Cell Death-Necrosis

BUSHRA AL-TARAWNEH, MD

PATHOLOGY, MICROBIOLOGY AND IMMUNLOGY DEPARTMENT

FACULTY OF MEDICINE/ MUTAH UNIVERSITY

When cells are injured, they die by different mechanisms, depending on the nature and severity of the insult:

1-Necrosis

2- Apoptosis

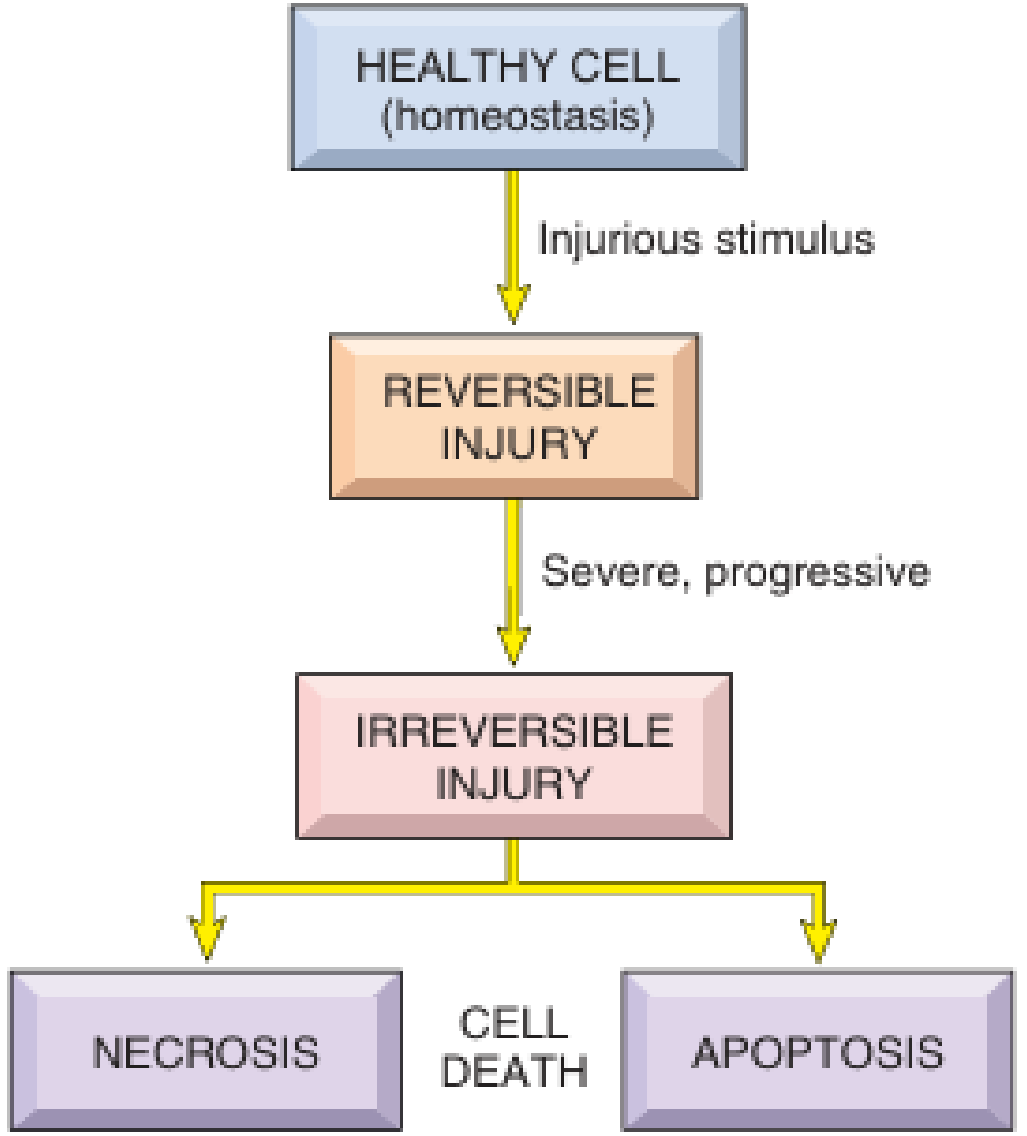
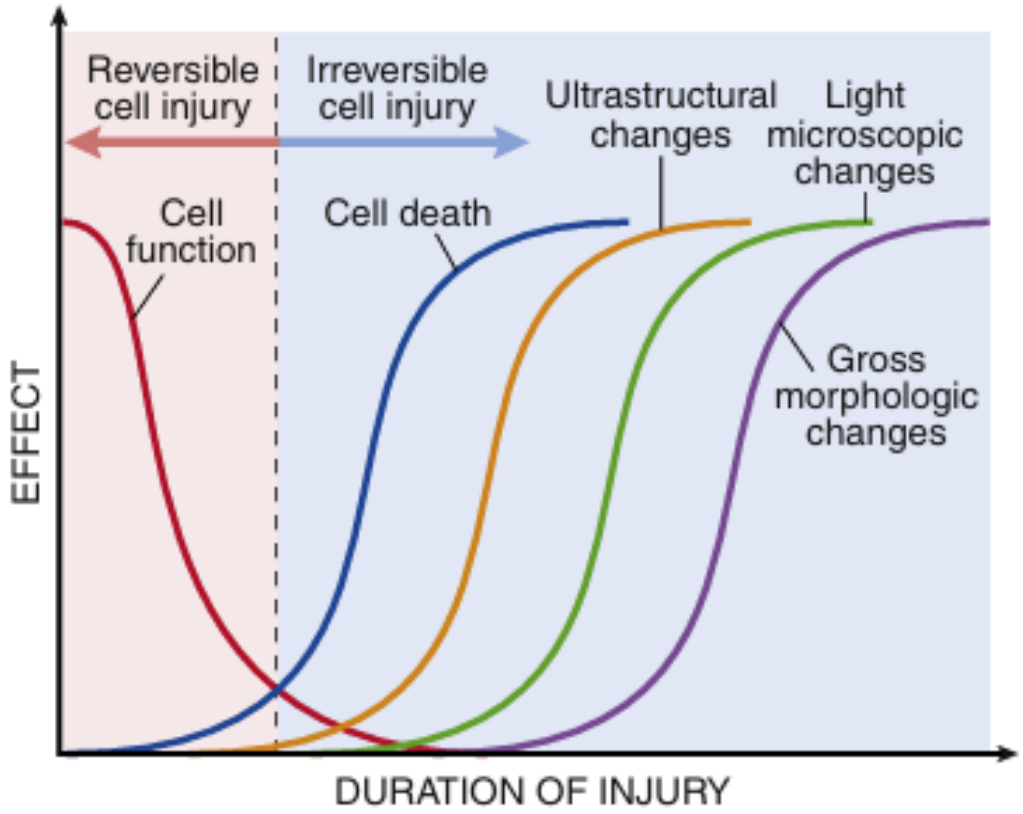


