Cell Injury, Adaptation and Cell Death

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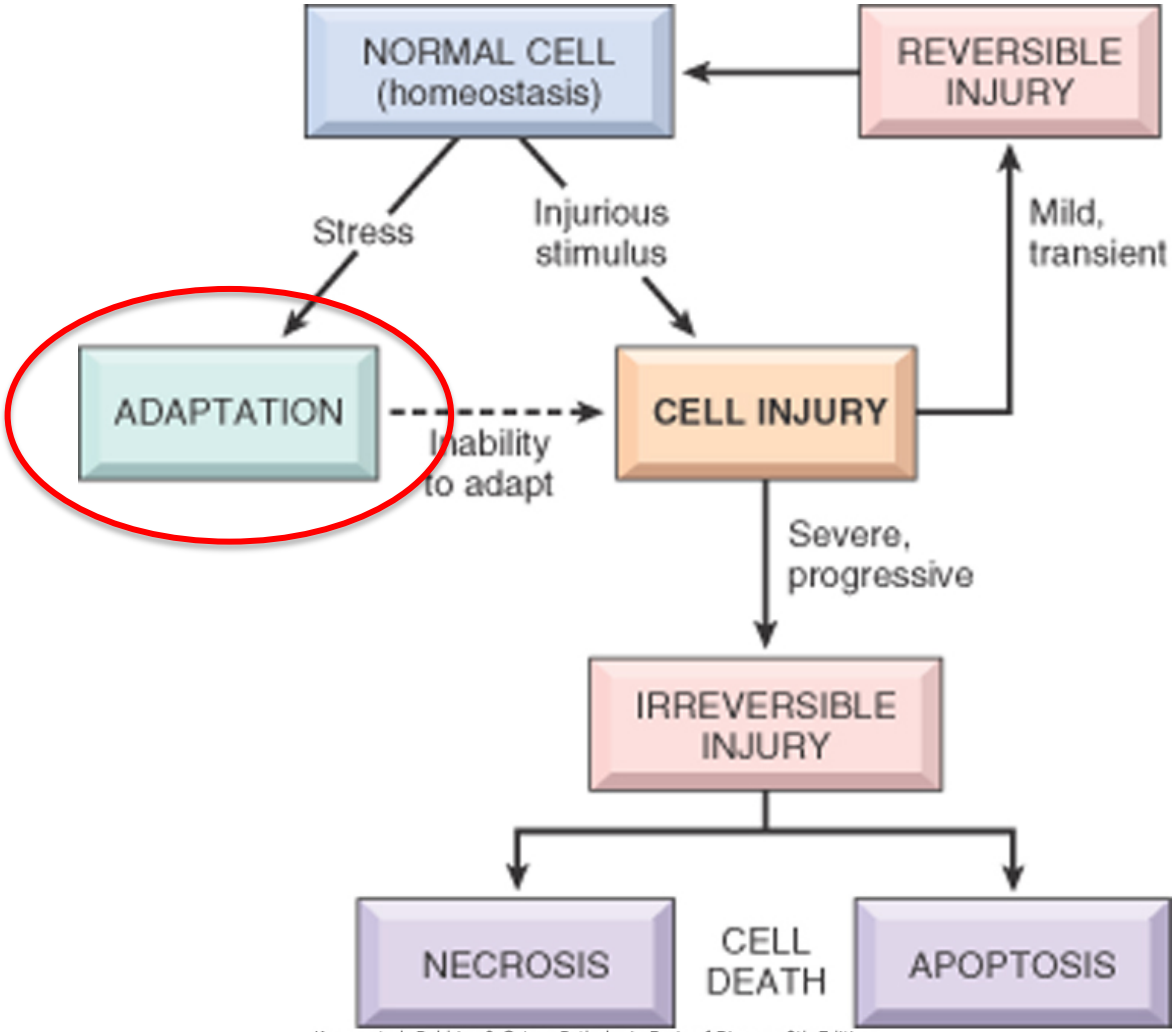
Objectives:

After learning, student should be able to

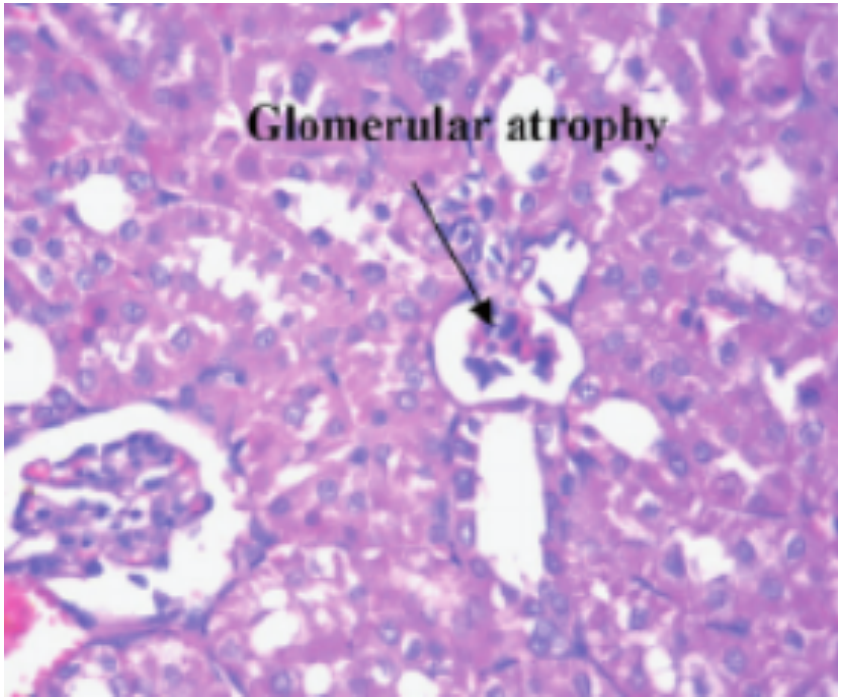
- Describe basic knowledge and pathology of cell adaptation, cell injury, and cell death
- Describe the patterns of intracellular accumulations and pathologic calcification
- Discuss patho-mechanisms of cell adaptation, cell injury, and cell death

Adaptation

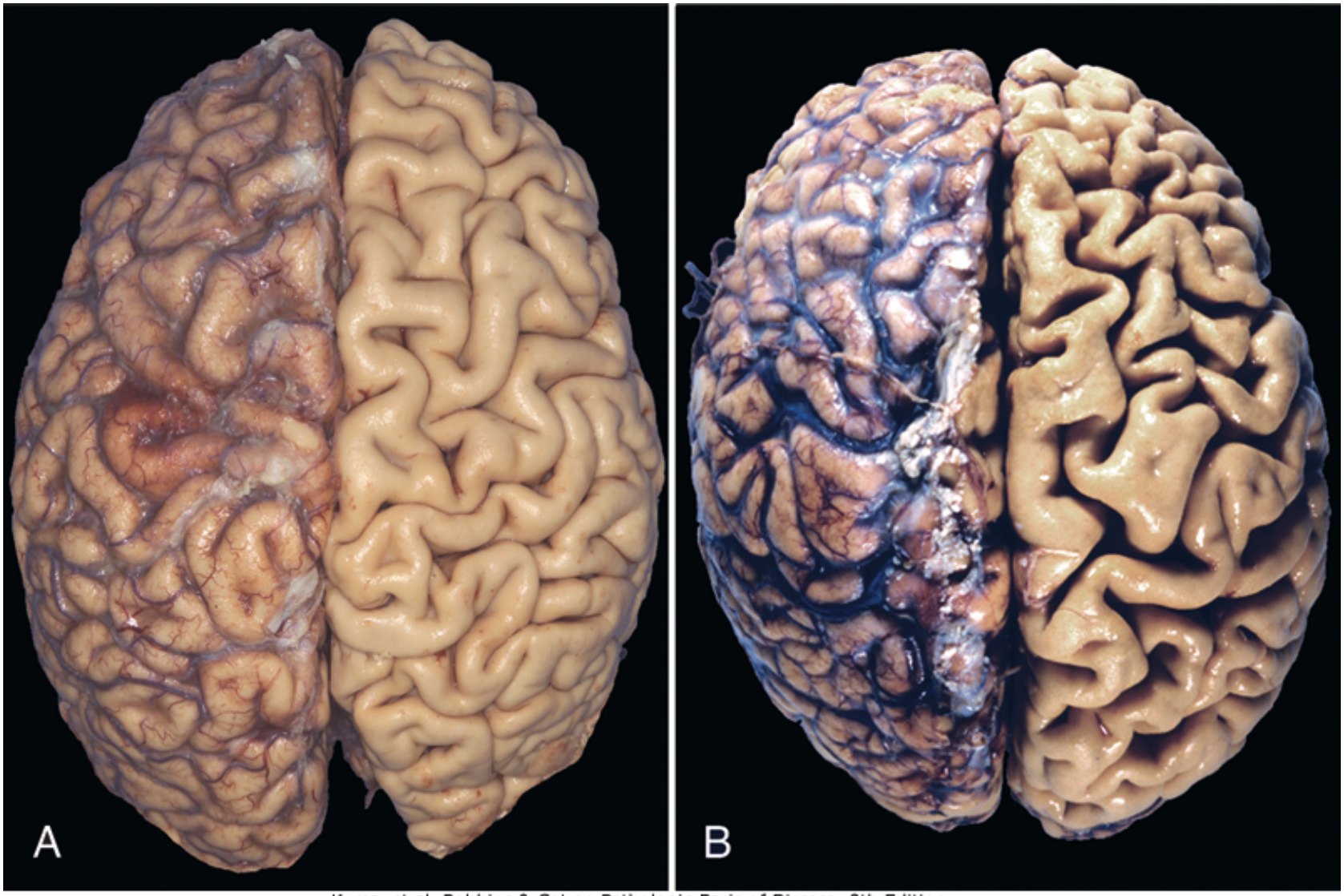


❑ Atrophy

- ❖ Decreased size and function
- ❖ Metabolic processes shut down to conserve energy
- ❖ Due to
  - decreased demand
  - ischemia
  - lack of nerve or hormonal stimulation
  - chronic inflammation

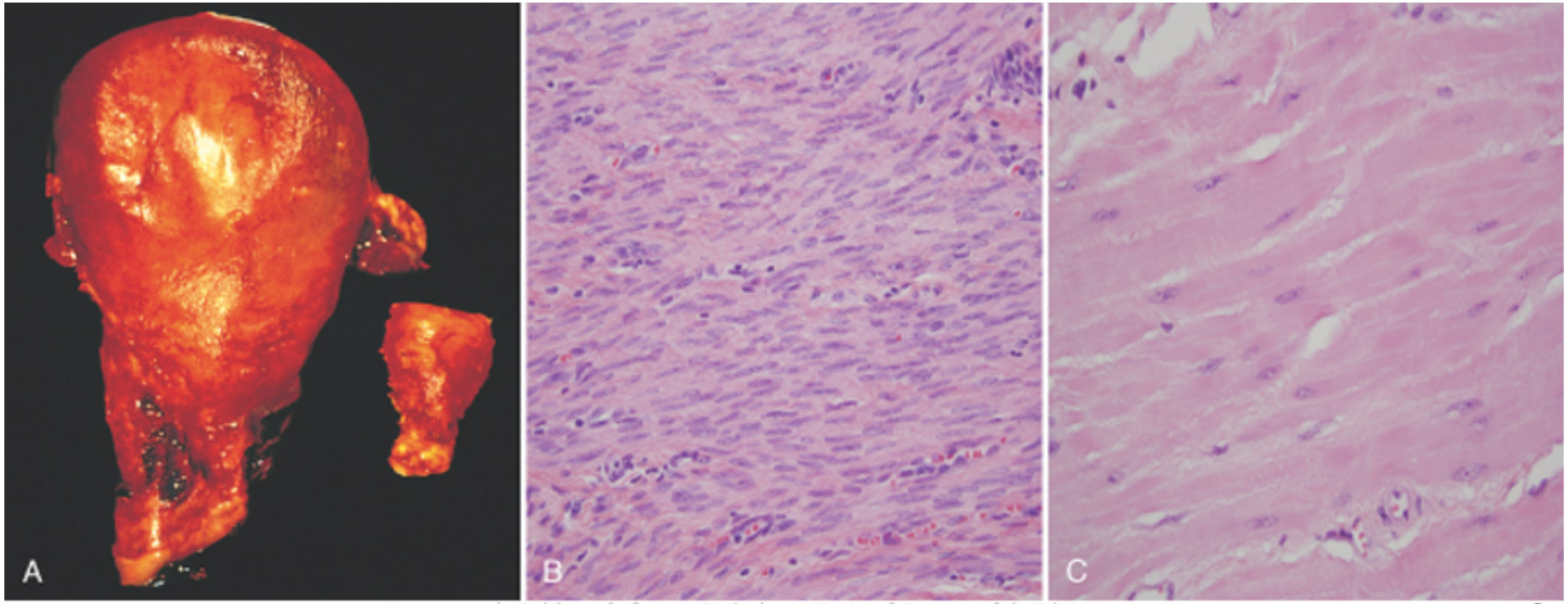


(https://www.researchgate.net)



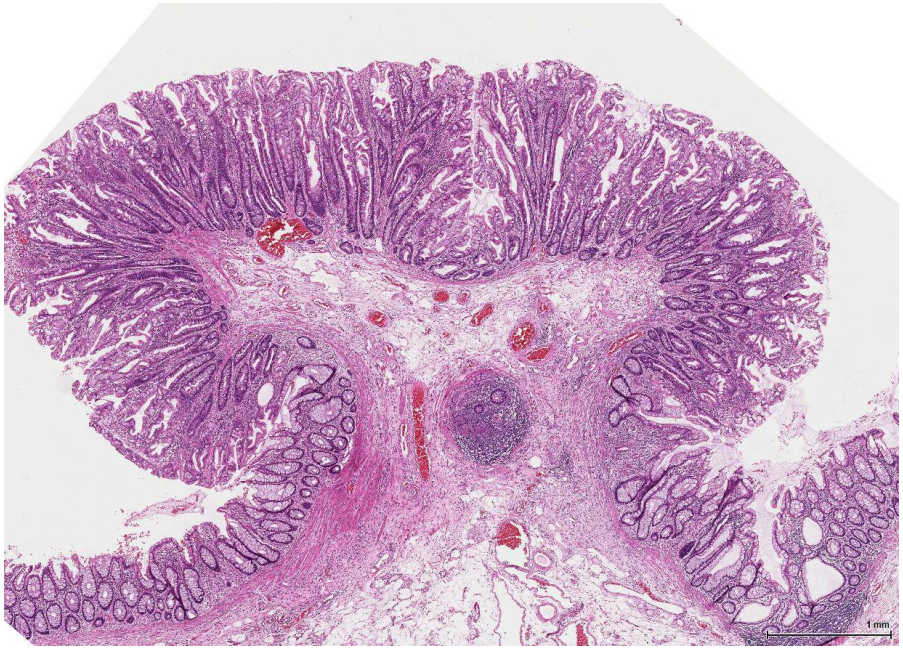
❑ Hypertrophy:

- ❖ Increased size and functional capacity
- ❖ Due to
  - hormonal stimulation
  - increased functional demand



❑ Hyperplasia

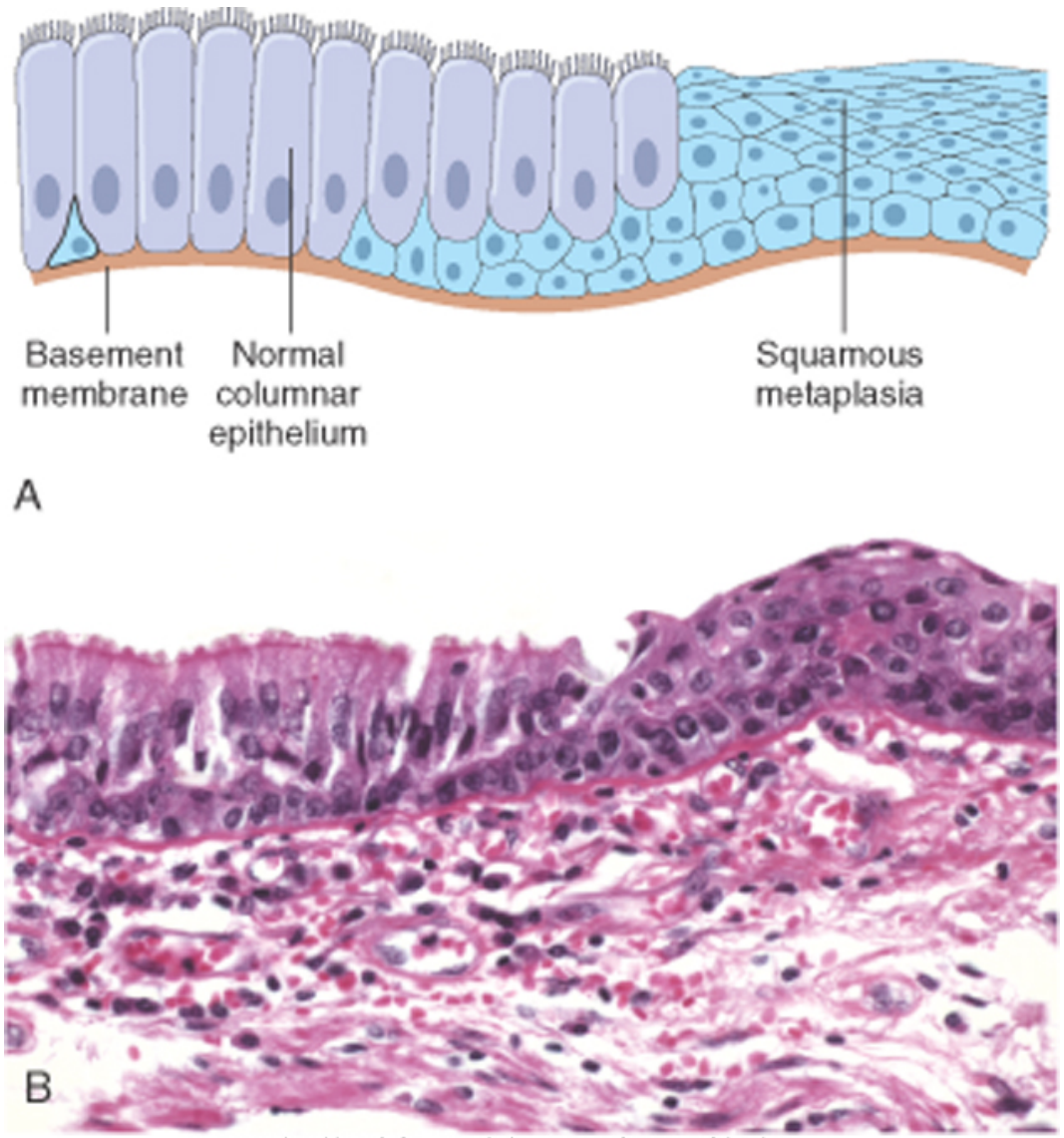
- ❖ Increase in number of cells
- ❖ Due to
  - – hormonal stimulation
  - – increased functional demand
  - – chronic stress or injury



(www.studyblue.com)

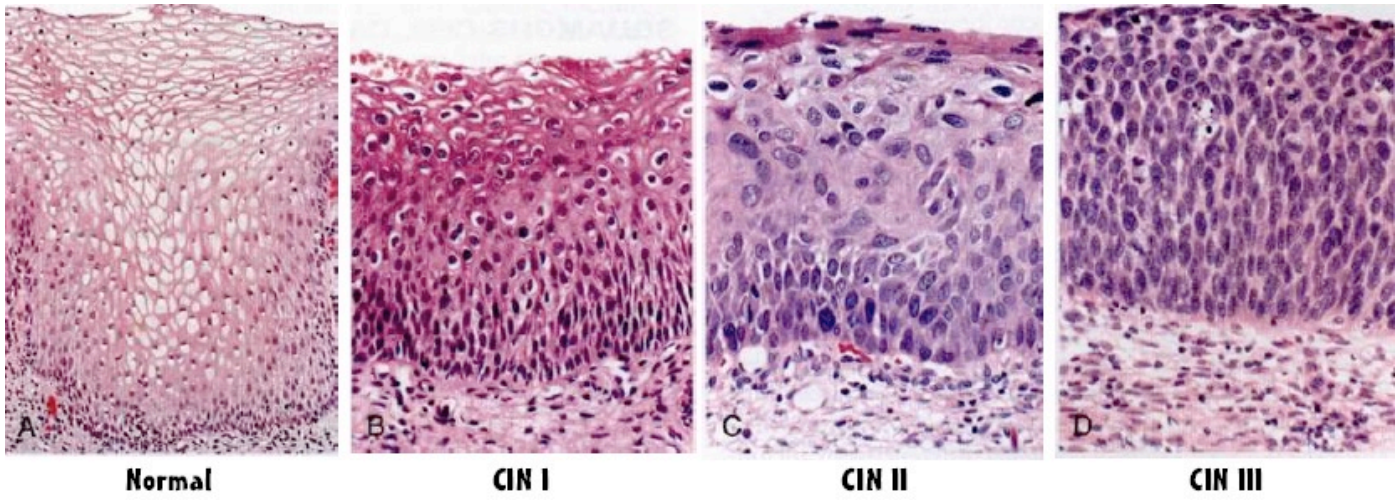
❑ Metaplasia

A reversible change in which one adult cell type is replaced by another adult cell type.



