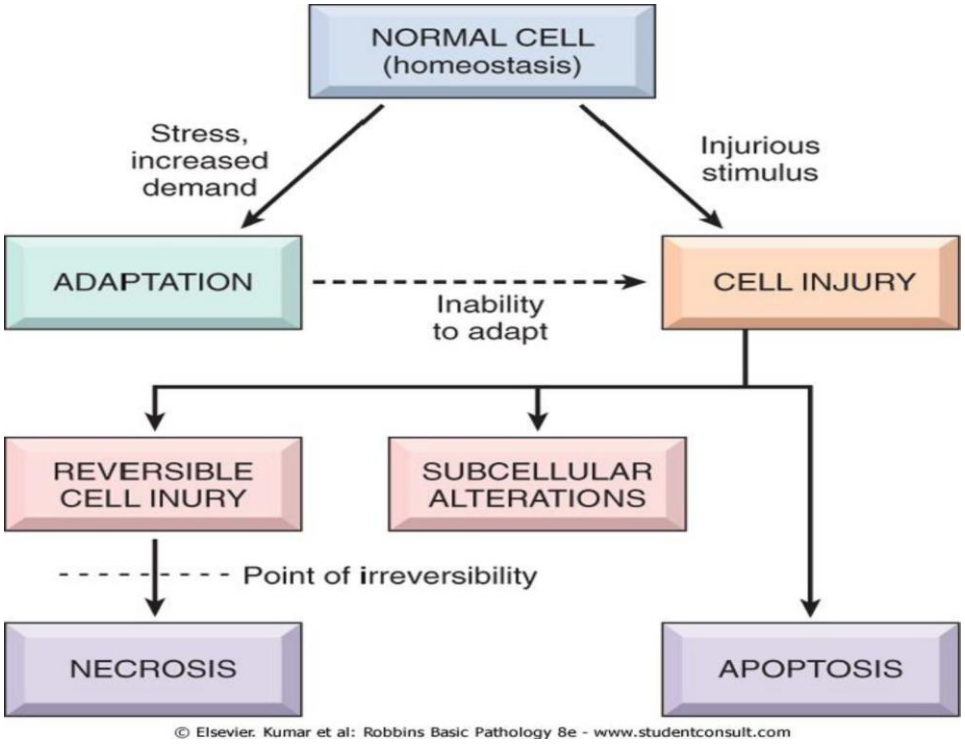
Lecture 2&3 General pathology

Cell Injury, Cell Death, and Adaptation

Cellular responses to stress and injurious stimuli:

Cells are the active part in their environment, maintaining normal homeostasis (staying stable) and adjusting their structure and function to accommodate any changes or extracellular stresses. Any physiologic stresses or pathologic stimuli on the cells, they can undergo **adaptation**, achieving a new steady state and preserving viability and function. Types of adaptation are: **Hypertrophy, Hyperplasia, Atrophy and Metaplasia.**

If the adaptive capability is exceeded or if the external stress is harmful, **cell injury** develops.



Cell injury is of two type:

1- Reversible injury: The cells return to a stable state.
2- Irreversible injury: Severe or persistent stress results in **cell death**

Cellular adaptations to stress:

Adaptations are reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to changes in their environment. Adaptation could be:

1- Physiologic adaptations: Responses of cells to **normal stimulation** by hormones or endogenous chemical materials, e.g.: the hormone-induced enlargement of the breast and uterus during pregnancy.

2- Pathologic adaptations: Responses to **stress** that allow cells to modulate their structure and function and thus escape injury.

Types of adaptations:

1- Hypertrophy:

An increase in the size of cells resulting in increase in the size of the organ. There are no new cells, just bigger cells, enlarged by an increased amount of structural proteins and organelles. Hypertrophy occurs when cells are incapable of dividing.

a- Physiologic hypertrophy: e.g.: in skeletal muscle cells of weight lifter.
b- Pathologic hypertrophy: e.g.: cardiac enlargement that occurs with hypertension or aortic valve disease.