FIG. 1.2 Sequence of reversible cell injury and cell death.

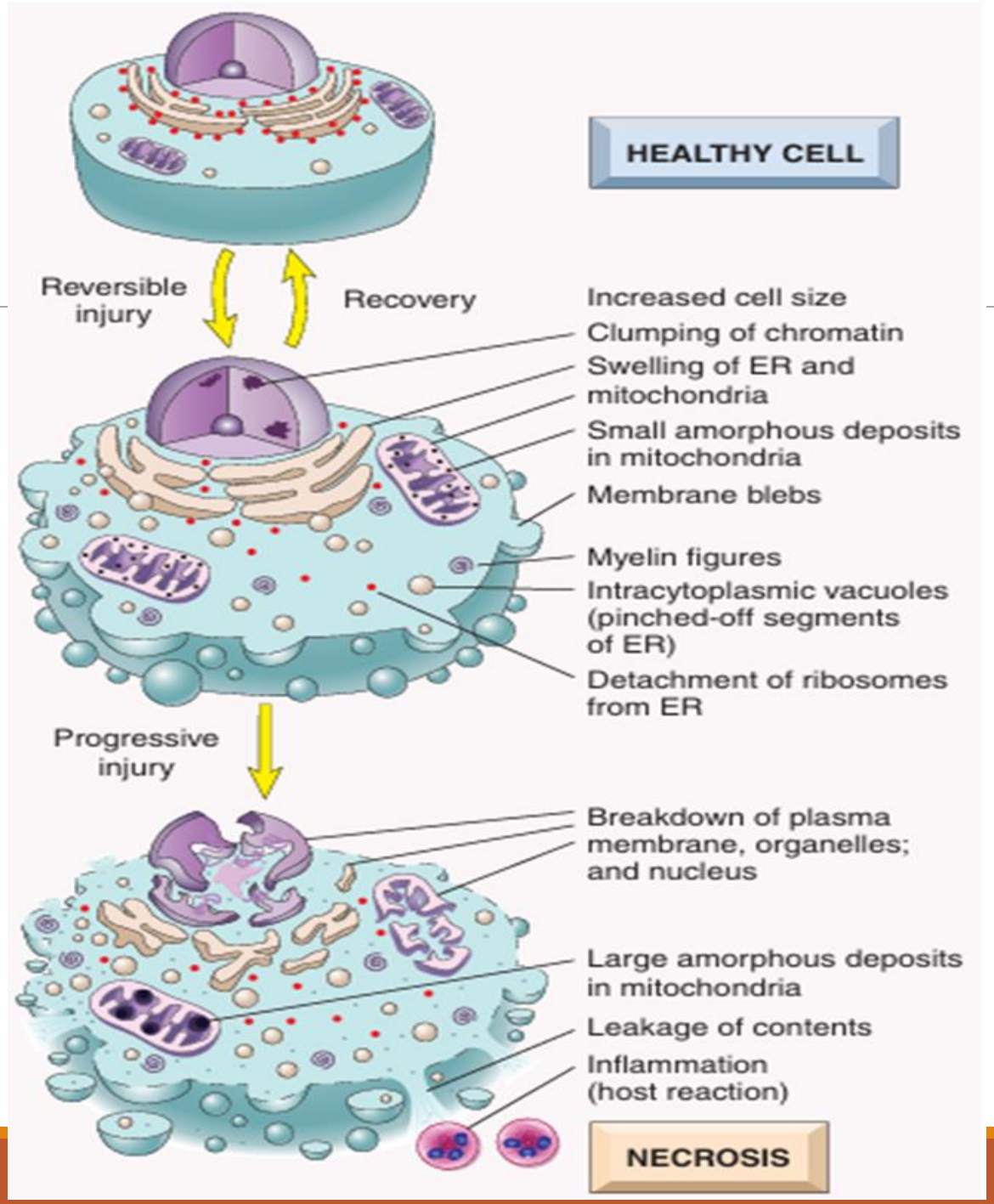
The relationship of cellular function, cell death, and the morphologic changes of cell injury

