Pathophysiology

Pathophysiology, cell injury, adaptation, and cell death

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Lecture 1

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Pathophysiology

- It is the science that study the functional or physiologic changes in the body which results from disease developments.
- It involves the study of the four aspects of disease:

➢Etiology (cause of the diseases)

➢Pathogenesis

➢Morphologic changes

➢Functional derangements and clinical significance

Etiology

- **The etiology of diseases can be**:

➢Genetic

➢Acquired (infectious, nutritional, chemical ,physical, etc).

- Idiopathic is a term used when the cause of the disease is unknown
- Multifactorial disease is a term used when the diseases caused by genetic and acquired factors.
- Iatrogenic is a term used when the disease is caused by medical treatment; it usually results from a mistake made in diagnosis or treatment and can also be the fault of any member of the healthcare team.

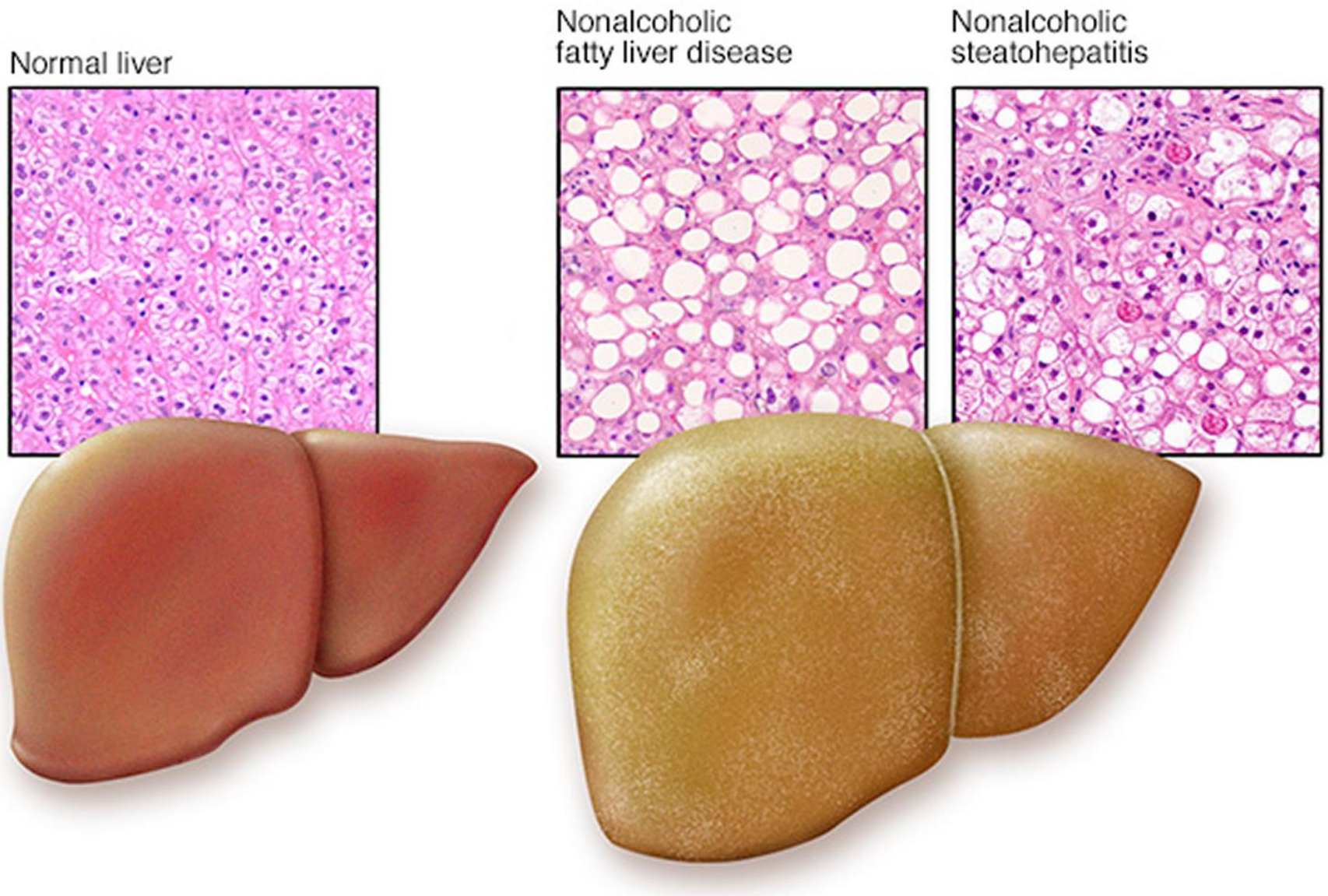
Pathogenesis

- It is the mechanism in which which the causative agent produce the pathological and clinical responses
- The pathogenetic mechanisms take place in the incubation period.

- **The morphologic changes** refer to the structural alterations in cells or tissues that occur following the pathogenetic mechanisms
- **The morphologic changes are**:

➢Gross morphologic changes (macroscopic changes): can be seen with the naked eye

➢Microscopic changes: can only be seen under microscope

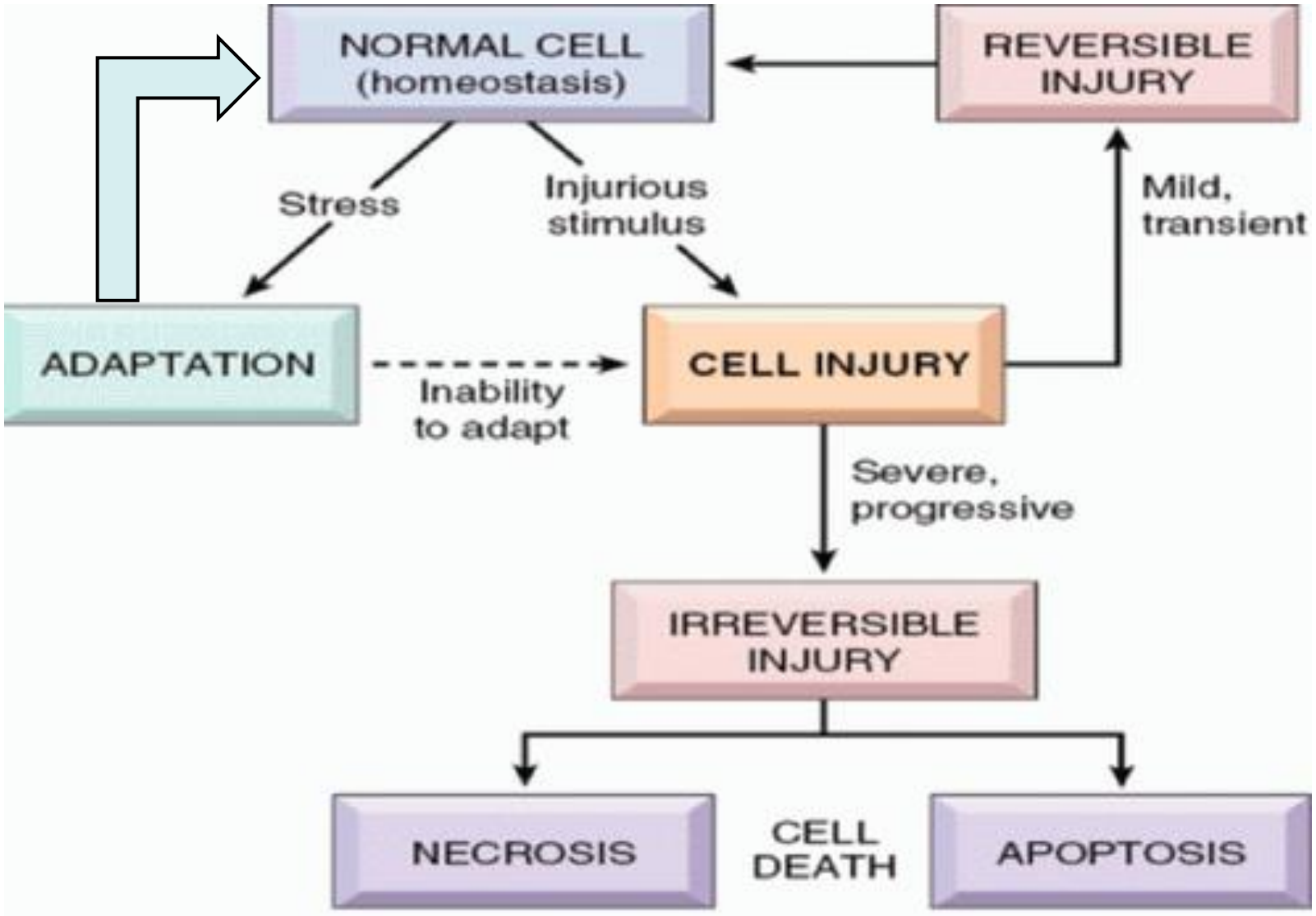

Normal liver
Nonalcoholic
fatty liver disease
Nonalcoholic
steatohepatitis

Functional derangements and clinical significance

- It is represented by the signs and symptoms
- Symptoms are feelings or sensations a person has, whereas signs are observable characteristics others can see. The doctor uses symptoms, signs, and testing to make a diagnosis.
- For example, pain and nausea are symptoms while cough and swelling are signs

Cell injury

- Cells can maintain their intracellular environment within a very narrow range of physiologic parameters (normal homeostasis). As cells encounter physiologic stresses or pathologic stimuli, they can undergo adaptation to achieve a new steady state and preserve viability and function.
- If physiologic stresses or pathologic stimuli exceeded the adaptation capacity of the cell, cell injury will develop, which is either reversible cell injury or irreversible (death)


NORMAL CELL
(homeostasis)
REVERSIBLE
INJURY
Stress
Injurious
stimulus
Mild,
transient
ADAPTATION
Inability
to adapt
CELL INJURY
Severe,
progressive
IRREVERSIBLE
INJURY
NECROSIS
CELL
DEATH
APOPTOSIS

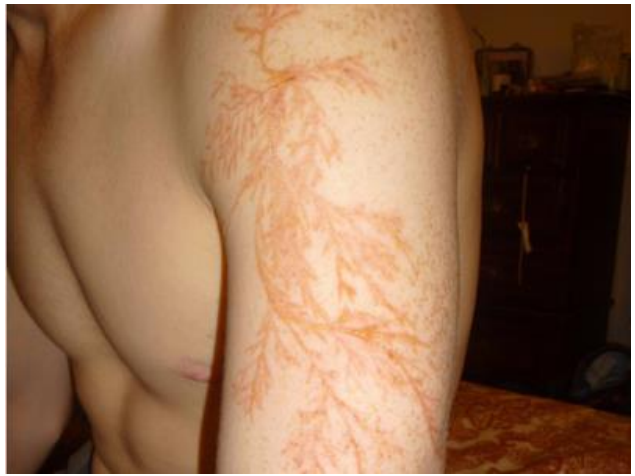
Causes of cell injury

- **The causes can be classified into five group**:

1. Injury from physical agents
2. Radiation injury
3. Chemical injury
4. Injury from biologic agents
5. Injury from nutritional imbalances

1. Injury from physical agents

- **Mechanical forces**; Injury or trauma caused by body impact with another object
- **Extremes of temperature**; Extremes of heat and cold cause damage to the cell, its organelles, and its enzyme systems.
- **Electrical forces**; affect the body through extensive tissue injury and disruption of neural and cardiac impulses.



2. Radiation injury

- Electromagnetic radiation comprises a wide spectrum of wave propagated energy, ranging from ionizing gamma rays to radiofrequency waves.
- **ionizing radiation** is radiation energy above the ultraviolet (UV) range. the photons have enough energy to knock electrons off atoms and molecules.
- **Nonionizing radiation** is radiation energy at frequencies below that of visible light. It includes infrared light, ultrasound, microwaves, and laser energy.
- **UV radiation** represents the portion of the spectrum of electromagnetic radiation just above the visible range. It contains increasingly energetic rays that are powerful enough to disrupt intracellular bonds and cause sunburn and increase chances of skin cancer.

3. Chemical injury

- **Chemicals capable of damaging cells are everywhere around us**:

➢Air and water pollution contain chemicals capable of tissue injury

➢Tobacco smoke

➢Some processed or preserved foods.