2- Hyperplasia:

An increase in number of cells that occur if the cell population is capable of dividing.

a- **Hormonal hyperplasia**: e.g. : The proliferation of the glandular epithelium of the female breast at puberty and during pregnancy.

b- **Compensatory hyperplasia**: occurs when a portion of the tissue is removed or diseased. e.g.: when a liver is partially resected, mitotic activity in the remaining cells begins to restore the liver to its normal weight.

c- **Pathologic hyperplasia**: caused by excessive hormonal or growth factor stimulation. e.g, endometrial hyperplasia that occurrs due to disturbances in the balance between estrogen and progesterone hormons causing abnormal menstrual bleeding. Another example is connective tissue hyperplasia in wound healing in which proliferating fibroblasts and blood vessels aid in repair.

3- Atrophy:

Shrinkage in the size of the cell by the loss of cell substance. Atrophic cells may have diminished function but they are not dead. Causes of atrophy include a decreased workload, e.g., immobilization of a limb to permit healing of a fracture, loss of innervation, diminished blood supply, inadequate nutrition, loss of endocrine stimulation, and aging (senile atrophy).

4- Metaplasia:

Change in which one adult cell type (epithelial or mesenchymal) by another adult cell type, e.g. in cigarette smokers, the normal ciliated columnar epithelial cells of the respiratory epithelium is replaced by stratified squamous epithelial cells.

Overview of cell injury and cell death

Cell injury results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents or suffer from intrinsic abnormalities. Injury may progress through a reversible stage and culminate in cell death.

1- Reversible cell injury: In early stages or mild forms of injury the functional and morphologic changes are reversible if the damaging stimulus is removed. At this stage, although there may be significant structural and functional abnormalities, the injury has typically not progressed to severe membrane damage and nuclear dissolution.

2- Cell death*:* With continuing damage, the injury becomes irreversible, at which time the cell cannot recover and it dies.

Types of cell death:

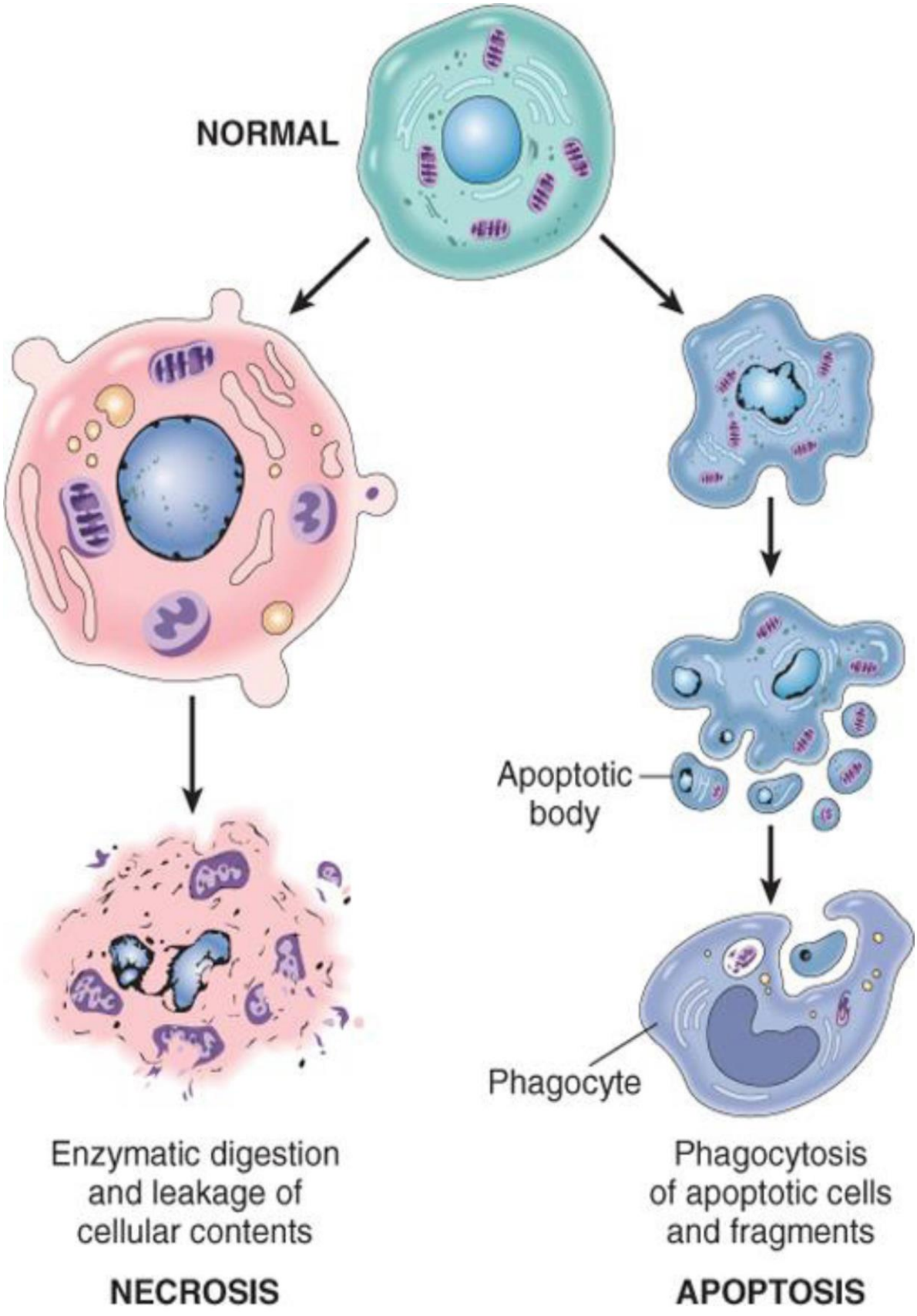
1- Necrosis: Occur when the damage to membranes is severe, enzymes leak out of lysosomes, enter the cytoplasm, and digest the cell. Cellular contents also leak out through the damaged plasma membrane and result in a host reaction (inflammation). Necrosis results from ischemia, exposure to toxins, various infections, and trauma.