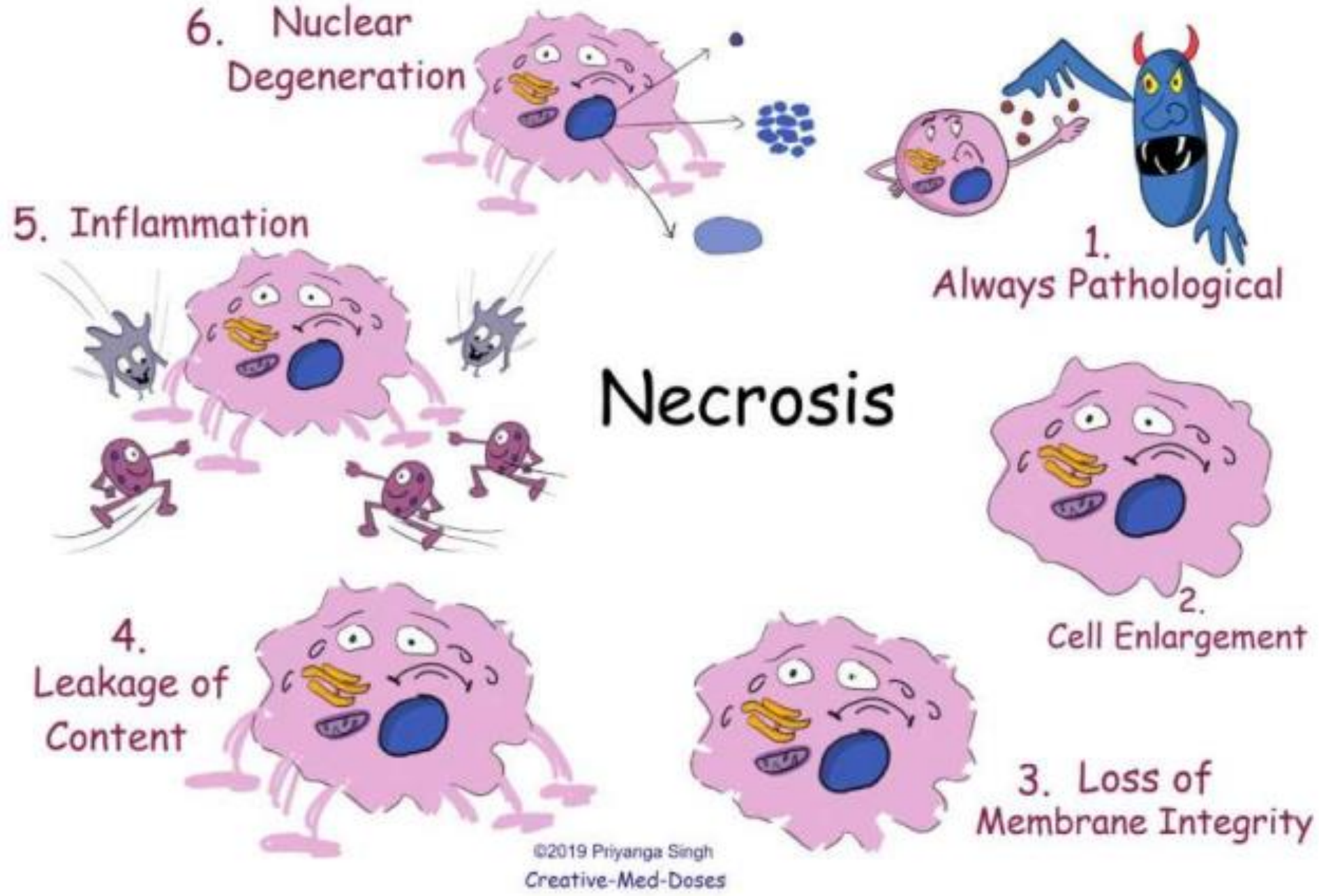
Note that cells may rapidly become nonfunctional after the onset of injury yet still be viable, with potentially reversible damage; with a longer duration of injury, irreversible injury and cell death may result. Cell death typically precedes ultrastructural, light microscopic, and grossly visible morphologic changes



Necrosis.

- The morphologic manifestation of accidental cell death is necrosis (Greek, necros :death).
- Necrosis is the major pathway of cell death in many commonly encountered injuries, such as those resulting from ischemia, exposure to toxins, various infections, and trauma. These severe disturbances, cause a rapid and uncontrollable form of death that has been called “accidental” cell death.
- **“ It is an uncontrolled cell death that results in swelling of the cell organelles, plasma membrane rupture and eventual lysis of the cell, and spillage of intracellular contents into the surrounding tissue leading to tissue damage.”**


HEALTHY CELL
Reversible injury
Recovery
Increased cell size
Clumping of chromatin
Swelling of ER and mitochondria
Small amorphous deposits in mitochondria
Membrane blebs
Myelin figures
Intracytoplasmic vacuoles (pinched-off segments of ER)
Detachment of ribosomes from ER
Progressive injury
Breakdown of plasma membrane, organelles; and nucleus
Large amorphous deposits in mitochondria
Leakage of contents
Inflammation (host reaction)
NECROSIS

