FirstHope Notes | B.Pharm Semester 1

Basic principles of Cell injury and Adaptation

Introduction to Cell Injury and Adaptation

- Cells, the basic units of life, are constantly exposed to various physical, chemical, and biological stimuli.
- While many of these stimuli are benign and essential for normal cell function, others can be harmful and lead to cell injury.
- Understanding how cells respond to these injurious stimuli is fundamental to comprehending various pathological conditions and diseases.

Cell Injury

- Cell injury occurs when cells are exposed to severe stress or harmful agents that they cannot adapt to.
- This can lead to reversible or irreversible changes, and in severe cases, it can result in cell death.

Types of Cell Injury

1. **Reversible Injury**
   - If the damaging stimulus is mild or of short duration, cells can often recover once the stimulus is removed.
   - Changes include cellular swelling and fatty change.
2. **Irreversible Injury**
   - If the stimulus persists or is severe, cells reach a point of no return, leading to cell death.
   - This can occur through necrosis or apoptosis.

Cell Adaptation

- Cell adaptation refers to the ability of cells to undergo changes in response to persistent stress or harmful stimuli, allowing them to survive and maintain function.
- These changes can be physiological (normal adaptation) or pathological (abnormal adaptation).

Types of Cell Adaptation

1. **Atrophy**
   - A decrease in cell size due to reduced functional demand or adverse conditions.
2. **Hypertrophy**
   - An increase in cell size in response to increased demand or stimulation.

3. **Hyperplasia**
   - An increase in the number of cells in a tissue or organ due to an increased rate of cell division.
4. **Metaplasia**
   - A reversible change in which one differentiated cell type is replaced by another cell type.
5. **Dysplasia**
   - Abnormal development or growth of cells, tissues, or organs, often considered a pre-neoplastic condition.

Homeostasis

- Homeostasis is the process by which living organisms maintain a stable internal environment despite changes in the external surroundings.
- Think of it like a thermostat in your home that keeps the temperature just right—neither too hot nor too cold.

Components of Homeostasis

To maintain homeostasis, three main components are involved:

1. **Receptor (Sensor)**
   - This detects changes in the environment.
   - For example, temperature sensors in your skin can detect when it's getting cold.
2. **Control Center**
   - This receives the signal from the receptor and processes the information.
   - In your body, the brain often acts as the control center.
3. **Effector**
   - This makes the necessary adjustments to bring things back to normal.
   - For example, muscles shiver to generate heat when you're cold.

Types of Feedback Systems

- Feedback systems help maintain homeostasis by regulating the internal environment.

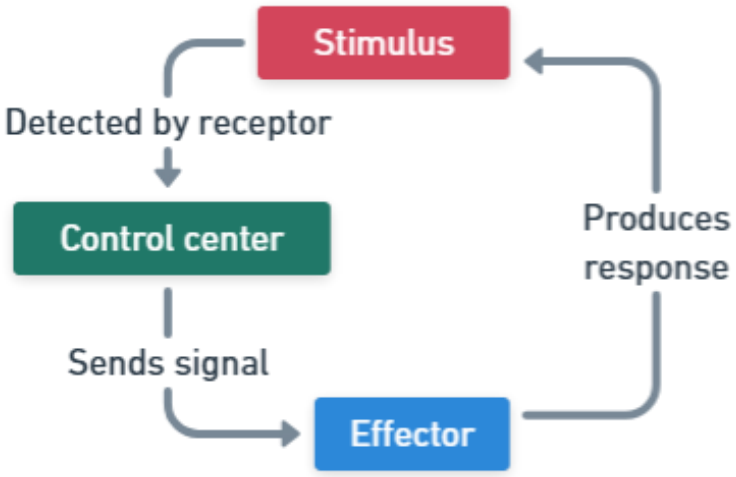
There are two main types:

A. Negative Feedback Systems

Mechanism of negative feedback system

- Negative feedback is like a loop that helps to counteract changes and bring the system back to its normal state.

- It's the most common type of feedback system in the body.



