MOLECULAR BASIS OF DISEASE

PATHOLOGENESIS

Pathologic processes that occur in human body

- Pathology is **the study (logos) of suffering (pathos).**
- It is a discipline that **bridges clinical practice and basic science**, and it involves the investigation of the causes (etiology) of disease as well as the underlying mechanisms (pathogenesis) that result in the presenting signs and symptoms of the patient.
- Pathologists use a variety of **molecular, microbiologic, and immunologic Techniques** to understand the **biochemical, structural, and functional changes that occur in cells, tissues, and organs.**
- To render **diagnoses and guide therapy, pathologists identify changes** in the gross or microscopic appearance (morphology) of cells and tissues, and biochemical alterations in body fluids (such as blood and urine).
- Traditionally the discipline is divided into **general pathology** and **systemic pathology**; the former focuses on the fundamental cellular and tissue responses to pathologic stimuli, while the latter examines the particular **responses of specialized organs**.

- The four aspects of a disease process that form the core of pathology are its cause (**etiology**), the mechanisms of its development (**pathogenesis**), the structural alterations induced in the cells and organs of the body (**morphologic changes**), and the functional consequences of the morphologic changes (**clinical significance**).

Etiology or Cause

- The concept that certain abnormal symptoms or diseases are "caused" is as ancient as recorded history. For the Arcadians (2500 BC), if someone became ill, it was the patient's own fault (for having sinned) or the makings of outside agents, such as bad smells, cold, evil spirits, or gods.
- In modern terms, there are two major classes of **etiologic factors: intrinsic or genetic, and acquired** (e.g., infectious, nutritional, chemical, physical). The concept, however, of one etiologic agent for one disease — developed from the study of infections or single-gene disorders — is no longer sufficient.
- Genetic factors are clearly involved in some of the common environmentally induced maladies, such as atherosclerosis and cancer, and the environment may also have profound influences on certain genetic diseases
- Knowledge or discovery of the primary cause remains the backbone on which a diagnosis can be made, a disease understood, or a treatment developed.

Pathogenesis

- Pathogenesis **refers to the sequence of events in the response of cells or tissues to the etiologic agent**, from the initial stimulus to the ultimate expression of the disease.
- The study of pathogenesis remains one of the main domains of **pathology**.

- For example, to understand cystic fibrosis is to know not only the defective gene and gene product, but also the biochemical, immunologic, and morphologic events leading to the formation of cysts and fibrosis in the lung, pancreas, and other organs.

Morphologic Changes.

- The morphologic changes **refer to the structural alterations in cells or tissues that are either characteristic of the disease or diagnostic of the etiologic process**.
- The practice of diagnostic pathology is devoted to identifying the nature and progression of disease by studying morphologic changes in tissues and chemical alterations in patients.
- Functional Derangements and Clinical Manifestations.
- The nature of the morphologic changes and their distribution in different organs or tissues influence normal function and determine the clinical features (symptoms and signs), course, and prognosis of the disease.

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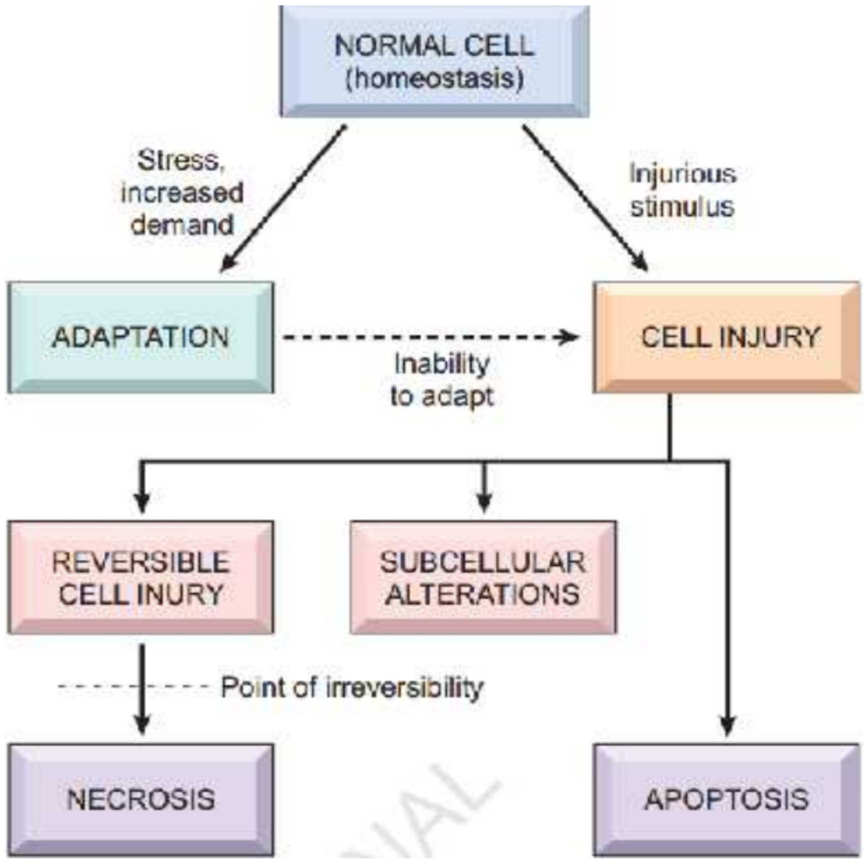
CELLULAR RESPONSES TO STRESS AND NOXIOUS STIMULI

- Cells are **active participants in their environment,** constantly adjusting their structure and function to accommodate changing demands and extracellular stresses.
- As cells encounter physiologic stresses or pathologic stimuli, they **can undergo adaptation,** achieving a new steady state and preserving viability and function.
- The principal adaptive responses are **hypertrophy, hyperplasia, atrophy, and metaplasia.**
- If the adaptive capability is exceeded or if the external stress is inherently harmful, cell injury develops.

- Within certain limits injury is reversible, and cells return to a stable baseline; however, **severe or persistent stress results in irreversible** injury and death of the affected cells.
- Cell death is one of the most crucial events in the evolution of disease in any tissue or organ. It results from diverse causes, including **ischemia (lack of blood flow), infections, toxins, and immune reactions**.
- Cell death is also a normal and essential process in embryogenesis,the development of organs, and the maintenance of homeostasis

MOLECULAR BASIS OF DISEASE



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.
- Physiologic adaptations usually represent **responses of cells to normal stimulation by hormones or endogenous chemical mediators(e.g**., the hormone-induced enlargement of the breast and uterus during pregnancy).
- **Pathologic adaptations** are responses to stress that allow cells to modulate their structure and function and thus escape injury.

- **Hypertrophy**

- Hypertrophy is an increase in the size of cells resulting in increase in the size of the organ.(In contrast, hyperplasia is characterized by an increase in cell Number)
- Hypertrophy can be physiologic or pathologic and is caused either by increased functional demand or by specific hormonal stimulation.
- Hypertrophy and hyperplasia can also occur together, and obviously both result in an enlarged (hypertrophic) organ.
- **Eg: physiologic**

- Thus, the massive physiologic enlargement of the uterus during pregnancy occurs as a consequence of estrogenstimulated smooth muscle hypertrophy and smooth muscle hyperplasia.
- In contrast, the striated muscle cells in both the skeletal muscle and the heart can undergo only hypertrophy in response to increased demand because in the adult they have limited capacity to divide.(Therefore, the avid weightlifter can develop a rippled physique only by hypertrophy of individual skeletal muscle cells induced by an increased workload.)