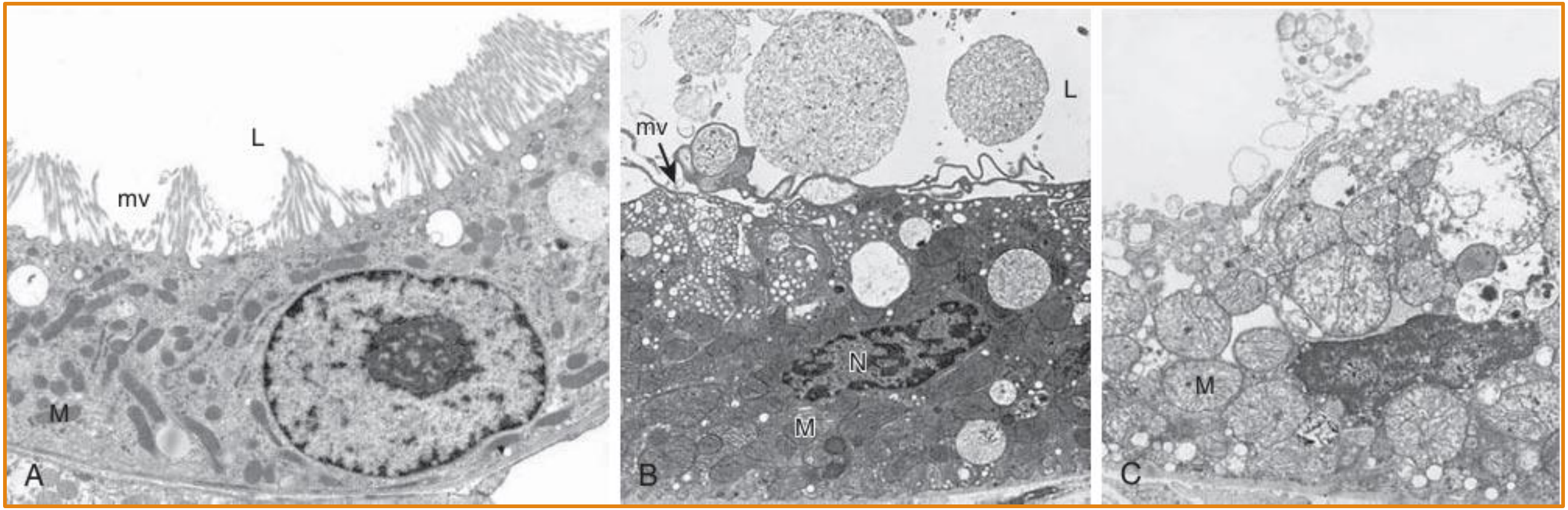

6. Nuclear Degeneration
1. Always Pathological
5. Inflammation
Necrosis
2. Cell Enlargement
4. Leakage of Content
3. Loss of Membrane Integrity
©2019 Priyanga Singh
Creative-Med-Doses

MORPHOLOGY : Cytoplasmic changes

- Necrotic cells show increased **eosiniphilia**, attributable in part to increased binding of eosin to denatured cytoplasmic proteins and in part to loss of basophilic ribonucleic acid (RNA) in the cytoplasm (basophilia stems from binding of the blue dye hematoxylindthe H in “H&E”).
- Compared with viable cells, necrotic cells may have a **glassy,** homogeneous appearance, mostly due to the loss of glycogen particles.
- When enzymes have digested cytoplasmic organelles, the cytoplasm becomes vacuolated and appears “**moth eaten**.”

MORPHOLOGY: Electron microscopy

Necrotic cells are characterized by discontinuities in plasma and organelle membranes, marked dilation of mitochondria associated with large amorphous intra-mitrochondrial densities, disruption of lysosomes, and intracytoplasmic myelin figures, which are more prominent in necrotic cells than in cells with reversible injury



A- Electron micrograph of a normal epithelial cell of the proximal kidney tubule

B- Epithelial cell of the proximal tubule showing early cell injury, the microvilli are lost and have been incorporated in apical cytoplasm; blebs have formed and are extruded in the lumen. Mitochondria (M) would have been swollen.

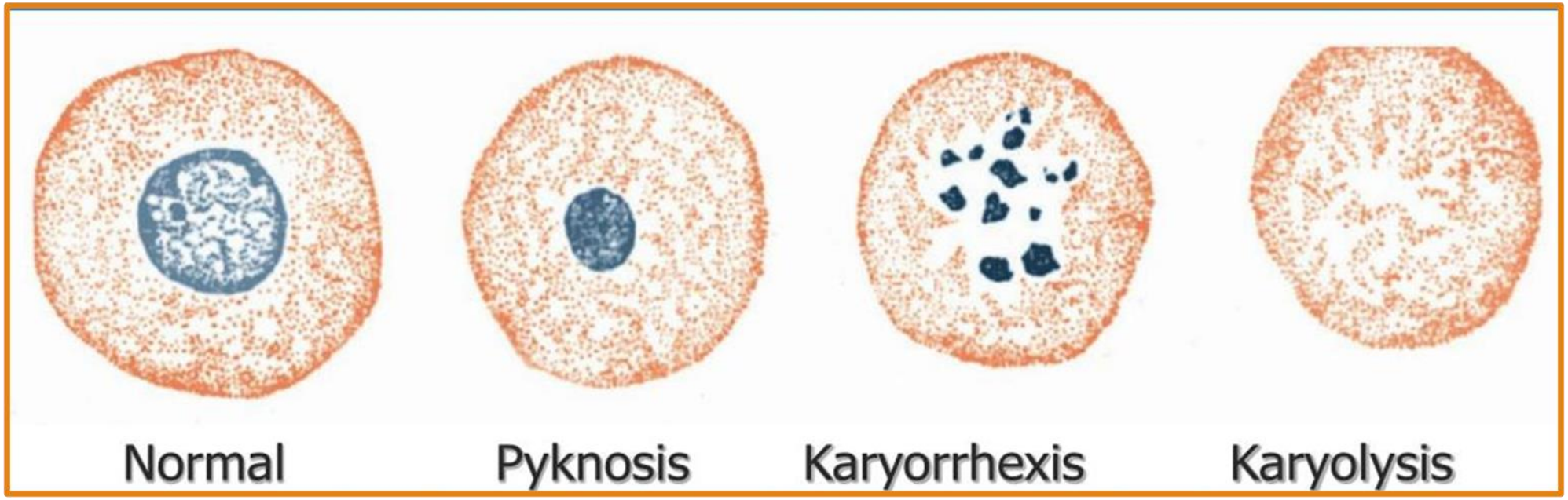
C-Proximal tubular cell showing irreversible injury. Note the markedly swollen mitochondria containing electron-dense deposits that contain precipitated calcium and proteins. Higher magnification micrographs of the cell would show disrupted plasma membrane and swelling and fragmentation of organelles

MORPHOLOGY: Nuclear changes.

Pyknosis is characterized by nuclear shrinkage and increased basophilia; the DNA condenses into a dark, shrunken mass.

- The **pyknotic** nucleus can subsequently undergo fragmentation; this change is called **karyorrhexis**.
- At the same time, the nucleus may undergo **karyolysis**, in which the basophilia fades due to digestion of deoxyribonucleic acid (DNA) by DNase.
- In 1 to 2 days, the nucleus in a dead cell may undergo complete dissolution.