Example: Temperature Regulation

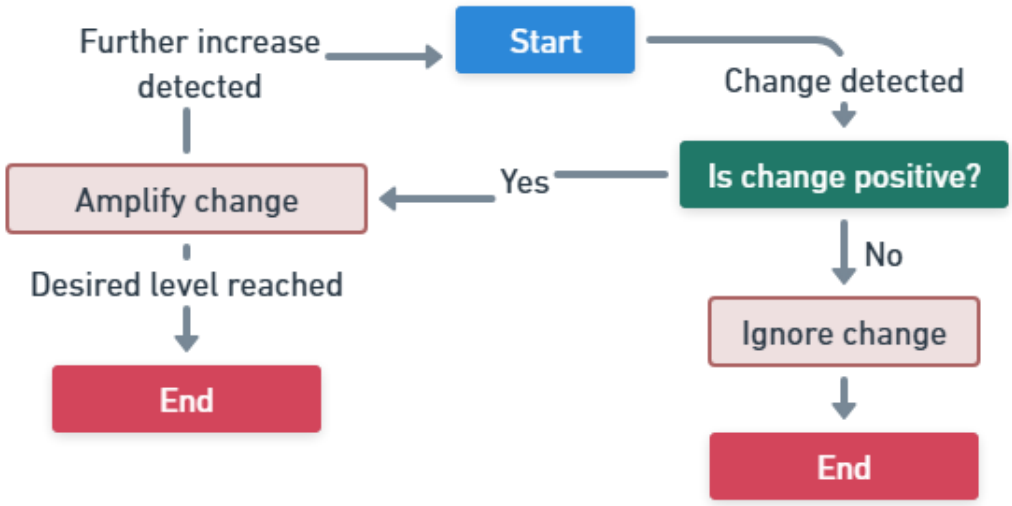
- **Receptor**: Temperature sensors in your skin detect that it's cold.
- **Control Center**: The brain receives this information and decides that action is needed.
- **Effector**: Your muscles start to shiver, generating heat and raising your body temperature back to normal.

This system "negates" the change (being cold) by producing heat, thus stabilizing the temperature.

B. Positive Feedback Systems

Mechanism of positive feedback system

- Positive feedback amplifies a change, making things move further from the normal state.
- It's less common but is used in certain situations.



Example: Blood Clotting

- **Receptor**: A blood vessel is damaged.

- **Control Center**: Platelets (a type of blood cell) recognize the injury and signal for more platelets.
- **Effector**: More platelets gather and release chemicals to attract even more platelets until the clot forms and stops the bleeding.

This system "amplifies" the initial signal (injury) to quickly produce a beneficial result (clotting).

Cause of Cell Injury

- **Cell injury** refers to the structural or functional impairment of a cell resulting from exposure to harmful stimuli or stressors.
- It can disrupt normal cellular processes and lead to cell dysfunction or death.

Types of Cell Injury

1. Reversible Cell Injury

- Occurs when a harmful stimulus is mild or removed.
- The cell can recover and regain normal function.
- Features include:
  - Cellular swelling
  - Fatty changes
  - Minor structural alterations

2. Irreversible Cell Injury

- Results from persistent or severe harmful stimuli, leading to cell death.
- Manifests as:
  - **Apoptosis:** Programmed cell death.
  - **Necrosis:** Uncontrolled cell death.

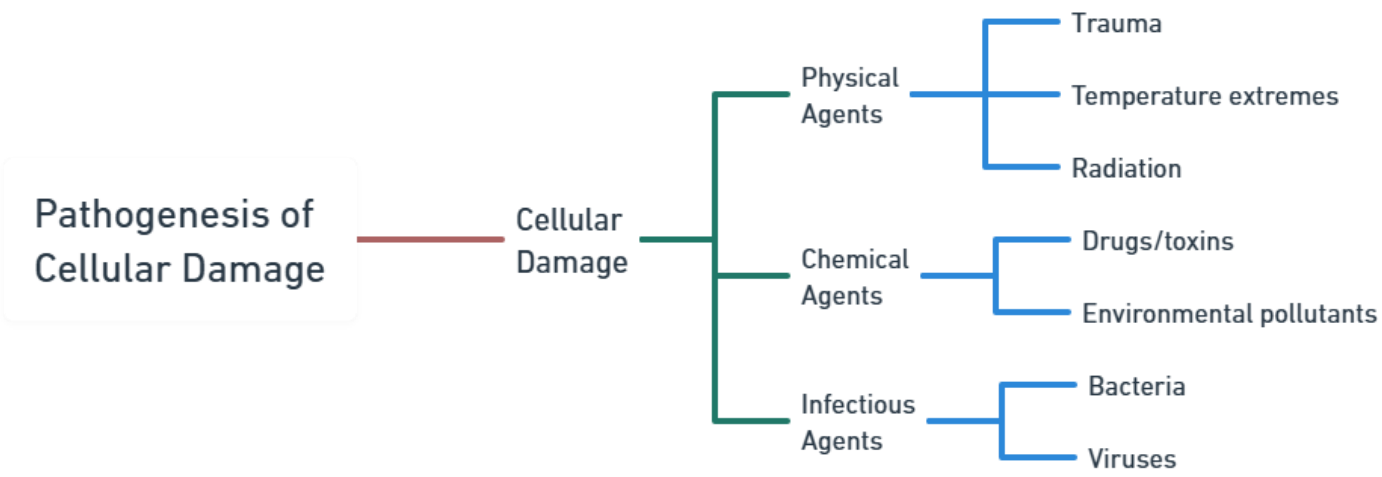
Causes of cell injury:

1. **Physical agents:** Mechanical trauma, extreme temperatures, radiation, or electrical injury.
2. **Chemical agents:** Toxic chemicals, heavy metals, drugs, poisons, or environmental pollutants.

3. **Infectious agents:** Bacteria, viruses, fungi, or parasites.
4. **Immunological reactions:** Autoimmune diseases or hypersensitivity reactions.
5. **Genetic factors:** Genetic mutations, chromosomal abnormalities, or inherited conditions.
6. **Nutritional imbalances:** Deficiencies or excesses of essential nutrients.
7. **Hypoxia and ischemia:** Reduced oxygen supply or blood flow to tissues.
8. **Aging:** Accumulation of damage and decline in cellular repair mechanisms.

Pathogenesis of Cellular Damage

- Cellular damage occurs when various factors disrupt the normal functioning of cellular components, such as cell membranes, mitochondria, ribosomes, and nuclei.
- Understanding the pathogenesis of this damage is crucial to comprehending how cells respond to stressors and how injury can lead to cell dysfunction or death.



Cell Membrane Damage

- The cell membrane is a critical structure responsible for maintaining cellular integrity, regulating the passage of molecules in and out of the cell, and facilitating communication with other cells.
- Damage to the cell membrane can result from:
    1. **Oxidative Stress**: Reactive oxygen species (ROS) can cause lipid peroxidation, altering the membrane's fluidity and permeability.
    2. **Toxins or Pathogens**: Certain bacterial toxins or viral infections can disrupt the cell membrane's integrity.
    3. **Mechanical Trauma**: Physical forces can cause membrane damage, leading to cell leakage or rupture.

Consequences:

- Loss of selective permeability.
- Impaired cellular communication.

- Uncontrolled influx of ions and molecules, leading to cell dysfunction or death.

Mitochondrial Damage

- Mitochondria are the cell's energy-producing organelles, generating ATP through oxidative phosphorylation.
- Mitochondrial damage can be caused by:
    1. **Hypoxia**: Insufficient oxygen impairs the electron transport chain, reducing ATP production and causing the formation of ROS.
    2. **Toxins or Drugs**: Some chemicals or medications can damage mitochondrial DNA, inhibit enzymes involved in ATP production, or increase ROS production.
    3. **Genetic Mutations**: Inherited mitochondrial disorders can lead to impaired energy production or increased susceptibility to damage.

Consequences:

- Reduced ATP production.
- Increased ROS generation.
- Release of pro-apoptotic factors, which can lead to cell dysfunction or apoptosis.

Ribosome Damage

- Ribosomes are responsible for protein synthesis, translating mRNA into polypeptides.
- Ribosome damage can be caused by:
    1. **Toxins**: Certain toxins, like those produced by some bacteria, can inhibit ribosomal function.
    2. **Oxidative Stress**: ROS can damage ribosomal RNA or proteins, impairing ribosome function.
    3. **Nutrient Deprivation**: Insufficient amino acids or energy can impair ribosomal function and protein synthesis.

Consequences:

- Reduced protein synthesis.
- Production of misfolded proteins.
- Impaired cellular function, resulting in cell injury or death.