➢Gases such as carbon monoxide (CO)

➢Insecticides

➢Trace metals such as lead

➢Drugs (ethanol, prescription drugs, over the counter drugs, and street drugs are capable of directly or indirectly damaging tissues)

➢Oxygen at high partial pressure is poisonous; affect the membrane permeability, osmotic homeostasis, integrity of enzymes

4. Injury From Biologic Agents

- These agents range from submicroscopic viruses to the larger parasites.
- Biologic agents differ from other injurious agents in that they are able to replicate and can continue to produce their injurious effects.
- Biologic agents injure cells by diverse mechanisms. Viruses enter the cell and become incorporated into its DNA synthetic machinery. Certain bacteria elaborate exotoxins that interfere with cellular production of ATP. Other bacteria, such as the gram-negative bacilli, release endotoxins that cause cell injury and increased capillary permeability.

5. Injury from nutritional imbalances

- Nutritional excesses and nutritional deficiencies predispose cells to injury.
- Obesity and diets high in saturated fats are thought to predispose persons to atherosclerosis
- Dietary deficiencies can occur in the form of starvation, in which there is a deficiency of all nutrients and vitamins, or because of a selective deficiency of a single nutrient or vitamin
- Iron-deficiency anemia, scurvy, beriberi, and pellagra are examples of injury caused by the lack of specific vitamins or minerals.

Mechanisms of Cell Injury

- There are at least **three major mechanisms** whereby most injurious agents exert their effects:

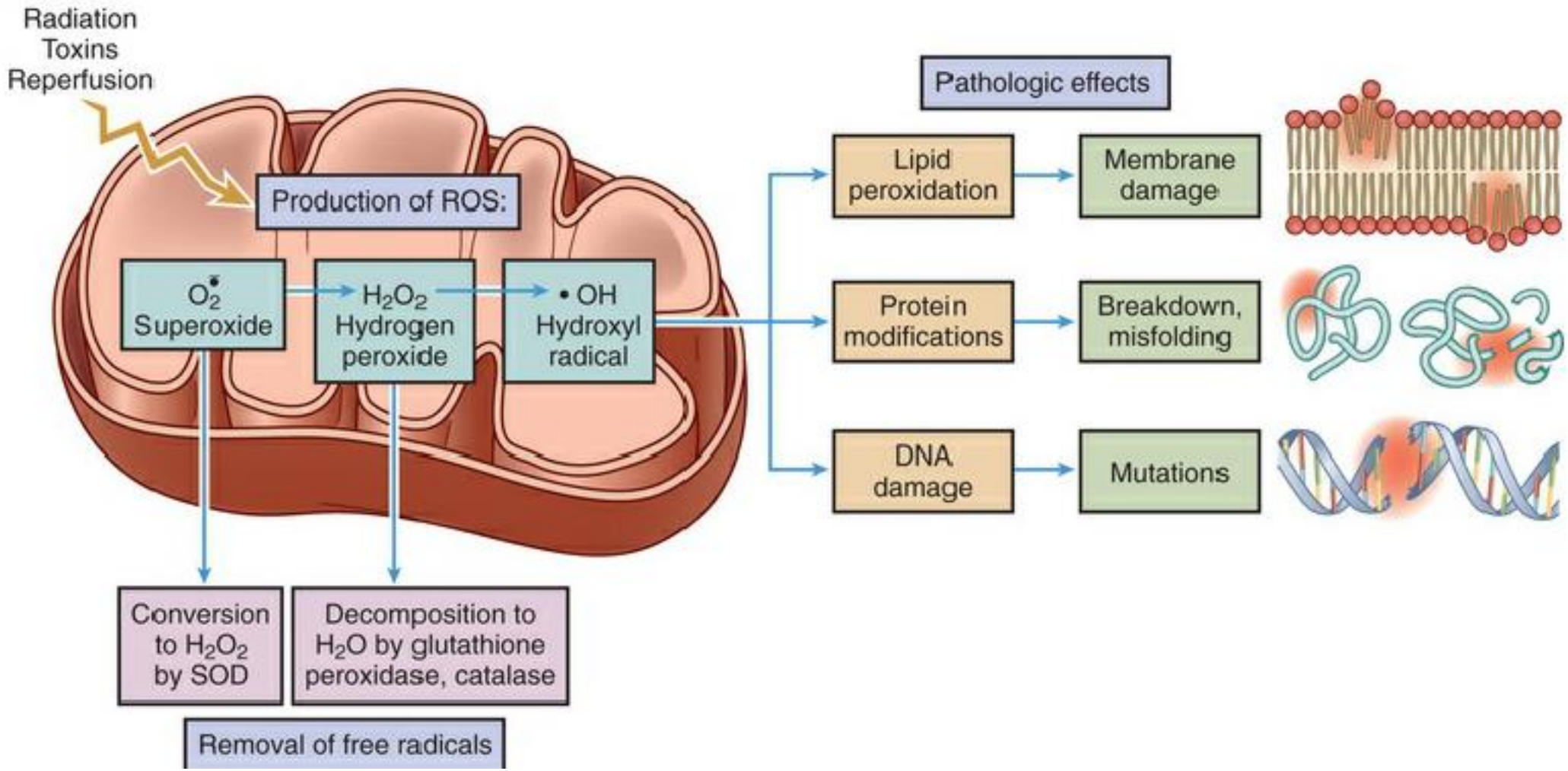
➢ Free radical formation

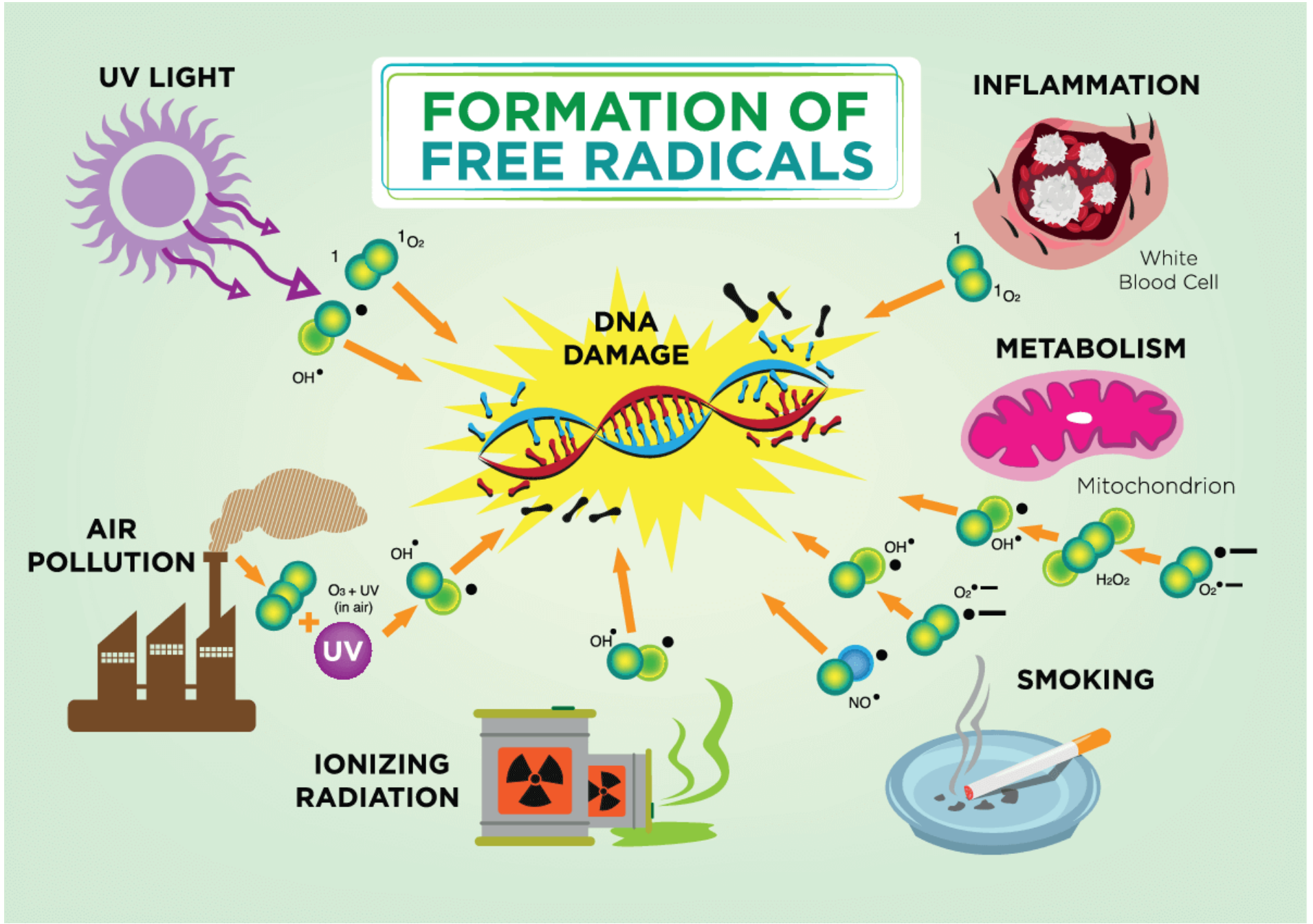
➢ Hypoxia and ATP depletion

➢ Disruption of intracellular calcium homeostasis

Free radical formation

- It is a highly reactive chemical species (also called reactive oxygen species) arising from an atom that has a single unpaired electron in an outer orbit. the radical is highly unstable and can enter reactions with cellular constituents, particularly key molecules in cell membranes and nucleic acids.
- Free radical formation is a by-product of many normal cellular reactions in the body, including energy generation, breakdown of lipids and proteins, and inflammatory processes
- Uncontrolled free radical production causes damage to cell membranes, cross-linking of cell proteins, inactivation of enzyme systems, or damage to the nucleic acids that make up DNA.
- Exogenous sources of free radicals include tobacco smoke, certain pollutants and organic solvents, pesticides, and radiation. Some of these compounds and certain medications are metabolized to free radical intermediates that cause oxidative damage to target tissues.


Radiation
Toxins
Reperfusion
Production of ROS:
$O_2^{\bullet}$ Superoxide
H_2O_2 Hydrogen peroxide
• OH Hydroxyl radical
Conversion to H_2O_2 by SOD
Decomposition to H_2O by glutathione peroxidase, catalase
Removal of free radicals
Pathologic effects
Lipid peroxidation
Membrane damage
Protein modifications
Breakdown, misfolding
DNA damage
Mutations


FORMATION OF FREE RADICALS
UV LIGHT
INFLAMMATION
White Blood Cell
DNA DAMAGE
METABOLISM
Mitochondrion
AIR POLLUTION
O_3 + UV (in air)
UV
IONIZING RADIATION
SMOKING
$^1O_2$
OH•
NO•
$O_2^{\bullet-}$
H_2O_2

