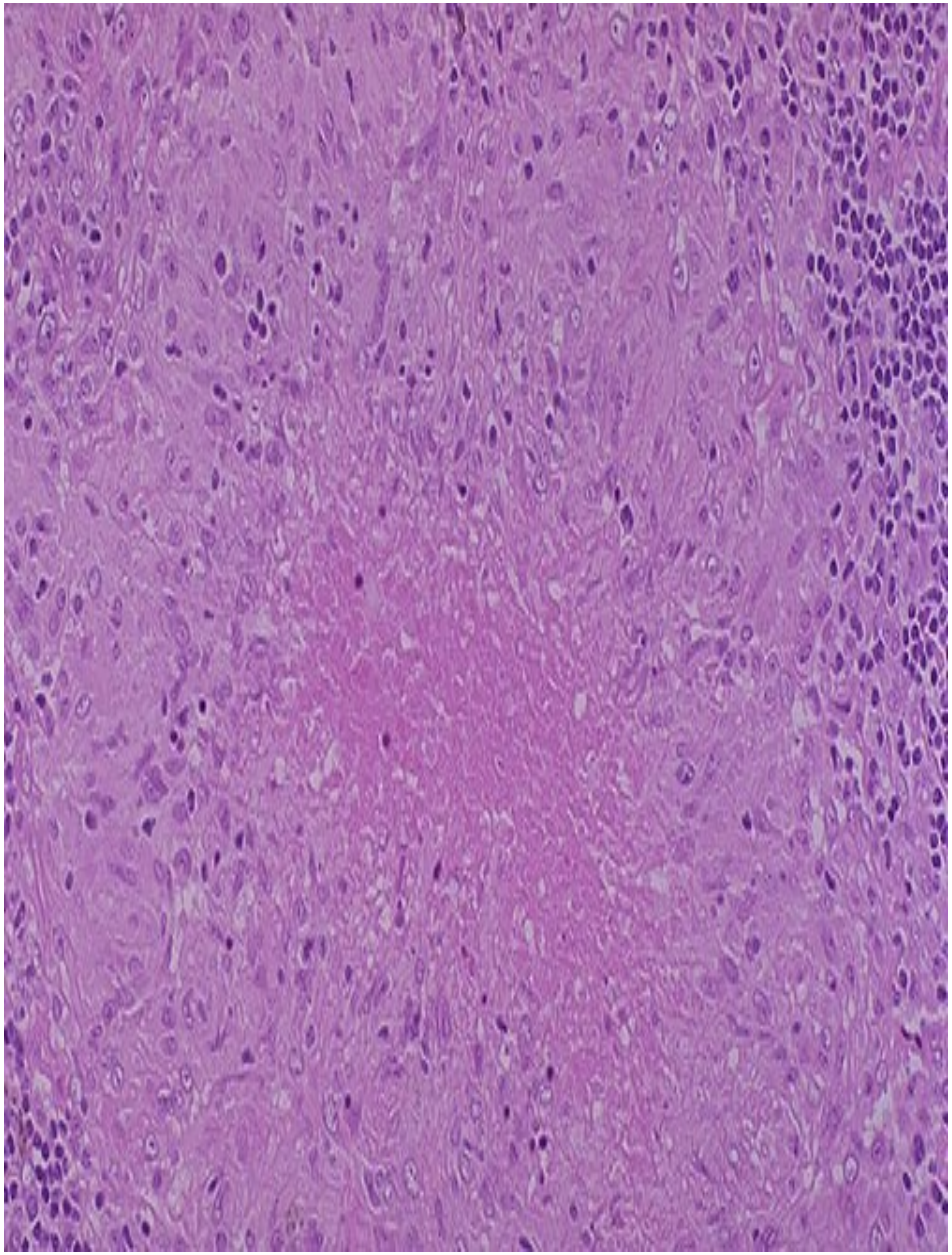


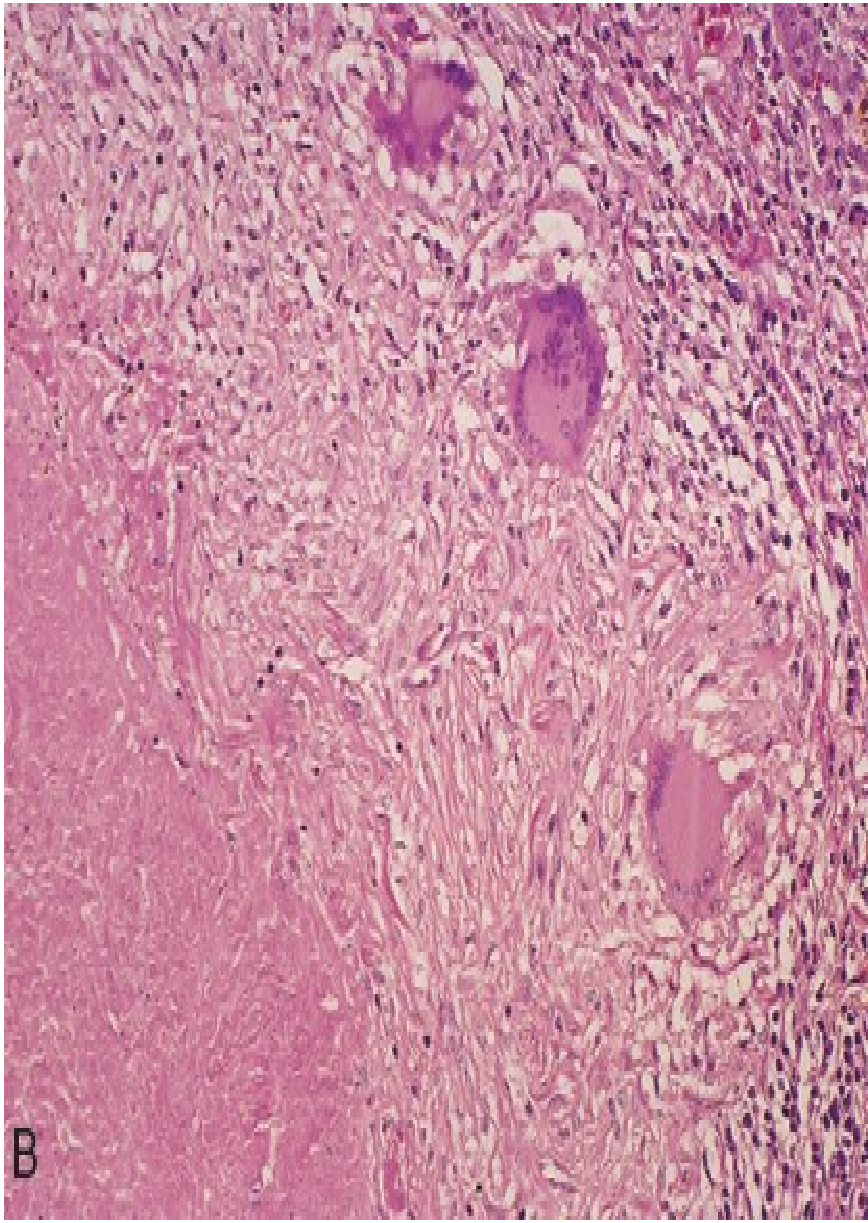
4 .Caseous necrosis
cheese like due to friable white yellow appearance grossly .

- microscopically appearance is a collection of fragmented or lysed cells and pink amorphous granular debris enclosed within a distinctive inflammatory border.