2- Apoptosis occurs when a cell is deprived of growth factors or the cell's DNA or proteins are damaged beyond repair, the cell kills itself by another type of death, called apoptosis, which is characterized by nuclear dissolution without complete loss of membrane integrity. Apoptosis is an active, energy-dependent, tightly regulated type of cell death that is seen in some specific situations.

Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with pathologic cell injury.

Table 1-1. Features 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



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Causes of cell injury

1- Hypoxia:
It is oxygen deficiency**,** caused by ischemia which is loss of blood supply in a tissue.

2- Chemical Agents:
Include air pollutants, insecticides, CO, asbestos, alchohol and therapeutic drugs if used excessively or inappropriately.

3- Infectious Agents:
Viruses, rickettsia, bacteria, fungi, protozoans and tapeworms.

4- Immunologic Reactions:
Although the immune system defends the body against pathogenic microbes, immune reactions can also result in cell and tissue injury like autoimmune reactions against one's own tissues and allergic reactions against environmental substances.

5- Genetic Defects:
Genetic defects can result in pathologic changes like congenital malformations associated with Down syndrome and sickle cell anemia.

6- Nutritional Imbalances:
Like protein-calorie insufficiency and specific vitamin deficiencies. Excesses of nutrition are also important causes of cell injury, e.g., obesity increases the risk for type 2 diabetes mellitus, and diets rich in animal fat lead to the development of atherosclerosis.

7- Physical Agents:
Trauma, extremes of temperatures, radiation, electric shock, and sudden changes in atmospheric pressure all have wide-ranging effects on cells.

8- Aging:
Cellular senescence leads to alterations in replicative and repair abilities of individual cells and tissues. All of these changes result in a diminished ability to respond to damage and, death of cells and of the organism.

The morphology of cell injury:

A- Morphology of reversible Injury:

1- **Cellular swelling** due to failure of energy-dependent ion pumps in the plasma membrane, leading to an inability to maintain ionic and fluid homeostasis. Microscopic examination may reveal small, clear vacuoles within the cytoplasm; these represent distended and pinched-off segments of the endoplasmic reticulum. This pattern of nonlethal injury is sometimes called **hydropic change** or **vacuolar degeneration.**

2- **Fatty change** occurs in hypoxic injury and various forms of toxic or metabolic injury. It is manifested by the appearance of small or large lipid vacuoles in the cytoplasm. It occurs mainly in cells involved in and dependent on fat metabolism, such as Hepatocytes in the liver and myocardial cells in the heart.