Three patterns of nuclear changes in Necrosis, all caused by breakdown of DNA and chromatin.



Feature	Necrosis
Cell size	Enlarged (swelling)
Nucleus	Pyknosis → karyorrhexis → karyolysis
Plasma membrane	Disrupted
Cellular contents	Enzymatic digestion; may leak out of cell
Adjacent inflammation	Frequent
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)

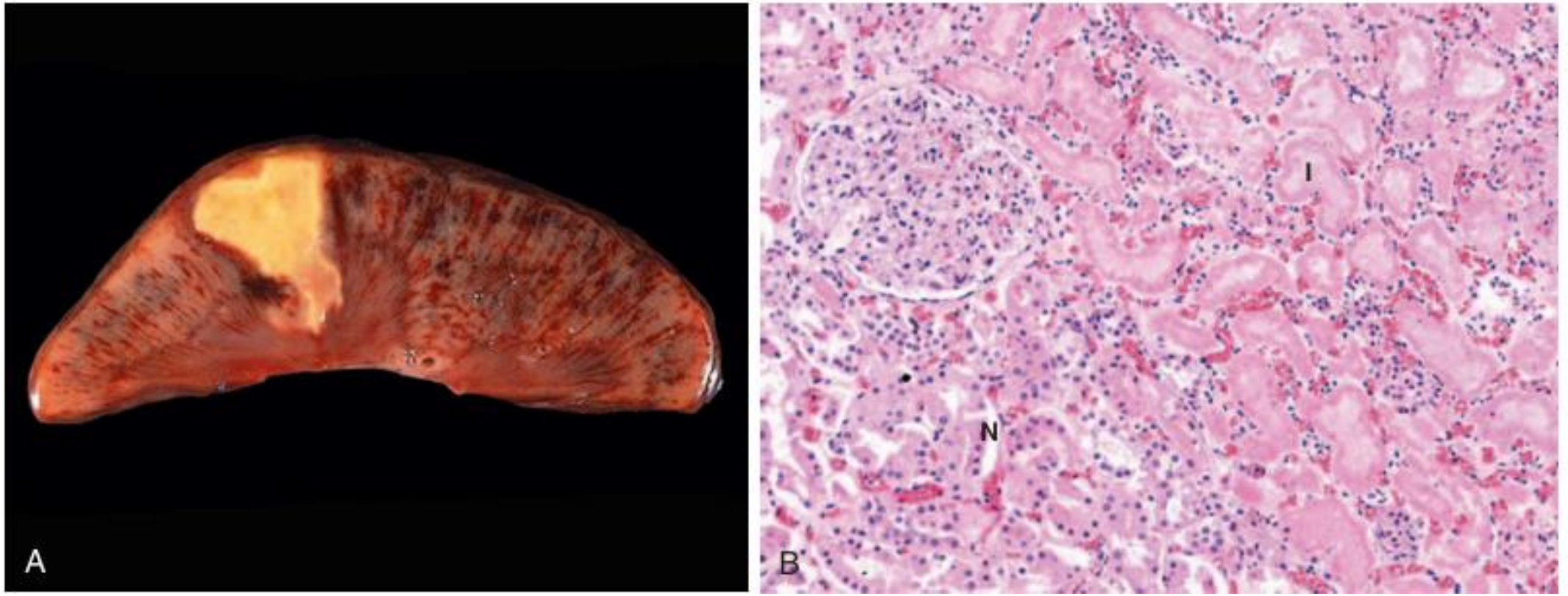
Morphologic Patterns of Tissue Necrosis

1. Coagulative necrosis
2. Liquefactive necrosis
3. Caseous necrosis
4. Fat necrosis
5. Fibrinoid necrosis

1- Coagulative necrosis

- The underlying tissue architecture is preserved for at least several days after the injury.
- The affected tissues take on a firm texture. Presumably, the injury denatures not only structural proteins but also enzymes, limiting the proteolysis of the dead cells; as a result, eosinophilic, anucleate cells may persist for days or weeks. Ultimately, the dead cells are digested by the lysosomal enzymes of recruited leukocytes and the cellular debris is removed by phagocytosis.
- Coagulative necrosis is characteristic of infarcts (areas of necrosis caused by ischemia) in all solid organs except the brain.

Coagulative necrosis.