Figure 2-13 Caseous necrosis. Tuberculosis of the lung, with a large area of caseous necrosis containing yellow-white and cheesy debris.





Photomicrograph showing caseous necrosis

5 . Fat necrosis is focal area of fat destructions .

- The released fatty acids combine with calcium to produce grossly visible chalky-white areas (fat saponification)
- ***Microscopically*** shadowy outline of necrotic fat cells surrounded by basophilic calcium deposit and inflammatory reaction

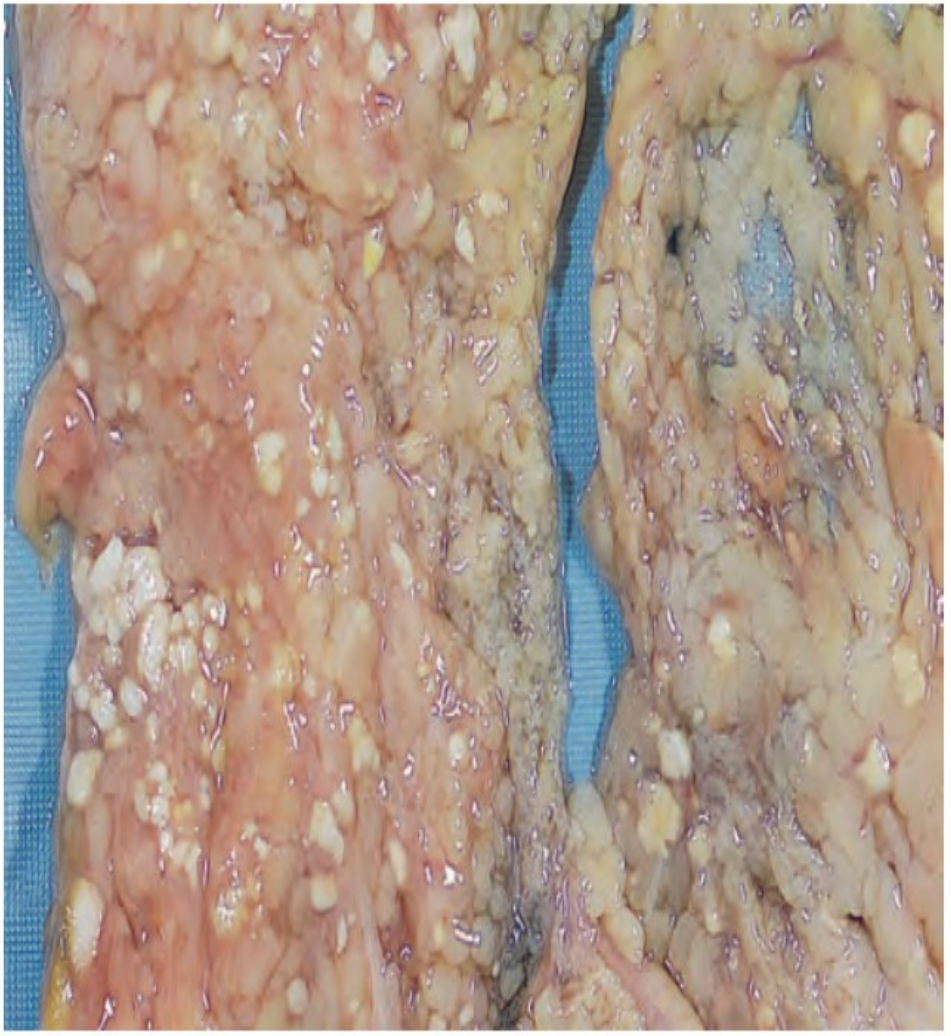
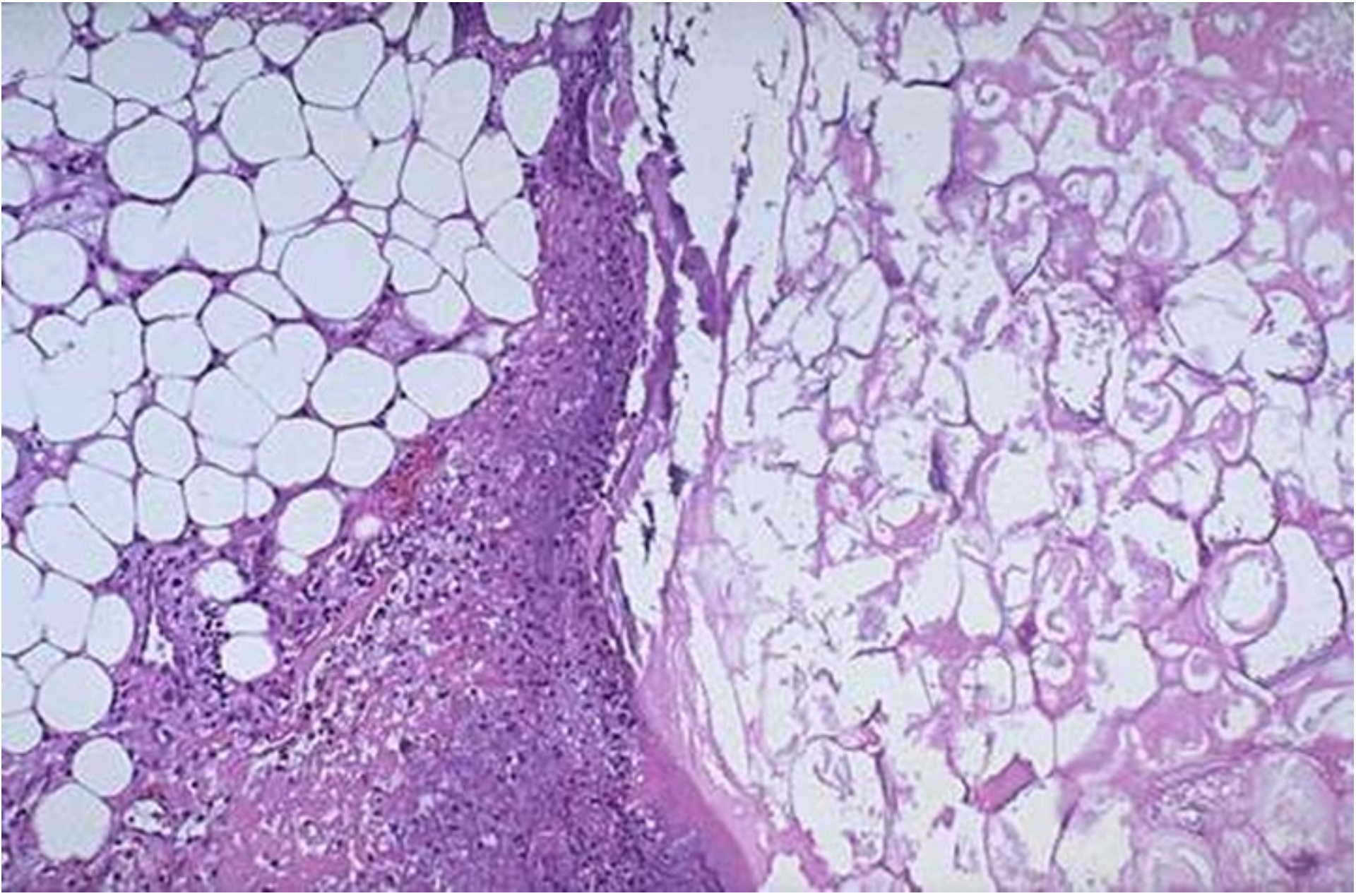


Figure 2-14 Fat necrosis. The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery.