Hypoxia and ATP depletion

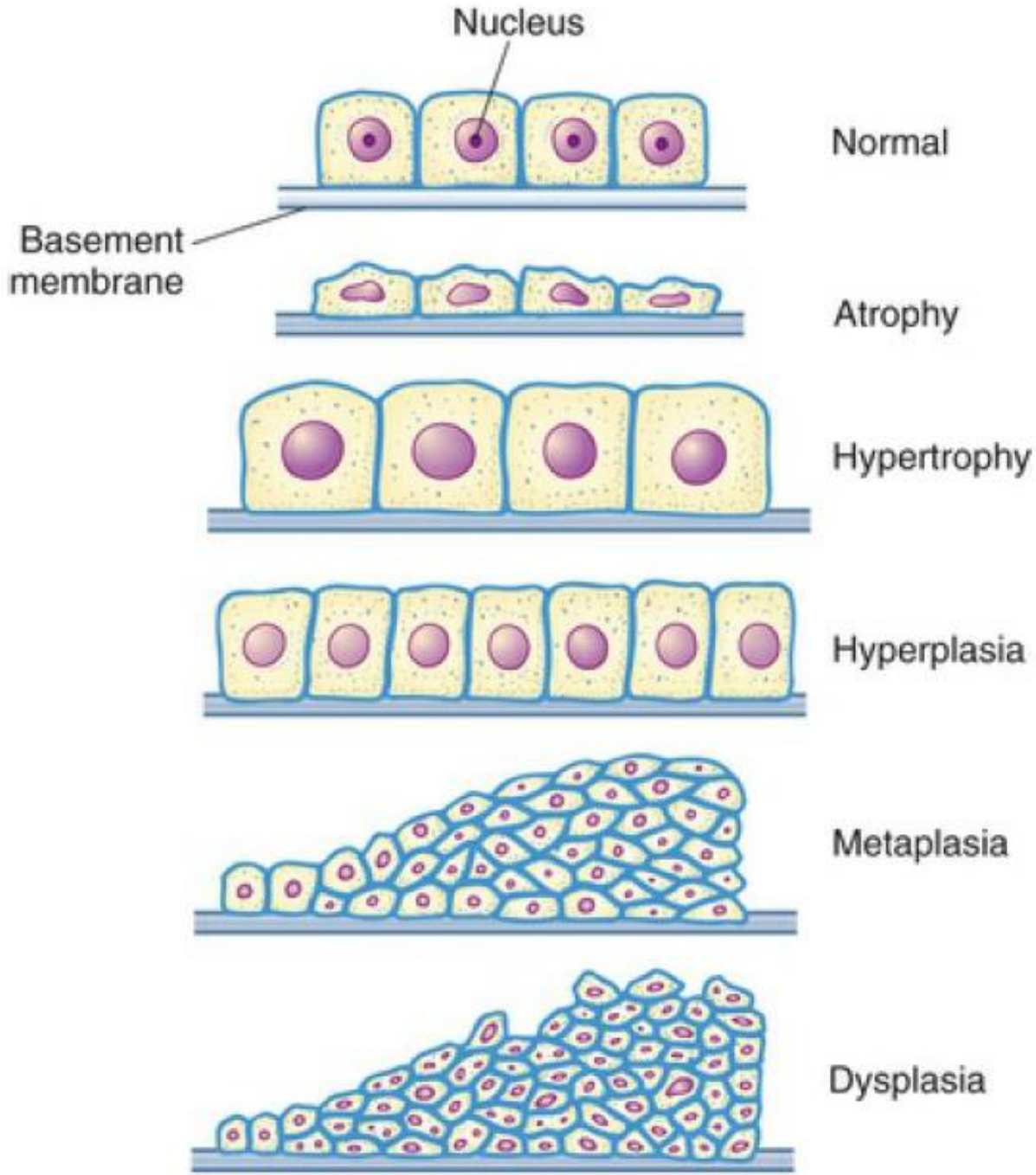
- Hypoxia (lack of sufficient oxygen) is the single most common mechanism of cellular injury.
- Hypoxia can result from **ischemia** (reduced blood supply), a reduced amount of oxygen in the air, loss of hemoglobin or hemoglobin function, decreased production of red blood cells, consequences of respiratory and cardiovascular system diseases, and poisoning of the oxidative enzymes (cytochromes) within the cells.
- Hypoxia can induce inflammation, and inflamed lesions can become hypoxic
- Hypoxia literally causes a power failure in the cell. As oxygen tension in the cell falls, oxidative metabolism ceases, and the cell reverts to anaerobic metabolism, using its limited glycogen stores to maintain vital cell functions. Cellular pH falls as lactic acid accumulates in the cell. This reduction in pH can have profound effects on intracellular structures. It will eventually lead to ATP depletion

Disruption of intracellular calcium homeostasis

- Calcium functions as a messenger for the release of many intracellular enzymes. Normally, intracellular calcium levels are kept extremely low compared with extracellular level by energy-dependent, membrane-associated calcium/magnesium (Ca^{2+}/Mg^{2+}) ATPase exchange systems.
- Ischemia and certain toxins lead to an increase in cytosolic calcium because of increased influx across the cell membrane and the release of calcium stored in the mitochondria and endoplasmic reticulum.
- The increased calcium level activates several enzymes with potentially damaging effects. The enzymes include the phospholipases responsible for damaging the cell membrane, proteases that damage the cytoskeleton and membrane proteins, ATPases that break down ATP and hasten its depletion, and endonucleases that fragment chromatin

Cellular Adaptation

- Cells adapt to their environment to escape and protect themselves from injury. An adapted cell is neither normal nor injured—its condition lies between these two states.
- Adaptations are **reversible changes** in cell size, number, phenotype, metabolic activity, or functions of cells.
- The most significant adaptive changes in cells include **atrophy** (decrease in cell size), **hypertrophy** (increase in cell size), **hyperplasia** (increase in cell number), and **metaplasia** (reversible replacement of one mature cell type by another less mature cell type or a change in the phenotype).
- Dysplasia (deranged cellular growth) is not considered a true cellular adaptation but rather an atypical hyperplasia


Nucleus
Basement membrane
Normal
Atrophy
Hypertrophy
Hyperplasia
Metaplasia
Dysplasia

Atrophy

- Atrophy is a decrease or shrinkage in cellular size. If atrophy occurs in a sufficient number of an organ's cells, the entire organ shrinks or becomes atrophic.
- Atrophy can affect any organ, but it is most common in skeletal muscle, the heart, secondary sex organs, and the brain
- Atrophy can be classified as physiologic or pathologic. Physiologic atrophy can occur with early development. For example, the thymus gland undergoes physiologic atrophy during childhood. It can also occur with aging, brain cells become atrophic and endocrine-dependent organs, such as the gonads, shrink as hormonal stimulation decreases.
- Pathologic atrophy can be grouped based on cause into five categories:

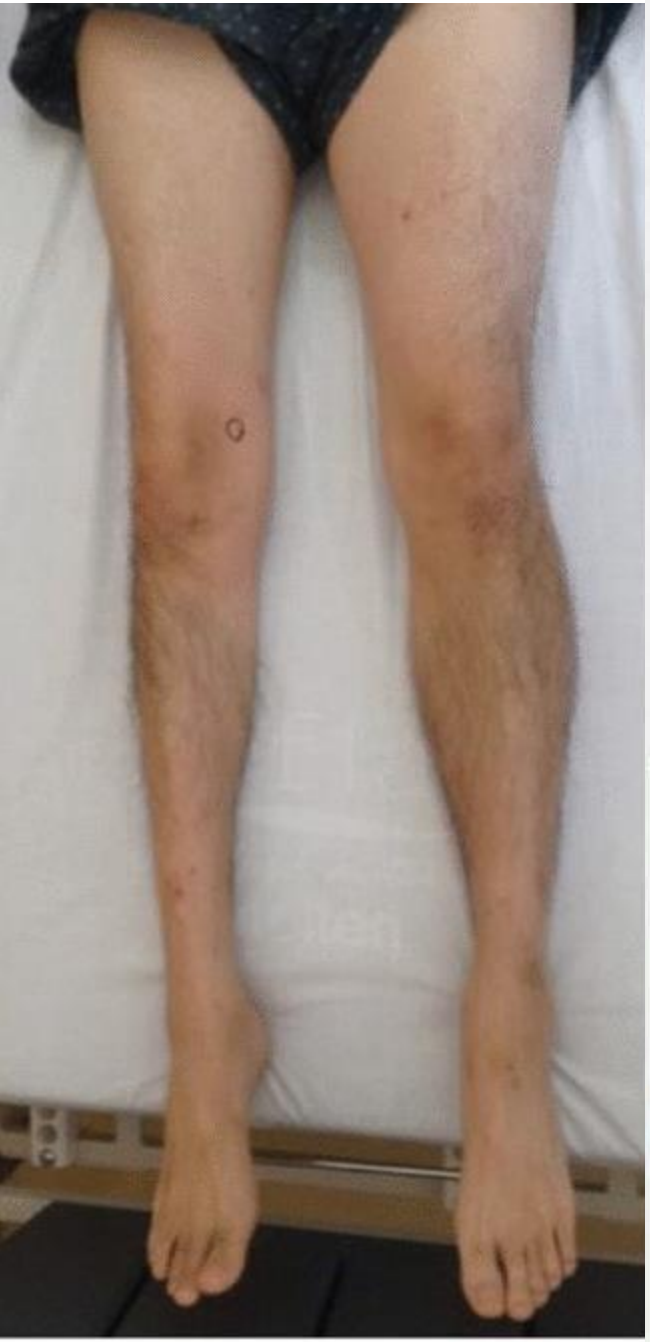
(1) disuse, (2) denervation, (3) loss of endocrine stimulation, (4) inadequate nutrition, and (5) ischemia

Pathologic atrophy

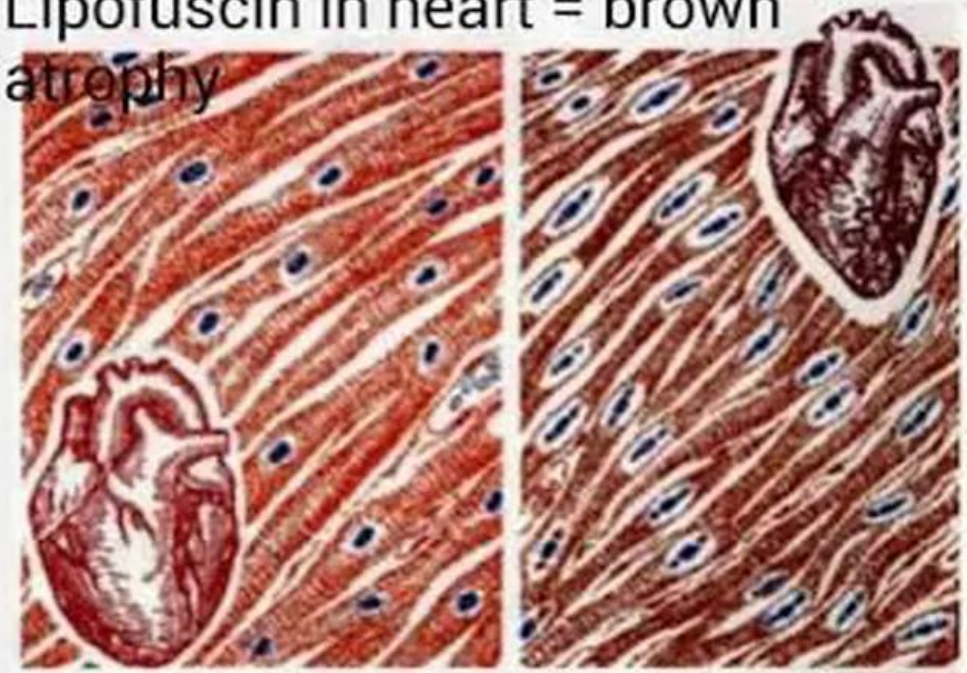
- Disuse atrophy occurs when there is a reduction in skeletal muscle use. example of disuse atrophy is seen in the muscles of extremities that have been encased in plaster casts. Because atrophy is adaptive and reversible, muscle size is restored after the cast is removed and muscle use is resumed.
- Denervation atrophy is a form of disuse atrophy that occurs in the muscles of paralyzed limbs.
- Lack of endocrine stimulation produces a form of disuse atrophy. In women, the loss of estrogen stimulation during menopause results in atrophic changes in the reproductive organs.
- With malnutrition and decreased blood flow, cells decrease their size and energy requirements as a means of survival.

Atrophy

- The atrophic muscle cell contains less endoplasmic reticulum (ER) and fewer mitochondria and myofilaments than does the normal cell
- The mechanisms of atrophy include decreased protein synthesis or increased protein degradation, or both.
- The degradation of proteins occurs mainly by the ubiquitin proteosome pathway
- Ubiquitin Proteasome System program is a multicomponent system that identifies and degrades unwanted proteins in the cytoplasm of all cells.
- In many situations, atrophy is also accompanied by increased autophagy, in which the starved cell eats its own components in an attempt to find nutrients and survive