Examples of pathologic cellular hypertrophy include the cardiac enlargement that occurs with hypertension or aortic valve disease

- The mechanisms driving cardiac hypertrophy involve at least two types of signals: mechanical triggers, such as stretch, and trophic triggers, such as activation of α-adrenergic receptors.
- These stimuli turn on signal transduction pathways that lead to the induction of a number of genes, which in turn stimulate synthesis of numerous cellular proteins, including growth factors and structural proteins.
- The result is the synthesis of more proteins and myofilaments per cell, which achieves improved performance and thus a balance between the demand and the cell's functional capacity.

- **Hyperplasia**

- Hyperplasia is characterized by **an increase in cell number.**
- Hyperplasia can be **physiologic or pathologic**.
- The **two types of physiologic hyperplasia** are

  (1)hormonal hyperplasia, exemplified by the **proliferation of the glandular epithelium of the female breast** at puberty and during pregnacy;

  (2) **Compensatory hyperplasia**, that is, **hyperplasia that occurs when a portion of the tissue is removed or diseased**.

  Forexample, when a **liver is partially resected, mitotic activity in the remaining cells begins as early as 12 hours later, eventually restoring the liver to its normal weight**.

The **stimuli** for hyperplasia in this setting are **polypeptide growth factors** produced by remnant **hepatocytes** as well as **nonparenchymal cells in the liver**.
After restoration of the liver mass, cell proliferation is **"turned off"** by various growth inhibitors.

- Most forms of **pathologic hyperplasia are caused by excessive hormonal or growth factor stimulation**.
- For example, after a normal menstrual period there is a burst of uterine epithelial proliferation that is normally tightly regulated by stimulation through pituitary hormones and ovarian estrogen and by inhibition through progesterone.
- However, **if the balance between estrogen and progesterone is disturbed,** endometrial hyperplasia ensues, a common cause of abnormal menstrual bleeding.

- **Hyperplasia is also an important response of connective tissue cells in wound healing,** in which proliferating fibroblasts and blood vessels aid in repair.

- In this process, **growth factors are produced** by **white blood cells (leukocytes)** responding to the **injury and by cells in the extracellular matrix.**
- Stimulation by growth factors is also involved in the **hyperplasia** that is associated with certain viral infections; **for example, papillomaviruses cause skin warts and mucosal lesions composed of masses of hyperplastic epithelium. Here the growth factors may be produced by the virus or by infected cells**.
- It is important to note that in all these situations, the hyperplastic process remains **controlled**; **if hormonal or growth factor stimulation abates, the hyperplasia disappears**.

Atrophy

- Shrinkage in the size of the cell by the loss of cell substance is known as atrophy.
- When a sufficient number of cells is involved, the entire tissue or organ diminishes in size, **becoming atrophic** .
- It should be emphasized that although **atrophic cells may have diminished function, 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).
- Although **some of these stimuli are physiologic** (e.g., the loss of hormone stimulation in menopause) and **others pathologi**c (e.g., denervation), **the fundamental cellular changes are identical.**
- Atrophy results from **decreased protein synthesis and increased protein degradation in cells**.
- Protein synthesis decreases because of **reduced metabolic activity**.
- The degradation of cellular proteins **occurs mainly by the ubiquitin-proteasome pathway.**
- Nutrient deficiency and disuse **may activate ubiquitin ligases, which attach multiple** copies of the **small peptide ubiquitin to cellular proteins** and target these proteins for degradation in **proteasomes.**

- This pathway is also **thought to be responsible for the accelerated proteolysis** seen in a variety of catabolic conditions, including cancer .
- In many situations, atrophy is also **accompanied by increased autophagy,** with resulting **increases in the number of autophagic vacuoles.**
- Autophagy ("selfeating") is the process in which the starved cell eats its own components in an attempt to find nutrients and survive.

Metaplasia

- Metaplasia is a reversible **change in which one adult cell type (epithelial or** mesenchymal**) is replaced by another adult cell type.**
- In this type of cellular adaptation, **cells sensitive to a particular stress are replaced by other cell types better able to withstand the adverse environment**.
- Metaplasia is thought to arise by genetic "reprogramming"of stem cells rather than trans differentiation of already differentiated cells.
- **Epithelial metaplasia** is exemplified by the squamous change that occurs in the respiratory epithelium in habitual cigarette smokers .
- The normal ciliated columnar epithelial cells of the trachea and bronchi are focally or widely replaced by stratified squamous epithelial cells.
- **Vitamin A deficiency may also induce squamous metaplasia** in the respiratory epithelium. **The "rugged" stratified squamous epithelium may be able to survive under circumstances that the more fragile specialized epithelium would not tolerate.**
- Although the **metaplastic squamous epithelium has survival advantages, important protective mechanisms are lost, such as mucus secretion and ciliary clearance of particulate matter.**

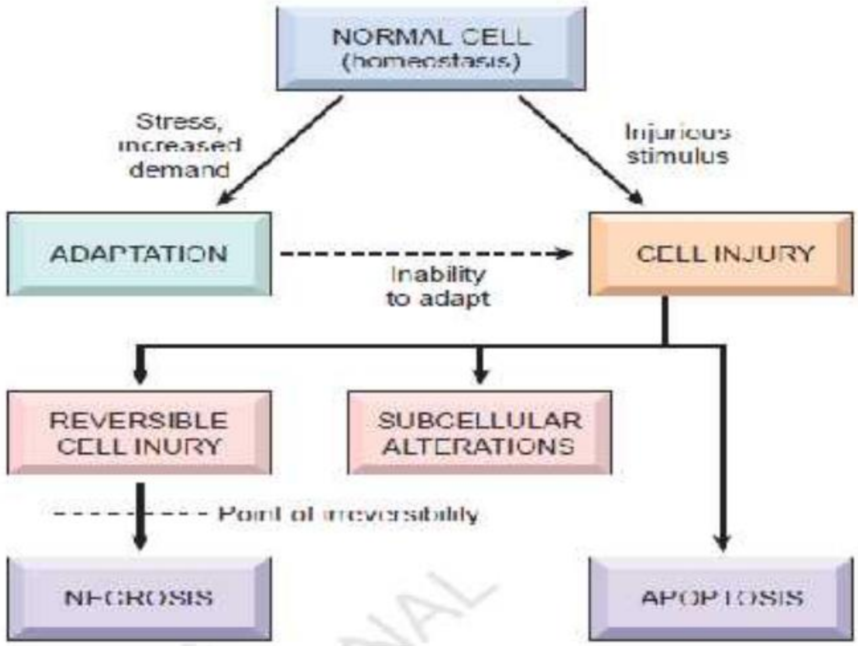
- **Epithelial metaplasia** is therefore a double-edged sword; moreover, the influences that induce **metaplastic transformation**, if persistent, may **predispose to malignant transformation of the epithelium**.
- In fact, in a common form of lung cancer, squamous metaplasia of the respiratory epithelium often coexists with **cancers composed of malignant squamous cells**.
- It is thought that **cigarette smoking** initially **causes squamous metaplasia**, and **cancers arise later in some of these altered foci**.

Cellular Adaptations to Stress

1. **Hypertrophy:** increased cell and organ size, often in response to increased workload; induced by mechanical stress and by growth factors; occurs in tissues incapable of cell division
2. **Hyperplasia:** increased cell numbers in response to hormones and other growth factors; occurs in tissues whose cells are able to divide

3. **Atrophy:** decreased cell and organ size, as a result of decreased nutrient supply or disuse; associated with decreased synthesis and increased proteolytic breakdown of cellular organelles
4. **Metaplasia:** change in phenotype of differentiated cells, often a response to chronic irritation that makes cells better able to withstand the stress; usually induced by altered differentiation pathway of tissue stem cells; may result in reduced functions or increased propensity for malignant transformation.