B- Morphology of irreversible Injury: Necrosis

Necrosis is a series of changes that accompany cell death, resulting from the digestive action of enzymes on injured cells. Necrotic cells are unable to maintain membrane integrity, and their contents often leak out.

Morphology

1- Increased eosinophilia**:** i.e., pink staining from the eosin dye, the "E" in "H&E" due to increased binding of eosin to denatured cytoplasmic proteins and to loss of the basophilia that is normally imparted by the ribonucleic acid (RNA) in the cytoplasm (basophilia is the blue staining from the hematoxylin dye, the "H" in "H&E").

2- The cell may have a more glassy homogeneous appearance than viable cells, because of the loss of glycogen particles.

3- When enzymes have digested the cytoplasmic organelles, the cytoplasm becomes vacuolated and appears motheaten.

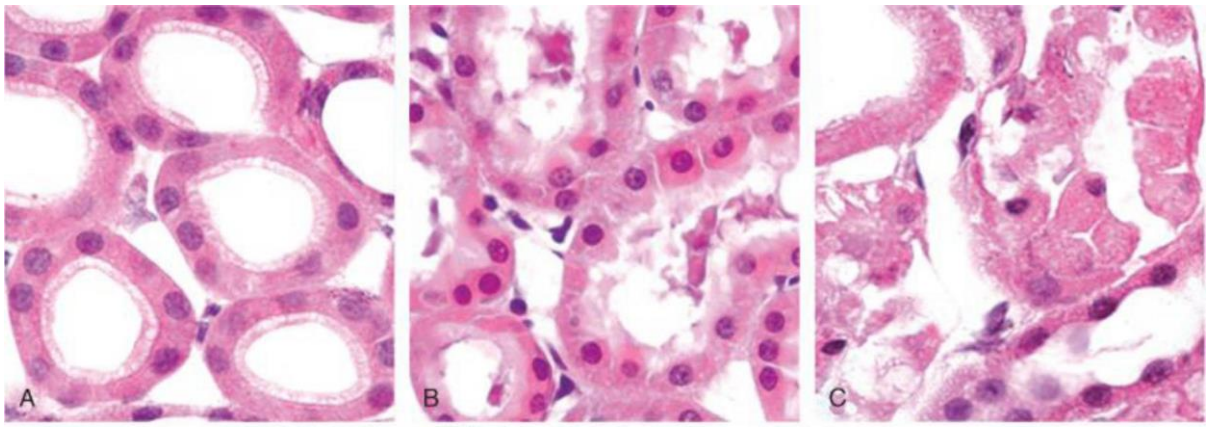
4- Dead cells may be replaced by large, whorled phospholipid masses which then either phagocytized by other cells or degraded into fatty acids which will be calcified resulting in the appearance of calcified dead cells.

5- Nuclear changes occur due to breakdown of DNA and chromatin and it include:

a- K**aryolysis:** The basophilia of the chromatin may fade, secondary to deoxyribonuclease (DNase) activity.