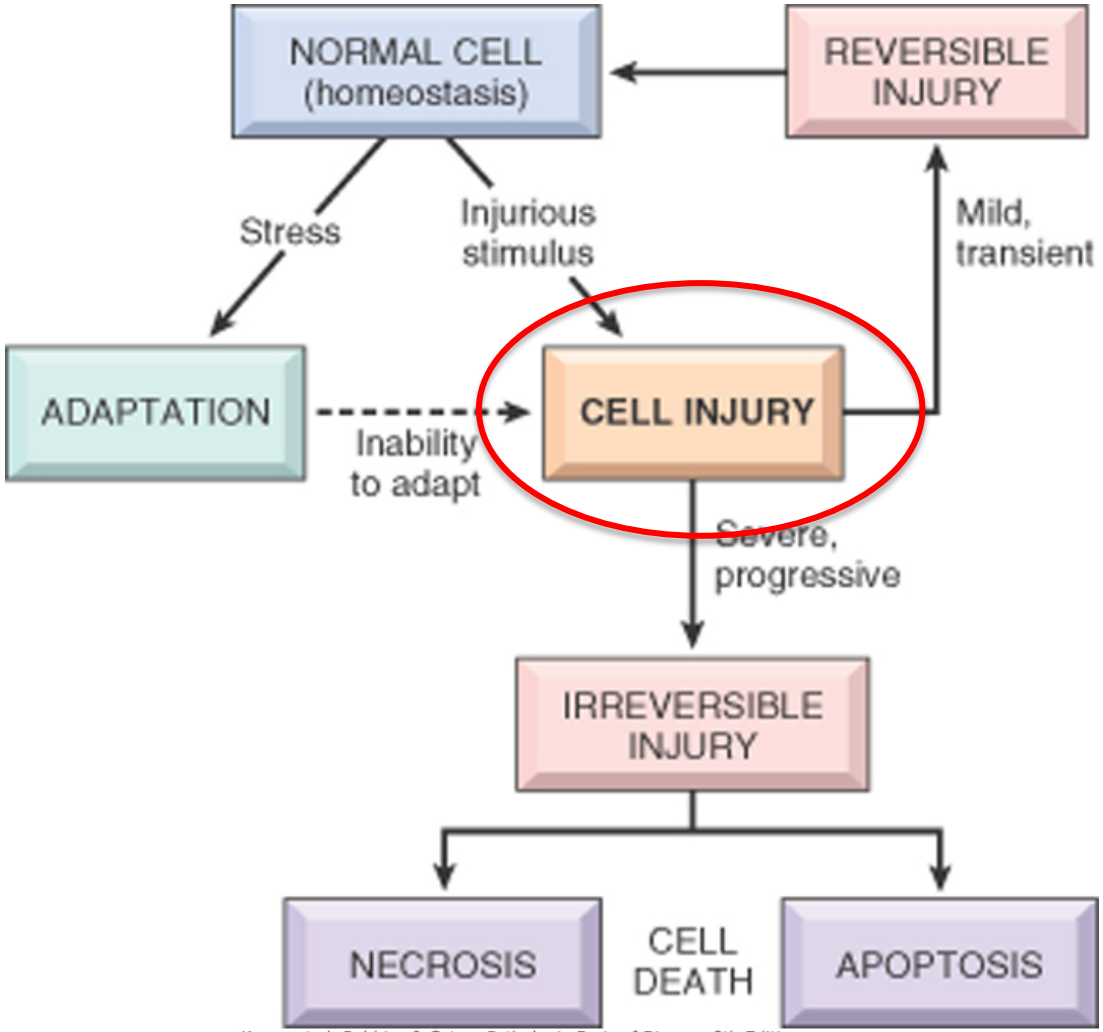
❑ Dysplasia:

- Is a disordered growth, it often occurs in metaplastic epithelium.
- Precancerous stage
- Dysplasia does *not necessarily progress* to cancer.



Cervical intraepithelial neoplasia,CIN (Robbin 7th, 2005: p1075)

Cell injury



Causes of Cell Injury

- ❑ Oxygen deprivation
- ❑ Chemical agents
- ❑ Physical agents
- ❑ Infectious agents
- ❑ Immunologic reactions
- ❑ Nutritional imbalances
- ❑ Genetic factors
- ❑ Aging

❑Oxygen Deprivation

- ❖ Hypoxia--- *deficiency of oxygen (inadequate oxygenation of the blood)*
- ❖ Ischemia--- *loss of blood supply (arterial flow or reduced venous drainage)*

❑ Chemical Agents

- ❖ The excess of glucose, salt, or water--- *the osmotic environment that can injury.*
- ❖ Toxic agents--- *air pollutants, insecticides, CO, asbestos*
- ❖ Some therapeutic drugs

❑ Physical Agents

- ❖ Mechanical trauma
- ❖ Extremes of temperature--- *burns*, *deep cold*
- ❖ Radiation
- ❖ Electric shock

❑ Infectious Agents

- ❖ Bacteria
- ❖ Parasites
- ❖ Viruses
- ❖ Fungi

❑ Immunologic Reactions

- ❖ Anaphylactic reaction
- ❖ Autoimmune diseases

❑ Nutritional Imbalances

- ❖ Protein-calorie deficiencies
- ❖ Vitamin deficiencies
- ❖ Excesses of lipids--- *Atherosclerosis*
- ❖ Metabolic diseases--- *Diabetes*

❑ Genetic Factors

- ❖ Congenital malformation--- *Down syndrome*
- ❖ Decreased life of red blood cell--- *Thalassemia*
- ❖ Inborn errors of metabolism--- *genetic variation (polymorphisms)*

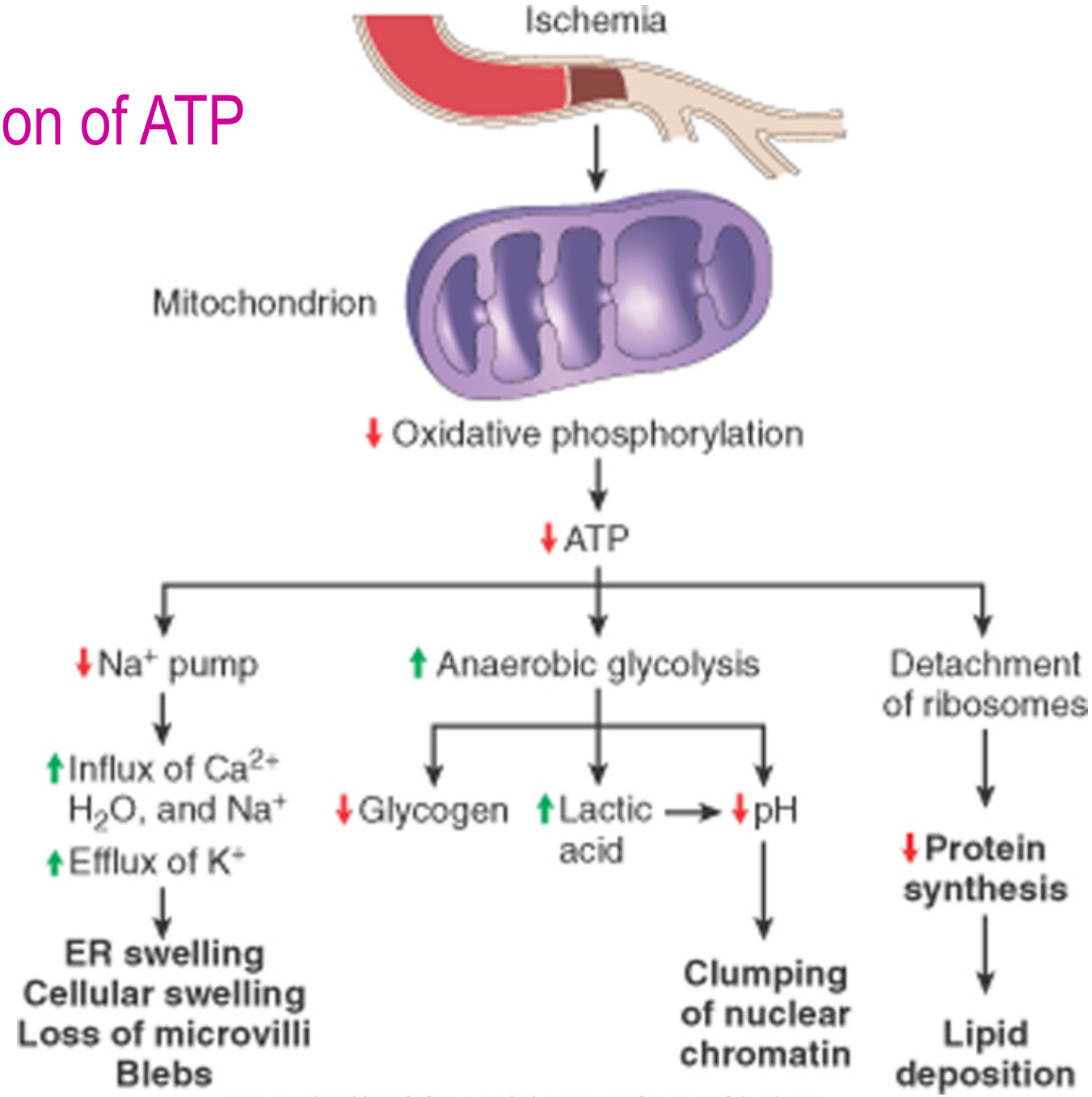
❑ Aging

- ❖ Cellular senescence
- ❖ Alterations in replicative and repair abilities

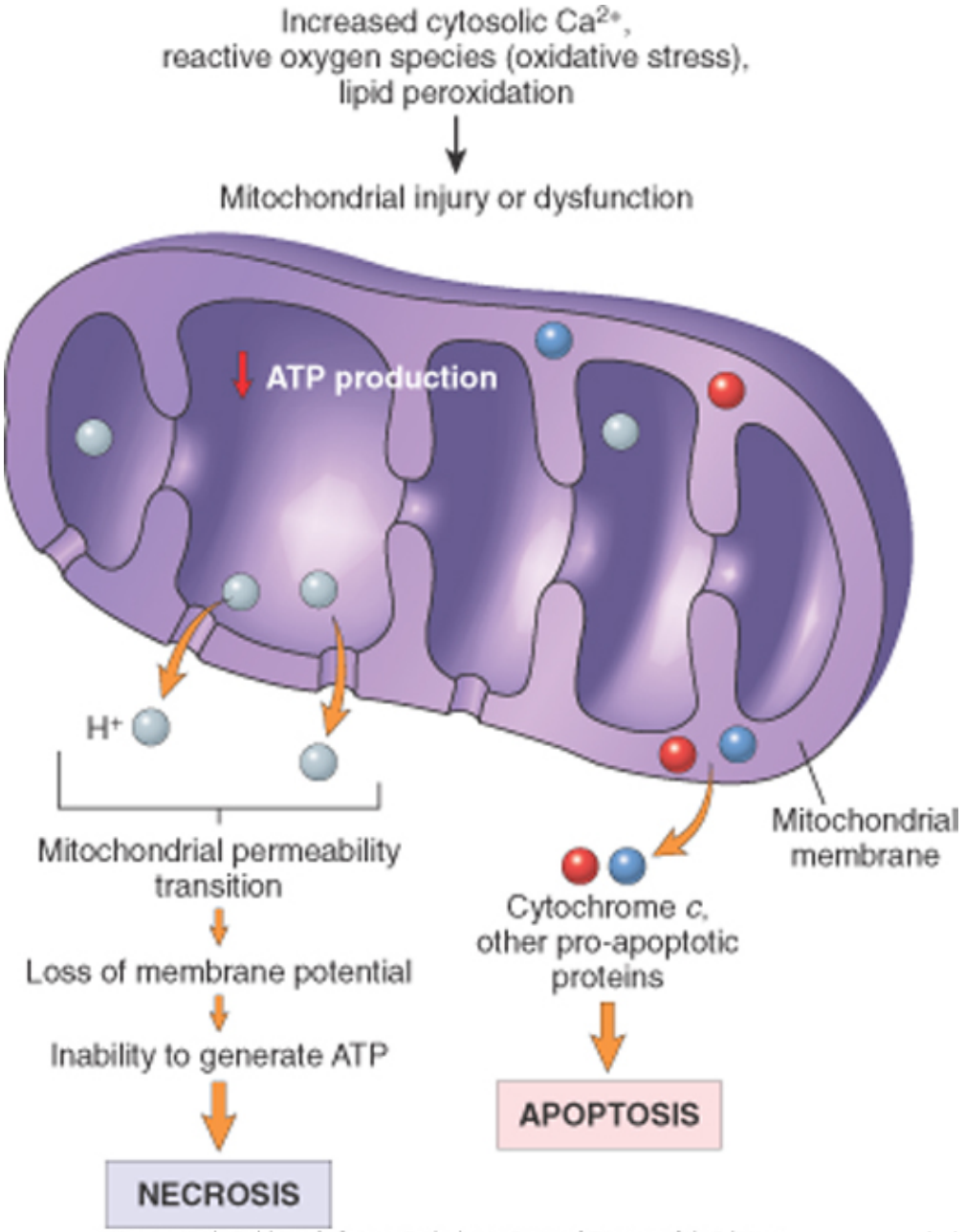
Mechanisms of cell injury

- Depletion of ATP
- Mitochondrial damage and dysfunction
- Influx of intracellular calcium
- Accumulation of oxygen derived free radicals--- *oxidative stress*
- Defects in membrane permeability