CELL INJURY AND CELL DEATH



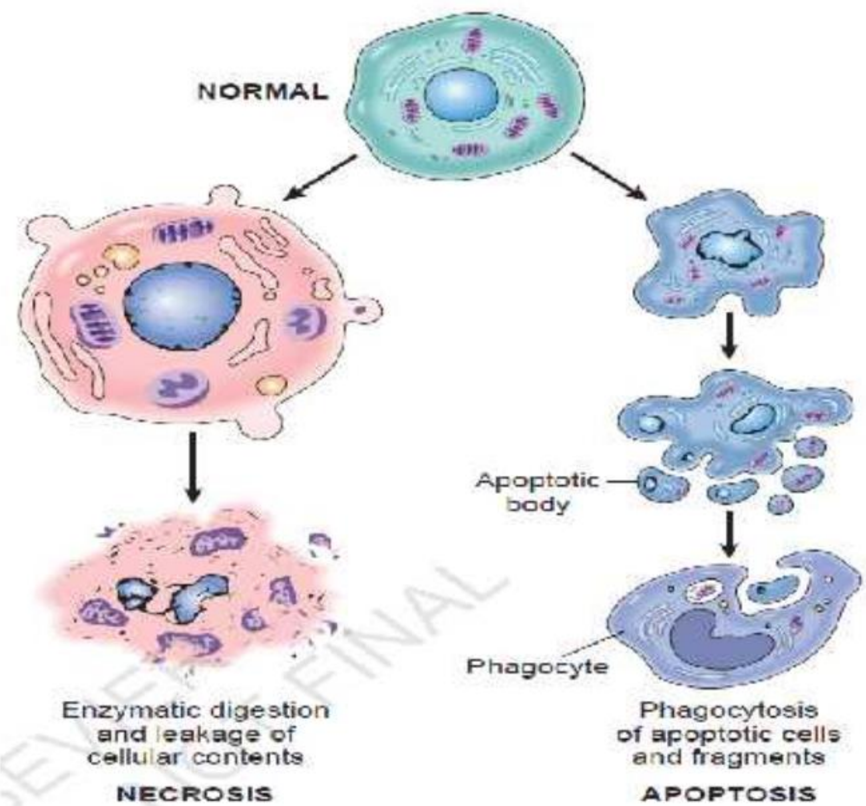
- Cell injury results when cells are stressed so severely that they are **no longer able to adapt** or when cells are exposed to **inherently damaging agents** or **suffer from intrinsic abnormalities**.
- Different injurious stimuli affect many metabolic pathways and cellular organelles. Injury may progress through a reversible stage and culminate in cell death.

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**.

Cell death

- *With continuing damage, the injury* becomes irreversible, at which time the cell cannot recover and it dies.
- *There are two types of cell death— necrosis and apoptosis—which differ in their morphology, mechanisms, and roles in disease and physiology.*
- When damage to membranes is severe, enzymes leak out of **lysosomes, enter the cytoplasm, and digest the cell, resulting in *necrosis.***
- *Cellular* contents also leak out through the damaged plasma membrane and elicit a host reaction (inflammation).
- 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.**



- 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 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.

CAUSES OF CELL INJURY

The causes of cell injury range from the gross physical trauma of a motor vehicle accident to the single gene defect that results in a **defective enzyme underlying a specific metabolic disease**. Most injurious stimuli can be grouped into the following categories.

1. **Oxygen Deprivation**
2. **Chemical Agents**
3. **Infectious Agents**
4. **Immunologic Reactions**
5. **Genetic Defects**
6. **Nutritional Imbalances**
7. **Physical Agents**
8. **Aging**

Oxygen Deprivation.

- ***Hypoxia, or oxygen deficiency,*** interferes with aerobic oxidative respiration and is an extremely important and common cause of cell injury and death.
- Hypoxia should be distinguished from *ischemia, which* is a loss of blood supply in a tissue due to impeded arterial flow or reduced venous drainage.
- While ischemia is the most common cause of hypoxia, oxygen deficiency can also result from inadequate oxygenation of the blood, **as in pneumonia, or reduction in the oxygen-carrying capacity of the blood, as in blood-loss, anemia or carbon monoxide (CO) poisoning**.
  (CO forms a stable complex with hemoglobin that prevents oxygen binding)

Chemical Agents

- An enormous number of chemical substances can injure cells; even innocuous substances such as **glucose or salt, if sufficiently concentrated**, can so derange the osmotic environment that cell injury or death results.

- Oxygen at **sufficiently high partial pressures is also toxic**.
- Agents commonly known **as poisons** cause severe damage at the cellular level by **altering membrane permeability, osmotic homeostasi**s, or the **integrity of an enzyme or cofactor**, and exposure to these poisons can culminate in the death of the whole organism.
- Other potentially toxic agents are **encountered daily in our environment; these include air pollutants, insecticides, CO, asbestos, and social "stimuli" such as ethanol.**
- Even **therapeutic drugs** can cause cell or tissue injury in a susceptible patient or if used excessively or inappropriately

Infectious Agents

These range from submicroscopic viruses to meter-long tapeworms; in between are the rickettsiae, bacteria, fungi, and protozoans

Immunologic Reactions

Although the immune system defends the body against pathogenic microbes, immune can also result in cell and tissue injury.

Examples include autoimmune reactions against one's own tissues and allergic reactions against environmental substances in genetically susceptible individuals

Genetic Defects

- Genetic defects can result in pathologic changes as conspicuous as the congenital malformations associated with Down syndrome or as subtle as the single amino acid substitution in hemoglobin S giving rise to sickle cell anemia.
- Genetic defects may cause cell injury because of deficiency of functional proteins, such as enzymes in inborn errors of metabolism, or accumulation of damaged DNA or misfolded proteins, both of which trigger cell death when they are beyond repair.
- Variations in the genetic makeup (SNP) can also influence the susceptibility of cells to injury by chemicals and other environmental insults

Nutritional Imbalances

- Nutritional deficiencies remain a major cause of cell injury.
- Protein-calorie insufficiency among underprivileged populations is only the most
- obvious example;
- specific vitamin deficiencies are not uncommon even in developed countries with high standards of living .

- Ironically, excesses of nutrition are also important causes of morbidity and mortality; **for example, obesity markedly increases the risk for type 2 diabetes mellitu**s. Moreover, diets rich in **animal fat** are strongly implicated in the development of atherosclerosis as well as in increased vulnerability to many disorders, including cancer.

Physical Agents

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

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, eventually, the death of cells and of the organism.

THE MORPHOLOGY OF CELL AND TISSUE INJURY

- All stresses and noxious influences exert their effects first at the molecular or biochemical level.
- Cellular function may be **lost long before cell death occurs, and the morphologic changes of cell injury (or death) lag far behind both.**
- **myocardial cells become noncontractile after 1 to 2 minutes of ischemia, although they do not die until 20 to 30 minutes of ischemia have elapsed.**

- The cellular derangements of reversible injury can be repaired and, if the injurious stimulus abates, the cell will return to normalcy.
- Persistent or excessive injury, however, causes cells to pass the nebulous "point of no return" into irreversible injury and cell death.
- The events that determine when reversible injury becomes irreversible and progresses to cell death remain poorly understood.