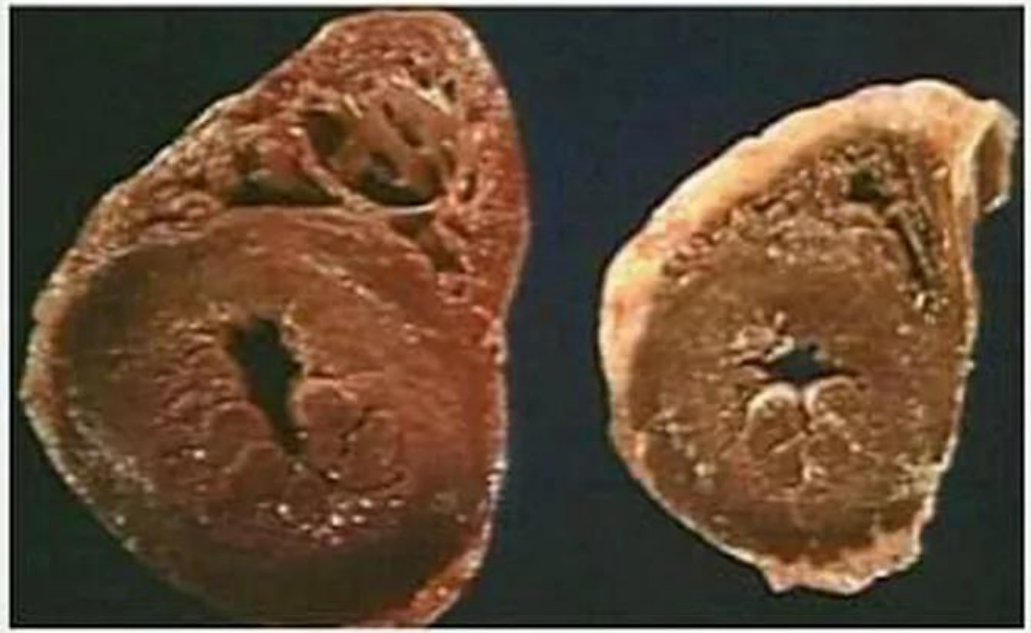


Lipofuscin in heart = brown atrophy



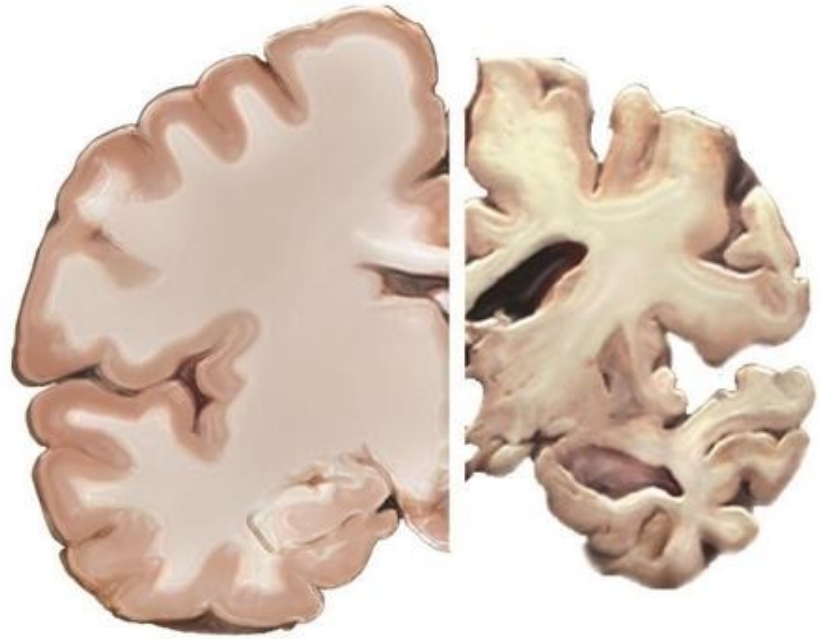
normal heart

Brown atrophy of the heart



Healthy Brain

Brain Atrophy

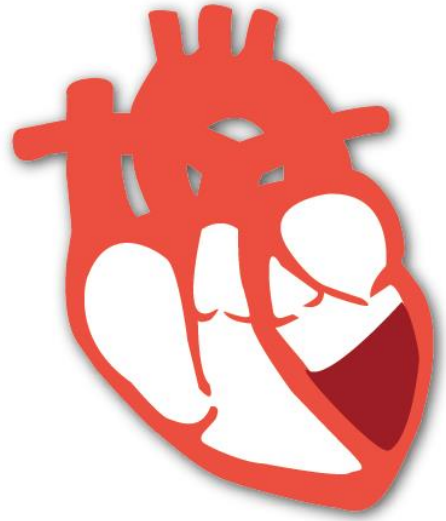


Hypertrophy

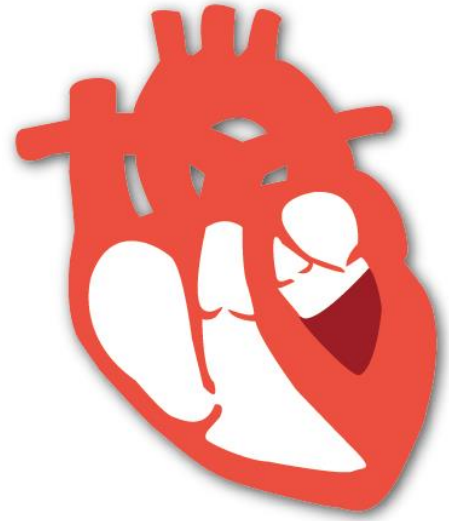
- Hypertrophy is an increase in the size of cells by increasing the amount of structural proteins and organelles. Thus, increases the size of the affected organ without increasing the number of these cells (the cells cannot be divided)
- The cells of the heart and kidneys are particularly responsive to enlargement.
- Hypertrophy can be physiologic or pathologic.
- Physiologic hypertrophy caused by increased demand, stimulation by hormones, and growth factors.
- Physiologic hypertrophy in avid weightlifter who develop a rippled physique only by hypertrophy of individual skeletal muscle cells induced by an increased workload. Pregnancy is an example of physiologic hypertrophy and hormone-induced uterine enlargement.

Pathologic hypertrophy

- Pathologic hypertrophy occurs as the result of disease conditions and may be adaptive or compensatory.
- Examples of adaptive hypertrophy are the thickening of the urinary bladder from long-continued obstruction of urinary outflow, and the myocardial hypertrophy that results from valvular heart disease or hypertension.
- Compensatory hypertrophy is the enlargement of a remaining organ or tissue after a portion has been surgically removed or rendered inactive. For instance, if one kidney is removed, the remaining kidney enlarges to compensate for the loss.
- Prolonged cardiac hypertrophy progresses to contractile dysfunction, decompensation, and finally heart failure. If not treated, it will result in death.



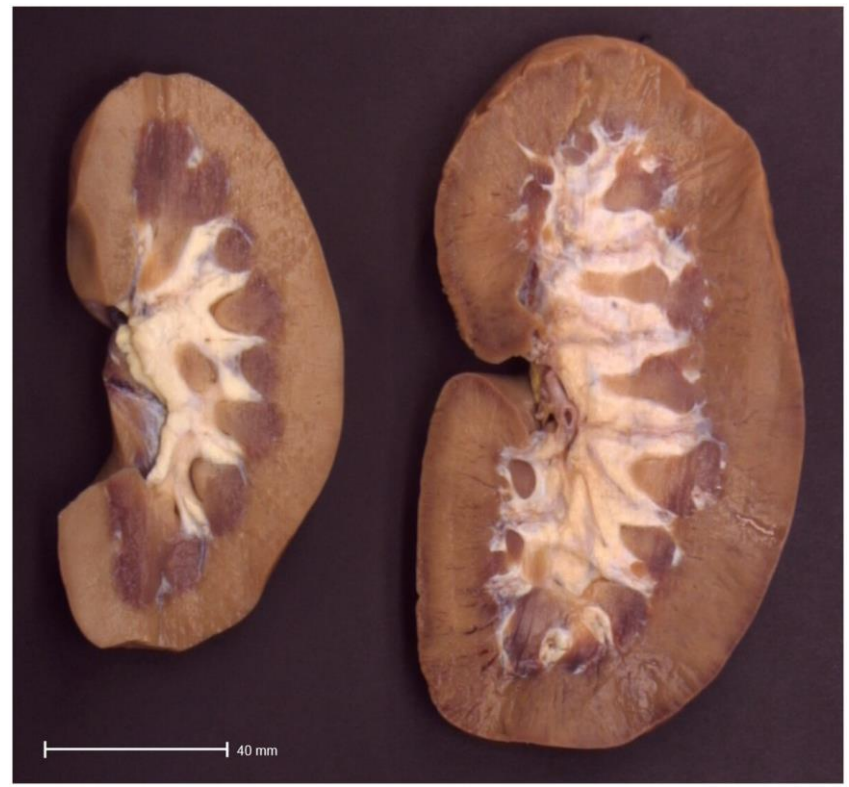
Normal



Thicker Walls

Less blood

Left Ventricular Hypertrophy



Hyperplasia

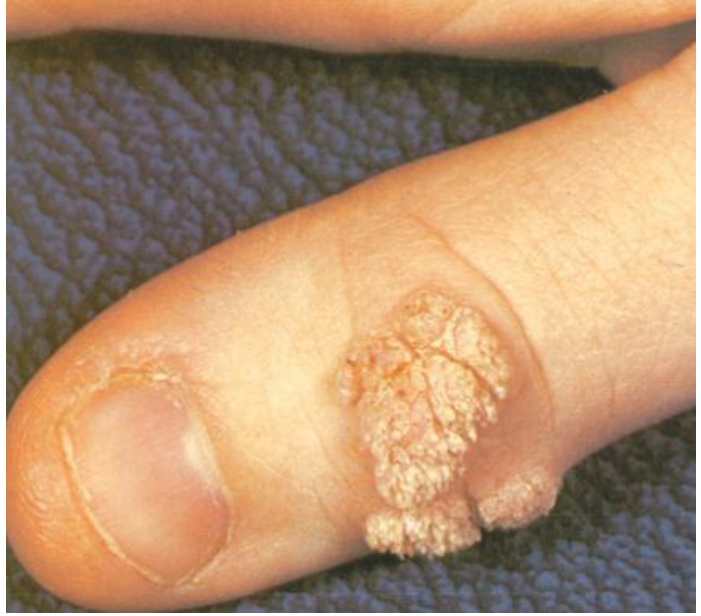
- Hyperplasia is an increase in the number of cells in an organ or tissue resulting from an increased rate of cellular division. Hyperplasia occurs as a response to injury that results when the injury has been severe and prolonged.
- The main mechanism for hyperplasia is the production of growth factors, which stimulate the remaining cells (after cell loss or injury) to synthesize new cell components and, ultimately, to divide. Another mechanism is increased output of new cells from tissue stem cells. For example, if liver cells are compromised, new cells can regenerate from intrahepatic stem cells.
- Hyperplasia and hypertrophy can occur together
- It occurs in tissues with cells that are capable of mitotic division, such as the epidermis, intestinal epithelium, and glandular tissue
- Hyperplasia can be physiologic or pathologic.

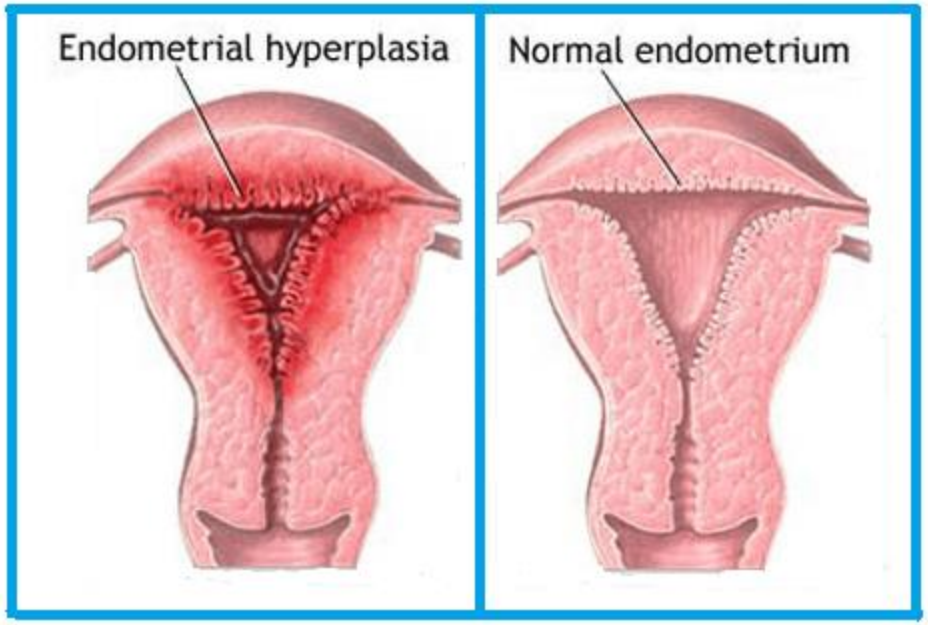
Physiologic hyperplasia

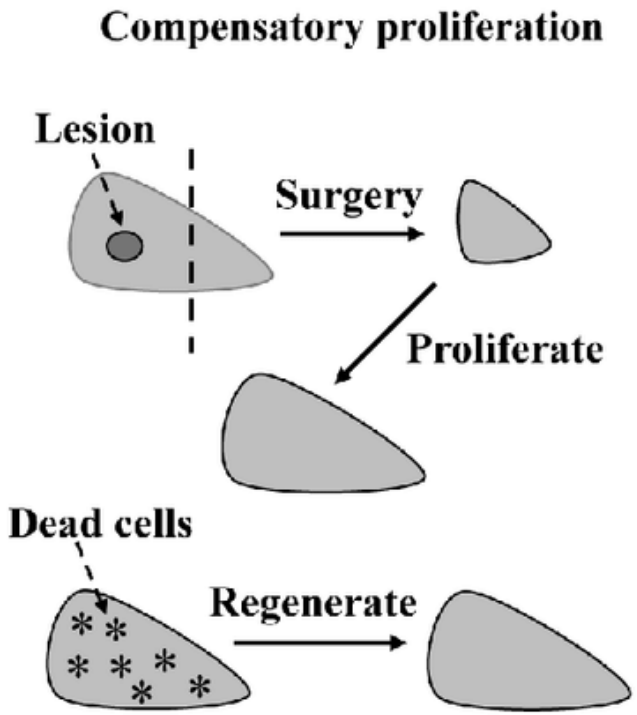
- There are two types of physiologic hyperplasia: compensatory hyperplasia and hormonal hyperplasia.
- **Compensatory hyperplasia** is an adaptive mechanism that enables certain organs to regenerate. For example, removal of part of the liver leads to hyperplasia of the remaining liver cells (hepatocytes) to compensate for the loss. Another example is the response to wound healing as part of the inflammation process
- **Hormonal hyperplasia** occurs chiefly in estrogen-dependent organs, such as the uterus and breast. After ovulation, for example, estrogen stimulates the endometrium to grow and thicken for reception of the fertilized ovum. If pregnancy occurs, hormonal hyperplasia, as well as hypertrophy, enables the uterus to enlarge.