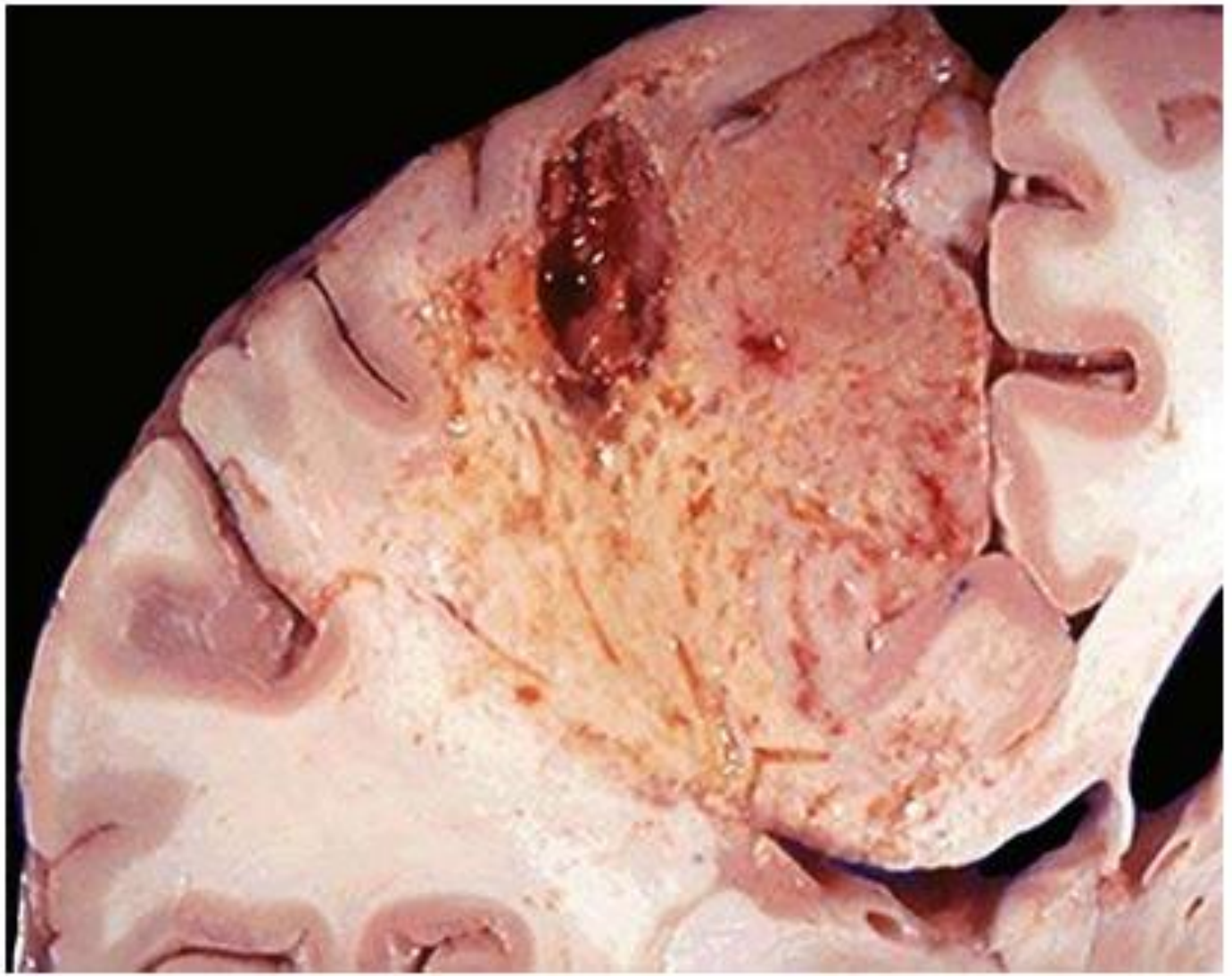
(A) A wedge-shaped kidney infarct (yellow) with distinct margins. (B) Micro scopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I). The necrotic cells show preserved outlines with loss of nuclei, and an inflammatory infiltrate is present (difficult to discern at this magnification).

2- Liquefactive necrosis

- Itis seen at sites of bacterial or, occasionally, fungal infections, because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digest (“liquefy”) the tissue.
- For obscure reasons, hypoxic death of cells within the central nervous system often causes liquefactive necrosis.
- In this form of necrosis, the dead cells are completely digested, transforming the tissue into a viscous liquid that is eventually removed by phagocytes.
- When the process is initiated by acute inflammation, as in a bacterial infection, the material is frequently creamy yellow and is called **pus.**
- A localized collection of pus is called an abscess

Liquefactive necrosis.

An infarct in the brain showing dissolution of the tissue.



Gangrenous necrosis

Although gangrenous necrosis is not a distinctive pattern of cell death, the term is still commonly used in clinical practice. It usually refers to the condition of 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, the morphologic appearance is often liquefactive because of destruction mediated by the contents of the bacteria and the attracted leukocytes (resulting in so-called wet gangrene).