- Although there are **no definitive morphologic or biochemical correlates of irreversibility**, two phenomena consistently characterize irreversibility:

1. **The inability to reverse mitochondrial dysfunction (lack of oxidative phosphorylationand ATP generation) even after resolution of the original injury,**
2. **Profound disturbances in membrane function.**

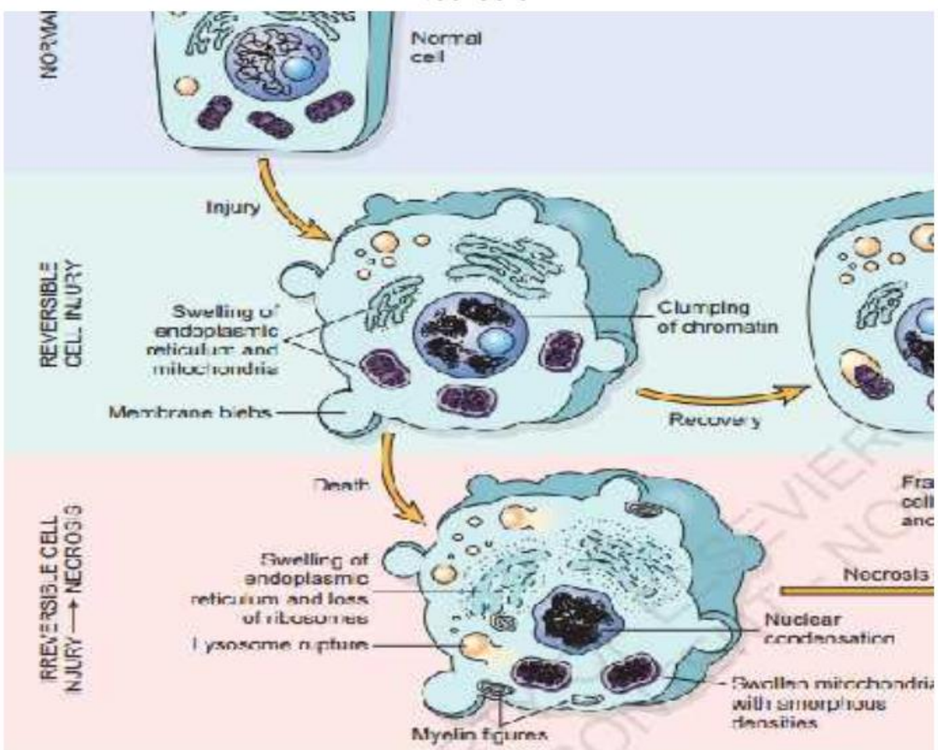
Reversible Injury

The two main morphologic correlates of reversible cell injury are

1. cellular swelling
2. fatty change.

- ❑ Cellular swelling is the result of **failure of energy-dependent ion pumps in the plasma membrane**, leading to an inability to maintain ionic and fluid homeostasis.
- ❑ Fatty change occurs in **hypoxic injury** and various forms of **toxic or metabolic injury**, and 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 and myocardial cells.

Necrosis



Necrosis

1. The term necrosis refers to a series of changes that accompany cell death, largely resulting from the degradative action of enzymes on lethally injured cells.
2. Necrotic cells are unable to maintain membrane integrity, and their contents often leak out.
3. The enzymes responsible for digestion of the cell are derived either from the lysosomes of the dying cells themselves or from the lysosomes of leukocytes that are recruited as part of the inflammatory reaction to the dead cells.

Causes of Necrosis

Necrosis is caused by factors external to the cell or tissue, such as infection, toxins, or trauma that result in the unregulated digestion of cell components

- Cells that die due to necrosis **do not follow the apoptotic signal transduction pathway** but rather various receptors are activated that result in the loss of cell membrane integrity and an uncontrolled release of products of cell death into the extracellular space.
- This initiates in the surrounding tissue aninflammatory response which prevents nearby phagocytes from locating and eliminating the dead cells by phagocytosis.
- For this reason, it is often necessary to remove necrotic tissue surgically, aprocedure known as **debridement.**
- Untreated necrosis results in a build-up of decomposing dead tissue and cell debris at or near the site of the cell death. A classic example is **gangrene.**

Causes of Necrosis

- Necrosis may occur due to external or internal factors.

External factors

1. mechanical trauma (physical damage to the body that causes cellular breakdown),
2. damage to blood vessels (which may disrupt blood supply to associated tissue), and ischemia.
3. Thermal effects (extremely high or low temperature) can result in necrosis due to the disruption of cells.
4. Infrostbite (Inadequate blood circulation when the ambient temperature is below freezing point leads to frostbite) crystals form, increasing the pressure of remaining tissue and fluid causing the cells to burst.

5. Under extreme conditions tissues and cells die through an unregulated process of destruction of membranes and cytosol.

Internal factors causing necrosis include

1. Trophoneurotic disorders;(a functional disease of a part due to failure of nutrition from defective nerve action in the parts involved)
2. Injury
3. Paralysis of nerve cells.
4. Pancreatic enzymes (lipases) are the major cause of fat necrosis.
5. Necrosis can be activated by components of the immune system, such as the complement system; bacterial toxins; activated natural killer cells; and peritoneal macrophages.

- Pathogen-induced necrosis programs in cells with immunological barriers (intestinal mucosa) may alleviate invasion of pathogens through surfaces affected by inflammation.
- Toxins and pathogens may cause necrosis; toxins such as snake venoms may inhibit enzymes and cause cell death.
- Necrotic wounds have also resulted from the stings of *vespa mandarinia.*

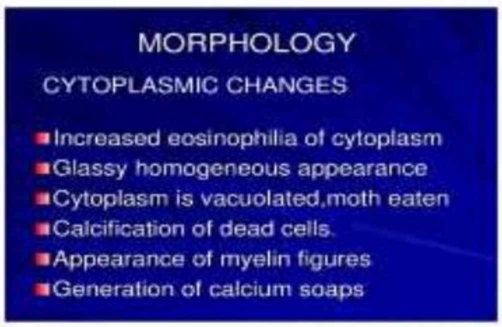
Morphology

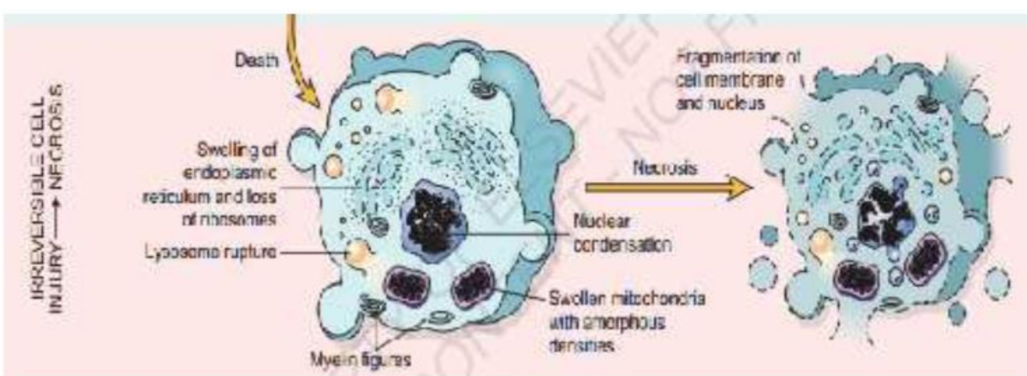
Morphology-cytoplasmic changes

- In one common pattern of cell death resulting from lack of oxygen, the necrotic cells show increased eosinophilia (i.e., pink staining from the eosin dye, the "E" in "H&E"). This is attributable in part to increased binding of eosin to denatured cytoplasmic proteins and in part 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").

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

- When enzymes have digested the cytoplasmic organelles, the cytoplasm becomes vacuolated and appears motheaten.
- Dead cells may be replaced by large, whorled phospholipid masses, called myelin figures, that are derived from damaged cellular membranes. They are thought to result from dissociation of lipoproteins with unmasking of phosphatide groups, promoting the uptake and intercalation of water between the lamellar stacks of membranes. These phospholipid precipitates are then either phagocytosed by other cells or further degraded into fatty acids; calcification of such fatty acid residues results in the generation of calcium soaps. Thus, the dead cells may ultimately become calcified.