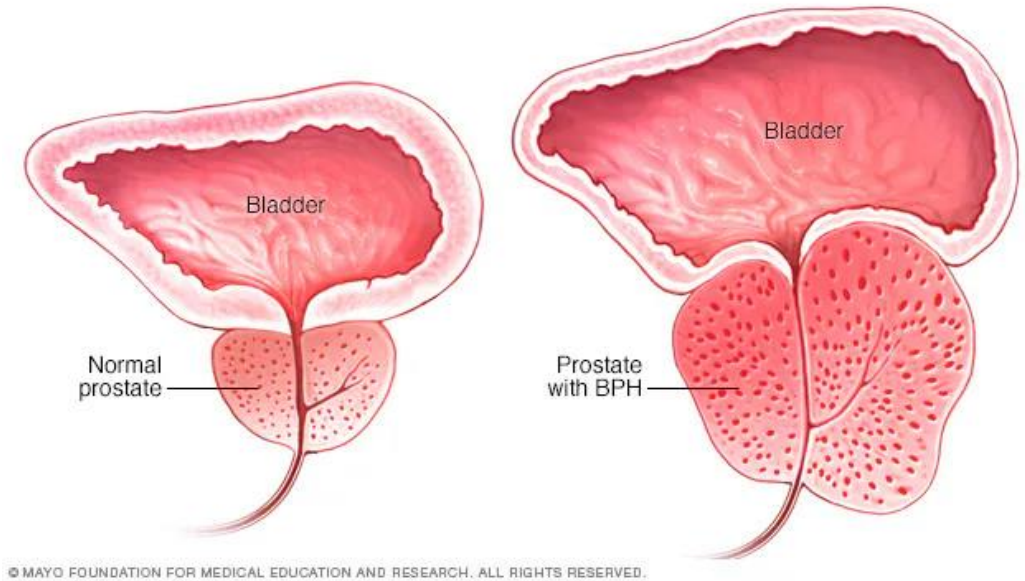
Pathologic hyperplasia

- Pathologic hyperplasia is the abnormal proliferation of normal cells and can occur as a response to excessive hormonal stimulation or the effects of growth factors on target cells
- The most common example is pathologic hyperplasia of the endometrium, which is caused by an imbalance between estrogen and progesterone levels with relative increases of estrogen. Pathologic endometrial hyperplasia, which causes excessive menstrual bleeding, is under the influence of regular growth-inhibition controls. If these controls fail, hyperplastic endometrial cells can undergo malignant transformation
- Benign prostatic hyperplasia, which is a common disorder of men older than 50 years, is thought to be related to the synergistic action of estrogen and androgens
- Skin warts are an example of hyperplasia caused by growth factors produced by the human papillomaviruses




Endometrial hyperplasia
Normal endometrium


Compensatory proliferation
Lesion
Surgery
Proliferate
Dead cells
Regenerate


Bladder
Normal prostate
Bladder
Prostate with BPH
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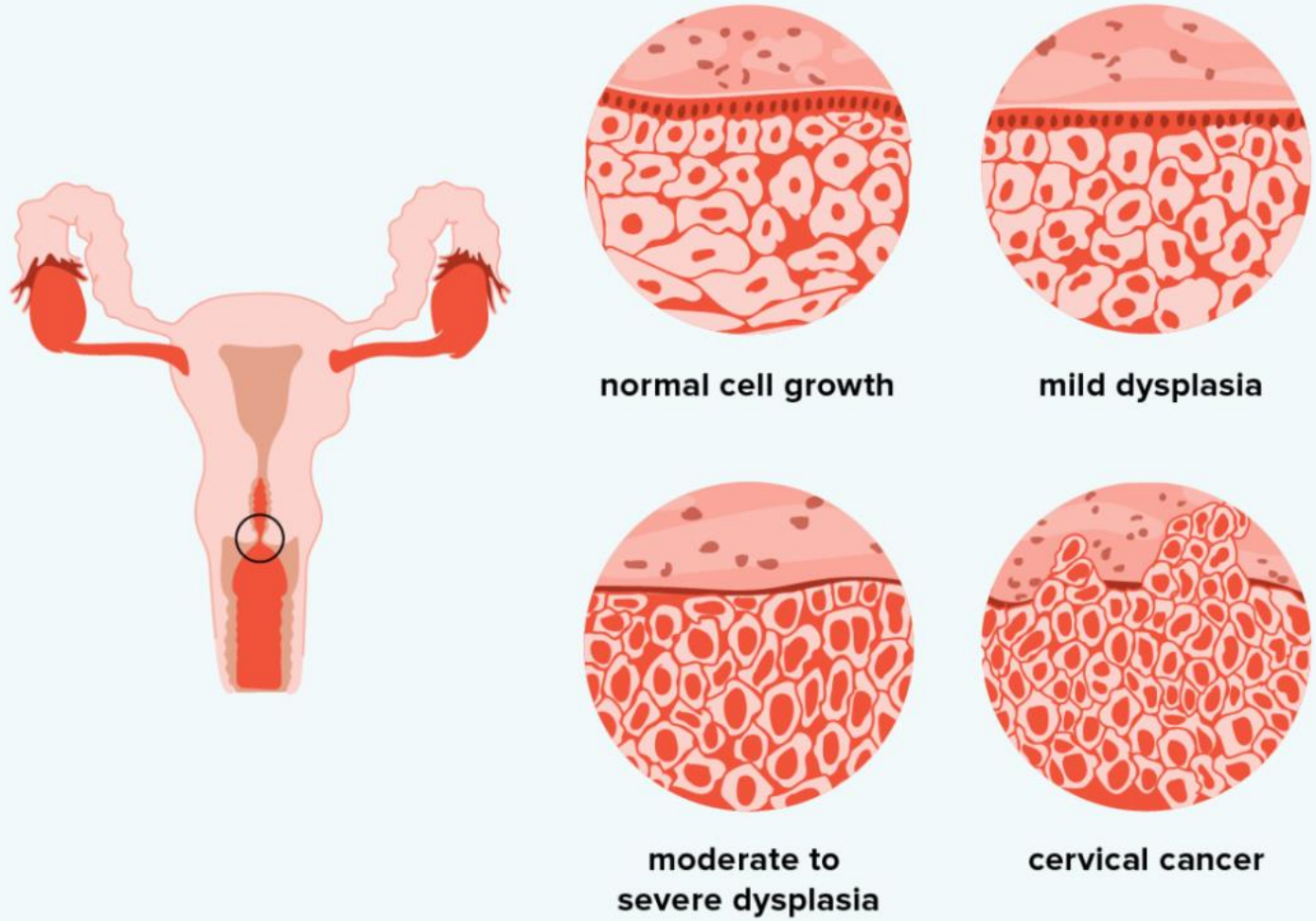
Dysplasia

- Dysplasia refers to abnormal changes in the size, shape, and organization of mature cells. Dysplasia is not considered a true adaptive process but is related to hyperplasia and is often called atypical hyperplasia.
- The architecture of the dysplastic tissue can be disorderly. Minor degrees of dysplasia are associated with chronic irritation or inflammation. The pattern is most frequently encountered in metaplastic squamous epithelium of the respiratory tract and uterine cervix
- Dysplasia is strongly implicated as a precursor of cancer. However, it may or may not progress to cancer.
- Dysplasia that do not involve the entire thickness of epithelium may be completely reversible.
- When dysplastic changes penetrate the basement membrane it is considered a preinvasive neoplasm and is known as carcinoma *in situ*.