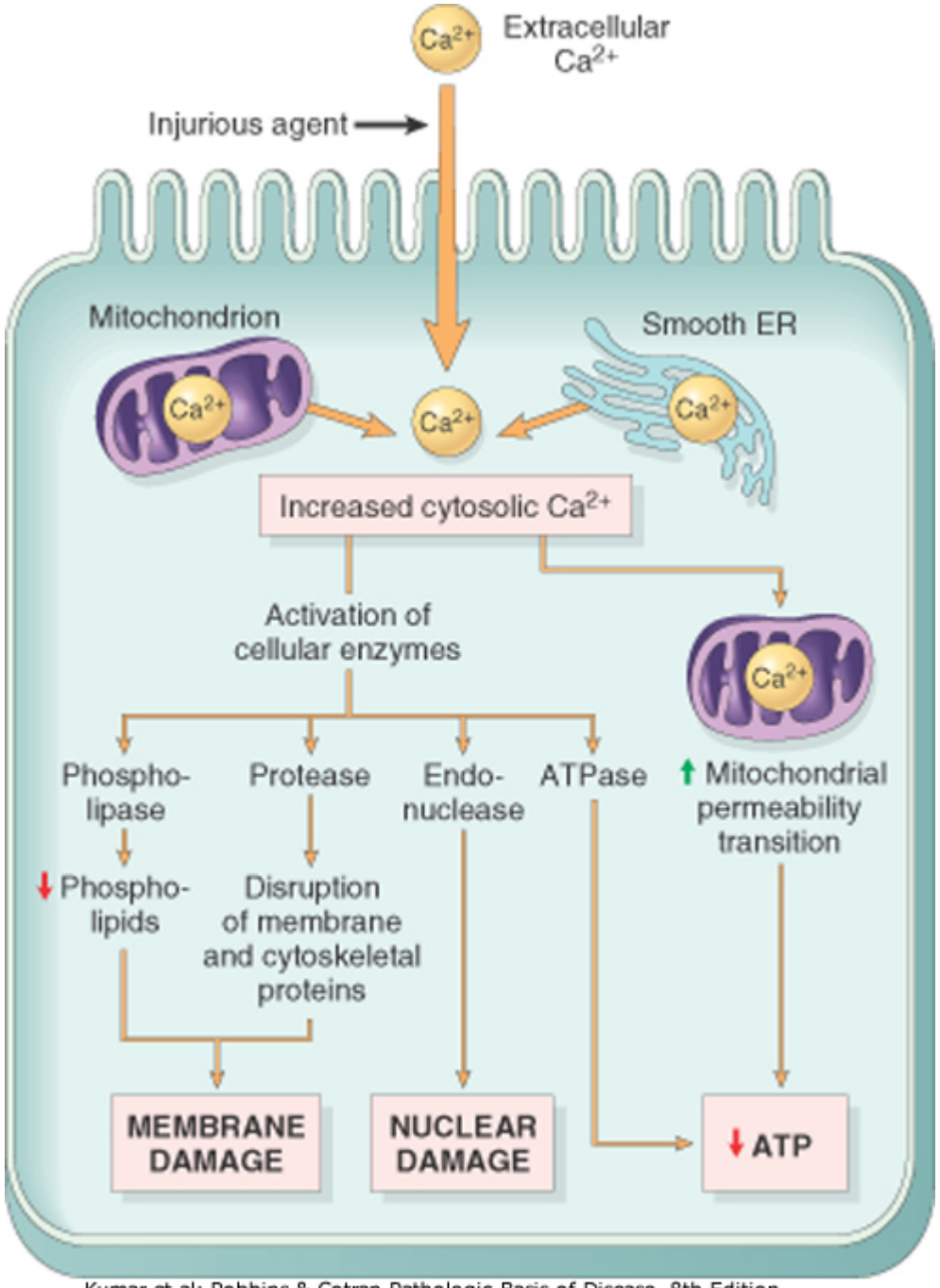
Depletion of ATP



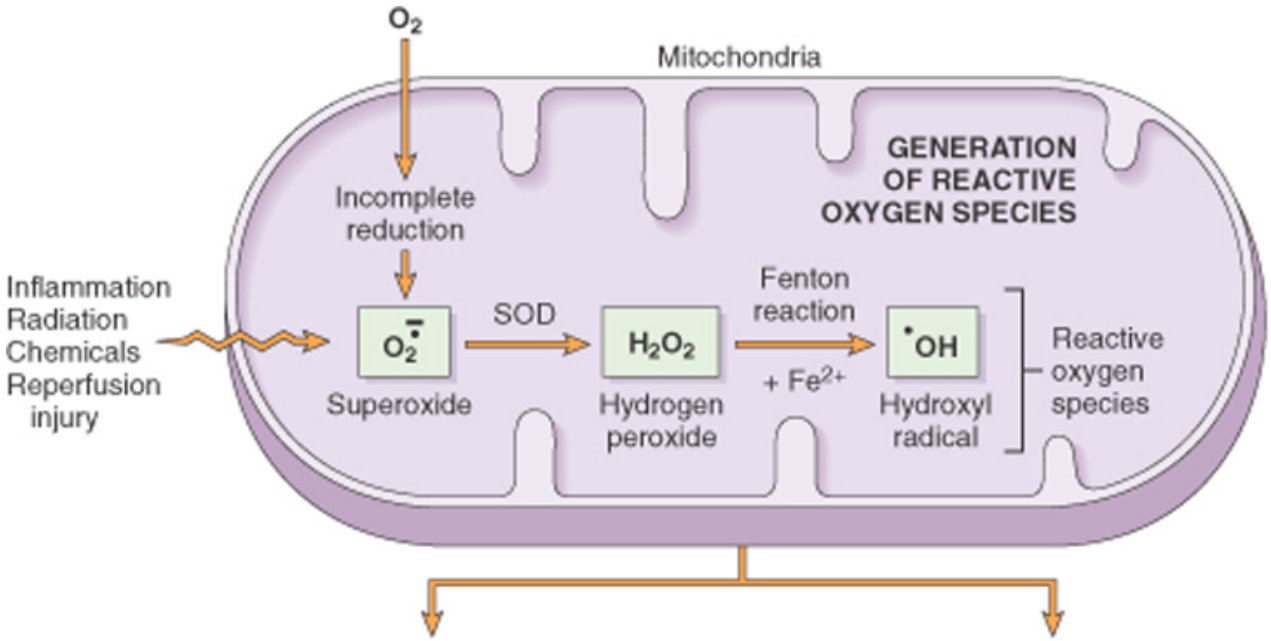
Mitochondrial damage and dysfunction



Influx of intracellular calcium



Accumulation of oxygen-derived free radicals



PATHOLOGIC EFFECTS OF ROS: CELL INJURY AND DEATH

ROS react with:

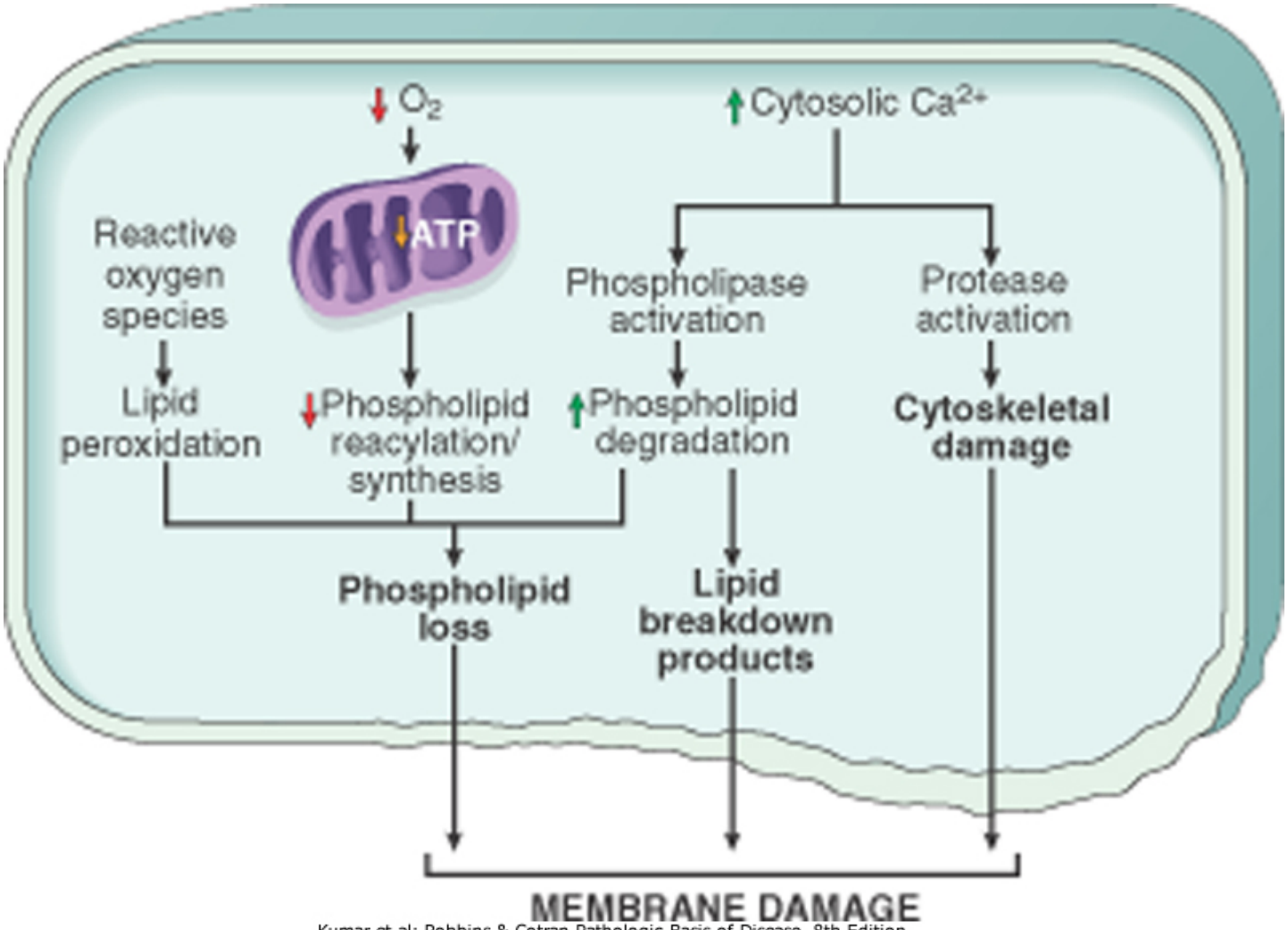
- Fatty acids → oxidation → generation of lipid peroxidases → disruption of plasma membrane, organelles
- Proteins → oxidation → loss of enzymatic activity, abnormal folding
- DNA → oxidation → mutations, breaks

REMOVAL OF FREE RADICALS

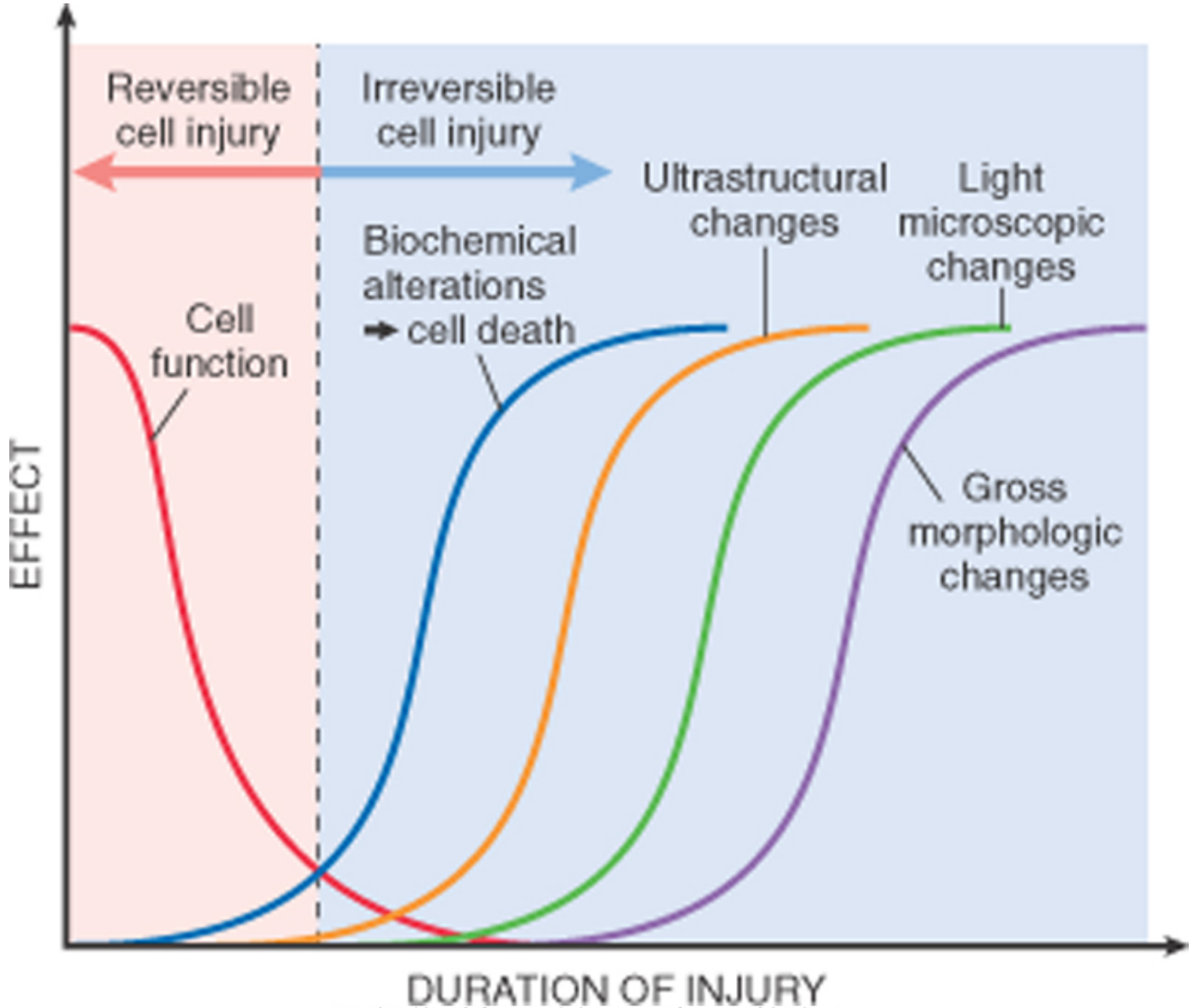
Antioxidant mechanisms:

- SOD (in mitochondria) converts $O_2^{\cdot-}$ → H_2O_2
- Glutathione peroxidase (in mitochondria) converts $^{\cdot}OH$ → H_2O_2 → $H_2O + O_2$
- Catalase (in peroxisomes) converts H_2O_2 → $H_2O + O_2$