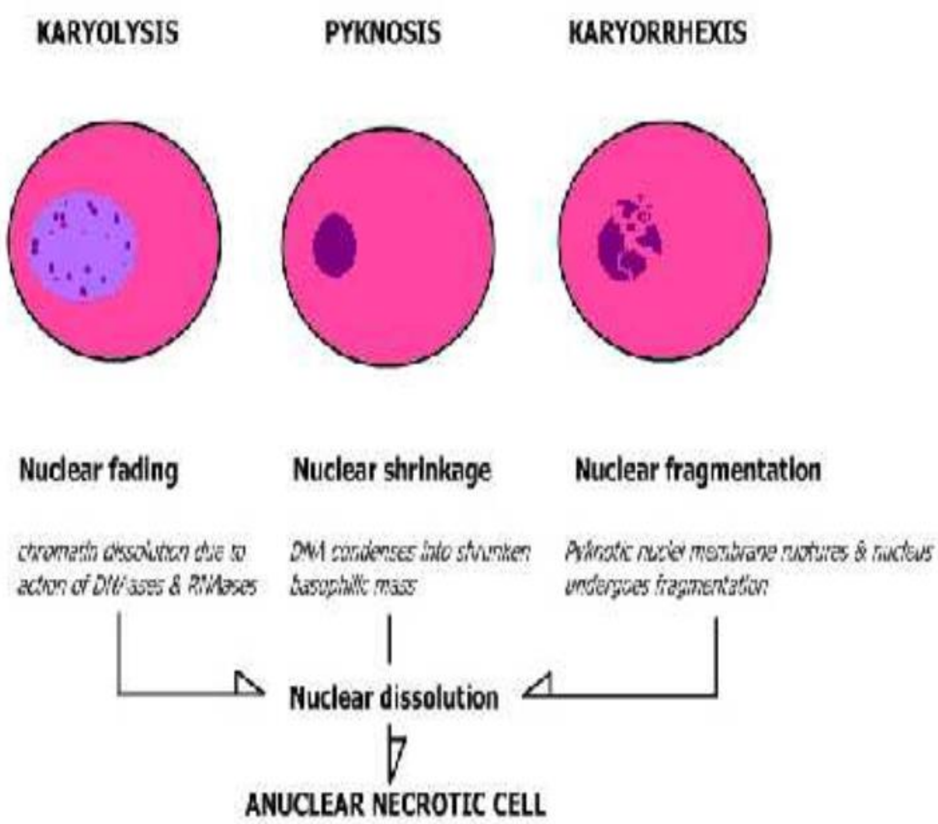


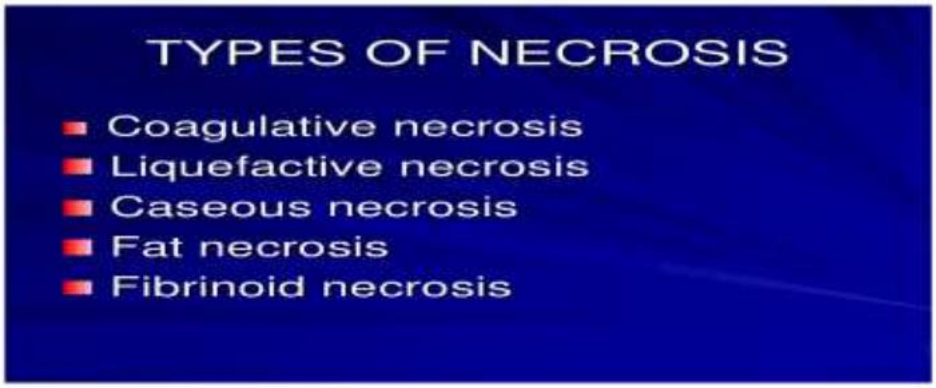
- By electron microscopy, necrotic cells are characterized by discontinuities in plasma and organelle membranes, marked dilation of mitochondria with the appearance of large amorphous densities, disruption of lysosomes, intracytoplasmic myelin figures, and profound nuclear changes culminating in nuclear dissolution.

Morphology-nuclear changes

Nuclear changes assume one of three patterns, all due to breakdown of DNA and chromatin.

- **karyolysis:** The basophilia of the chromatin may fade **due** to deoxyribonuclease (DNase) activity.
- **Pyknosis, characterized by** nuclear shrinkage and increased basophilia; the DNA condenses into a solid shrunken mass.
- **Karyorrhexis, the pyknotic nucleus undergoes** fragmentation. In 1 to 2 days, the nucleus in a dead cell completely disappears.





Coagulative necrosis

- **Coagulative necrosis is a form of tissue necrosis in which** the component cells are dead but the basic tissue architecture is preserved for at least several days.
- The affected tissues take on a firm texture.
- Presumably the **injury denatures not only structural proteins but also enzymes and so blocks the proteolysis of the dead cells; as a result, eosinophilic, anucleate cells may persist for days or weeks.**
- Ultimately, the necrotic cells are removed by phagocytosis of the cellular debris by infiltrating leukocytes and by digestion of the dead cells by the action of lysosomal enzymes of the leukocytes.
- Coagulative necrosis is characteristic of **infarcts (areas of** ischemic necrosis) in all solid organs except the brain.

Liquefactive necrosis

- **Liquefactive necrosis is seen** in focal bacterial or, occasionally, fungal infections, because microbes stimulate the accumulation of inflammatory cells and the **enzymes of leukocytes digest ("liquefy") the tissue**.
- Whatever the pathogenesis, 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**

Gangrenous necrosis

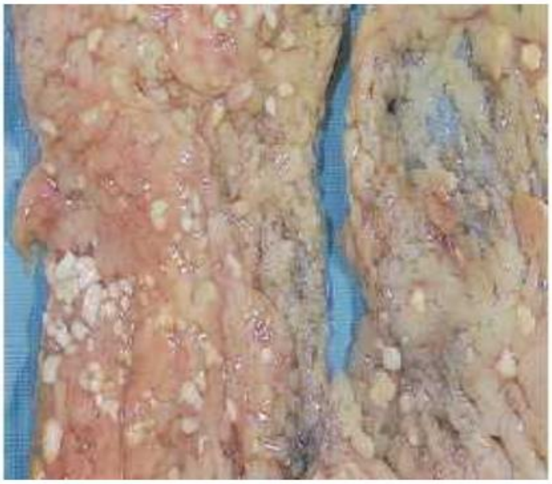
- **gangrenous necrosis is not a distinctive** pattern of cell death, the term is still commonly used in clinical practice.
- It is usually **applied to a limb**, generally the lower leg, that has lost its blood supply and has **undergone coagulative necrosis** involving multiple tissue layers.
- **When bacterial infection is superimposed**,coagulative necrosis is modified by the **liquefactive action of the bacteria and the attracted leukocytes (socalled wet gangrene).**

Caseous necrosis

- **Caseous necrosis is encountered most often in foci** of tuberculous infection.
- The term **"caseous" (cheeselike)** is derived from the **friable yellow-white appearance of the area of necrosis** .
- Caseous necrosis is often enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a **granuloma**

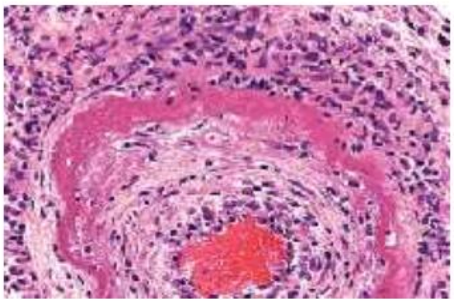
Fat necrosis

- **Fat necrosis,** refers to focal areas of fat destruction, typically resulting from release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. This occurs in the calamitous abdominal emergency known as **acute pancreatitis .**
- The released fatty acids combine with calcium to produce grossly visible chalky white areas (fat saponification), which enable the surgeon and the pathologist to identify the lesions



Fibrinoid necrosis

- **Fibrinoid necrosis is a special form of necrosis** usually seen in immune **reactions involving blood vessels**.
- This pattern of **necrosis is prominent when complexes of antigens and antibodies are deposited in the walls of arteries**. Deposits of these **"immune complexes,"** 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) by Pathologists .
- The immunologically **mediated diseases (e.g., polyarteritis nodosa)** in which this type of necrosis.