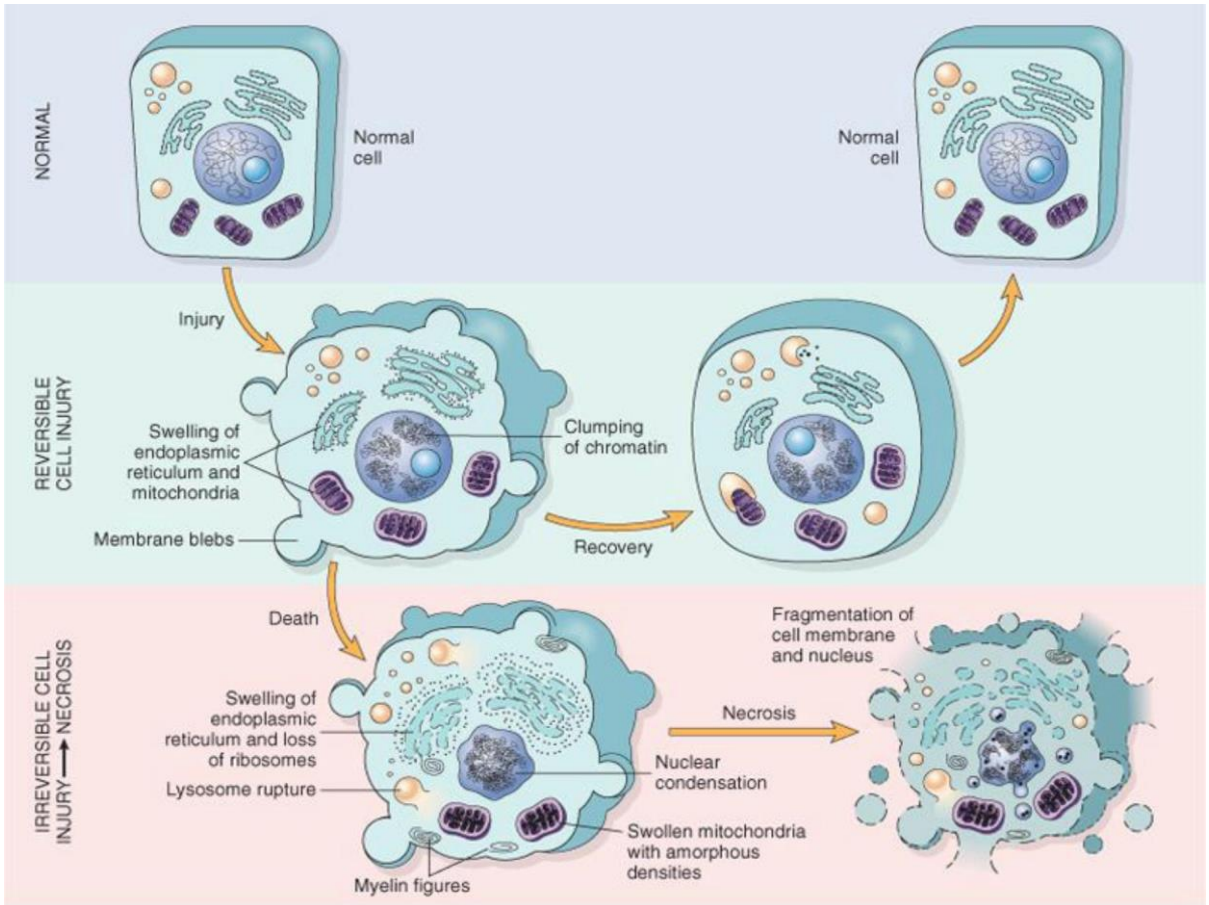
b- Pyknosis: Nuclear shrinkage and increased basophilia; the DNA condenses into a solid shrunken mass.

c- K**aryorrhexis:** The pyknotic nucleus undergoes fragmentation and then completely disappears.



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Morphologic changes in reversible and irreversible cell injury (necrosis).
A, Normal kidney tubules with viable epithelial cells. **B,** Early (reversible) ischemic injury showing surface blebs, increased eosinophilia of cytoplasm, and swelling of occasional cells. **C,** Necrotic (irreversible) injury of epithelial cells, with loss of nuclei and fragmentation of cells and leakage of contents.



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A normal cell and the changes in reversible and irreversible cell injury (necrosis).

Patterns of Tissue Necrosis

1- Coagulative necrosis: The component cells are dead but the basic tissue architecture is preserved for at least several days. Coagulative necrosis is characteristic of **infarcts** (areas of ischemic necrosis) in all solid organs except the brain.

2- Liquefactive necrosis: Seen in focal bacterial or, occasionally, fungal infections, because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes will digest ("liquefy") the tissue and it occur within the dead cells of the central nervous system. Liquefaction completely digests the dead cells, resulting in transformation of the tissue into a liquid viscous mass. If the process was initiated by acute inflammation, the material is frequently creamy yellow and is called **pus**.