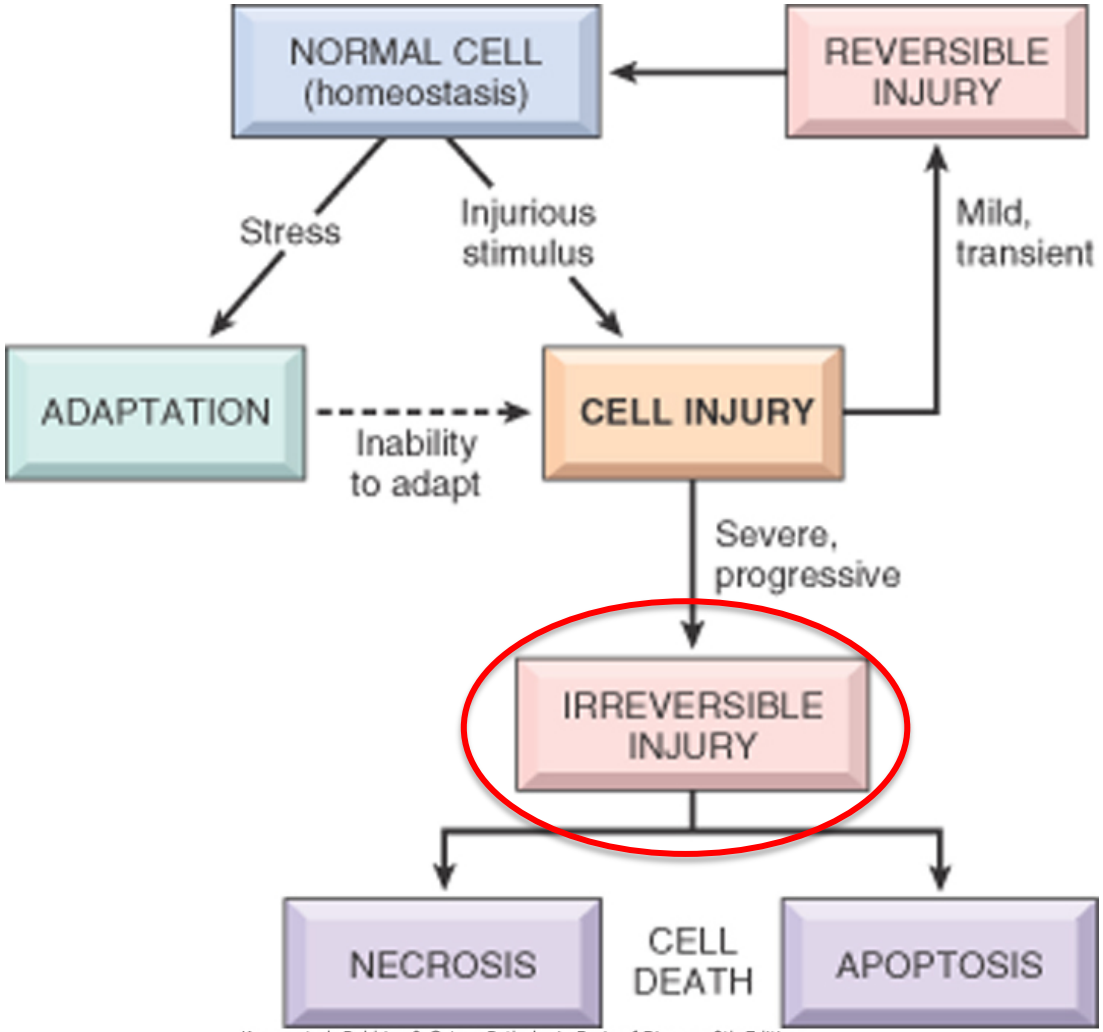
Defects in membrane permeability

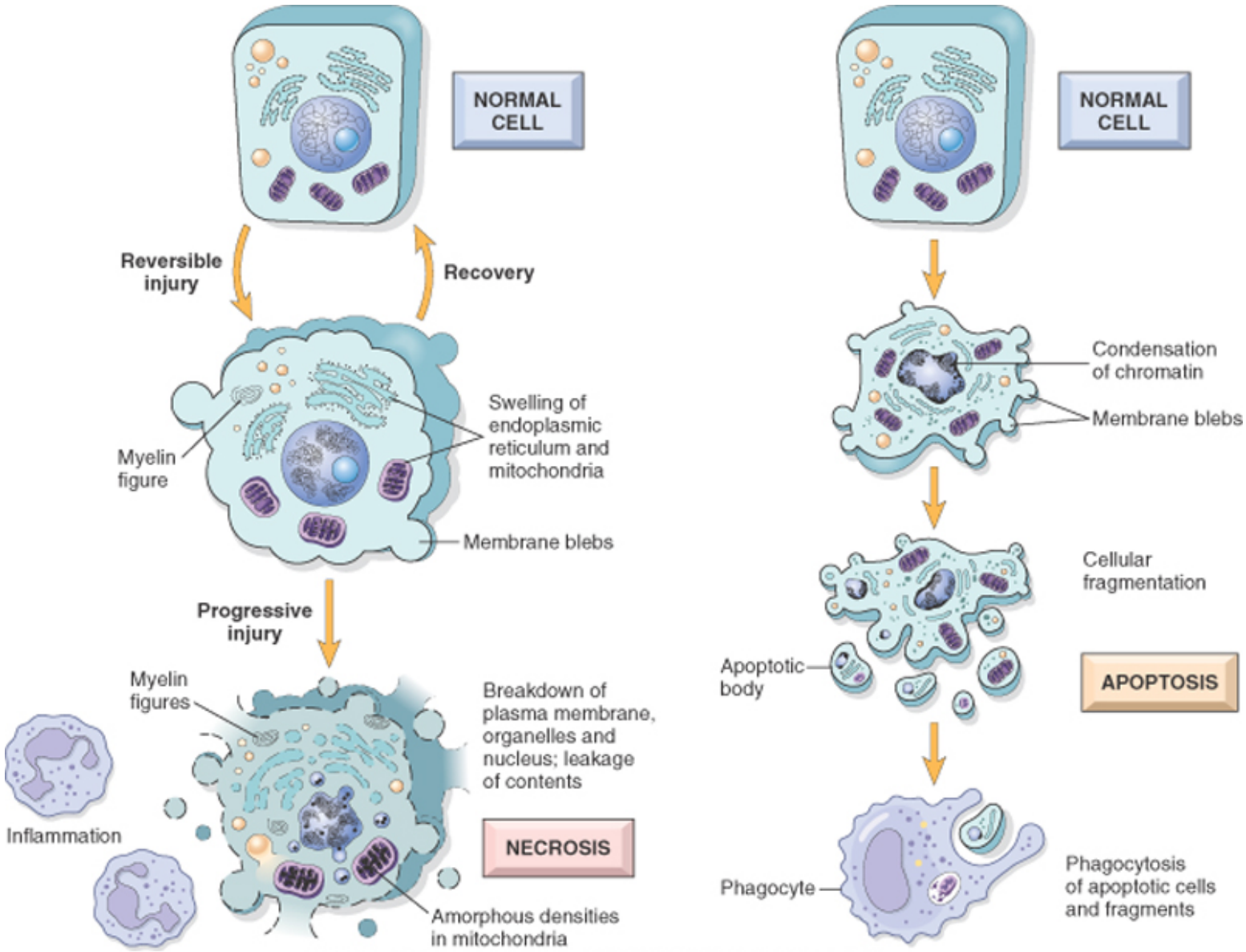


Duration of Injury

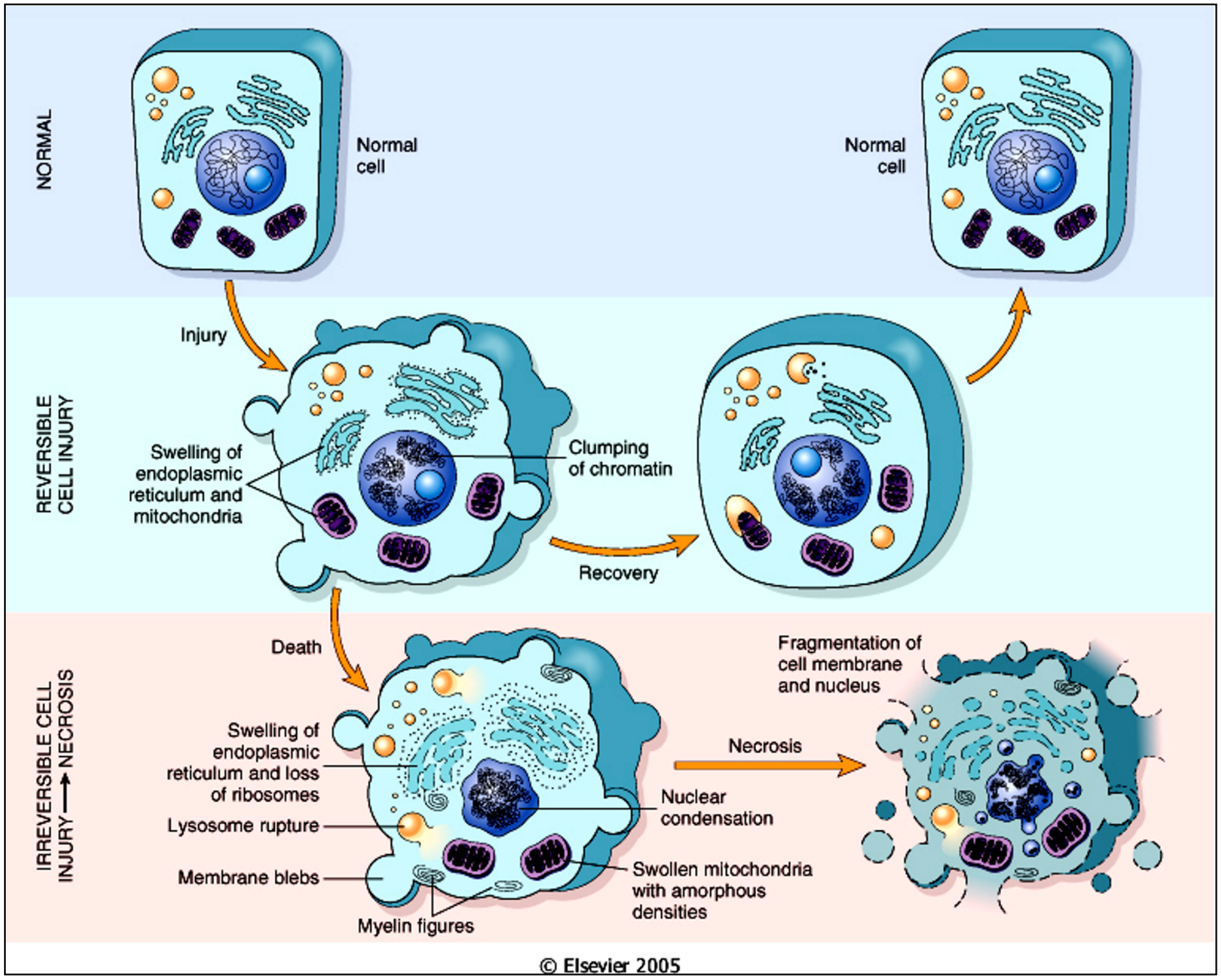


Cell death

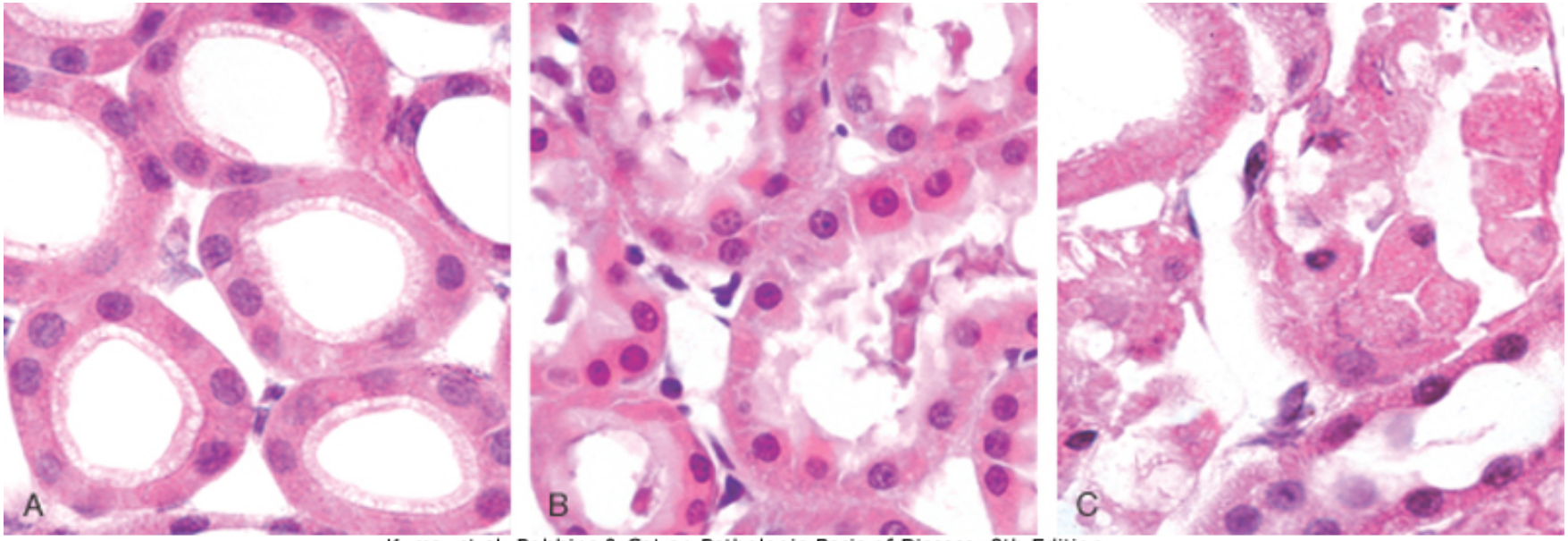




❑ Reversible and Irreversible Cell Injury



❖ Morphologic changes in reversible and irreversible cells

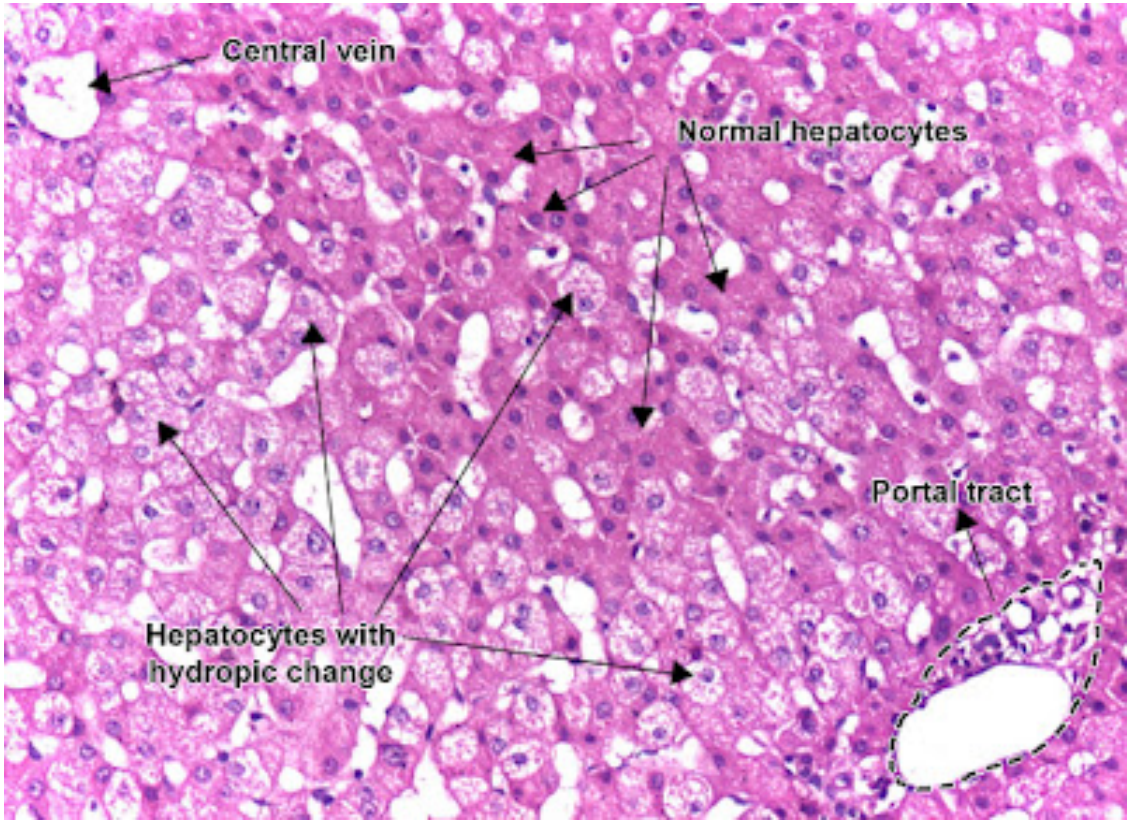


❑ Reversible cell injury

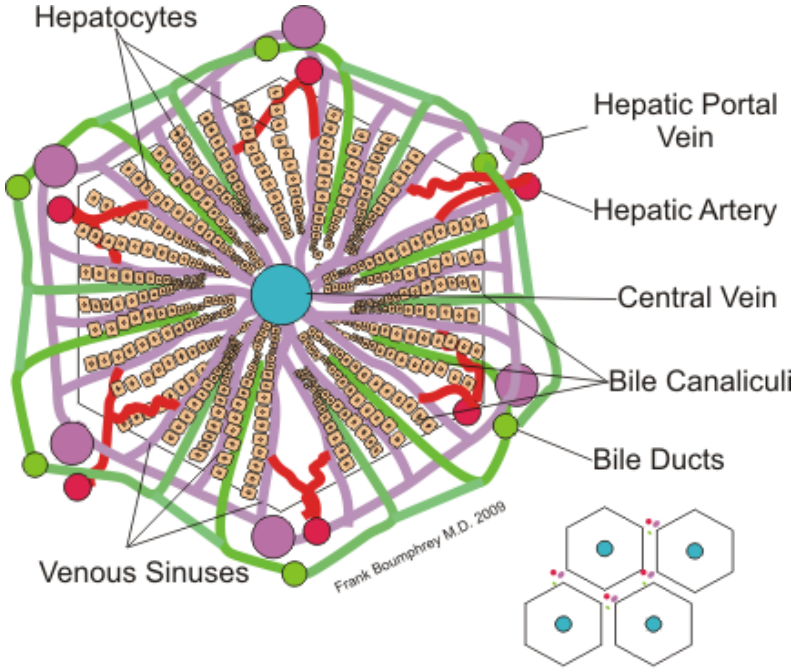
- ❖ The responses of cell to toxic injury may be transient and reversible once
  - The stress has been removed
  - The compensatory cellular changes made
- ❖ Two commonly specific cell changes to toxic exposure are
  - Cell swelling
  - Fatty change (Steatosis)

Cell swelling:

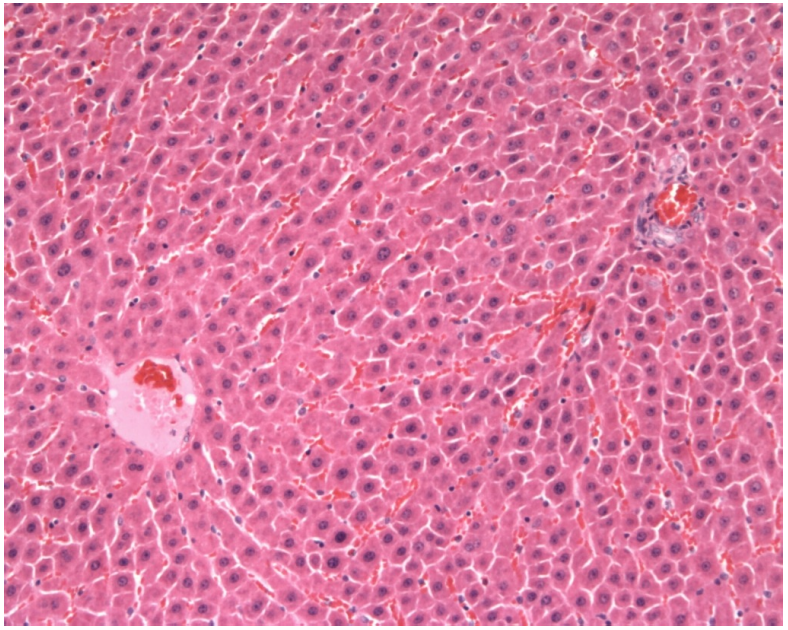
- Early change in most types of *acute injury*
- Histologically, cells are typically enlarged in size, vacuolar degeneration, cellular edema.
- Staining affinity is often diminished, giving the cells a pale or cloudy appearance.



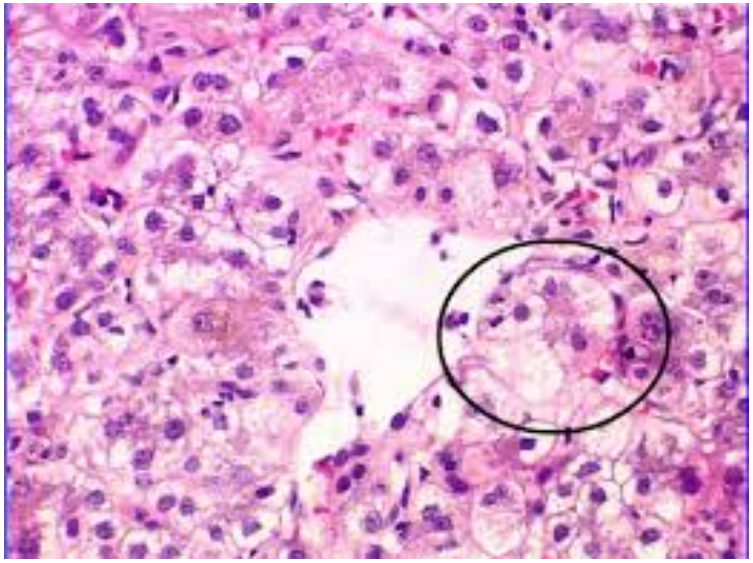
(http://ahmadkelhy.blogspot.com)



Basic Structure of Liver Lobule



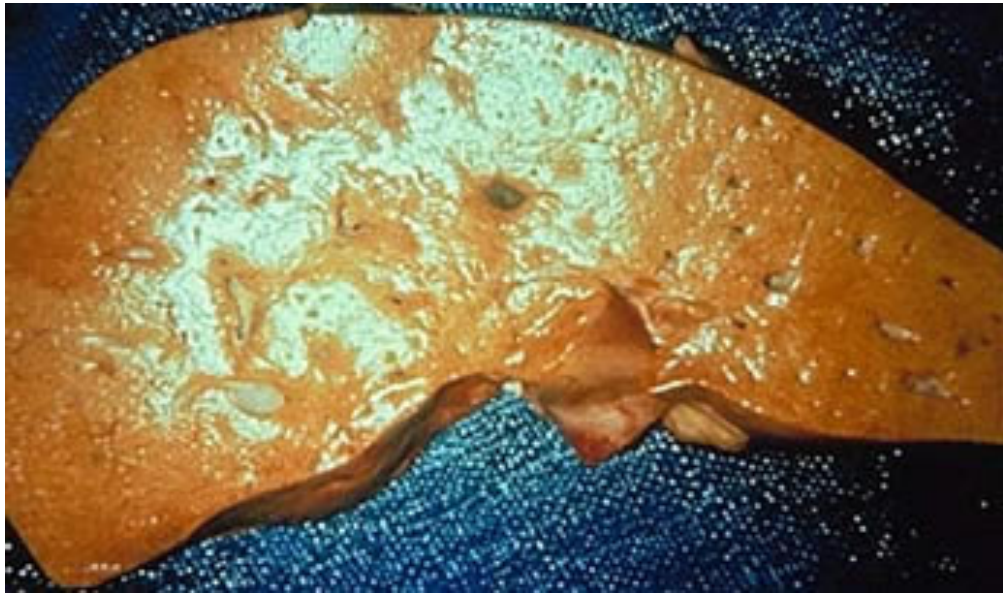
(http://pathology.tistory.com)

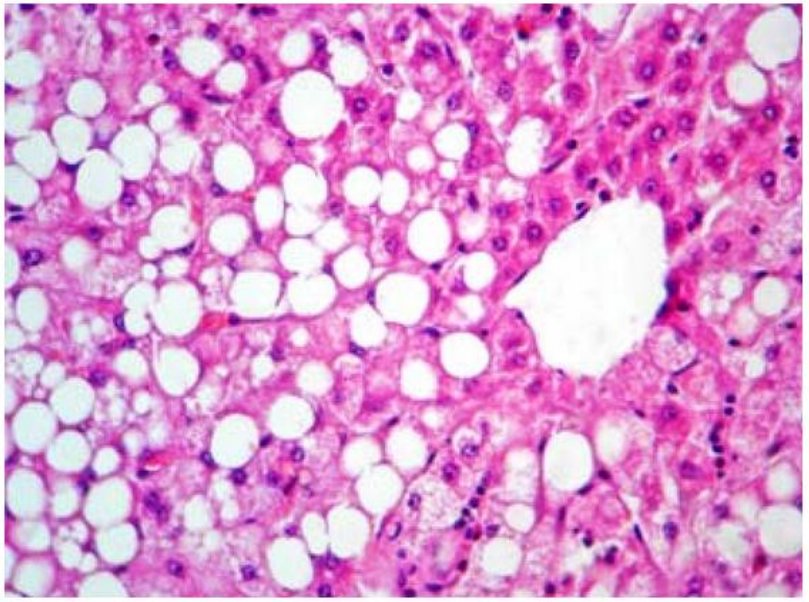


(www.studyblue.com)

Fatty change (Steatosis):