MECHANISMS OF CELL INJURY

we have discussed the causes of cell injury and necrosis and their morphologic and functional correlates, we next consider in more detail the molecular basis of cell injury.

Factors that determine reversible or irreversible cell injury

1.The cellular response to injurious stimuli depends ***on the type of injury, its duration, and its severity.***

- *Thus, **low doses of toxins or a brief duration of ischemia*** may lead to reversible cell injury, whereas ***larger toxin doses or longer ischemic intervals may result in irreversible injury and cell death***.

*2.The **consequences of an injurious stimulus depend on the type, status, adaptability, and genetic makeup of the injured cell**.*

Example:

- The same injury has vastly **different outcomes depending on the cell type**; thus, striated **skeletal muscle in the leg accommodates complete ischemia for 2 to 3 hours** without irreversible injury, whereas **cardiac muscle dies after only 20 to 30 minutes**.
- The **nutritional (or hormonal) status can also be important**; clearly, a **glycogen-replete hepatocyte** will **tolerate ischemia** much better than **one that has just burned its last glucose molecule.**
- **Genetically determined diversity in metabolic pathways** can also be important. For instance, when exposed to the **same dose of a toxin**, individuals who inherit **variants in genes** encoding **cytochrome P-450** may **catabolize the toxin** at different rates, leading to different outcomes.
- Much effort is now directed toward **understanding the role of genetic polymorphisms in responses to drugs and toxins and in disease susceptibility**. The study of such interactions is called pharmacogenomics.

*3.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

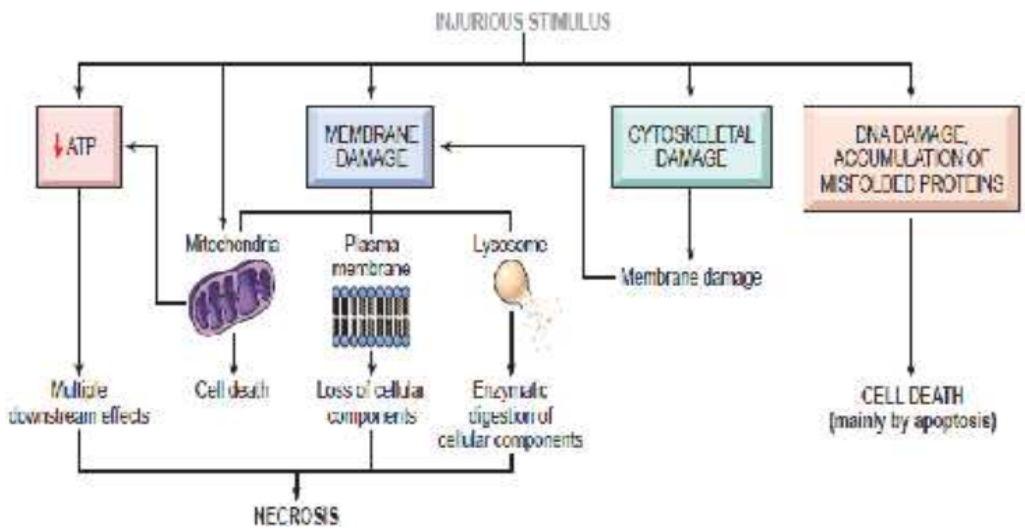
(1) mitochondria, the sites of ATP generation;

(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.



What is ATP? How it is produced ?

- ATP, the energy store of cells, is produced mainly by **oxidative phosphorylation** of adenosine diphosphate (ADP) during reduction of oxygen in the electron transport system of mitochondria.
- In addition, the glycolytic pathway can generate ATP in the absence of oxygen using glucose derived either from the circulation or from the hydrolysis of intracellular glycogen.

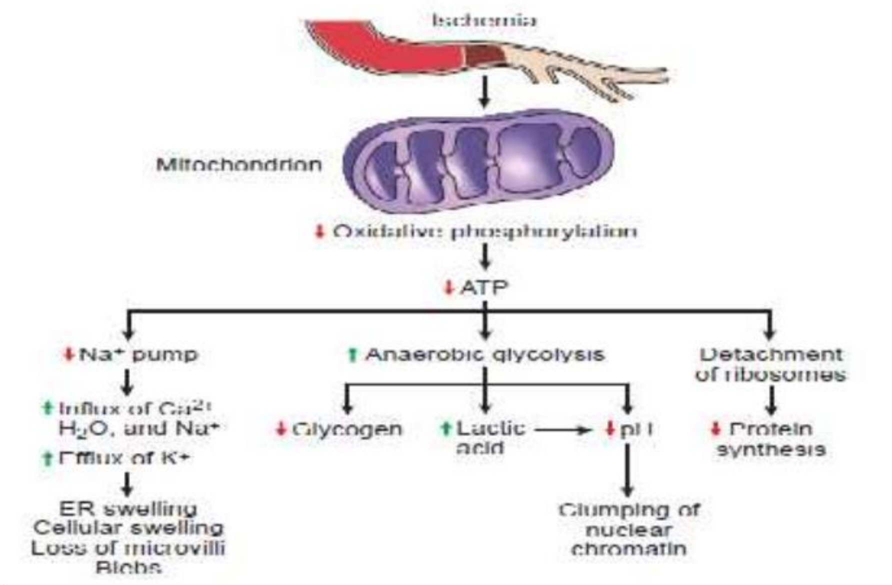
How ATP depletion happened?

- The major causes of ATP depletion are

1. **Reduced supply of oxygen and nutrients,**
2. **Mitochondrial damage,**
3. **Actions of some toxins (e.G., Cyanide).**

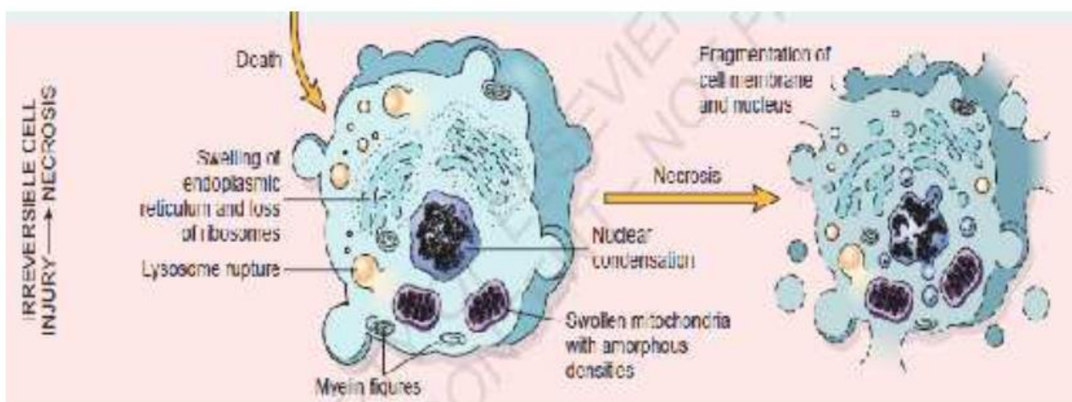
- Tissues with a **greater glycolytic capacity** (e.g., the liver) are able to survive ***loss of oxygen and decreased oxidative phosphorylation*** better than are **tissues with limited capacity** for glycolysis (e.g., the brain).
- **High-energy phosphate in the form of ATP** is required for virtually all synthetic and degradative processes within the cell, including membrane transport, protein synthesis, lipogenesis.
- *Depletion of **ATP to less than 5% to 10% of normal levels** has widespread effects on many critical cellular systems.*