3- G**angrenous necrosis:** Applied to 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, coagulative necrosis is modified by the liquefactive action of the bacteria and the attracted leukocytes, so-called **wet gangrene**.

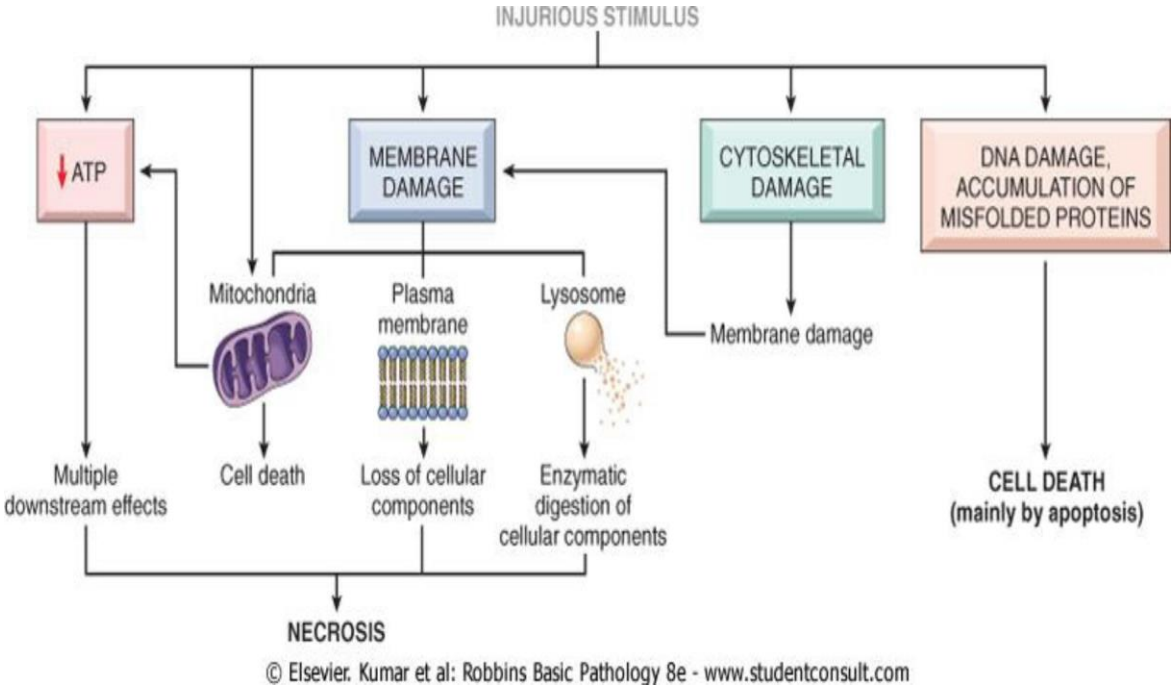
4- Caseous necrosis: The term "caseous" (cheese-like) is derived from the friable yellow-white appearance of the area of necrosis. The necrotic focus appears as a collection of fragmented or lysed cells with an amorphous granular appearance. Unlike coagulative necrosis, the tissue architecture is completely lost and cellular outlines cannot be seen. Caseous necrosis is often enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a **granuloma**. It is seen most often in foci of tuberculous infection.

5- Fat necrosis: Focal areas of fat destruction, resulting from release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. Histologically, the foci of necrosis contain shadowy outlines of necrotic fat cells with basophilic calcium deposits, surrounded by an inflammatory reaction.

6- Fibrinoid necrosis: Seen in immune reactions involving blood vessels. This pattern of necrosis is prominent when complexes of antigens-antibodies are deposited in the walls of arteries together with fibrin that has leaked out of vessels; result in a bright pink and amorphous appearance in H&E stains, called "fibrinoid" (fibrin-like).

Mechanisms of cell injury

Cell injury results from functional and biochemical abnormalities in one or more of several essential cellular components.



The most important targets of injurious stimuli are:

(1) Mitochondria, the sites of ATP generation (the energy store of cells).
(2) Cell membranes, on which the ionic and osmotic homeostasis of the cell and its organelles depends.
(3) Protein synthesis.
(4) The cytoskeleton.
(5) The genetic apparatus of the cell.