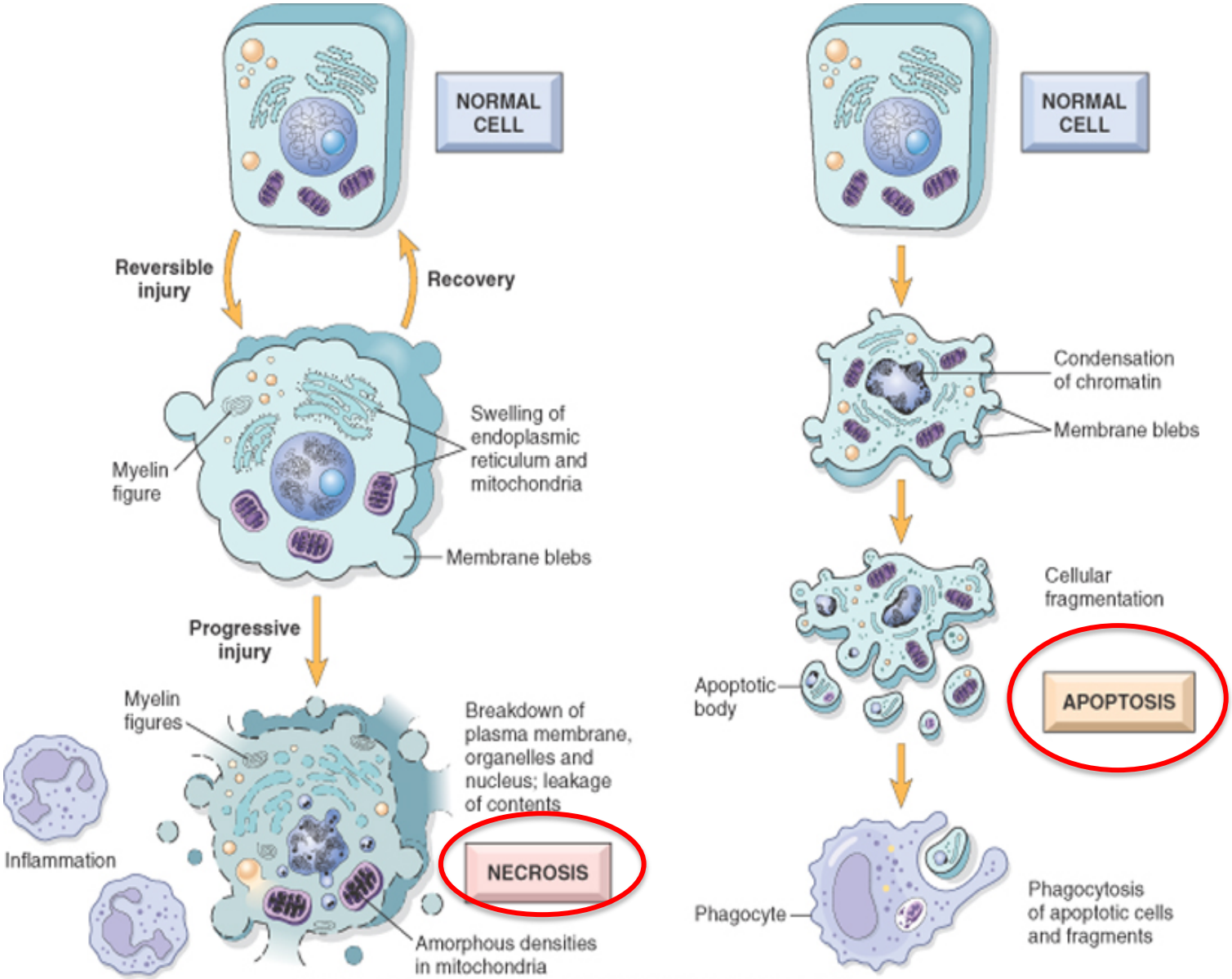
- Any abnormal accumulation of triglycerides within parenchymal cells
- Histologically, small (microvesicular) or large (macrovesicular) fat vacuoles can be seen within the cytoplasm.



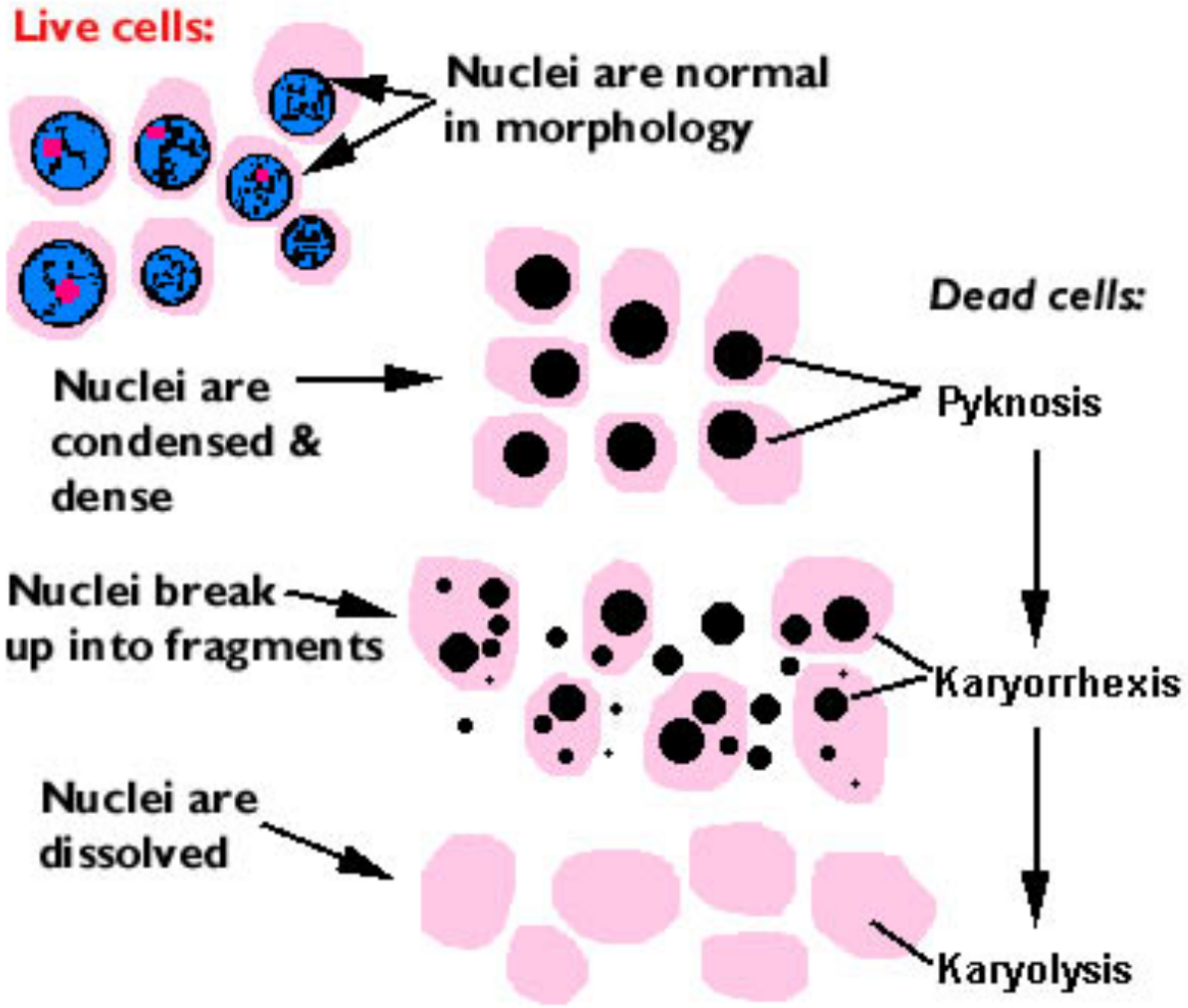


Fatty change (liver): Grossly, the liver is swollen, heavier than normal, yellowish and greasy.

(www.pathology.vcu.edu)

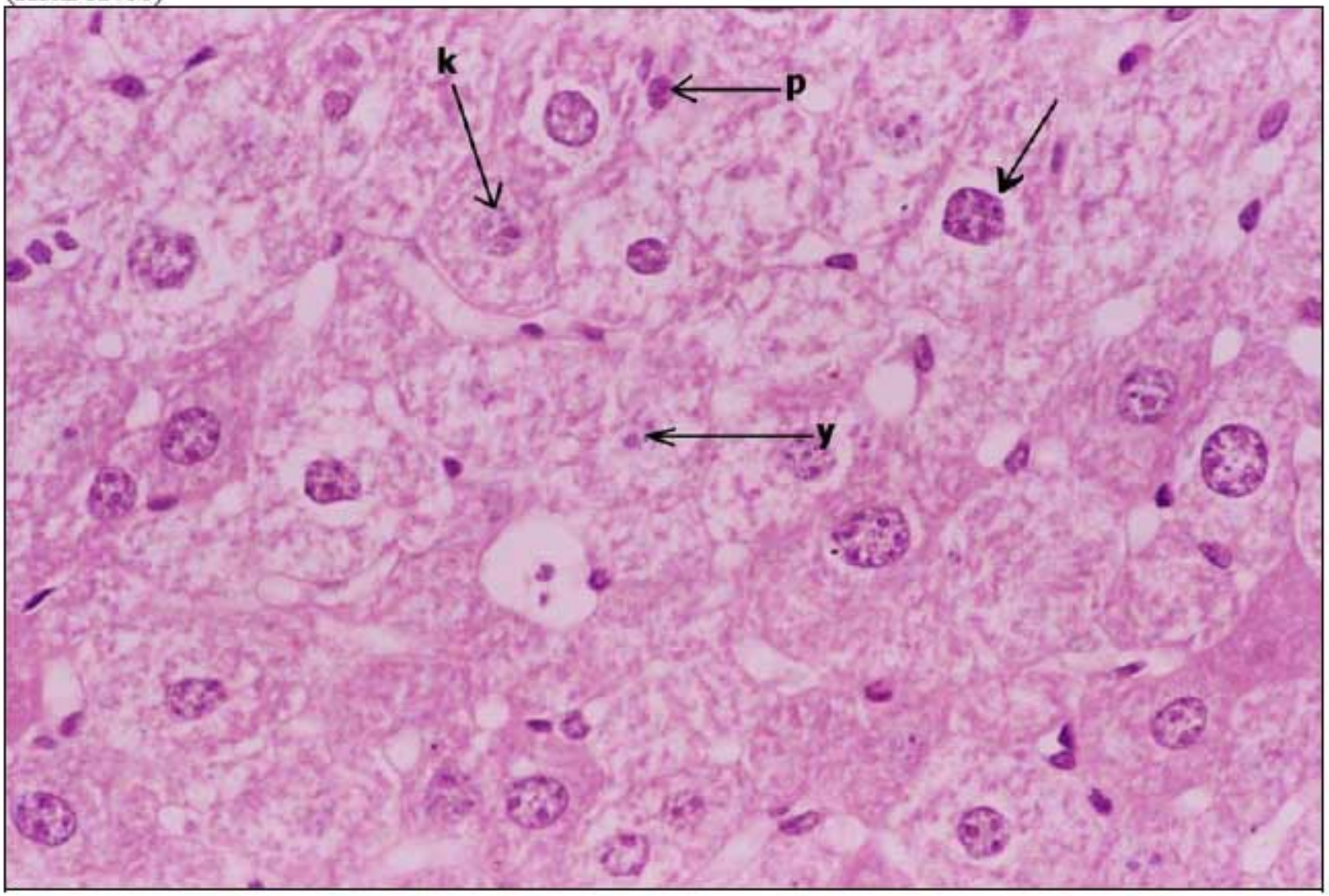


❑ Necrosis

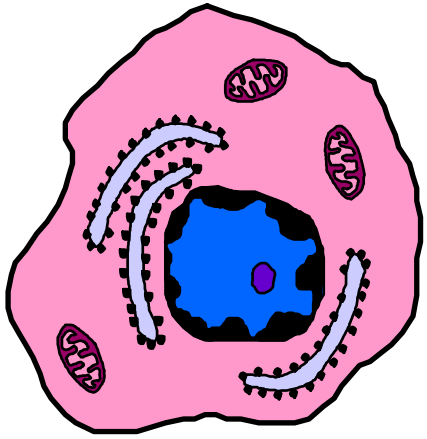


(http://www.vetmed.vt.edu)

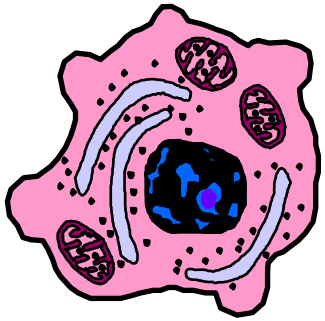
Fig. 4: Section in the liver of a green tea control mouse showing cellular necrosis in most hepatocytes in the form of vaculated cytoplasm (arrow) with pyknotic (p), karyorrhetic (k) or karyolytic (y) nuclei. (H&E X400)



(http://www.bioline.org.br)



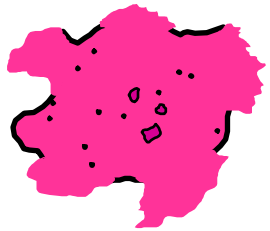
Normal cell



Reversible cell injury with cytoplasmic & organelle swelling, blebbing & ribosome detachment

Irreversible cell injury with rupture of membrane & organelles, & nuclear *pyknosis*

Karyorrhexis



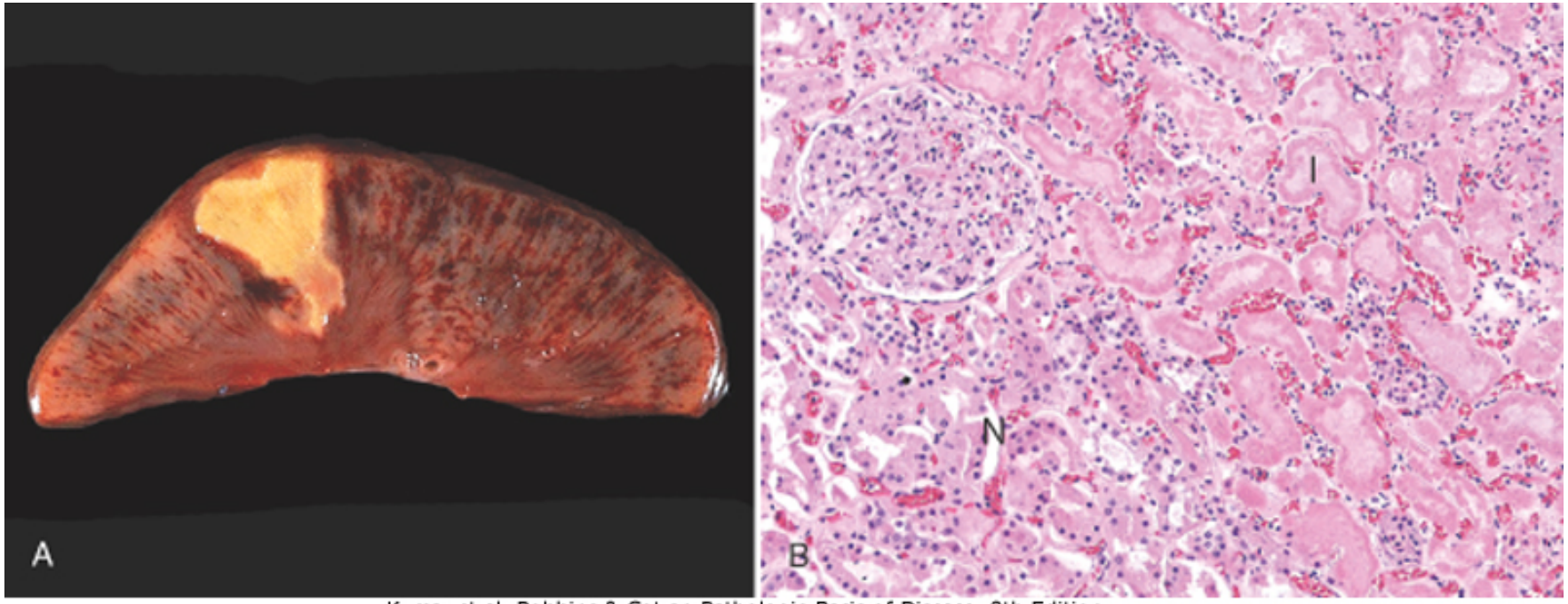
Karyolysis

The morphology of necrosis

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

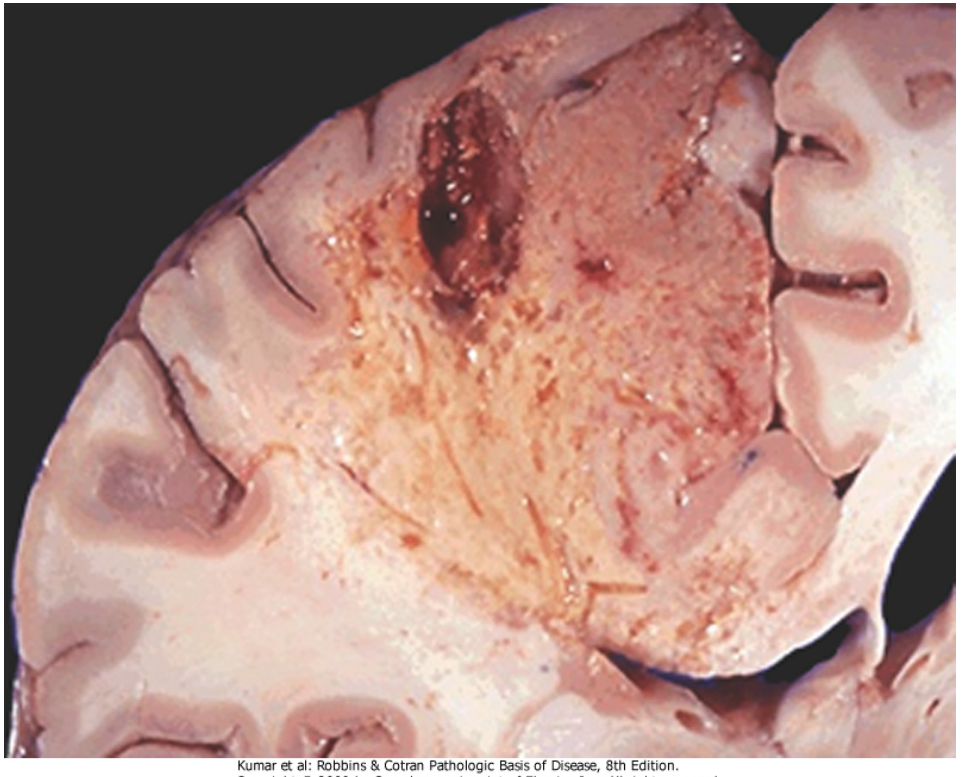
❑ Coagulative necrosis

Is a form of necrosis in which the underlying tissue architecture is preserved for at least several days.