- **Depletion of ATP-due to Reduced supply of oxygen and nutrients,**



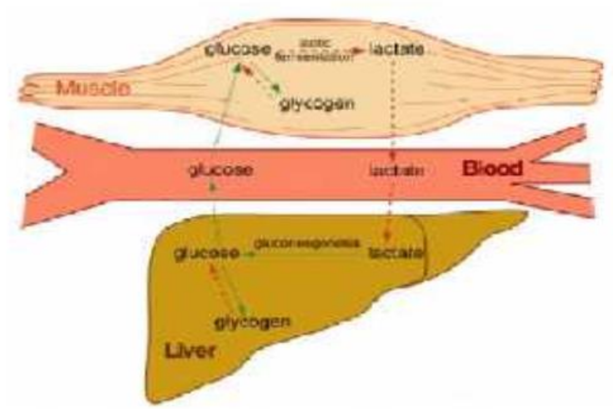
1.The activity of the *plasma membrane energy dependent sodium pump is reduced, resulting in* intracellular **accumulation of sodium** and **efflux of potassium**.

• ***Failure of the Ca2+ pump*** *leads to* **influx of Ca2+,** *with* damaging effects on numerous cellular components. The net gain of solute is accompanied by iso-osmotic gain of water, causing ***cell swelling and*** **dilation of the ER.**



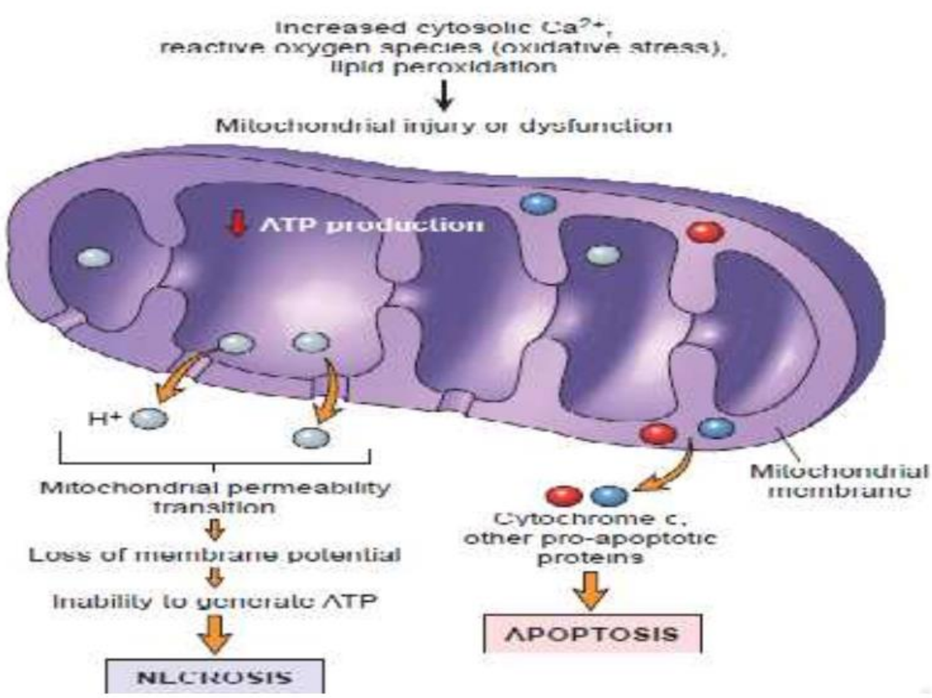
2. There is ***a compensatory increase in anaerobic glycolysis in an attempt to maintain the cell's energy sources***.

- As a consequence, **intracellular glycogen stores are rapidly depleted**, and **lactic acid accumulates**, leading to decreased **<u>intracellular pH and decreased activity of many cellular enzymes</u>**.



3. **<u>Prolonged or worsening depletion of ATP</u>** causes ***structural disruption of the protein synthetic apparatus,*** manifested as **detachment of ribosomes from the rough endoplastic reticulum (RER)** and **dissociation of polysomes into monosomes, with a consequent reduction in protein synthesis**.
Ultimately, there is irreversible damage to mitochondrial and the **cell undergoes necrosis.**

Depletion of ATP-due to damage to mitochondria



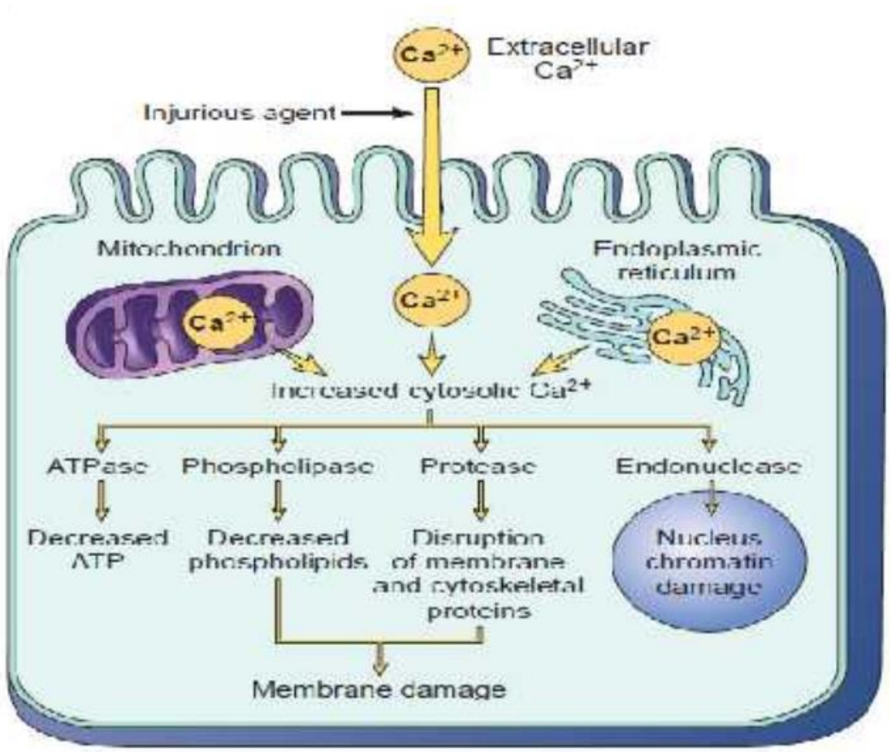
Damage to Mitochondria

- Mitochondria are the cell's suppliers of life-sustaining energy in the form of ATP, but they are also critical players in cell injury and death.
- Mitochondria can be damaged by

1. Increases of cytosolic ca2+,
2. Reactive oxygen species(ros),
3. Oxygen deprivation,
4. Sensitive to virtually all types of injurious stimuli, including hypoxia and toxins.

Influx of Calcium

- **Cytosolic free calcium is normally maintained by ATP dependent calcium transporters at concentrations** that are as **much as 10,000 times lower than the concentration of extracellular calcium or of sequestered intracellular mitochondrial and ER calcium**.
- Ischemia and certain toxins cause an increase in cytosolic calcium concentration, initially because of release of Ca2+ from the intracellular stores, and later resulting from increased influx across the plasma membrane.
- The importance of Ca2+ in cell injury was established by the finding that depleting extracellular Ca2+ delays cell death after hypoxia and exposure to some toxins.