Cervical Dysplasia

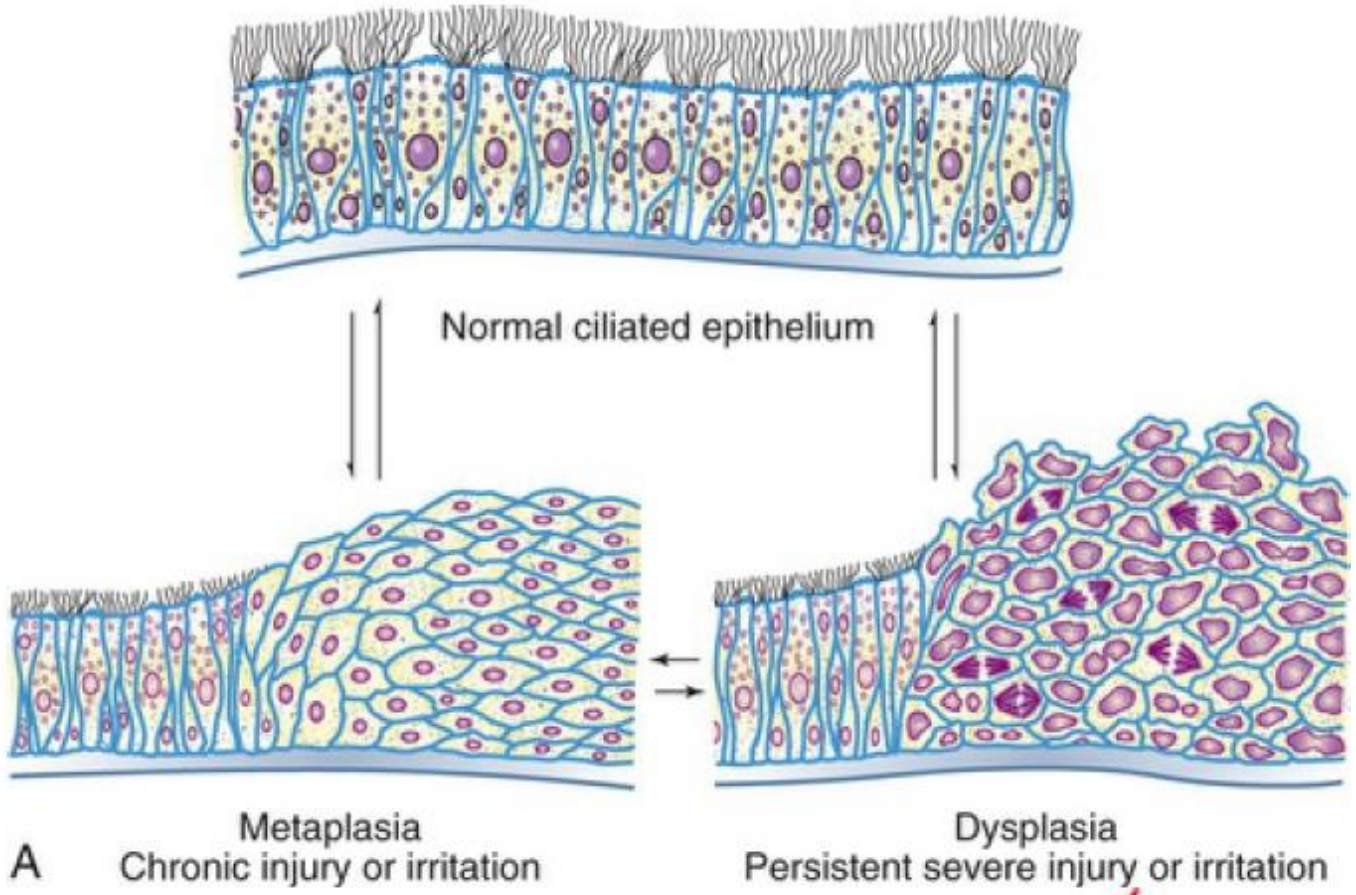
Abnormal cell growth in the cervix

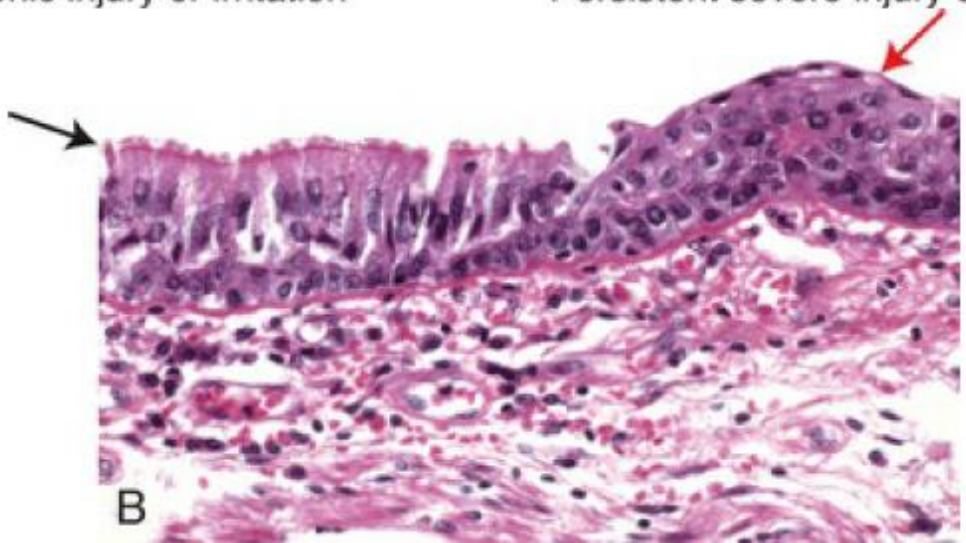


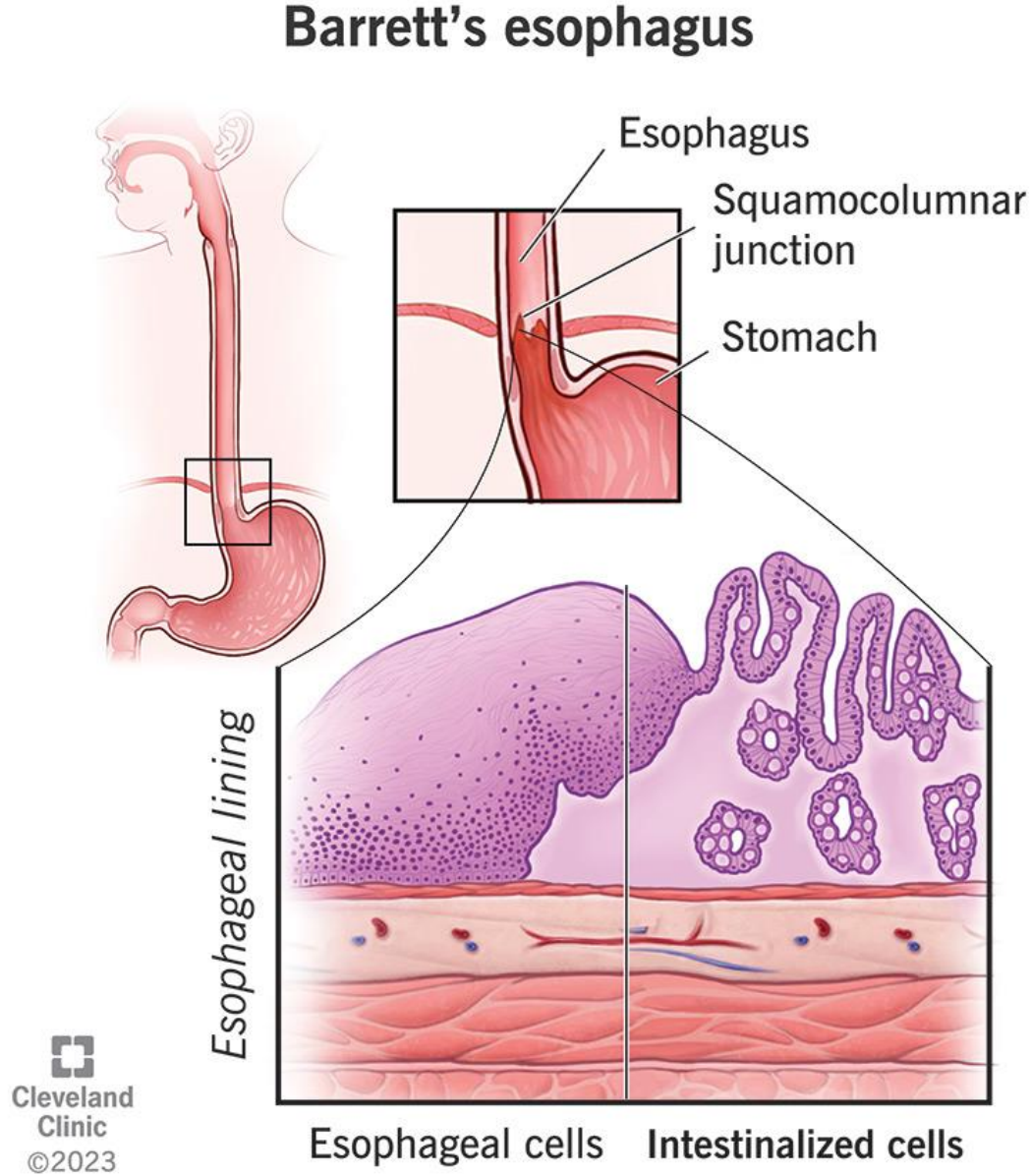
healthline

Metaplasia

- Metaplasia is the reversible replacement of one mature cell type (epithelial or mesenchymal) by another, less differentiated, cell type.
- Sometimes, the adaptive replacement cell type may be more suitable to the changed conditions in the surrounding environment. For example, gastroesophageal reflux damages squamous epithelium of the esophagus, and the adapted change or replacement by glandular epithelium may better tolerate the acidic environment.
- The change is not always beneficial. In the long-term cigarette smoker, the chronic irritation from the smoke causes the normal ciliated columnar epithelial cells of the trachea and bronchi to be replaced by stratified squamous epithelial cells. The newly formed squamous epithelial cells have better survival chances, but they do not secrete mucus or have ciliary clear the particulate matter, causing loss of a vital protective mechanism.
- Bronchial metaplasia can be reversed if the inducing stimulus is removed. If the inducing stimulus is persistent, it can initiate malignant transformation in the metaplastic epithelium.


Normal ciliated epithelium
Metaplasia
Chronic injury or irritation
Dysplasia
Persistent severe injury or irritation
A


B


Barrett's esophagus
Esophagus
Squamocolumnar junction
Stomach
Esophageal lining
Esophageal cells
Intestinalized cells
Cleveland Clinic
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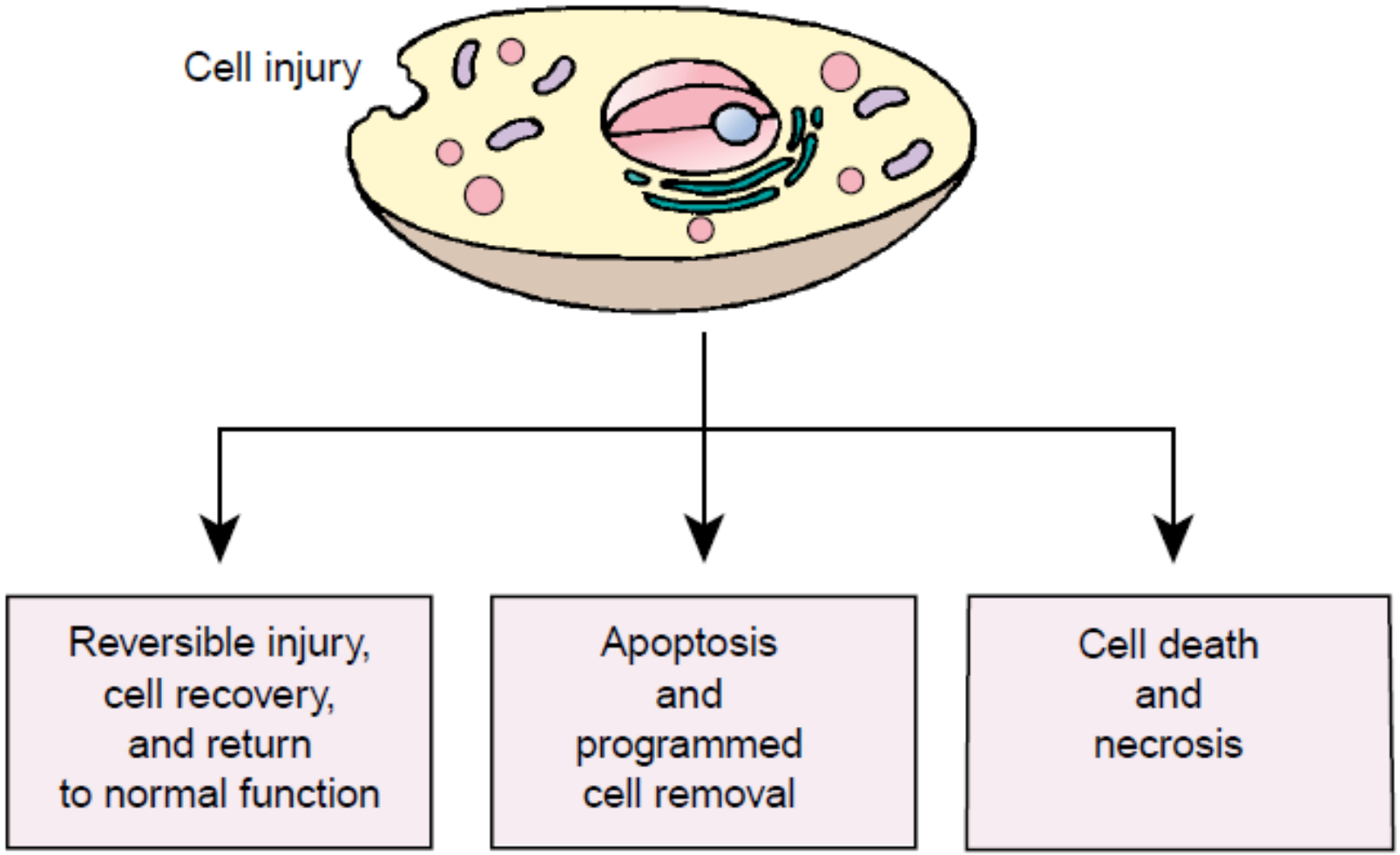
Reversible Cell Injury and Cell Death



Reversible Cell Injury

- Reversible cell injury, although impairing cell function, does not result in cell death.
- Two patterns of reversible cell injury can be observed under the microscope: cellular swelling and fatty change.
- Cellular swelling occurs with impairment of the energy-dependent Na^+/K^+ ATPase membrane pump, usually as the result of hypoxic cell injury.
- Fatty changes are linked to intracellular accumulation of fat. When fatty changes occur, small vacuoles of fat disperse throughout the cytoplasm

Apoptosis

- Apoptosis (cell suicide or programmed cell death) is a form of cell death in which a programmed sequence of events leads to the elimination of cells without releasing harmful substances into the surrounding area
- It involves controlled cell destruction and is required in normal cell deletion and renewal. For example, blood cells which undergo constant renewal from precursor cells in the bone marrow are removed by apoptotic cell death.
- Apoptotic cell death eliminates cells that are worn out, have been produced in excess, have developed improperly, or have genetic damage.