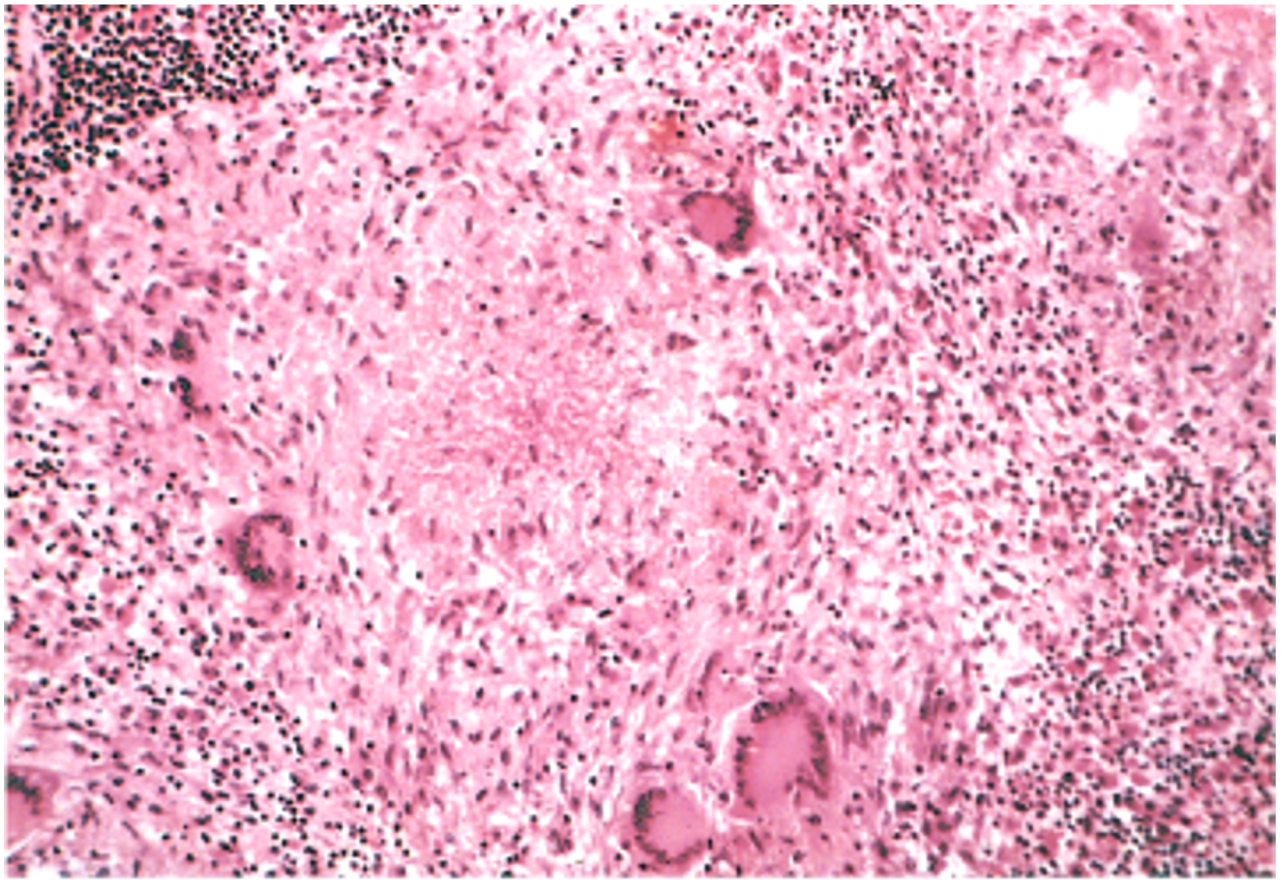
❑ Liquefactive necrosis

- ❖ Focal bacterial or fungal infections--- *accumulation of inflammatory cells*
- ❖ Hypoxic death of cells within CNS--- *liquid viscous mass*



❑ Caseous necrosis

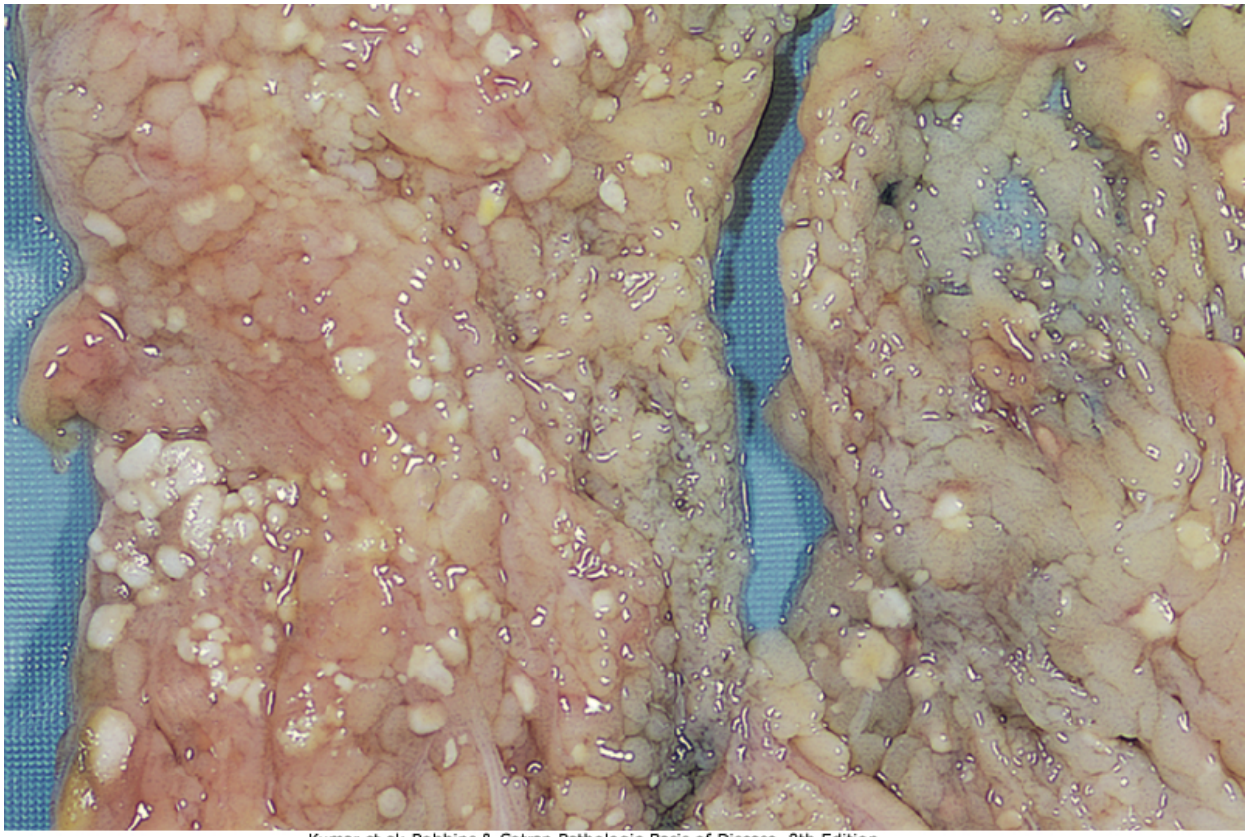
- ❖ Granulomatous inflammation
- ❖ Cheese-like--- *friable yellow-white appearance of the necrotic area*



Granuloma---- caseous necrosis, epithelioid cells, Langhans-giant cells, and Inflammatory cells

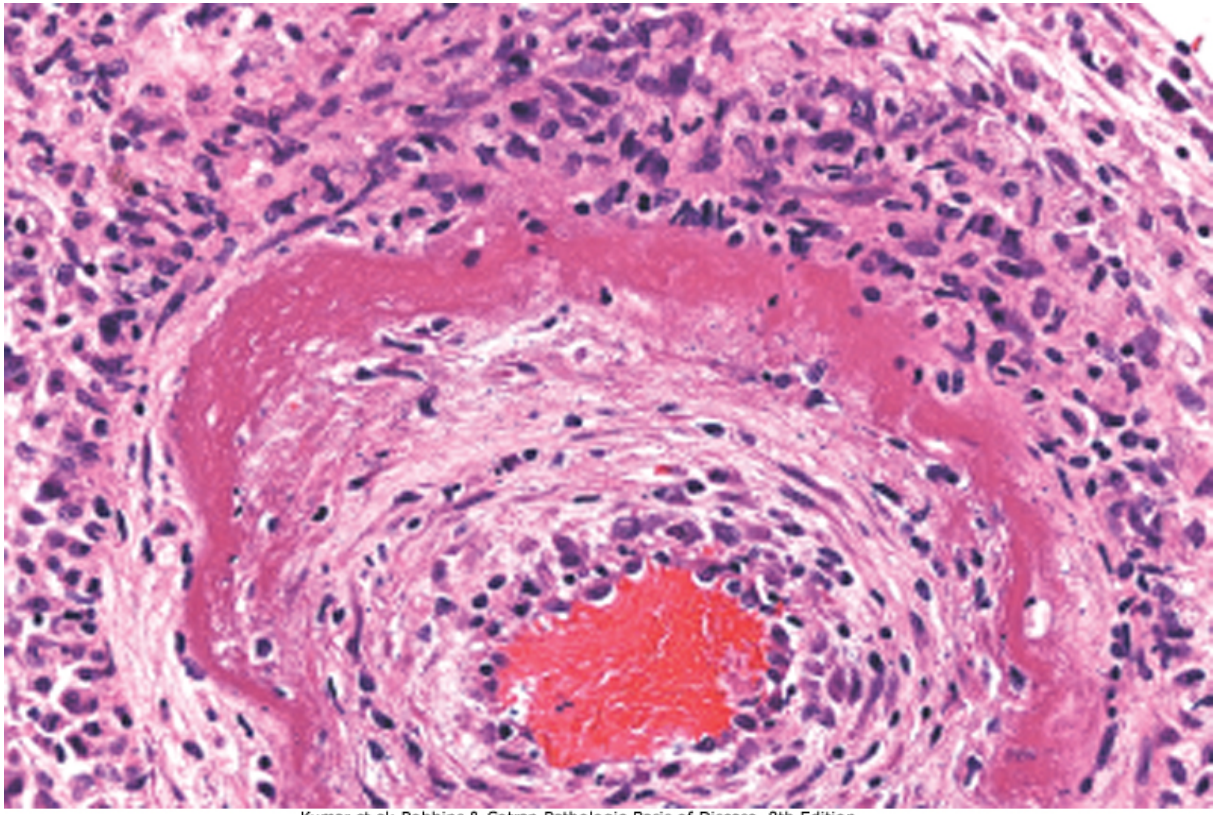
❑ Fat necrosis

- ❖ Area of fat destruction
- ❖ Typically, activated pancreatic lipases



❑ Fibrinoid necrosis

- ❖ Special form of necrosis, visible by light microscopy
- ❖ Fibrin-like--- *in immune reactions*

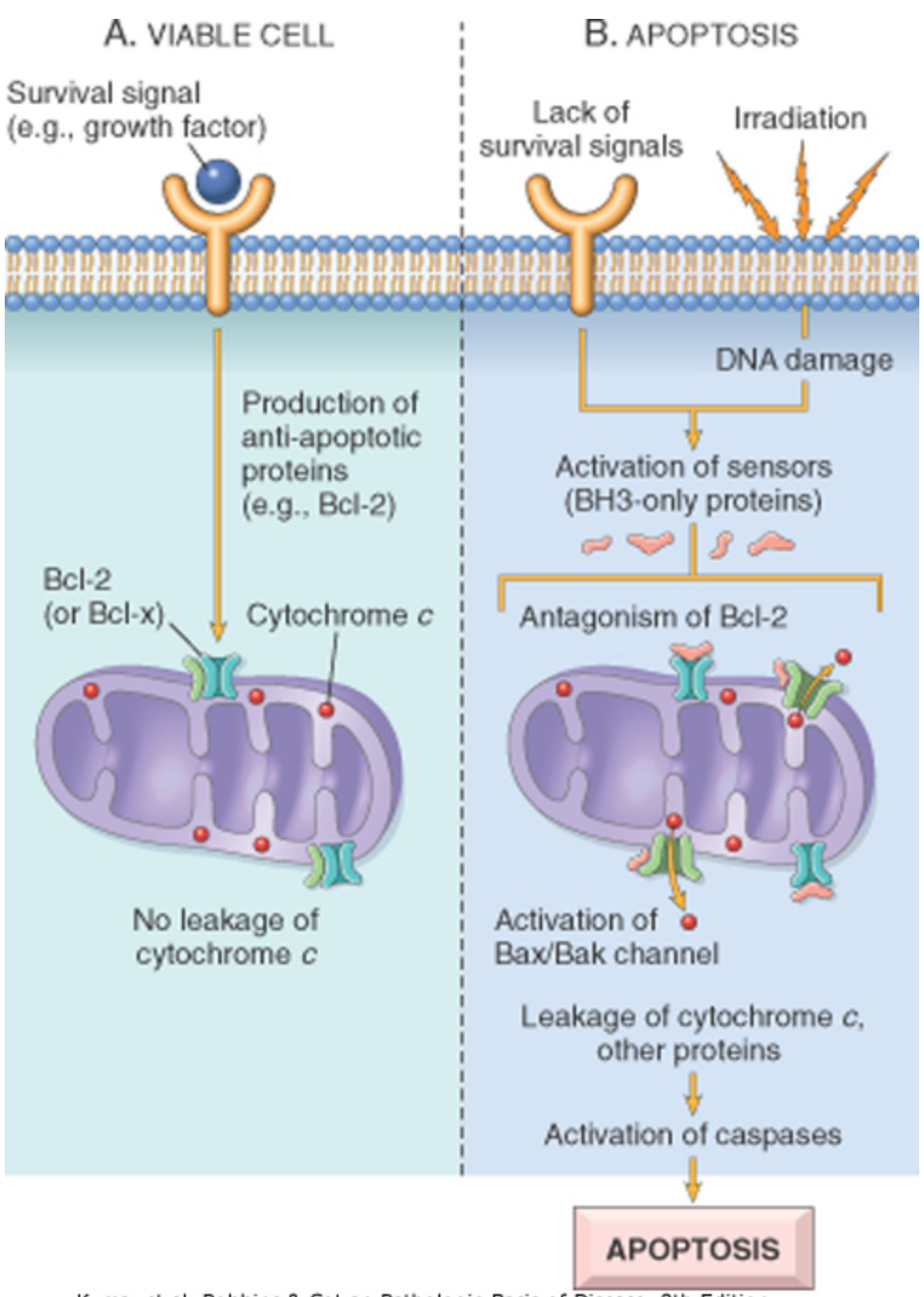


❑ Gangrenous necrosis

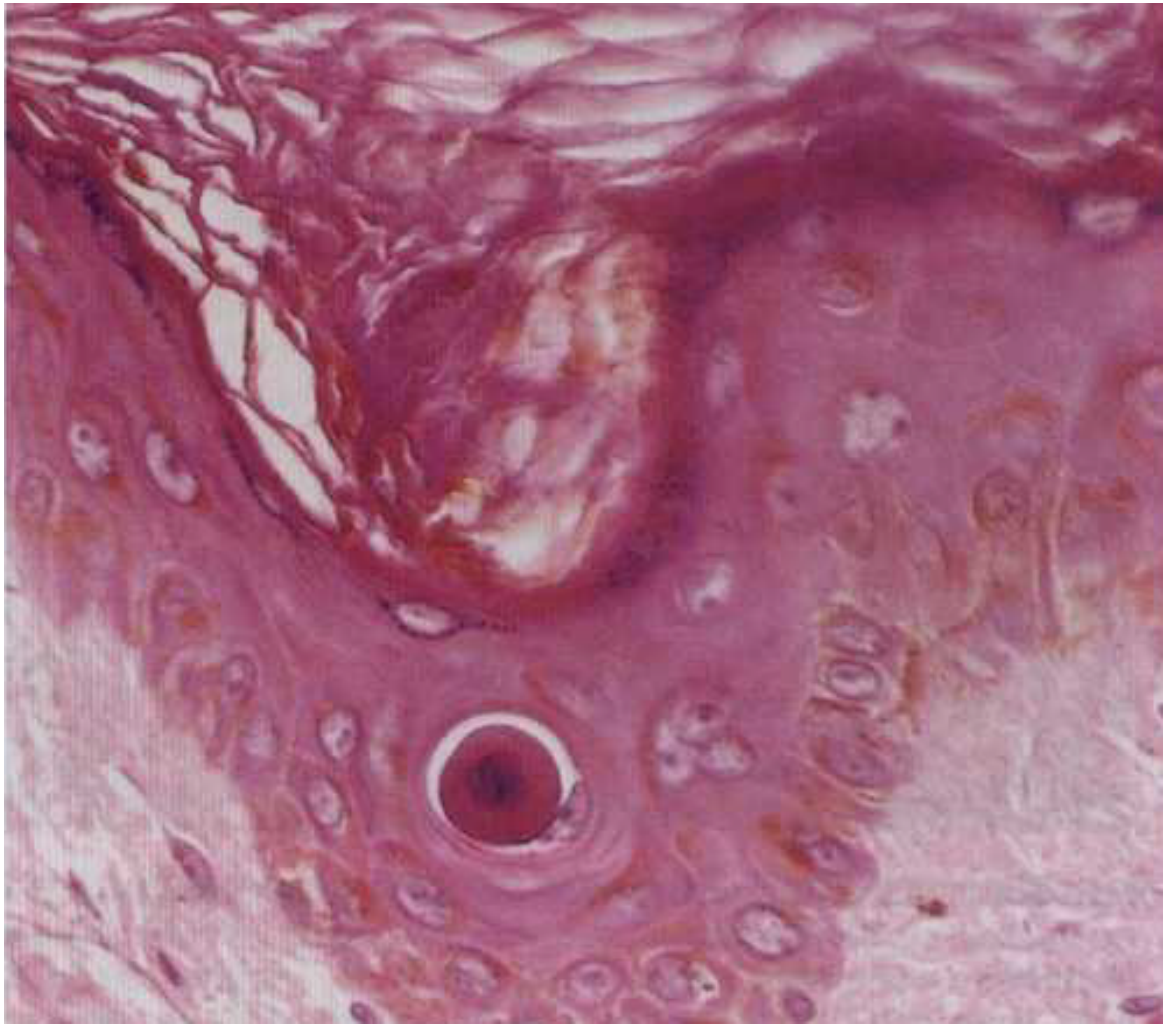
- ❖ Loss of blood supply--- infarction
- ❖ Infarct + Infect

Apoptosis

- Is a pathway of cell death in which cells active enzymes that degrade the cells' own nuclear DNA, nuclear, and cytoplasmic proteins.
- The activation of caspases
- Apoptosis in physiologic situations and pathologic conditions