Photomicrograph showing fat necrosis

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6. Fibrinous necrosis – occurs due to immune reaction in blood vessel, immune complex deposition results in bright pink and amorphous appearance

- It has no distinctive gross appearance

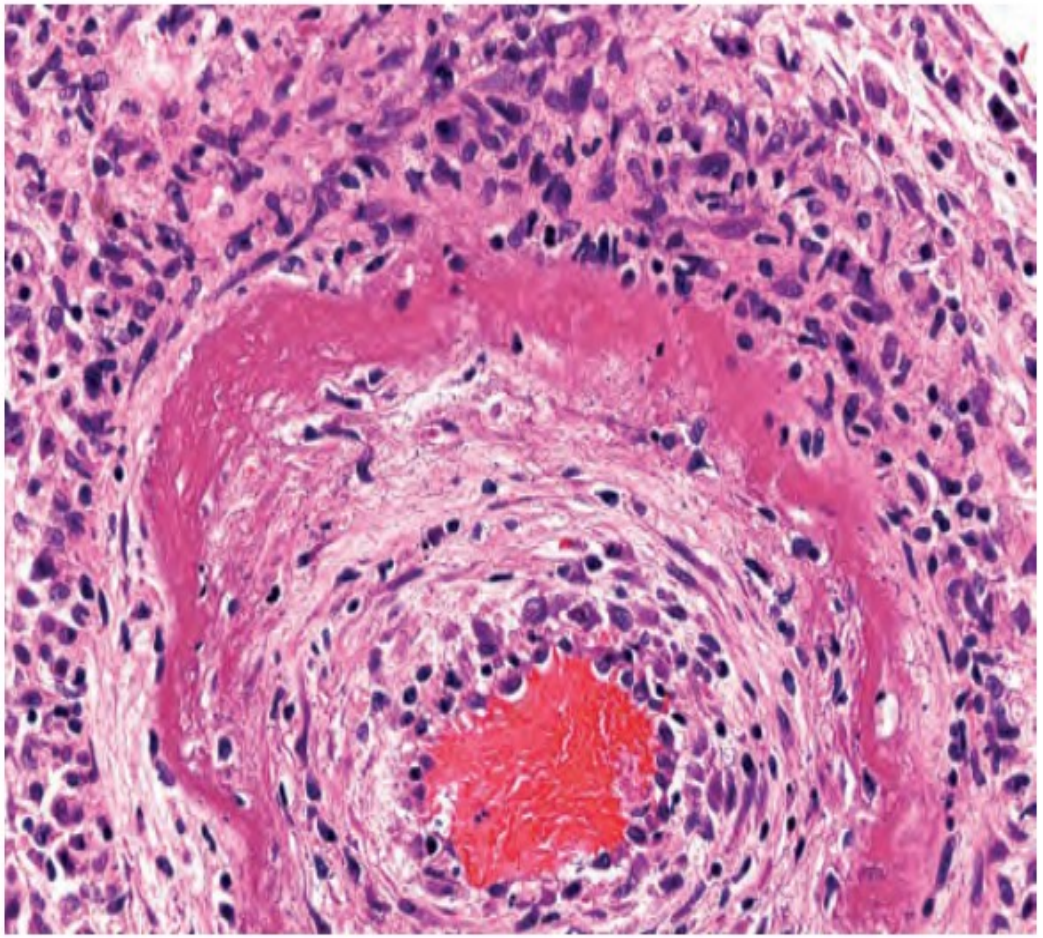


Figure 2-15 Fibrinoid necrosis in an artery. The wall of the artery shows a circumferential bright pink area of necrosis with inflammation (neutrophils with dark nuclei).

Apoptosis

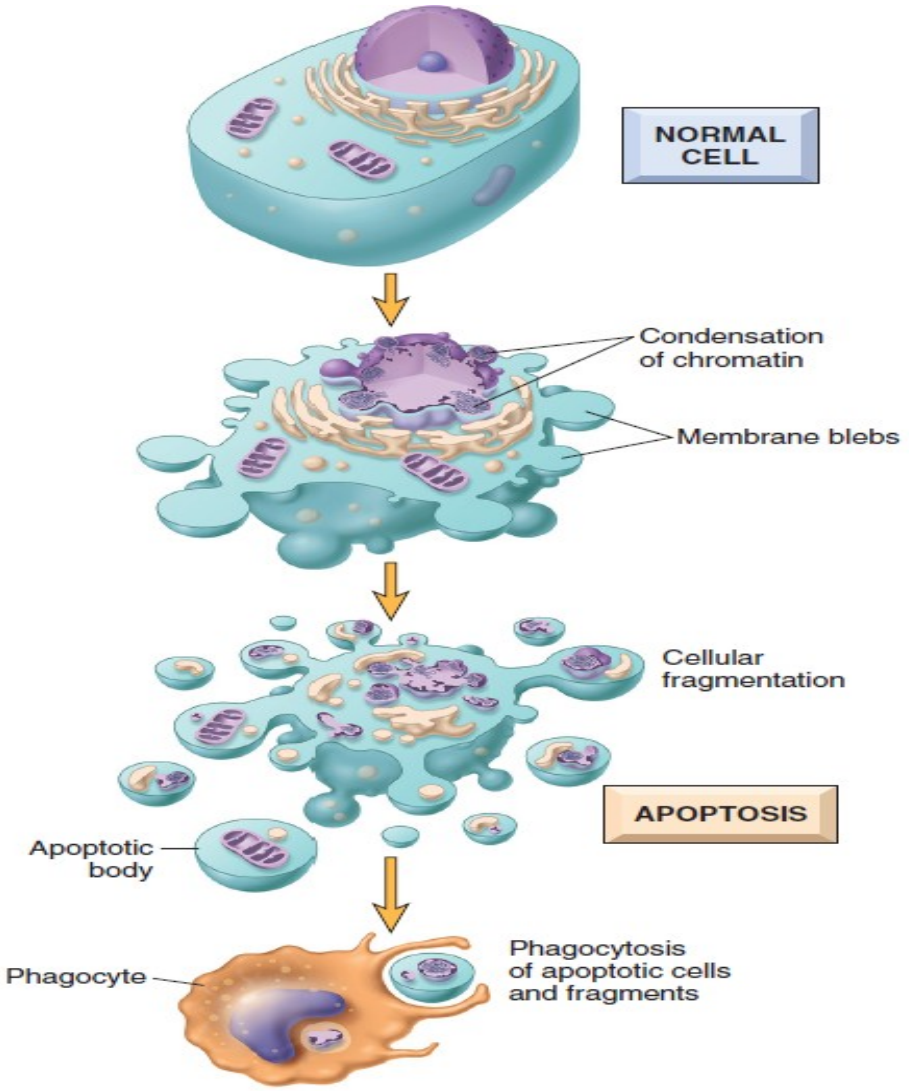
- Is a path way of cell death in which enzymes activated and degrade their own nuclear and cytoplasmic proteins but the plasma membrane is intact .
- It doesn't elicit inflammation .
- **Physiologic apoptosis**
- ✓ The programmed death of cells during embryogenesis
- ✓ Involution of hormone dependent tissue