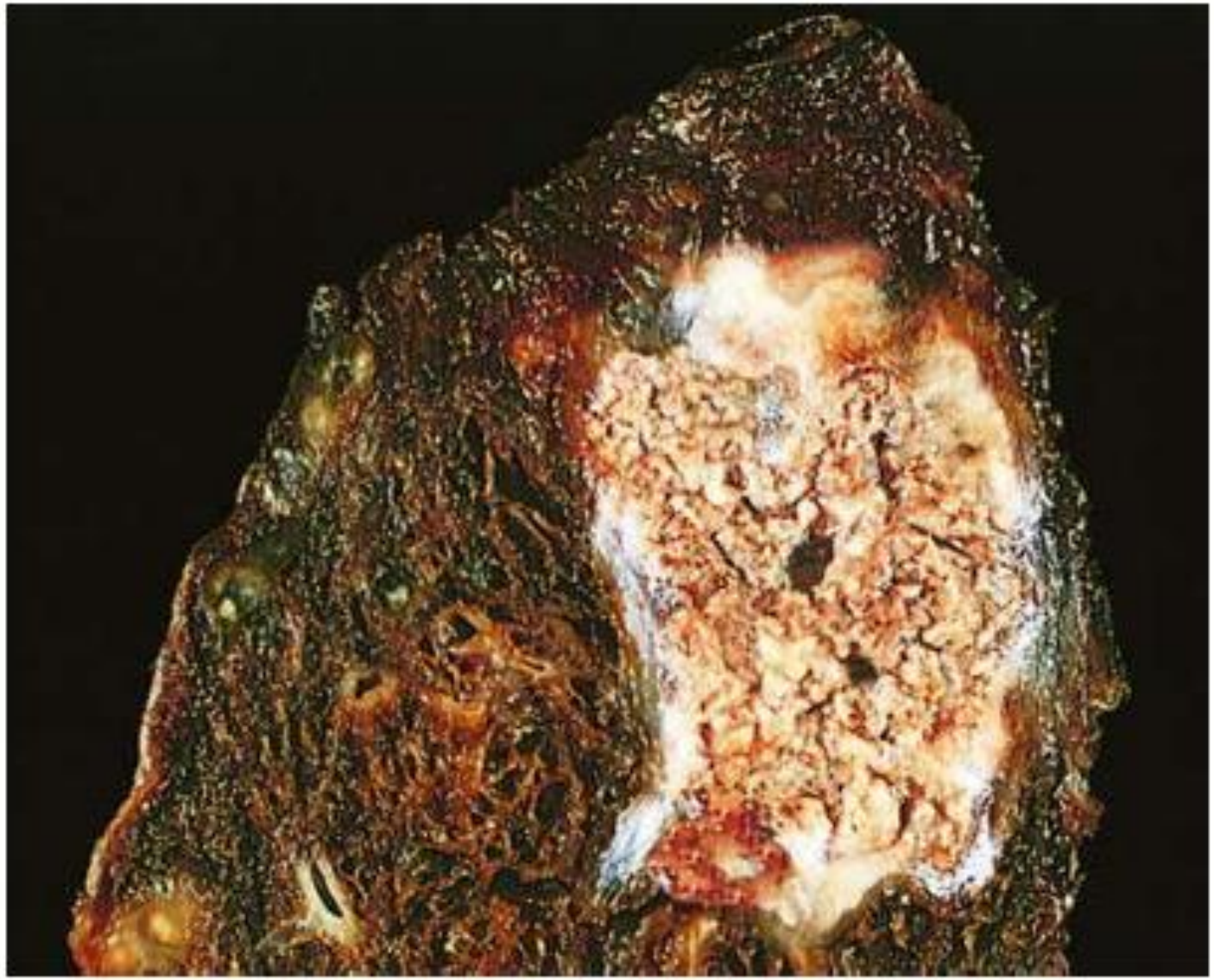
3- Caseous necrosis

- Caseous necrosis is encountered most often in foci of tuberculous infection.
- Caseous means “cheese-like,” referring to the friable yellow-white appearance of the area of necrosis.
- On microscopic examination, the necrotic focus appears as a collection of cellular debris with an amorphous granular pink appearance in H&E-stained tissue sections.
- Unlike coagulative necrosis, the tissue architecture is obliterated, and cellular outlines cannot be discerned.
- Caseous necrosis is often surrounded by a collection of macro phages and other inflammatory cells; this appearance is characteristic of a nodular inflammatory lesion called a granuloma.

Caseous necrosis.

- Caseous necrosis.

Tuberculosis of the lung, with a large area of caseous necrosis containing yellow-white (cheesy) debris.

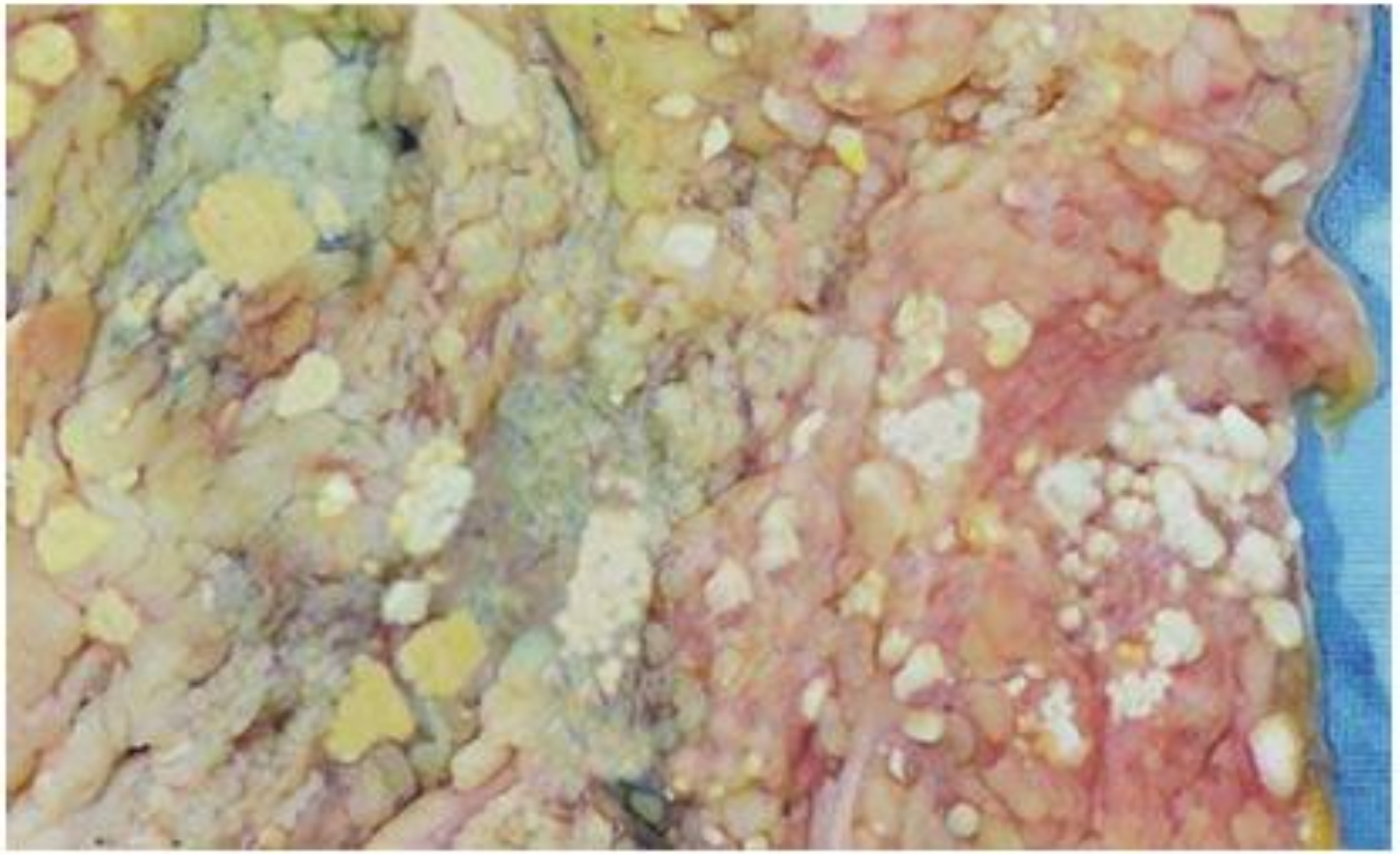


4- Fat necrosis

- Fat necrosis refers to focal areas of fat destruction, which can be due to abdominal trauma or acute pancreatitis, in which enzymes leak out of damaged pancreatic acinar cells and ducts and digest peritoneal fat cells and their contents, including stored triglycerides.
- The released fatty acids combine with calcium to produce grossly identifiable chalky white lesions.
- On histologic examination, the foci of necrosis contain shadowy outlines of necrotic fat cells surrounded by granular basophilic calcium deposits and an inflammatory reaction.