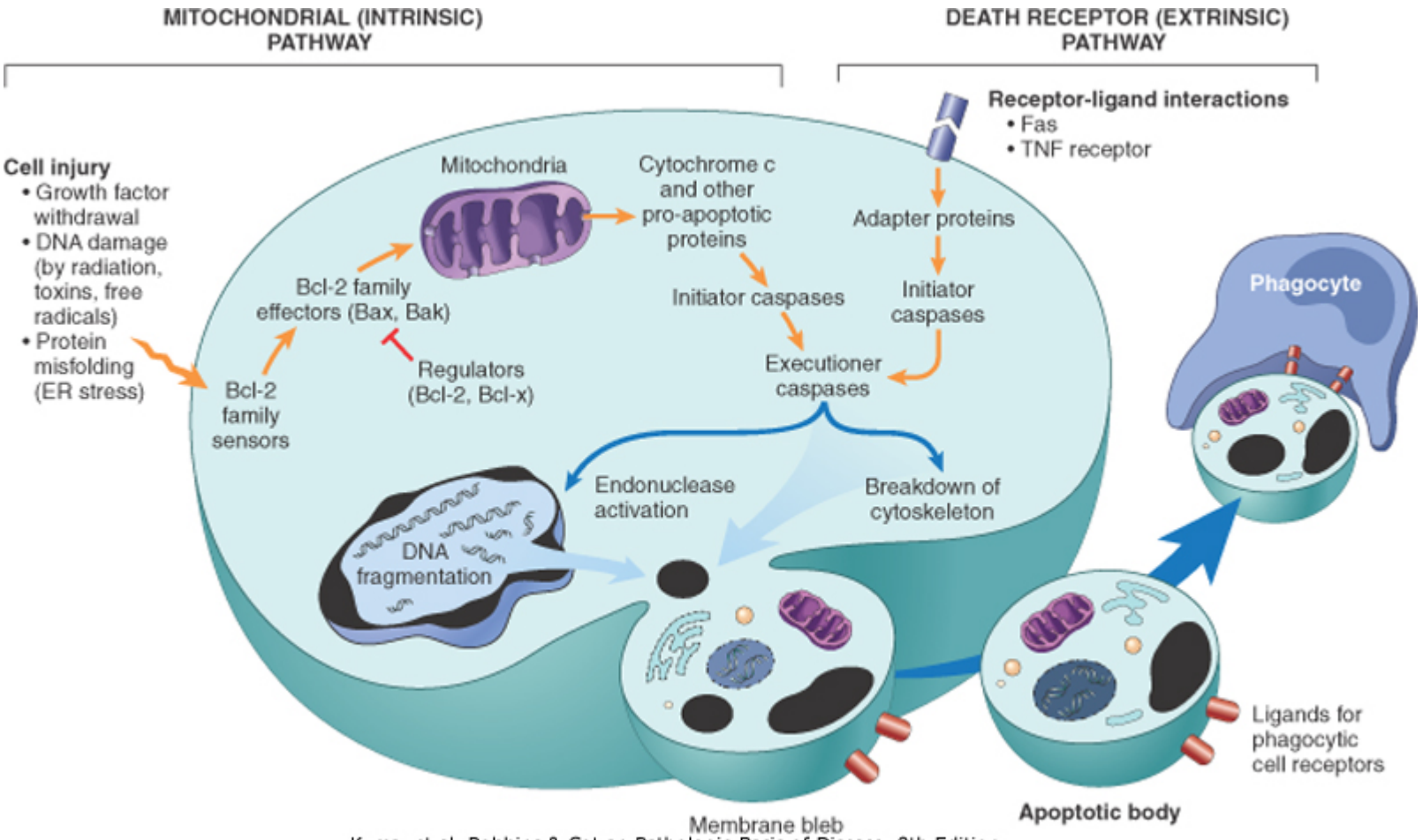


- Apoptosis of epidermal cells in an immune-mediated reaction

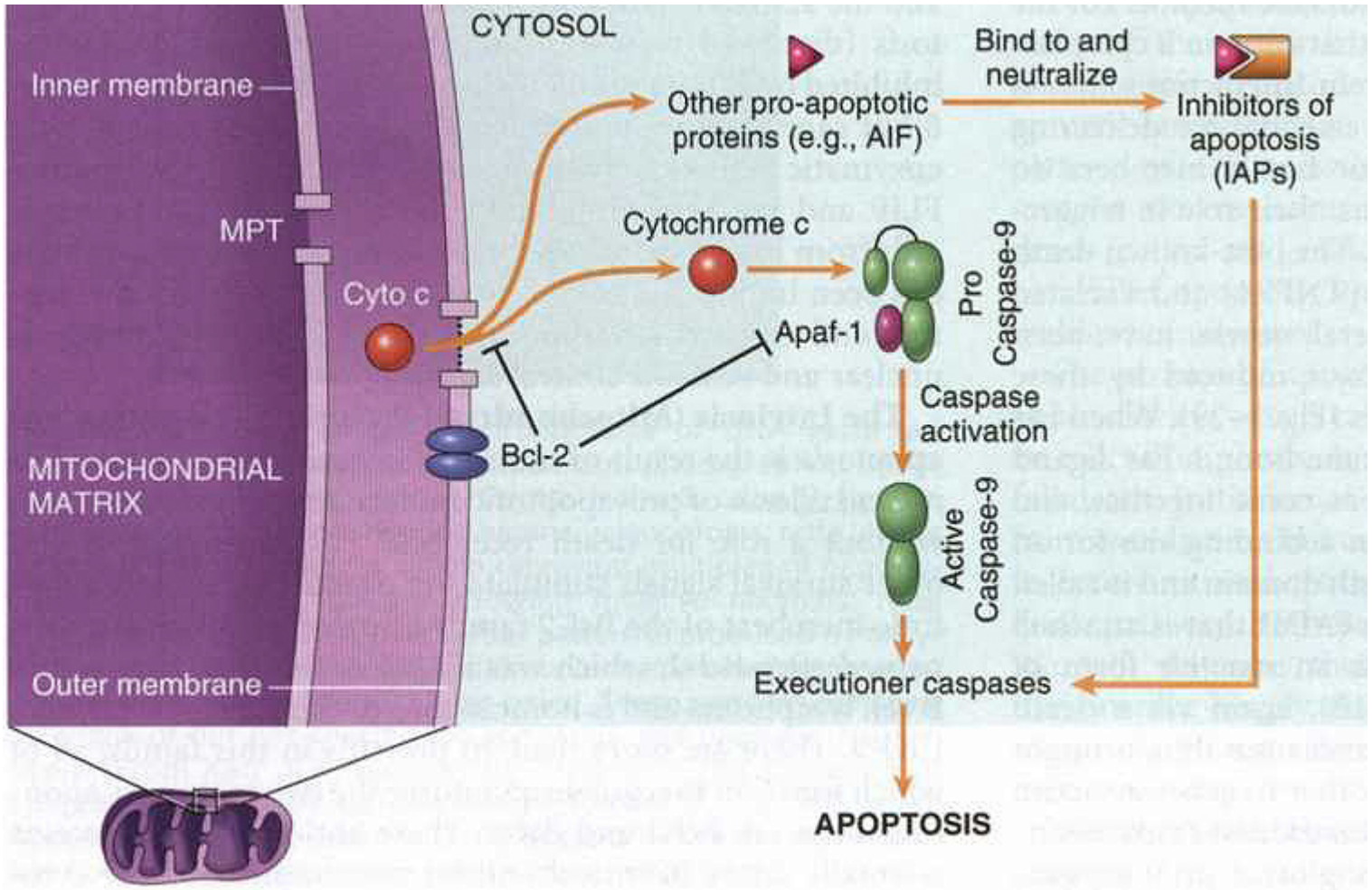


(Kumar, 2015)

Mechanism of apoptosis

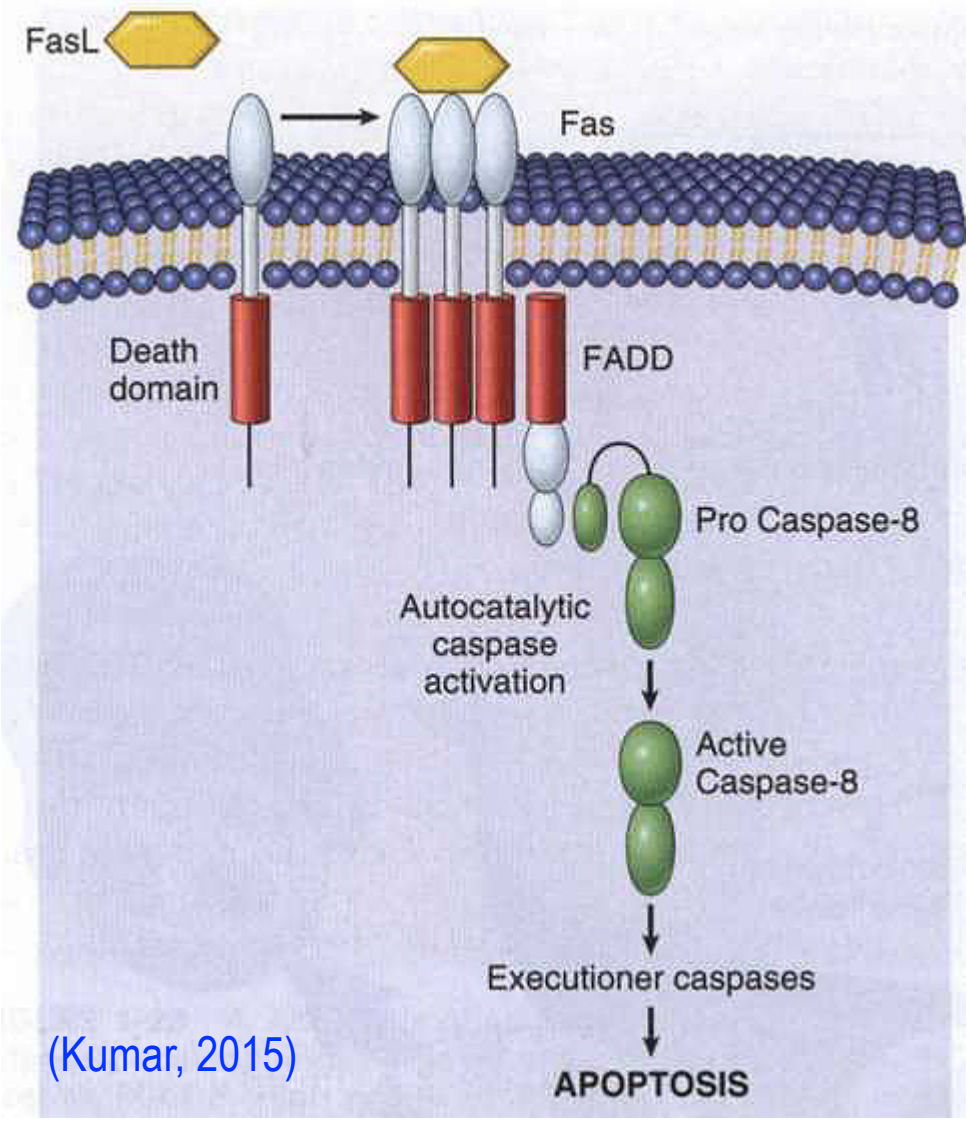


❑ Intrinsic pathway



(Kumar, 2015)

❑ Extrinsic pathway



(Kumar, 2015)

Characteristics of necrosis and apoptosis

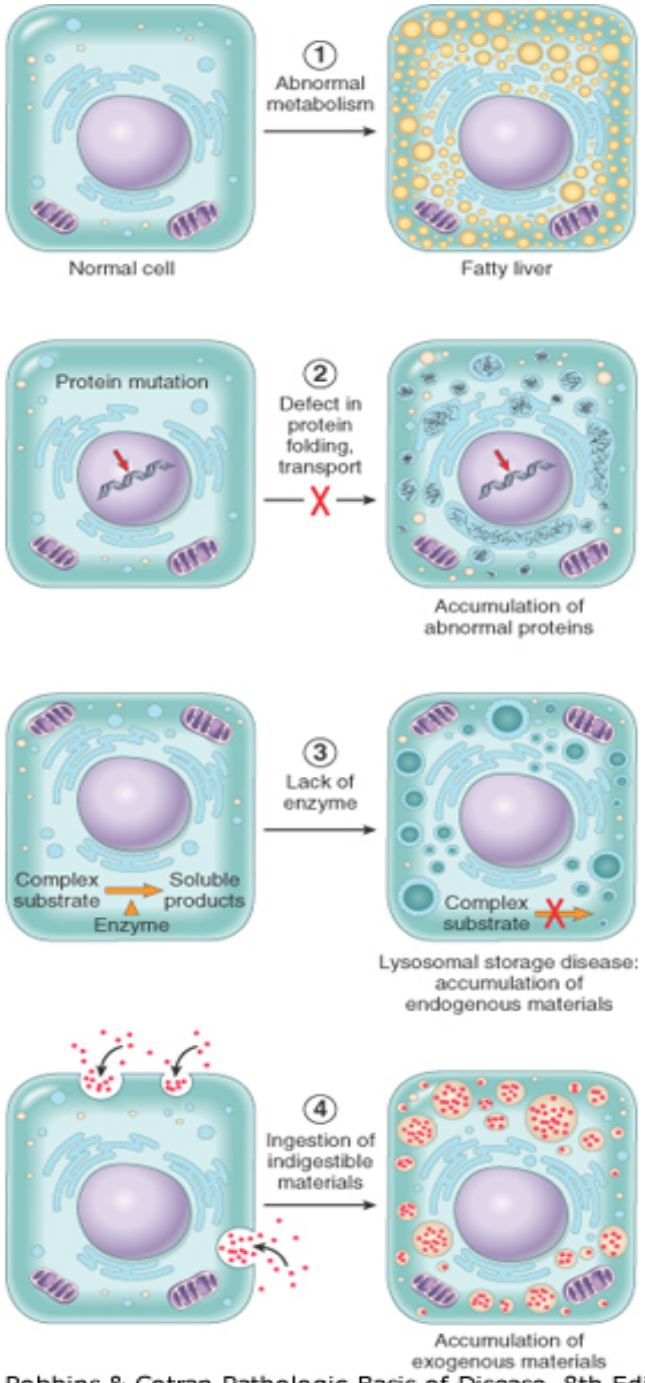
Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak 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

(Kumar, 2015)

Intracellular accumulations

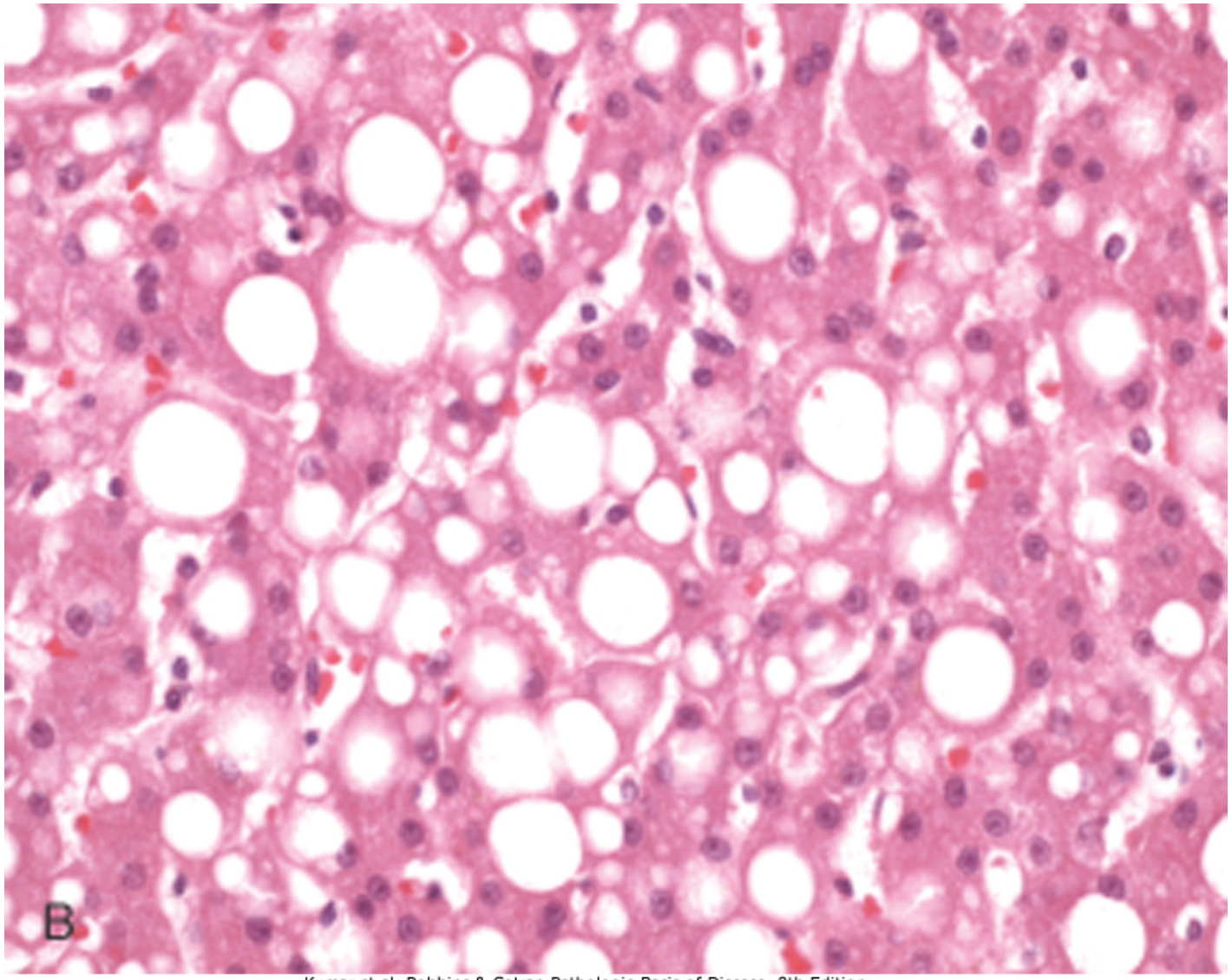
- Located in the cytoplasm, organelles, or nucleus
- There are 4 main pathways

  - Inadequate removal of a normal substance
  - Accumulation of an abnormal endogenous substance
  - Failure to degrade a metabolite
  - Deposition and accumulation of an abnormal exogenous substance



❑ Fatty change (Steatosis)

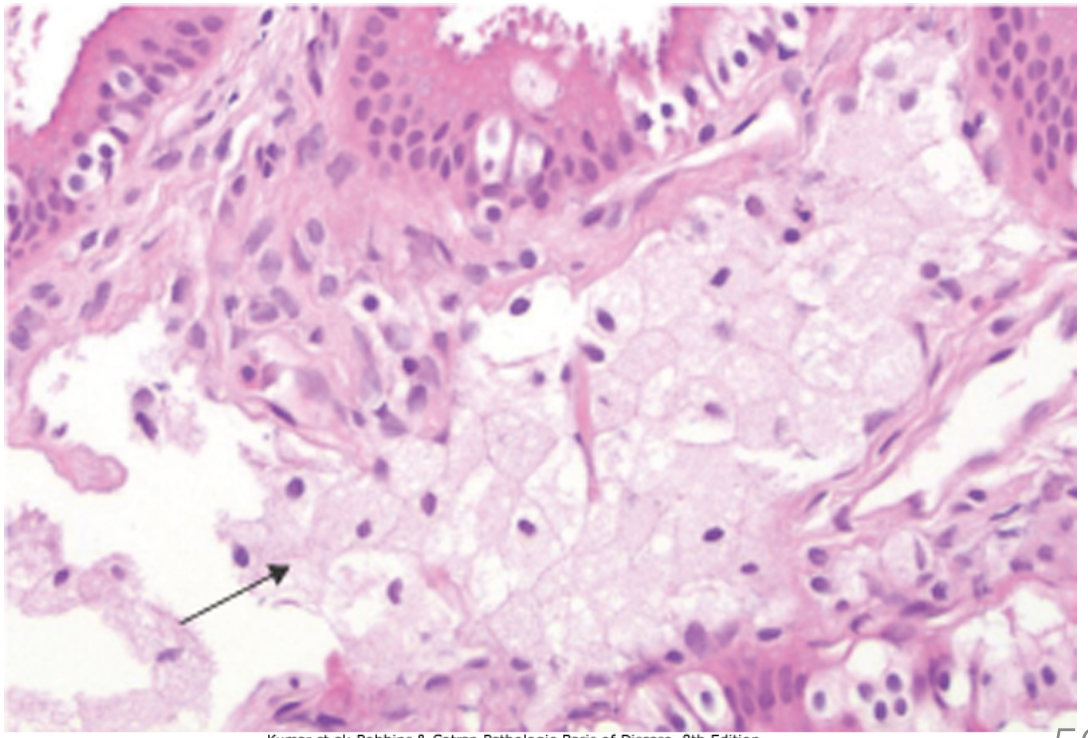
- ❖ Any abnormal accumulation of triglycerides within parenchymal cells
- ❖ Alcohol abuse and diabetes--- *fatty liver*
- ❖ Toxins, malnutrition, diabetes mellitus, obesity