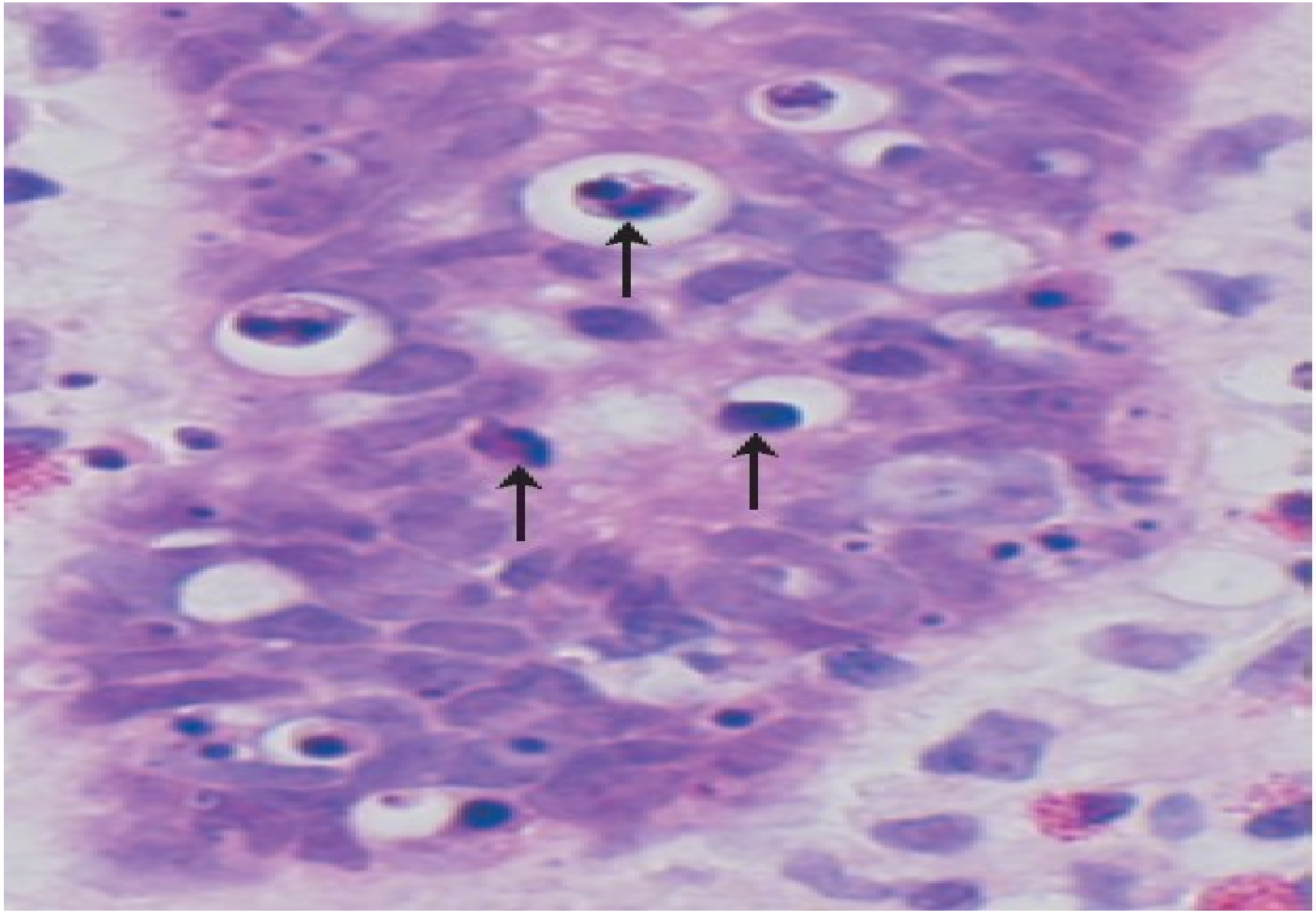
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- ✓Removal of cells that have served their useful purpose
- ✓Removal of harmful self reacting lymphocyte
- ✓*Cell loss in proliferating cell population*
- ➢***Pathologic apoptosis***
- ✓DNA damage due to radiation ,anticancer drugs or hypoxia
- ✓Accumulation of misfolded proteins
- ✓Cell death in certain infections
- ✓Pathological atrophy after duct obstruction

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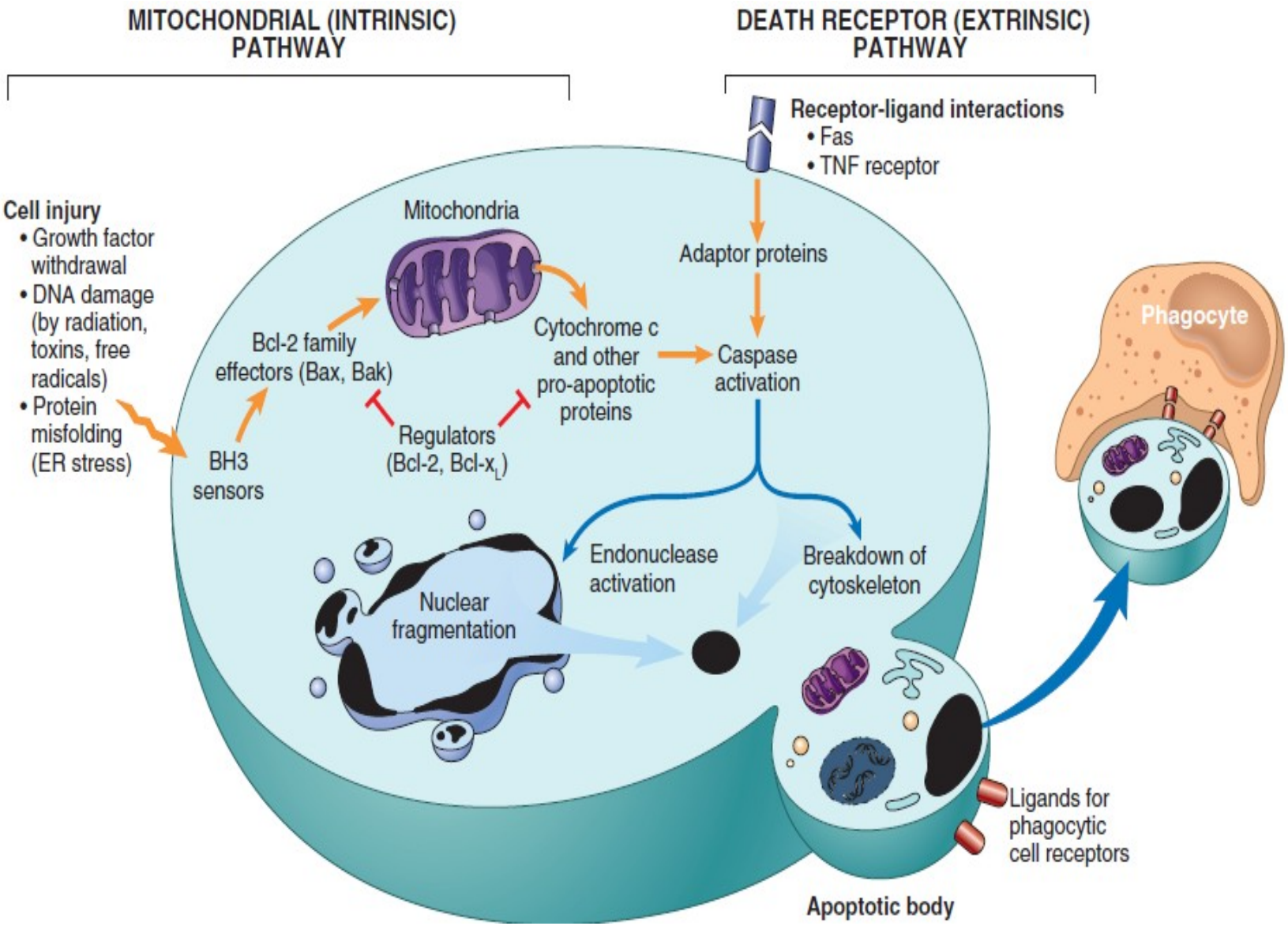
- **Morphologic changes**
- ✓ Cell shrinkage
- ✓ Chromatin condensation and aggregation then karyorrhexis
- ✓ Formation of cytoplasmic buds and fragment in to apoptotic bodies
- ✓ Phagocytosis of apoptotic cells or cell bodies