Fat necrosis.

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

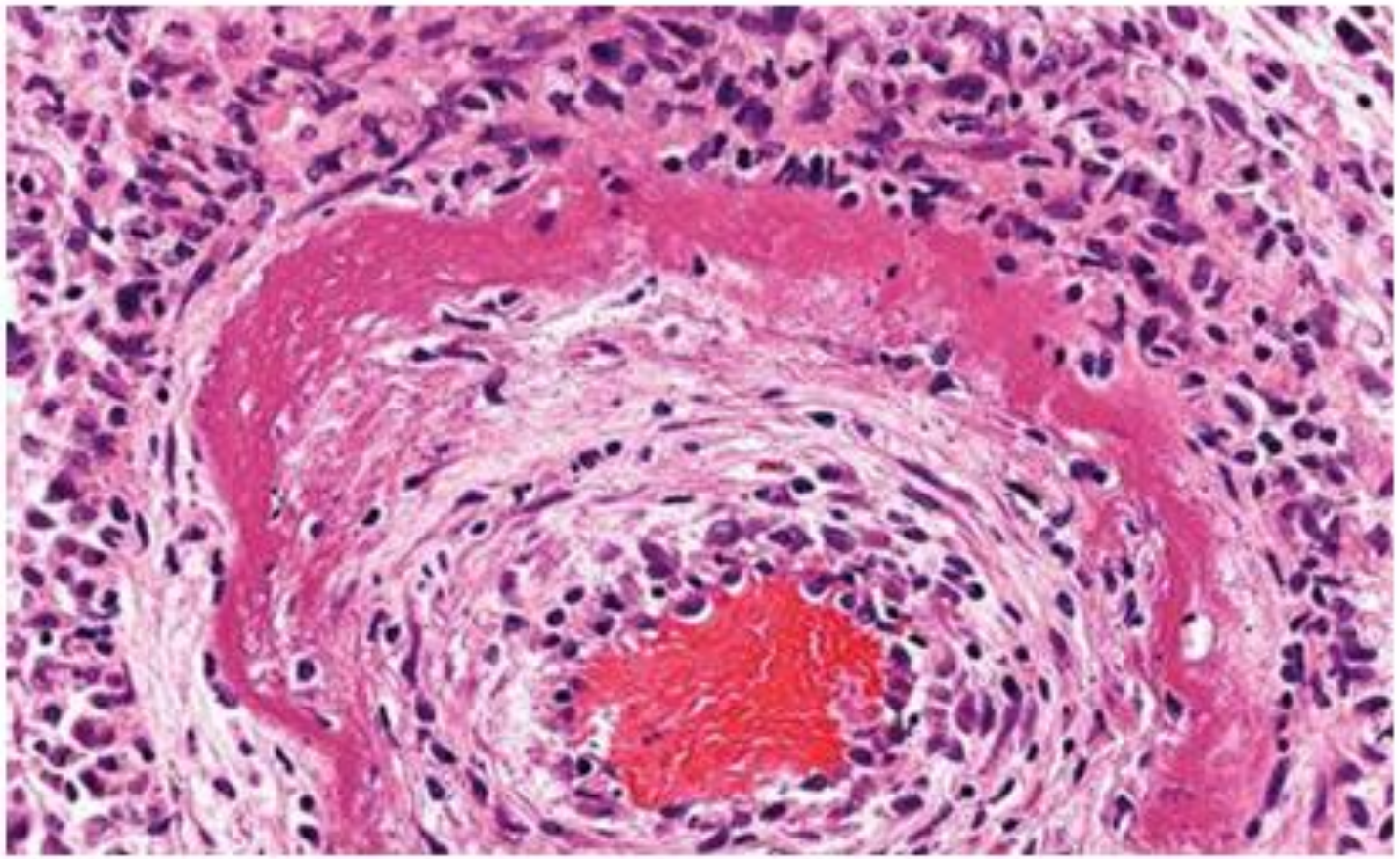


5- Fibrinoid necrosis

- Fibrinoid necrosis is a special form of necrosis, visible by light microscopy.
- It may be seen in immune reactions in which complexes of antigens and antibodies are deposited in the walls of blood vessels, and in severe hypertension.
- Deposited immune complexes and plasma proteins that have leaked into the walls of injured vessels produce a bright pink, amorphous appearance on H&E preparations called fibrinoid (fibrin-like) by pathologists
- Fibrinoid necrosis is seen most often in certain forms of vasculitis and in transplanted organs undergoing rejection

Fibrinoid necrosis

- In an artery in a patient with polyarteritis nodosa, a form of vasculitis.
- The wall of the artery shows a circumferential bright pink area of necrosis with protein deposition and inflammation.



Fates of necrotic cells

- Necrotic cells may persist for some time or may be digested by enzymes and disappear.
- Dead cells may be replaced by myelin figures, which are either phagocytosed by other cells or further degraded into fatty acids. These fatty acids bind calcium salts, which may result in the dead cells ultimately becoming calcified (dystrophic calcification)