Nuclear Damage

- The nucleus contains the cell's genetic material (DNA) and is responsible for controlling gene expression and regulating cellular processes.
- Nuclear damage can result from:
    1. **DNA-Damaging Agents**: Ionizing radiation, chemicals, or ROS can cause DNA lesions, such as base modifications, cross-links, or strand breaks.

2. **Replication Errors**: Errors during DNA replication can introduce mutations or genomic instability.
3. **Chromosomal Abnormalities**: Structural or numerical chromosomal alterations can disrupt gene function or regulation.

Consequences:

- Impaired gene expression and altered cellular processes.
- Genomic instability and increased risk of malignant transformation.
- Cells have DNA repair mechanisms, but if these fail or become overwhelmed, cell dysfunction or death (apoptosis or necrosis) may occur.

Morphology of cell injury

- The morphology of cell injury refers to the structural and functional changes in cells due to harmful stimuli or stressors.
- These changes can be reversible or irreversible, observable through various microscopy and biochemical techniques.

Reversible Cell Injury

- Reversible cell injury involves changes that can be reversed if the stressor is removed.

Common changes include:

1. **Cellular Swelling**
   - Early sign caused by water and ion influx due to malfunctioning ion pumps, visible as enlarged, pale, and turgid cells.
2. **Fatty Change (Steatosis)**
   - Accumulation of lipid droplets in cells, particularly in the liver, heart, and kidney, due to impaired lipid metabolism.
   - Affected cells appear vacuolated.
3. **Hydropic Degeneration**
   - A form of cellular swelling with clear, water-filled vacuoles in the cytoplasm.

Irreversible Cell Injury

- Irreversible cell injury occurs with persistent or severe stress, leading to cell death, either by apoptosis or necrosis.

1. Apoptosis

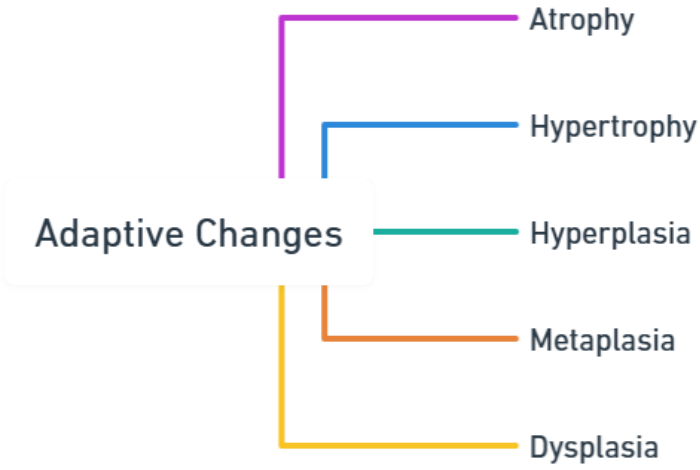
- Regulated cell death involving caspases, characterized by:
  - Cell shrinkage
  - Chromatin condensation
  - Nuclear fragmentation
  - Formation of apoptotic bodies
  - Phagocytosis without inflammation

2. Necrosis

- Unregulated cell death due to severe injury, marked by:
  - Cell swelling
  - Membrane rupture
  - Leakage of contents
  - Inflammation
- **Subtypes** include:
  - Coagulative
  - Liquefactive
  - Caseous
  - Gangrenous necrosis, each with distinct features

Adaptive Changes

- Adaptive changes are modifications that cells undergo in response to chronic stress or injurious stimuli, allowing them to survive and maintain function.
- These changes can be either physiological (normal) or pathological (abnormal).
- The main types of adaptive changes include atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia.



1. Atrophy

Description:

- Reduction in cell size and function due to decreased demand or insufficient nutrients. Cells shrink, losing organelles and reducing metabolic activity.

Causes:

- Disuse (e.g., muscle atrophy from immobility)
- Denervation (e.g., muscle atrophy from nerve loss)
- Ischemia (e.g., reduced blood supply)
- Malnutrition
- Loss of endocrine stimulation (e.g., menopause-related endometrial atrophy)

Microscopic Appearance:

- Smaller cells with fewer organelles
- Presence of autophagic vacuoles and lipofuscin granules

2. Hypertrophy

Description:

- Increase in cell size due to greater functional demand or hormonal stimulation. Cells grow larger and gain more structural proteins and organelles.