Mechanisms of apoptosis

- *Apoptosis is regulated by biochemical path way with the activation of proenzymes called* ***caspases***
- There are two path ways for activation of caspases
  1 . Intrinsic (mitochondrial) path way
  2. Extrinsic (death receptor) path way


MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor-ligand interactions
• Fas
• TNF receptor
Cell injury
• Growth factor withdrawal
• DNA damage (by radiation, toxins, free radicals)
• Protein misfolding (ER stress)
Mitochondria
Adaptor proteins
Bcl-2 family effectors (Bax, Bak)
Cytochrome c and other pro-apoptotic proteins
Caspase activation
Regulators (Bcl-2, Bcl-xL)
BH3 sensors
Endonuclease activation
Breakdown of cytoskeleton
Nuclear fragmentation
Phagocyte
Ligands for phagocytic cell receptors
Apoptotic body

Cont'd…

- **Clearance of apoptotic cells –**apoptotic cells are phagocytes by producing "eat me" signals
- Plasma membrane alternation and secreted protein facilitate recruitment of macrophages
- Efflux of phosphatidilserine to outer membrane attracts phagocytosing cells .

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size 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 damage

Mechanism of cell injury

- Cell injury results from different biochemical mechanisms acting on several essential cellular components
- Cellular response to injurious stimuli depends on type , duration and severity of injury .
- The consequence also depends on type , status , adaptability and genetic make up of the injured cell .

Mechanisms of Cell Injury

- The mechanisms responsible for cell injury are complex.
- The cellular components that are most frequently damaged by injurious stimuli include
- Mitochondria
- Cell membranes
- The machinery of protein synthesis and Packaging, and
- The DNA in nuclei

Basic mechanisms of cell injury

- DEPLETION OF ATP
- MITOCHONDRIAL DAMAGE

- INFLUX OF CALCIUM AND LOSS OF CALCIUM HOMEOSTASIS
- ACCUMULATION OF OXYGEN-DERIVED FREE RADICALS (OXIDATIVE STRESS)

- DEFECTS IN MEMBRANE PERMEABILITY
- DAMAGE TO DNA AND PROTEINS

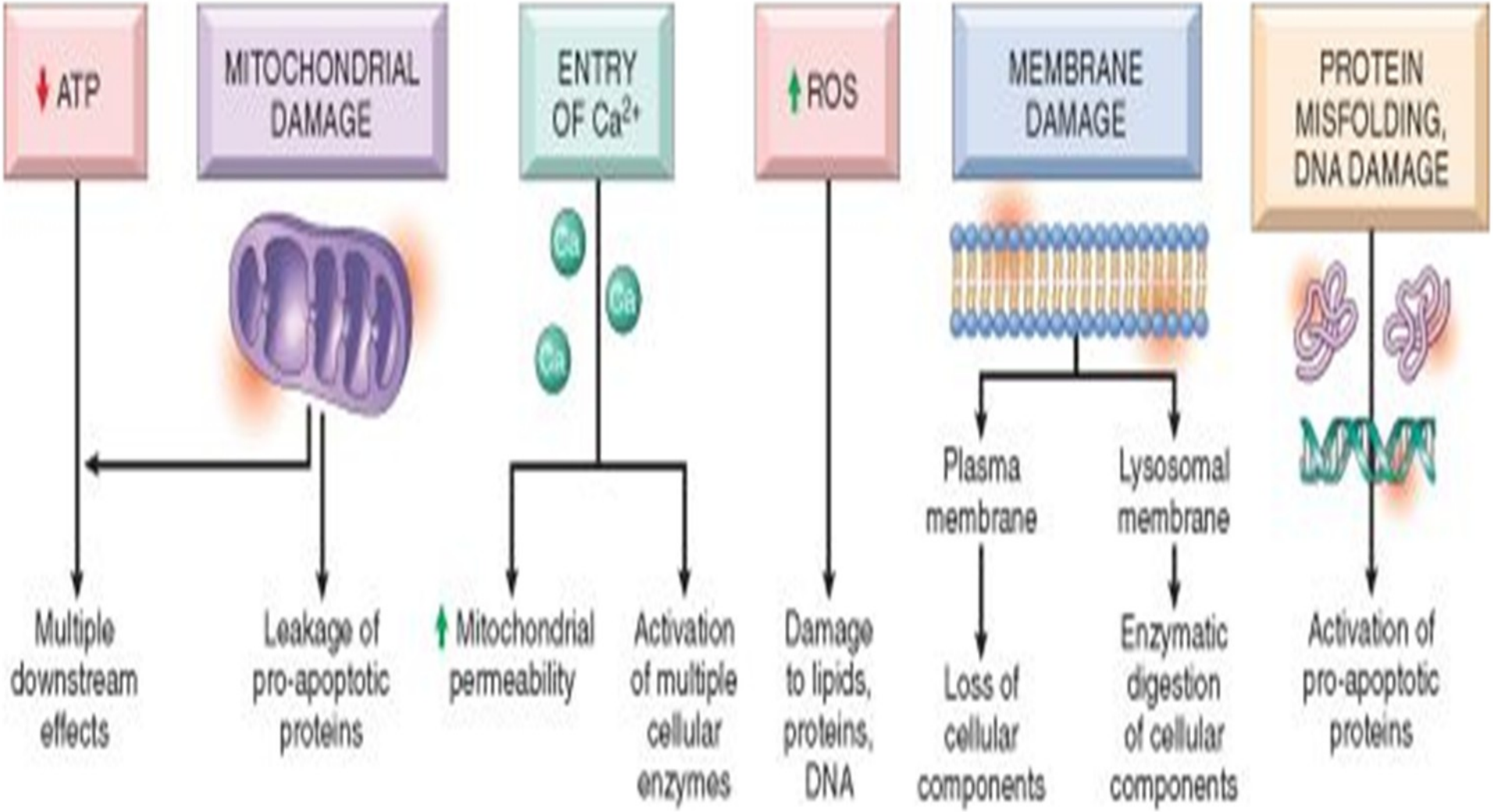
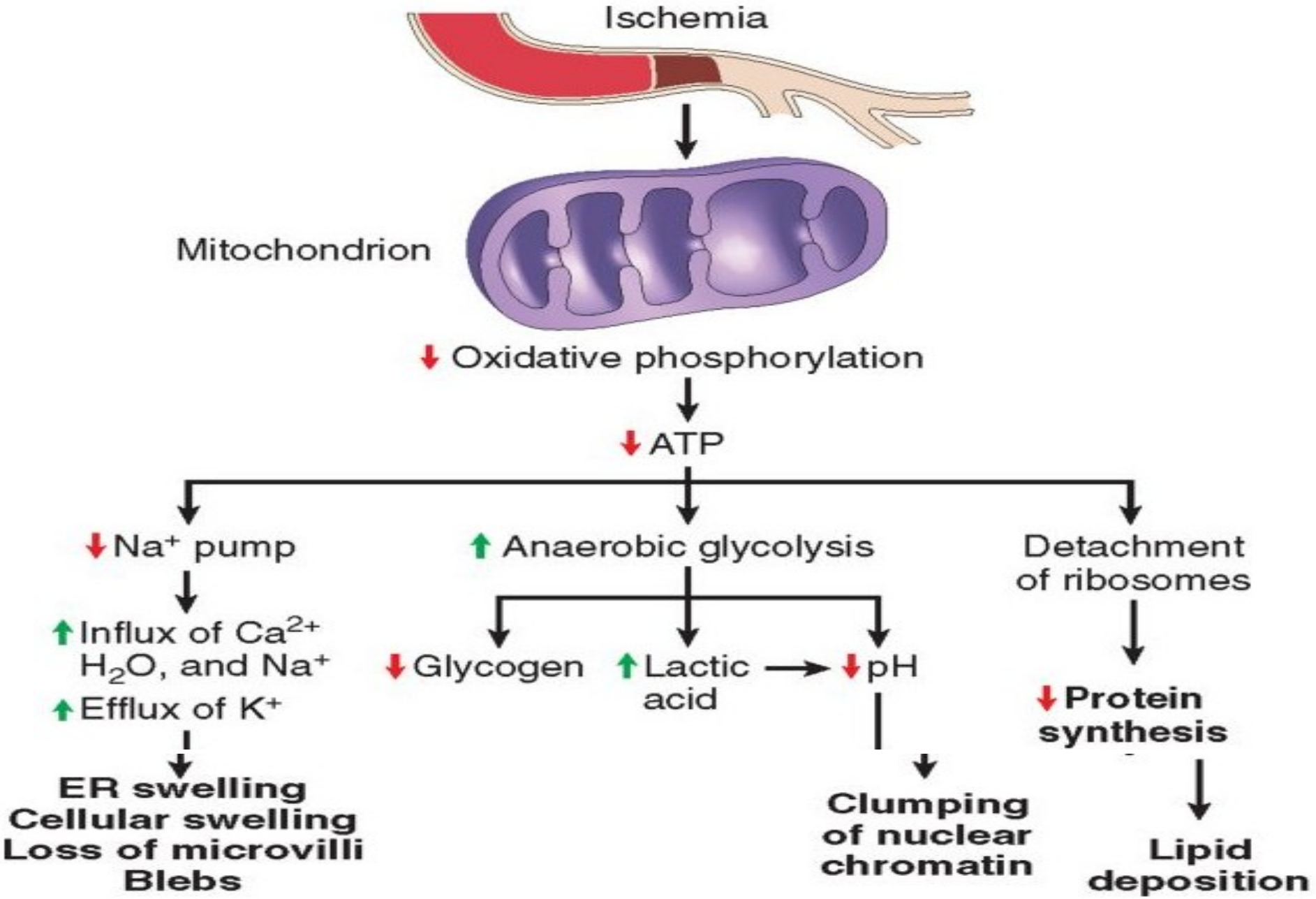