Apoptosis

- Apoptotic cell death is characterized by controlled autodigestion of cell components.
- Cells appear to initiate their own death through the activation of endogenous enzymes. This results in cell shrinkage brought about by disruption of the cytoskeleton, condensation of the cytoplasmic organelles, disruption and clumping of nuclear DNA, and a distinctive wrinkling of the cell membrane.
- As the cell shrinks, the nucleus breaks into spheres, and the cell eventually divides into membrane covered fragments.
- During the process, membrane changes occur, signaling surrounding phagocytic cells to engulf the cell fragments and complete the degradation process (no inflammation)

Apoptosis

- Apoptosis can be linked to several physiological process. Such as, the separation of the webbed fingers and toes of the developing embryo, the control of immune cell numbers and destruction of autoreactive T cells in the thymus, the hormone dependent involution of endometrial cells during the menstrual cycle and in the regression of breast tissue after weaning from breast-feeding
- Apoptosis also involved in pathological process. Such as, neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Also, In hepatitis B and C, the virus seems to sensitize the hepatocytes to apoptosis. Certain oncogenes and suppressor genes involved in the development of cancer seem to play an active role in stimulation or suppression of apoptosis. Injured cells may induce apoptotic cell death through increased cytoplasmic calcium, which leads to activation of nuclear enzymes that break down DNA

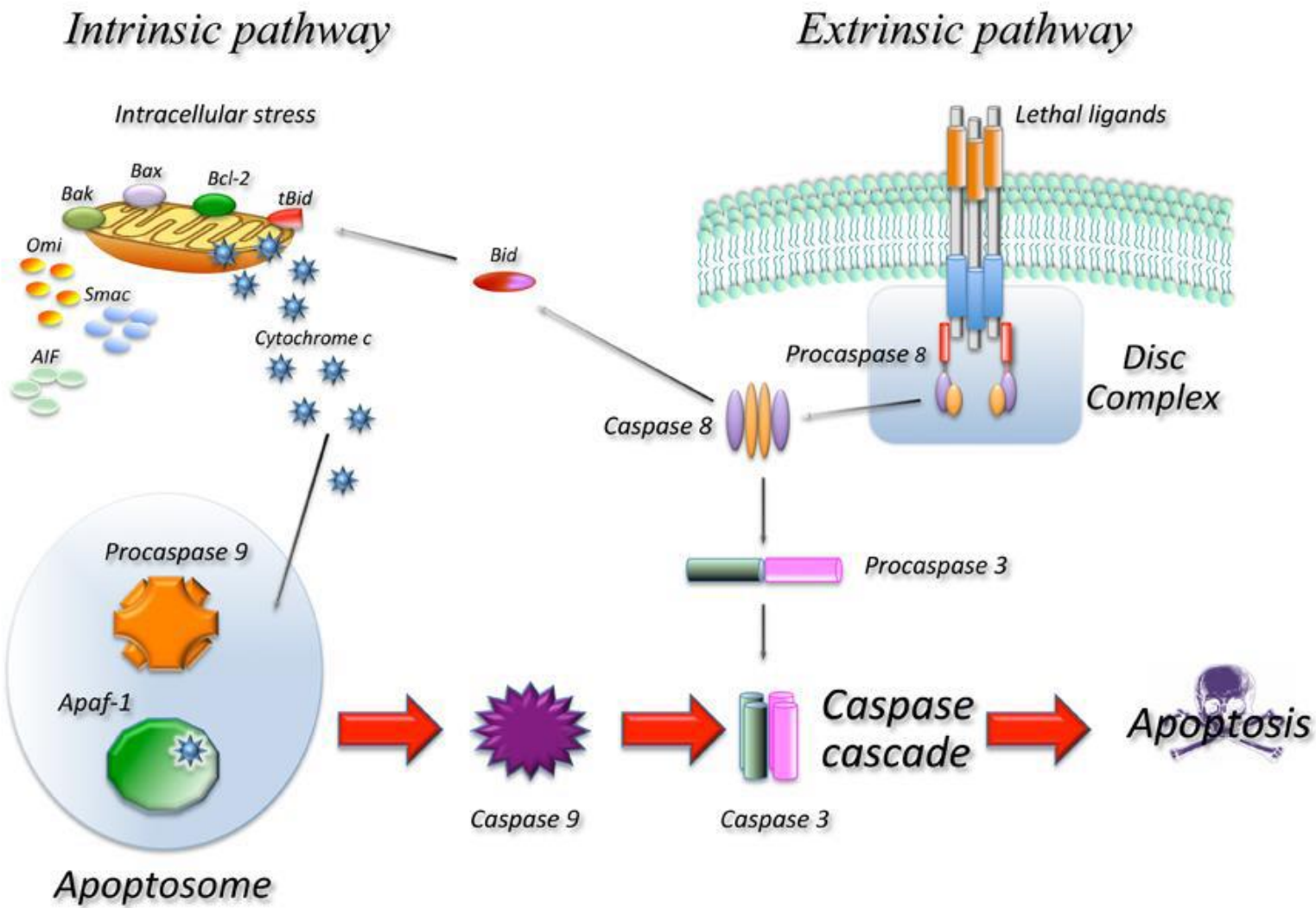
Apoptosis

- **It is initiated by two pathways**:

1. **Mitochondrial (intrinsic) pathway** is triggered by Loss of survival signals, DNA damage beyond repair, accumulation of misfolded proteins (ER stress). E.g Aging, cystic fibrosis and Neurodegenerative Diseases.

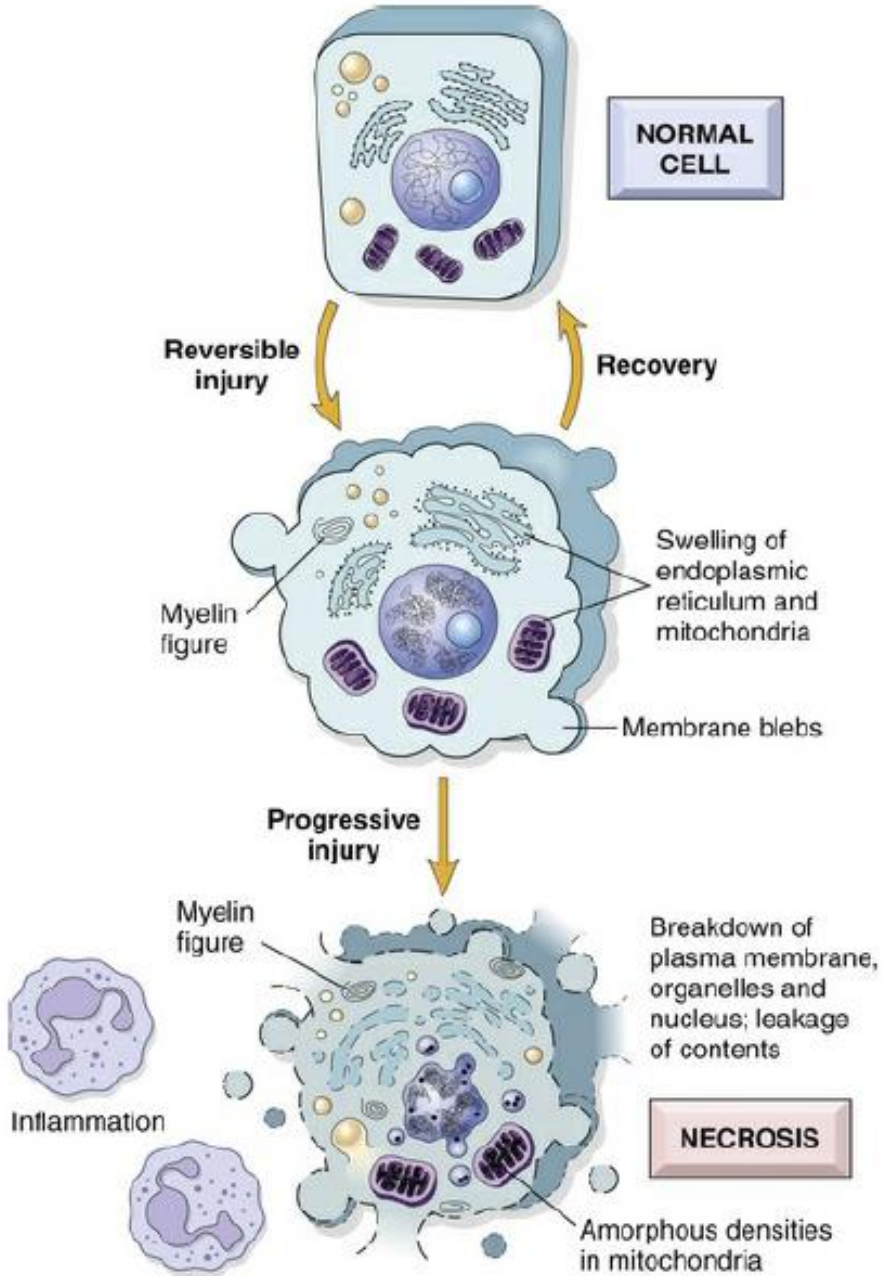
All these will lead to leakage of pro-apoptotic proteins from mitochondrial membrane into the cytoplasm and Trigger Caspase activation

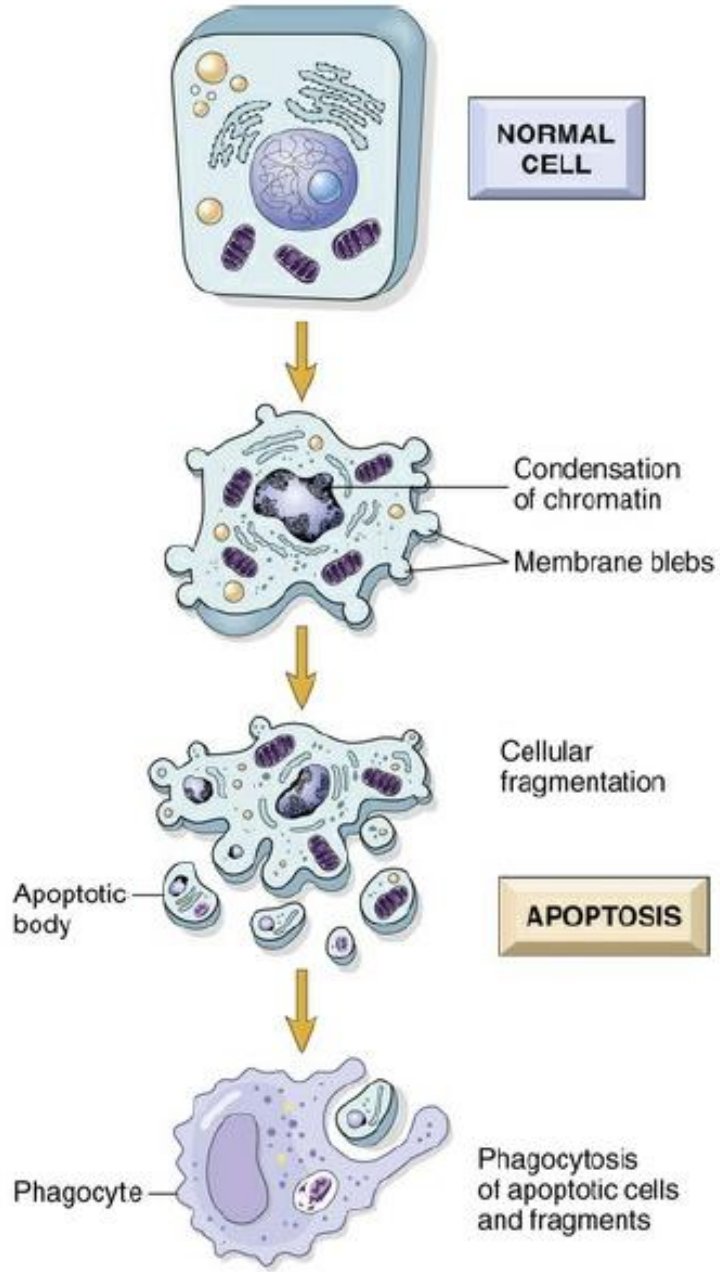
2- **Death receptor (extrinsic) pathway** is responsible for elimination of self-reactive lymphocytes and damage by cytotoxic T lymphocytes. It is initiated by engagement of death receptors (members of the Tumor necrotizing factor (TNF) receptor family) by ligands on adjacent cells.


Intrinsic pathway
Extrinsic pathway
Intracellular stress
Bax
Bak
Bcl-2
tBid
Omi
Smac
AIF
Cytochrome c
Bid
Lethal ligands
Procaspase 8
Disc
Complex
Caspase 8
Procaspase 3
Procaspase 9
Apaf-1
Apoptosome
Caspase 9
Caspase 3
Caspase
cascade
Apoptosis

Necrosis

- Necrosis is death of group of cells within a living body caused by an irritant
- Necrosis differs from apoptosis in that it involves unregulated enzymatic digestion of cell components, swelling, loss of cell membrane integrity with uncontrolled release of the products of cell death into the intracellular space, and initiation of the inflammatory response.
- Necrosis often interferes with cell replacement and tissue regeneration.


NORMAL CELL
Reversible injury
Recovery
Swelling of endoplasmic reticulum and mitochondria
Myelin figure
Membrane blebs
Progressive injury
Myelin figure
Breakdown of plasma membrane, organelles and nucleus; leakage of contents
Inflammation
NECROSIS
Amorphous densities in mitochondria


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

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

Types of necrosis

1. Coagulative necrosis:

occurs primarily in the kidneys, heart, and adrenal glands, commonly results from hypoxia caused by severe ischemia or hypoxia caused by chemical injury, especially ingestion of mercuric chloride.