ATP depletion*:* The major causes of ATP depletion are reduced supply of oxygen and nutrients, mitochondrial damage, and the actions of some toxins (e.g., cyanide). Failure of energy-dependent functions → reversible injury → necrosis

Mitochondrial damage*:* ATP depletion → failure of energy-dependent cellular functions → necrosis; under some conditions, leakage of proteins that cause apoptosis

Influx of calcium*:* activation of enzymes that damage cellular components and may also trigger apoptosis. Failure of the Ca^{2+} pump leads to influx of Ca^{2+}, with damaging effects on numerous cellular components.

Accumulation of reactive oxygen species*:* covalent modification of cellular proteins, lipids, nucleic acids.

Increased permeability of cellular membranes. The activity of the plasma membrane energy-dependent sodium pump is reduced, resulting in intracellular accumulation of sodium and efflux of potassium, causing cell swelling.

Accumulation of damaged DNA and misfolded proteins triggers apoptosis. Cells have mechanisms that repair damage to DNA, but if this damage is too severe to be corrected (e.g., after radiation injury), the cell initiates its suicide program and dies 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.

Apoptosis: (Programmed cell death)

Apoptosis is regulated mechanism of cell death that serves to eliminate unwanted and irreparably damaged cells. Characterized by: enzymatic degradation of proteins and DNA, initiated by caspases enzyme; and recognition and removal of dead cells by phagocytes.

This cell death is induced by a tightly regulated suicide program in which the cells activate enzymes capable of degrading the cells' own nuclear DNA and nuclear and cytoplasmic proteins. Fragments of the apoptotic cells then break off; giving the appearance that is responsible for the name: Apoptosis = "falling off.

The plasma membrane of the apoptotic cell remains intact, but the membrane is altered in such a way that the cell and its fragments will be phagocytized and rapidly cleared before its contents have leaked out, and therefore cell death by this pathway does not elicit an inflammatory reaction in the host.
Thus, apoptosis differs from necrosis, which is characterized by loss of membrane integrity, enzymatic digestion of cells, leakage of cellular contents, and frequently a host inflammatory reaction.

Causes of Apoptosis

1- Apoptosis in Physiologic Situations:

1-The programmed destruction of cells during embryogenesis, including implantation, organogenesis, developmental involution, and metamorphosis.

2- "Involution of hormone-dependent tissues upon hormone deprivation, such as endometrial cell breakdown during the menstrual cycle, and regression of the lactating breast after weaning.

3- Cell loss in proliferating cell populations, such as intestinal crypt epithelia and oral epithelium so as to maintain a constant number of epithelial cells.

4- Death of cells that have served their useful purpose, such as neutrophils in an acute inflammatory response, and lymphocytes at the end of an immune response.

5- Elimination of potentially harmful self-reactive lymphocytes, either before or after they have completed their maturation, in order to prevent reactions against one's own tissues.

6- Cell death induced by cytotoxic T lymphocytes, a defense mechanism against viruses and tumors that serves to kill and eliminate virus-infected and neoplastic cells.

2- Apoptosis in Pathologic Conditions

Apoptosis eliminates cells that are genetically altered or injured beyond repair without eliciting a severe host reaction, thus keeping the damage as contained as possible. Death by apoptosis is responsible for loss of cells in a variety of pathologic states:

1- DNA damage. Radiation, cytotoxic anticancer drugs, extremes of temperature, and even hypoxia can damage DNA. If repair mechanisms cannot cope with the injury, the cell triggers intrinsic mechanisms that induce apoptosis.

2- Accumulation of improperly folded proteins leads to apoptotic death of cells.

3- Cell injury in certain infections, particularly viral infections, in which loss of infected cells is largely due to apoptotic death that may be induced by the virus.

4- Pathologic atrophy in parenchymal organs after duct obstruction, such as occurs in the
pancreas, parotid gland, and kidney.

Morphology of apoptosis:

In H&E-stained tissue sections, apoptotic cells may appear as round or oval masses with intensely eosinophilic cytoplasm. Nuclei show various stages of chromatin condensation, aggregation and karyorrhexis.