FIGURE 1-16 The principal mechanisms of cell injury, and their biochemical and functional effects, are shown. These are described in detail in the text.

DEPLETION OF ATP

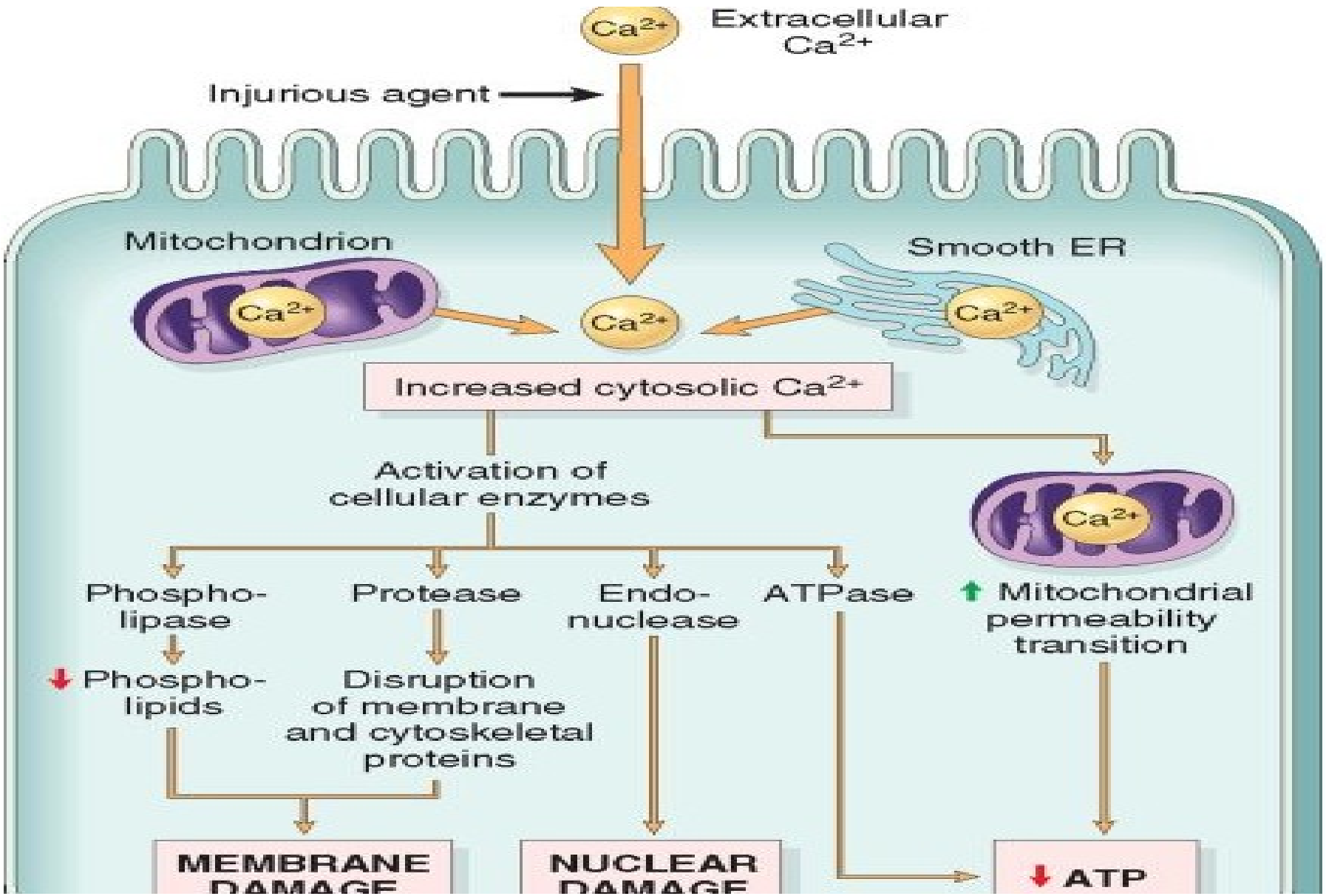
- ATP depletion and decreased ATP synthesis are frequently associated with both hypoxic and chemical (toxic) injury.
- The major causes of ATP depletion are

✓ Reduced supply of oxygen and nutrients,
✓ Mitochondrial damage, and
✓ The actions of some toxins (e.g., cyanide).