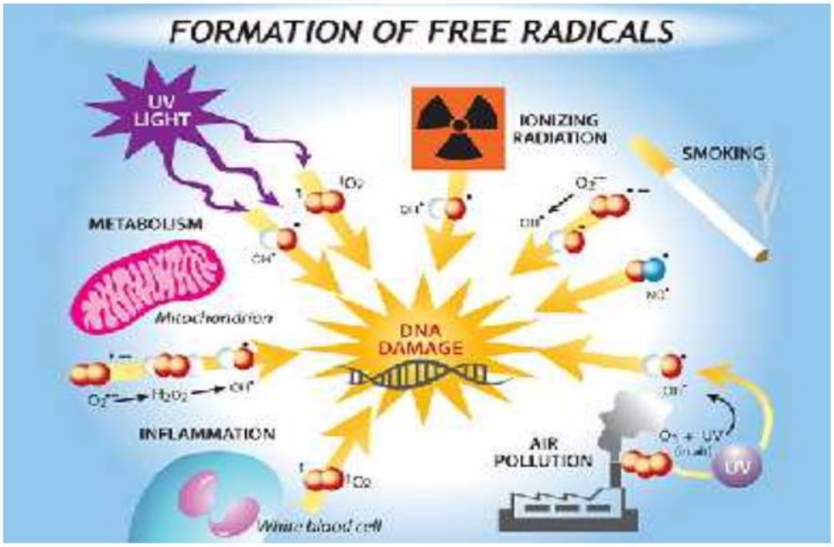
- ***<u>Increased cytosolic Ca2+ activates a number of enzymes</u>***, *with* ***<u>potentially deleterious cellular</u> <u>effects</u>***.

1. **Phospholipases (which cause membrane damage),**
2. **Proteases (which break down both membrane and cytoskeletal proteins),**
3. **Endonucleases (which are responsible for DNA and chromatin fragmentation),**
4. **adenosine triphosphatases (atpases; thereby hastening ATP depletion).**

Increased intracellular Ca2+ levels also **result in the induction of apoptosis, by direct activation of caspases and by increasing mitochondrial permeability**

Accumulation of Oxygen-Derived Free Radicals (Oxidative Stress)

- Free radicals are chemical species with a single unpaired electron in an outer orbital.
- Such chemical states are extremely unstable and readily react with inorganic and organic chemicals; when generated in cells they avidly attack nucleic acids as well as a variety of cellular proteins and lipids.
- In addition, free radicals **initiate autocatalytic reactions**; molecules that **<u>react with free radicals are in turn converted into free radicals</u>**, thus propagating the chain of damage.



The accumulation of free radicals is determined by their rates of production and removal

Several reactions are responsible for the *generation of free radicals.*

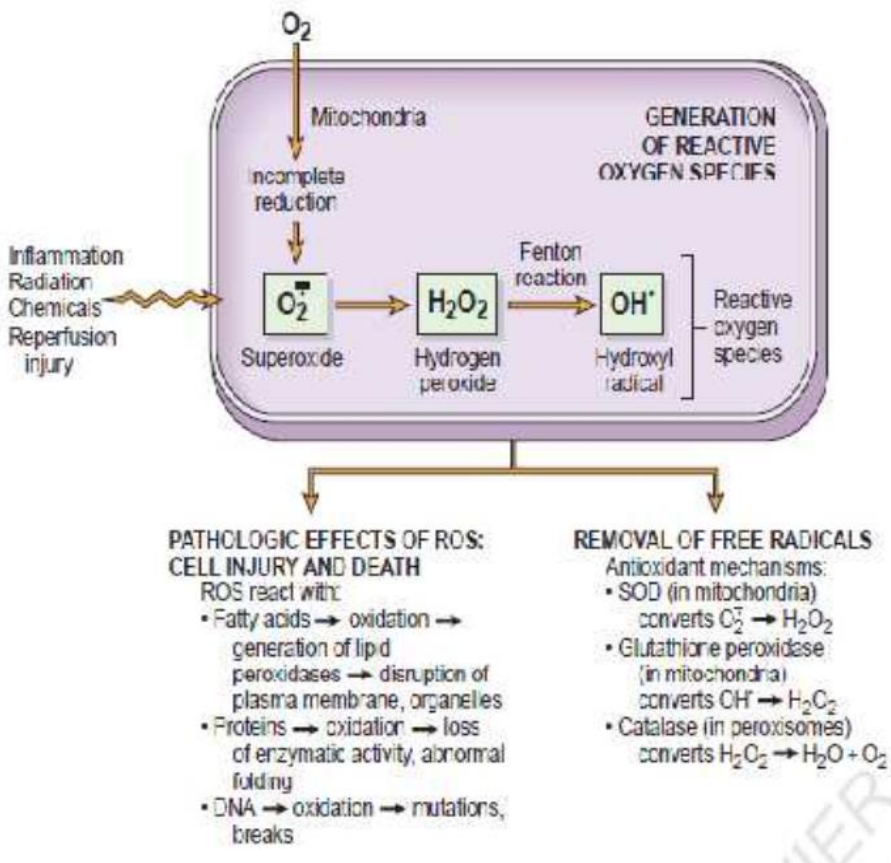
1. The reduction-oxidation (redox) reactions
2. The absorption of radiant energy
3. The enzymatic metabolism of exogenous chemicals
4. Inflammation
5. Nitric oxide (NO)

- ***Reactive oxygen species (ROS) are* a type of oxygen-derived free radical whose role in cell injury is well established.**
- They are produced normally in cells during mitochondrial respiration and energy generation, but they are degraded and removed by cellular defense systems.
- **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*.**

- **The reduction-oxidation (redox) reactions that occur during normal mitochondrial metabolism.**
- During normal respiration, for example, molecular oxygen is sequentially reduced in mitochondria by the addition of four electrons to generate water.
- In the process, small amounts of toxic intermediate species are generated by partial reduction of oxygen; these include superoxide radicals ($O2 \bullet -$), hydrogen peroxide ($H2O2$), and $OH\bullet$.
- **Transition metals such as copper and iron also acceptor donate free electrons during certain intracellular reactions and thereby catalyze free-radical formation,** as in the Fenton reaction ($Fe2+ + H2O2 \rightarrow Fe3+ + OH\bullet + OH-$).

The role of reactive oxygen species (ROS) in cell injury.

- O2 is converted to superoxide by oxidative enzymes in the endoplasmic reticulum, mitochondria, plasma membrane, peroxisomes, and cytosol.
- superoxide is converted to H2O2 by **dismutation** and thence to $OH^{\bullet}$ by the **Cu2+/Fe2+-catalyzed Fenton reaction**.
- H2O2 is also derived directly from **oxidases in peroxisomes**(not shown).
- **Also not shown** is another potentially injurious free radical, **singlet oxygen**.
- **Resultant free-radical damage** to **lipid** (by peroxidation), **proteins**, and deoxy ribonucleic acid (**DNA**) leads to various forms of cell injury.
- The major antioxidant enzymes are **superoxide dismutase (SOD), catalase, and glutathione peroxidase.**



- **The absorption of radiant energy** (e.g., ultraviolet light, x-rays). Ionizing radiation can hydrolyze water into hydroxyl (OH•) and hydrogen (H•) free radicals.

- The enzymatic metabolism of exogenous chemicals (e.g., **carbon tetrachloride**)
- **Inflammation**, since free radicals are produced by leukocytes that enter tissues.
- **Nitric oxide (NO),** an important chemical mediator
  normally synthesized by a variety of cell types, can act as a free radical or can be converted into highly reactive nitrite species