Coagulation is caused by protein denaturation, which causes the protein albumin to change from a gelatinous, transparent state to a firm, opaque state, similar to that of a cooked egg white.

The necrotic tissues appear firm and slightly swollen. The area of coagulative necrosis is called an infarct

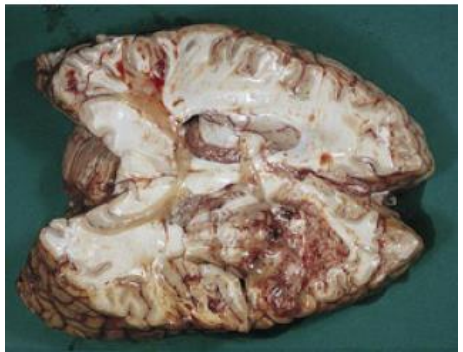
Coagulative necrosis of myocardium of posterior wall of left ventricle of heart. A large anemic (white) infarct is readily apparent

Types of necrosis

2. **Liquefactive necrosis**: commonly results from ischemic injury to neurons and glial cells in the brain. Dead brain tissue is readily affected by liquefactive necrosis because brain cells are rich in the digestive hydrolytic enzymes and lipids, and the brain contains little connective tissue.

As the cells are digested by their own hydrolases, the tissue becomes soft, liquefies, and is walled off from healthy tissue, forming cysts

Liquefactive necrosis can also result from bacterial infection (staphylococci, streptococci, and *Escherichia coli*). In this case the hydrolases are released from the lysosomes of neutrophils (phagocytes attracted to the infected area to kill the bacteria). Liquefaction of bacterial cells and neighboring tissue cells by neutrophilic hydrolases results in the accumulation of pus

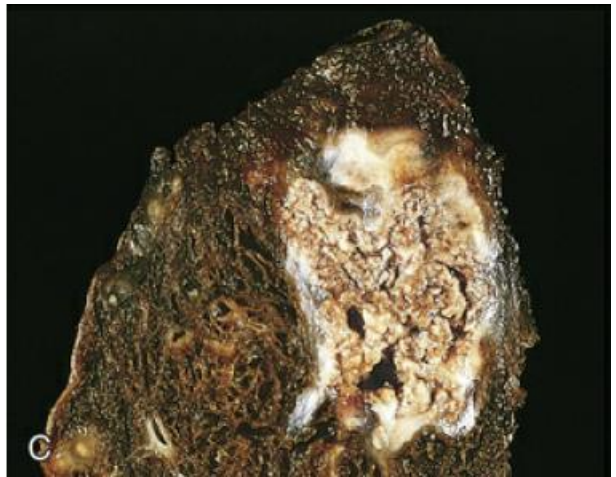


Liquefactive necrosis of the brain.
The area of infarction is softened as
a result of liquefactive necrosis

Types of necrosis

3. **Caseous necrosis**: commonly results from tuberculous pulmonary infection, particularly Mycobacterium tuberculosis, is a combination of coagulative and liquefactive necrosis

The dead cells disintegrate, but the debris is not digested completely by hydrolases. Tissues appear soft and granular and resemble clumped cheese, hence its name. A granulomatous inflammatory wall encloses areas of caseous necrosis.

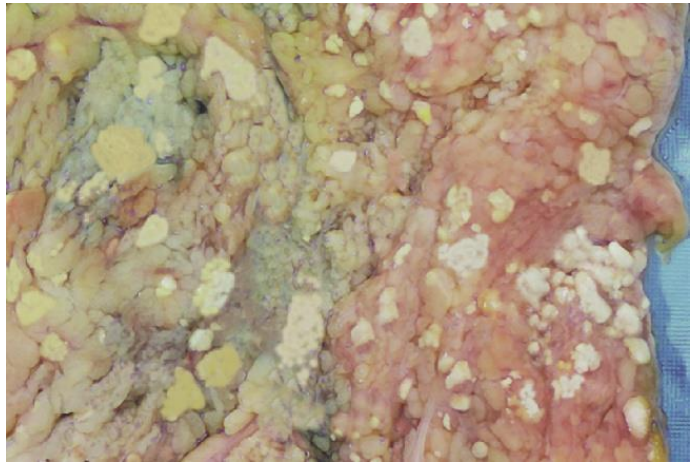


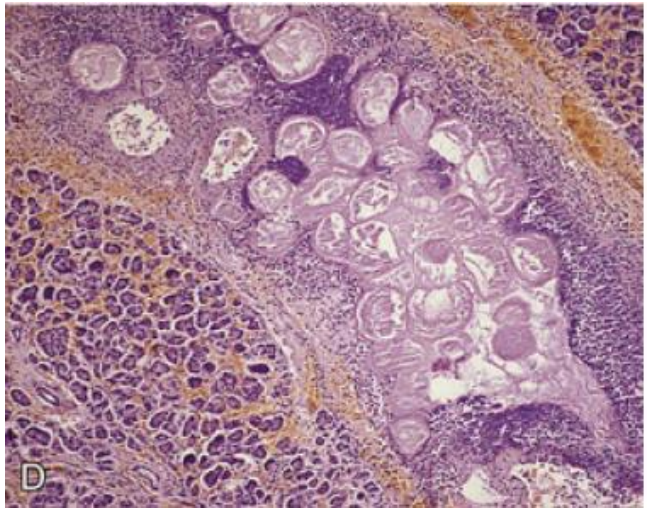
Tuberculosis of the lung, with a large area of caseous necrosis containing yellow-white and cheesy debris

Types of necrosis

4. **Fat necrosis**: occurs in the breast, pancreas, and other abdominal structures, is cellular dissolution caused by powerful enzymes called lipases.

Lipases break down triglycerides, releasing free fatty acids, which then combine with calcium, magnesium, and sodium ions, creating soaps (a process known as saponification). The necrotic tissue appears opaque and chalk white





Fat necrosis of pancreas. Interlobular adipocytes are necrotic; these are surrounded by acute inflammatory cells

Types of necrosis

5. **Gangrenous necrosis**: a term commonly used in surgical clinical practice, refers to death of tissue and results from severe hypoxic injury, commonly occurring because of arteriosclerosis, or blockage of major arteries, especially in the lower leg. With hypoxia and subsequent bacterial invasion, the tissues can undergo necrosis

It is classified as dry, wet, and gas gangrene

Dry gangrene is usually the result of coagulative necrosis. The skin becomes very dry and shrinks, resulting in wrinkles, and its color changes to dark brown or black

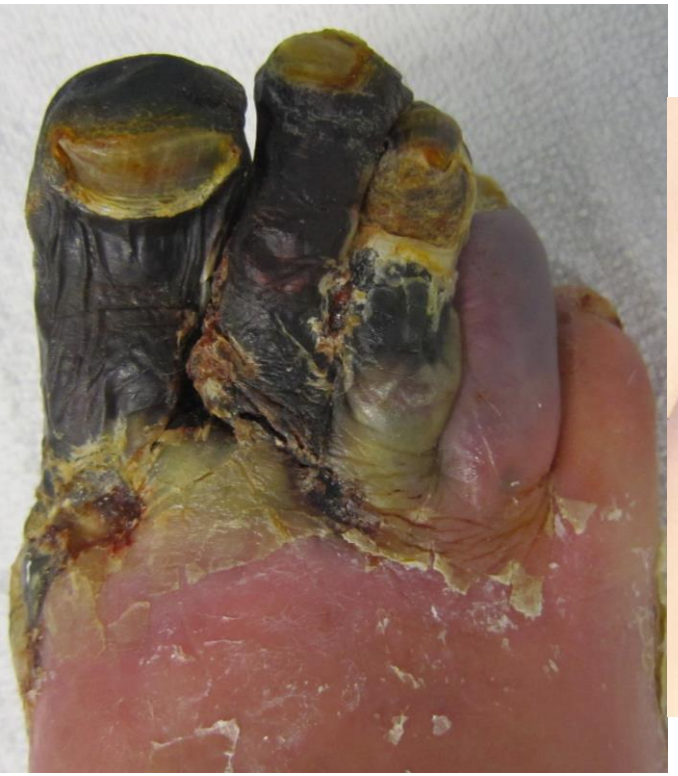
Wet gangrene develops when neutrophils invade the site, causing liquefactive necrosis. This usually occurs in internal organs and extremities unlike dry gangrene, causing the site to become cold, swollen, and black. A foul odor is present caused by bacterial action that produce pus, and if systemic symptoms become severe, death can ensue. Dry gangrene can be converted to wet gangrene by bacterial involvement

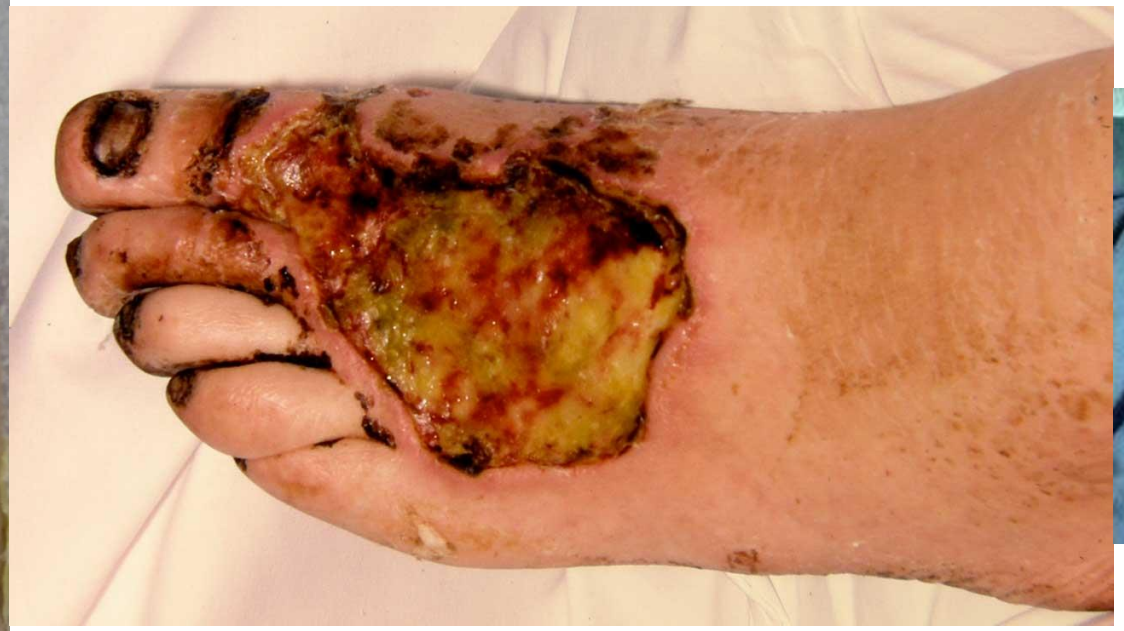
Types of necrosis

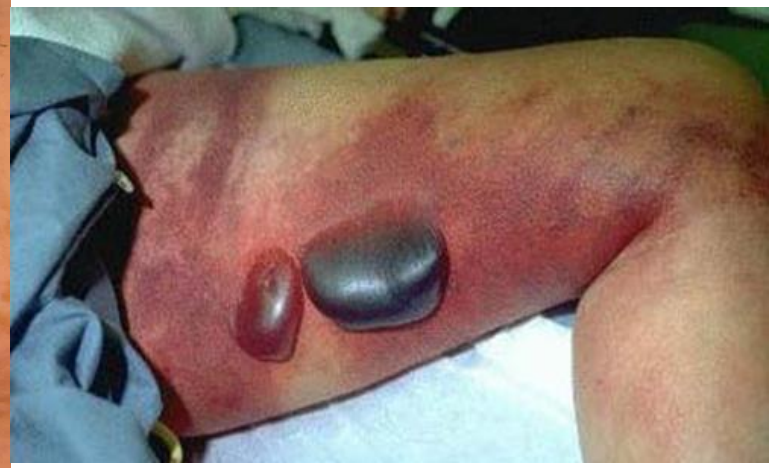
Gas gangrene, a special type of gangrene, is caused by infection of injured tissue by one of many species of *Clostridium*. These anaerobic bacteria produce hydrolytic enzymes and toxins that destroy connective tissue and cellular membranes and cause bubbles of gas to form in muscle cells.

Gas gangrene can be fatal if enzymes lyse the membranes of red blood cells, destroying their oxygen-carrying capacity. Death is the result of shock.

The condition is treated with antitoxins and supplemental oxygen delivered in a hyperbaric (pressurized) chamber.







Thank you for listening