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

INFLUX OF CALCIUM AND LOSS OF CALCIUM HOMEOSTASIS

- Ischemia and certain toxins cause an increase in cytosolic calcium concentration.
- Initially because of release of Ca2+ from intracellular stores, and
- Later resulting from increased influx across the plasma membrane
- Increased intracellular Ca2+ causes cell injury by several mechanisms.
- Increased intracellular Ca2+ levels also result in the induction of apoptosis
- Increased cytosolic Ca2+ activates a number of enzymes, with potentially deleterious cellular effects.


Ca2+
Extracellular Ca2+
Injurious agent
Mitochondrion
Ca2+
Ca2+
Smooth ER
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

ACCUMULATION OF OXYGEN-DERIVED FREE RADICALS (OXIDATIVE STRESS)

- ROS are produced normally in cells during mitochondrial respiration and energy generation, but they are degraded and removed by cellular defense systems.

- Thus, cells are able to maintain a steady state in which free radicals may be present transiently at low concentrations but do not cause damage

- When the production of ROS increases or the scavenging systems are ineffective, the result is an excess of these free radicals, leading to a condition called oxidative stress.

- Oxidative stress has been implicated in a wide variety of pathologic processes, including cell injury, cancer, aging, and some degenerative diseases such as Alzheimer disease.

Continued…

- Normal redox reactions generate free radicals
- ✓ Nitric oxide (NO) can act as a free radical

- Ionizing radiation (UV, X-rays) can hydrolyze water into hydroxyl (OH•) and hydrogen (H•) free radicals

- Metabolism of exogenous chemicals such as CCl4can generate free radicals

- Free radical generation is a “physiological” antimicrobial reaction

Pathologic Effects of Free Radicals.

- The effects of ROS and other free radicals are wide-ranging, but three reactions are particularly relevant to cell injury
  - Lipid peroxidation in membranes.
  - Oxidative modification of proteins.
  - Lesions in DNA

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 (except apoptosis)

Mechanisms of Membrane Damage.

The plasma membrane can also be damaged directly by various.

- Bacterial toxins
- Viral proteins
- Lytic complement components, and
- A variety of physical and chemical agents.

➢ Several biochemical mechanisms may contribute to membrane damage

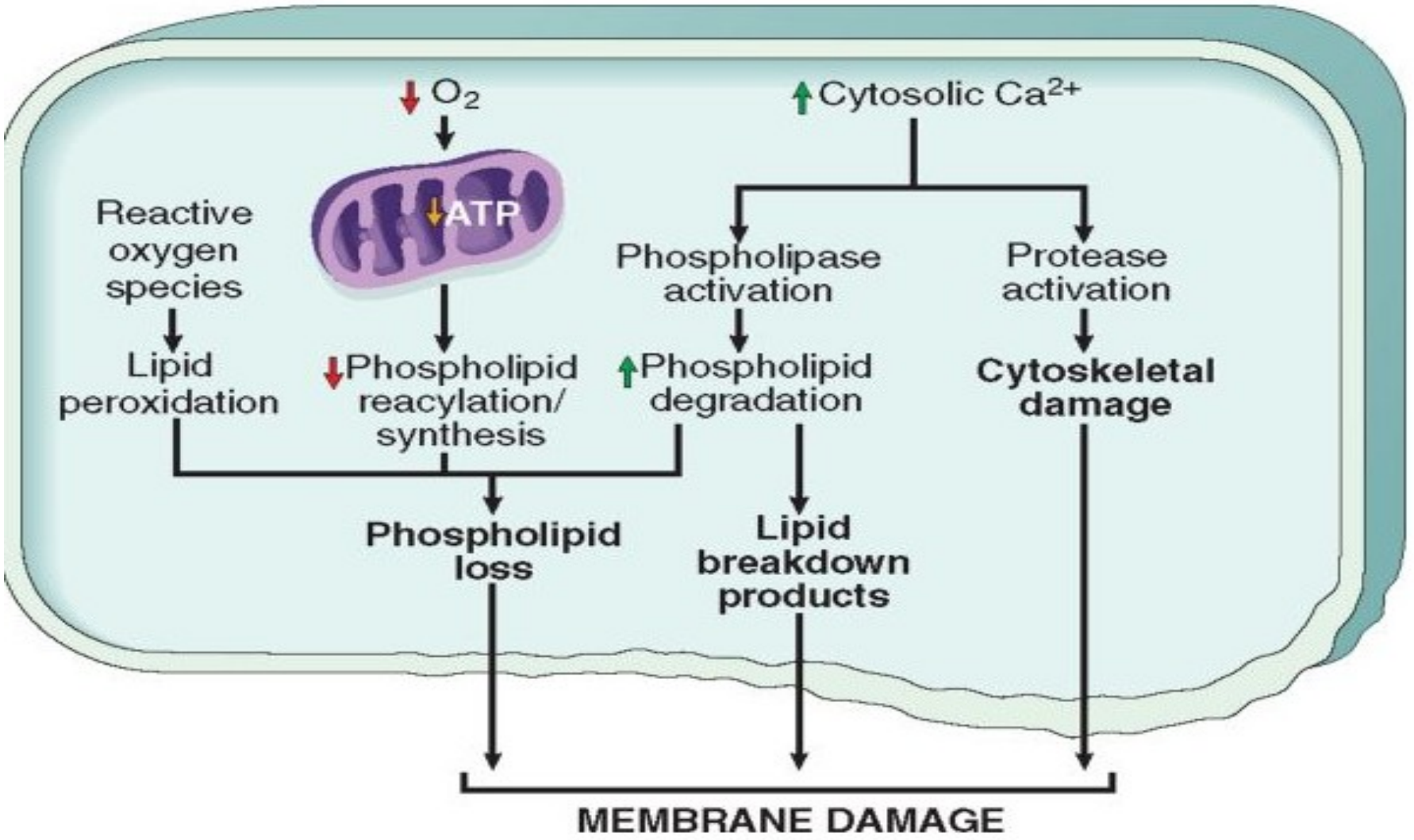


FIGURE 1-21 Mechanisms of membrane damage in cell injury. Decreased O_2 and increased cytosolic Ca^{2+} are typically seen in ischemia but may accompany other forms of cell injury. Reactive oxygen species, which are often produced on reperfusion of ischemic tissues, also cause membrane damage (not shown).

Reperfusion Damage

- If cells are reversibly injured due to ischemia, restoration of blood flow can paradoxically result in accelerated injury.
- Reperfusion damage is a clinically important process that significantly contributes to myocardial and cerebral infarctions
- Exact mechanisms are unclear
- Restoration of flow may expose compromised cells to high concentrations of calcium
- Reperfusion can result in increase free radicals production from compromised mitochondria and the circulating inflammatory cells

Consequences of Membrane Damage.

- The most important sites of membrane damage during cell injury are
  - ✓ The mitochondrial membrane
  - ✓ The plasma membrane
  - ✓ Membranes of lysosomes

DAMAGE TO DNA AND PROTEINS

- Cells have mechanisms that repair damage to DNA, but if this damage is too severe to be corrected , the cell initiates a suicide program that results in death by apoptosis.