❑ Cholesterol and cholesterol esters

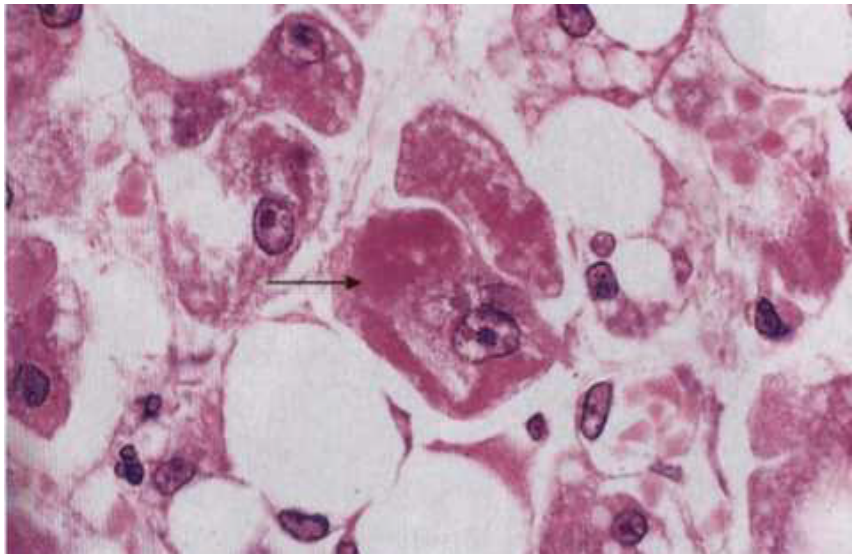
❖ Overload with lipid of phagocytic cells

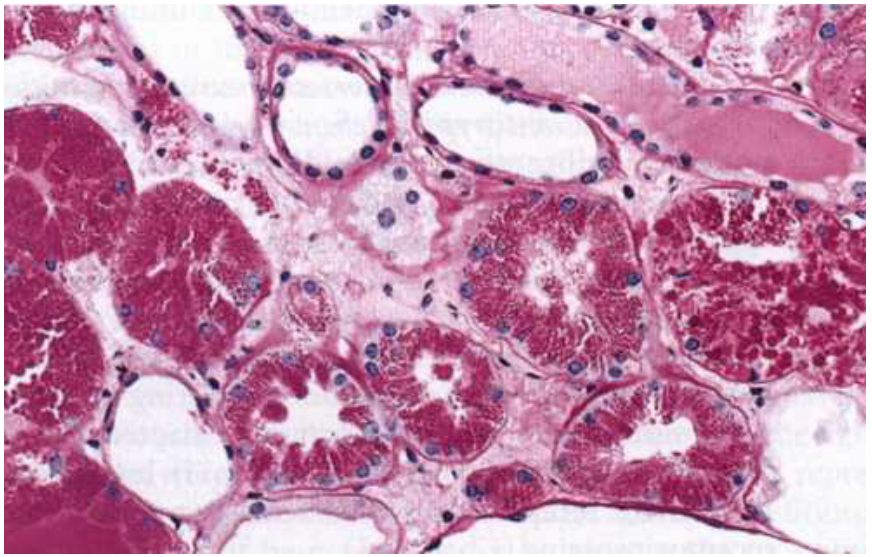
❖ Cholesterol-laden macrophages (foam cells)



❑ Proteins

❖ Appearance of pink, hyaline cytoplasmic droplets--- *in liver and kidney*



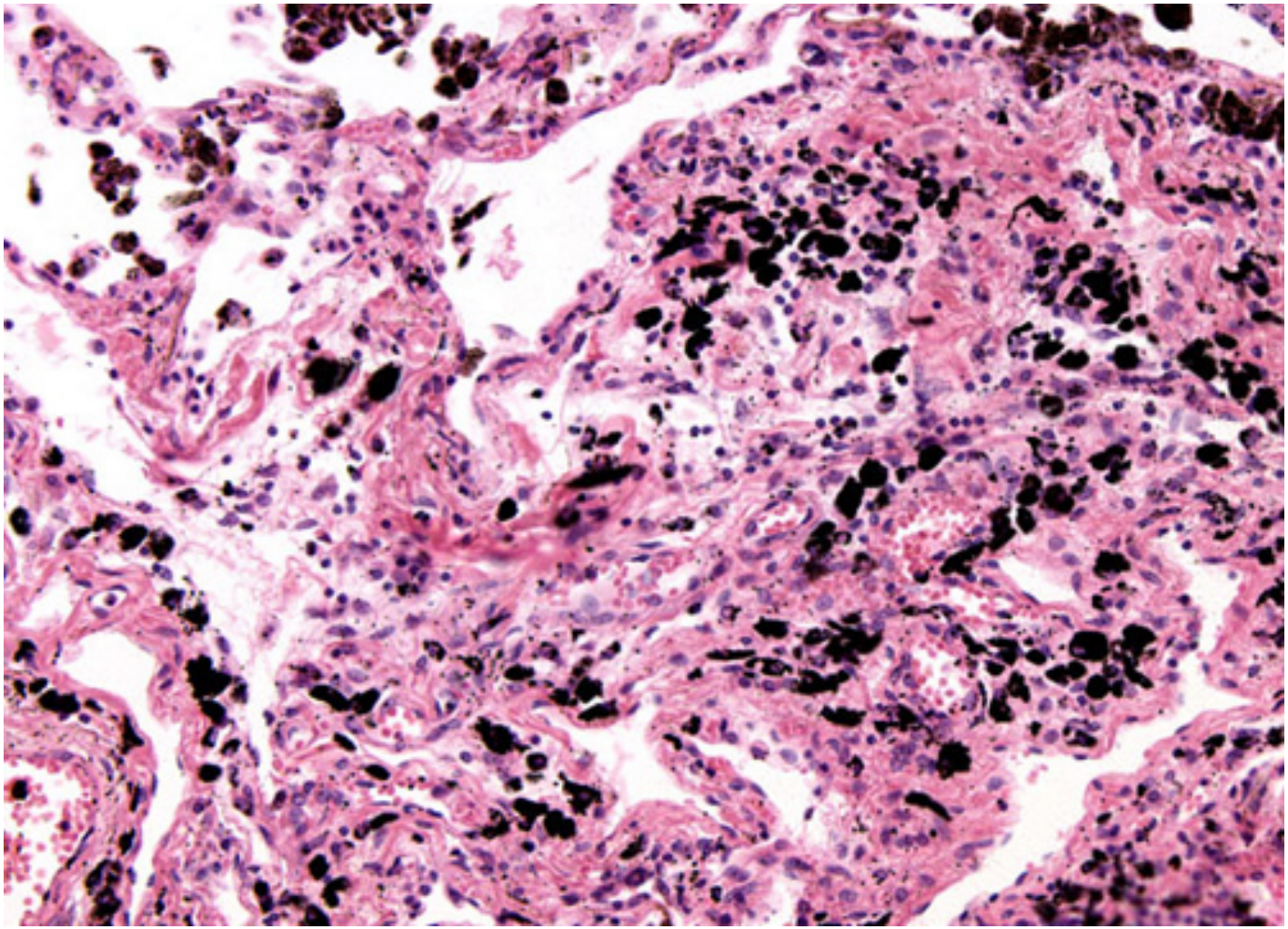


(Kumar, 2015)

❑ Pigments

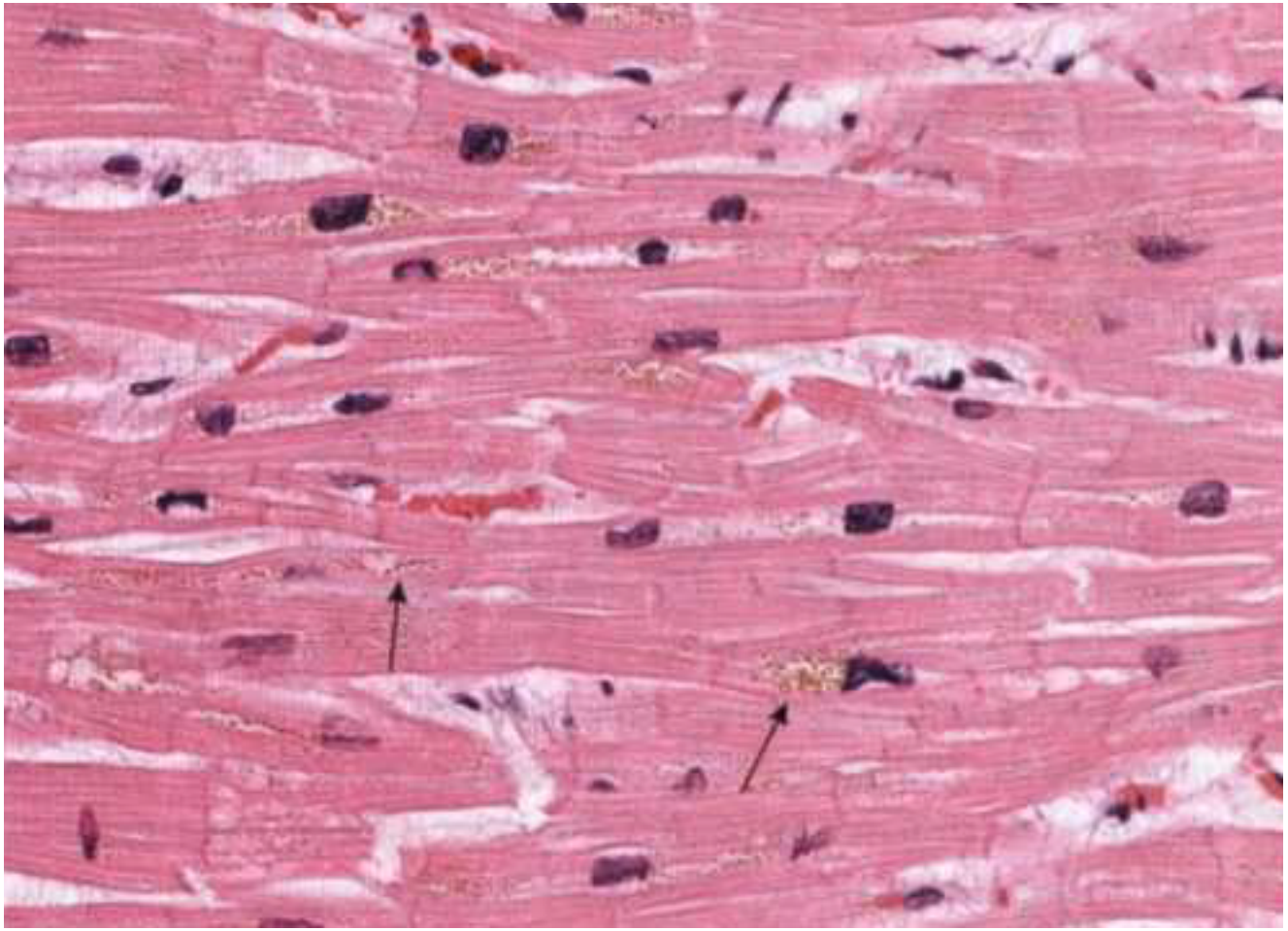
- ❖ They are colored substances that are either exogenous, coming from outside the body
- ❖ Anthracosis--- *carbon (the pigment blacken)*
- ❖ Lipofuscin--- *wear and tear pigment (brownish-yellow)*
- ❖ Hemosiderin--- *a hemoglobin drived granular pigment*

❑ Anthracosis in lung



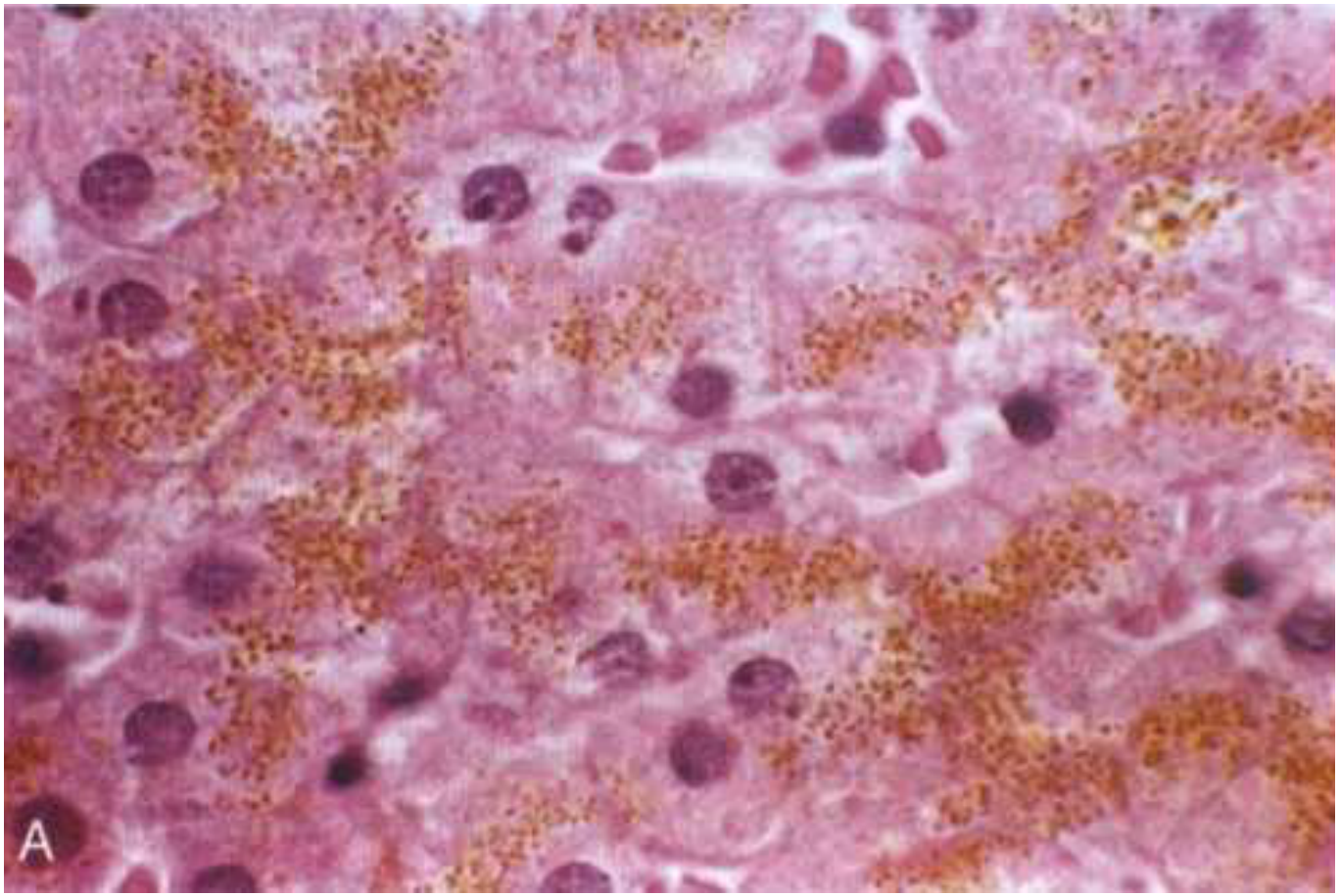
(www.microscopyu.com)

❑ Lipofuscin granules in a cardiac myocyte



(Kumar, 2015)

❑ Hemosiderin in liver cells



(Kumar, 2015)

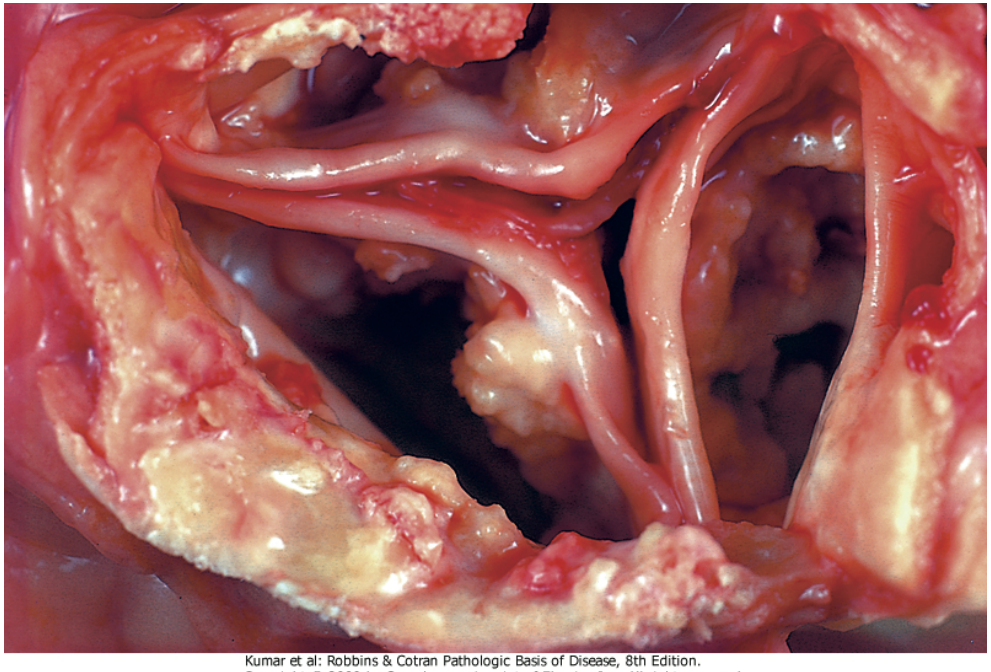
Pathologic calcification

- Common process in a wide variety of disease states
- Deposition of calcium salts (small amounts of iron, magnesium, and other minerals)

Dystrophic Calcification

- Dystrophic calcification is encountered *in areas of necrosis,* whether they are of coagulative, caseous, or liquefactive type, and in foci of enzymatic necrosis of fat.
- Calcification is almost inevitable in the atheromas of *advanced atherosclerosis*. It also commonly develops in aging or damaged heart valves, further hampering their function.

❑ Dystrophic calcification in aortic valve



the calcium salts appear macroscopically as fine, white granules or clumps, often felt as gritty deposits. Sometimes a tuberculous lymph node is virtually converted to stone.

Metastatic calcification

- Metastatic calcification may occur in normal tissues whenever there is *hypercalcemia.*
- Metastatic calcification may occur widely throughout the body but principally affects the *interstitial tissues* of the gastric mucosa, kidneys, lungs, systemic arteries, and pulmonary veins.

References

- Vinay Kumar, Abul K. Abbas, Nelson Fausto, Jon C Aster. Robbins and Cotran, Pathologic Basis of Disease; 2015
- J.C.E Underwood and S.S. Cross. General and Systemic Pathology; 2009.