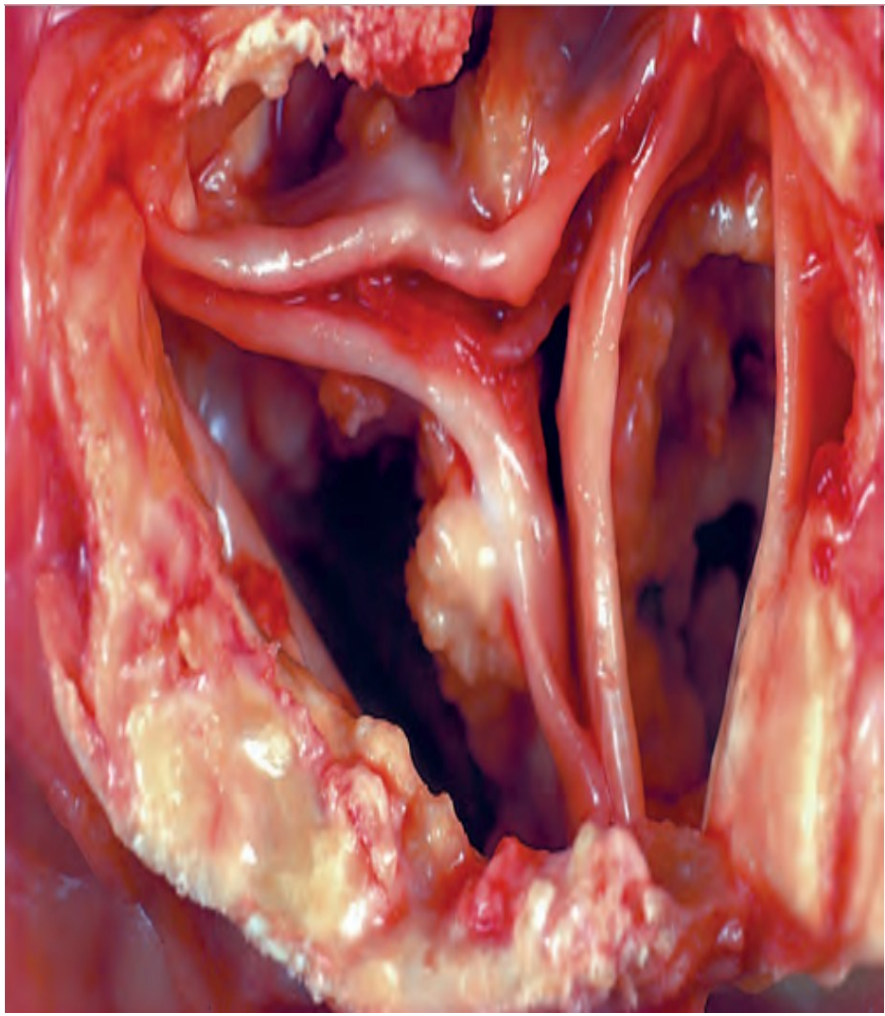
- A similar reaction is triggered by improperly folded proteins, which may be the result of inherited mutations or external triggers such as free radicals.

Pathologic calcification

- Pathologic calcification is a result of abnormal deposition of calcium salt by two ways , these are

1 . Dystrophic calcification *is initiated by extracellular deposition calcium phosphate membrane bound vesicles which may be derived from injured cells but calcium metabolism is normal* .

- Grossly it is white granules or clumps and on histology it appears as intracellular or extracellular basophilic deposits .
- It is a sign of previous injury and common in caseous necrosis of TB .

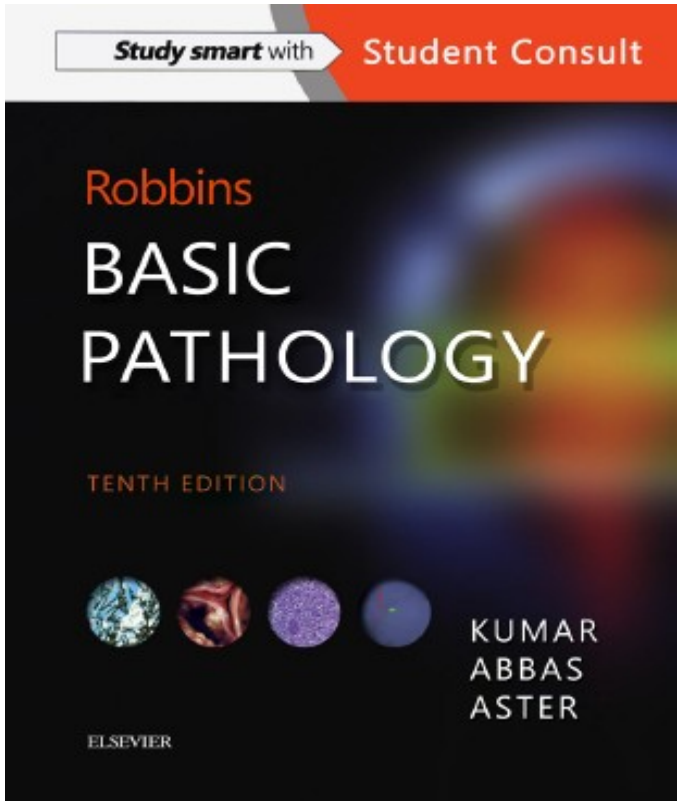


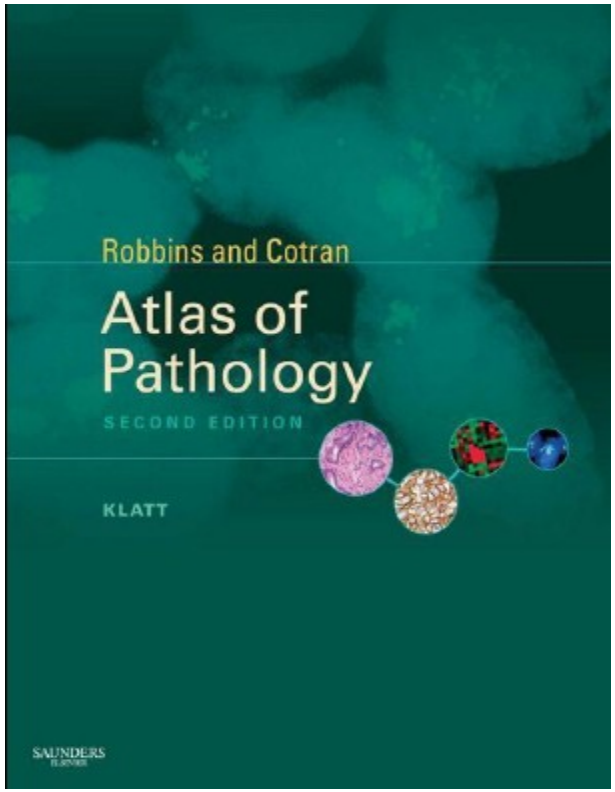
Cont'd…

2 . Metastatic calcification –due to hypercalcemia affects gastric mucosa ,kidney, lung ,systemic arteries and pulmonary veins .

- Caused by increased PTH, destruction of bone, vitamin D related disorders and renal failure .
- Usually they don't cause clinical dysfunction.

References


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