Causes:

- Increased workload (e.g., skeletal muscle hypertrophy from exercise)
- Hormonal stimulation (e.g., uterine hypertrophy during pregnancy)

Microscopic Appearance:

- Enlarged cells with more cytoplasm and larger nuclei
- No increase in cell number

3. Hyperplasia

Description:

- Increase in the number of cells in a tissue or organ due to higher demand or hormonal influence.

Causes:

- Hormonal (e.g., breast glandular proliferation during pregnancy)
- Compensatory (e.g., liver regeneration)
- Pathological (e.g., endometrial hyperplasia due to excessive estrogen)

Microscopic Appearance:

- More cells, but with normal morphology
- Intact tissue architecture

4. Metaplasia

Description:

- Reversible replacement of one differentiated cell type with another better suited to handle stress, often due to chronic irritation.

Causes:

- Chronic irritation or inflammation (e.g., squamous metaplasia in smokers' airways)

Microscopic Appearance:

- New, normal-appearing cell type in an abnormal location (e.g., squamous cells replacing columnar epithelium)

5. Dysplasia

Description:

- Abnormal growth and differentiation of cells often considered pre-cancerous. Cells display loss of uniformity and disordered growth.

Causes:

- Chronic irritation or inflammation (e.g., cervical dysplasia from HPV)
- Genetic mutations

Microscopic Appearance:

- Pleomorphism (variability in size and shape)
- Increased nuclear-to-cytoplasmic ratio
- Hyperchromatic, irregular nuclei
- Loss of normal tissue architecture

Morphological Features of Cell Injury

Cell Swelling

- **Also Known As**: Hydropic change or vacuolar degeneration
- **Definition**: One of the earliest signs of cellular injury. Occurs when cells lose their ability to maintain ionic and fluid homeostasis due to damage to the plasma membrane, leading to an influx of water.

Causes:

- Malfunction of energy-dependent ion pumps caused by hypoxia, toxins, or other disruptions to energy production.

Mechanism:

- ATP depletion impairs the function of membrane ion pumps, leading to sodium and water influx, which causes the cell to swell.
- Organelles like mitochondria and the endoplasmic reticulum also swell, which may disrupt cellular functions further.

Microscopy:

- Enlarged, pale, and turgid cells.

Outcome:

- Reversible if the stressor is removed; may progress to irreversible injury and cell death if persistent.

Intracellular Accumulation

- **Definition**: Abnormal build-up of substances within the cell, which can be endogenous (proteins, lipids, carbohydrates) or exogenous (infectious agents, minerals, pigments).

Types of Accumulations:

- **Lipids**: Fatty change (steatosis) in the liver due to excessive fat deposition (e.g., from alcohol, diabetes, or obesity).
- **Proteins**: Accumulation of misfolded proteins (e.g., neurodegenerative diseases like Alzheimer's).
- **Pigments**: Accumulation of endogenous pigments (e.g., melanin, bilirubin, lipofuscin) or exogenous pigments (e.g., carbon in anthracosis).
- **Glycogen**: Abnormal accumulation in glycogen storage diseases.
- **Calcium**: Pathological calcification, discussed below.

Mechanism:

- Accumulation may result from increased production, reduced degradation, or an inability to metabolize certain substances, leading to their deposition in the cytoplasm or organelles.

Examples:

- **Fatty Change**: Lipid accumulation.

- **Hyaline Change**: Protein accumulation.
- **Hemosiderin Deposition**: Iron accumulation.

Outcome:

- Can cause cellular dysfunction, injury, or death depending on the nature and severity of the accumulation.

Calcification

- **Definition**: Abnormal deposition of calcium salts in tissues. It can be classified as dystrophic or metastatic.

Mechanism:

- In dystrophic calcification, dead or damaged cells release intracellular contents that act as a nidus for calcium deposition.
- In metastatic calcification, elevated blood calcium levels cause calcium to be deposited in otherwise normal tissues.

Types:

- **Dystrophic Calcification**: Localized deposition in injured or dead tissues (e.g., necrotic areas, heart valves, atherosclerotic plaques), unrelated to calcium metabolism disturbances.
- **Metastatic Calcification**: Occurs in normal tissues due to hypercalcemia or calcium metabolism disturbances, affecting organs such as kidneys, lungs, blood vessels, and stomach.

Outcome:

- Impairs organ function and may lead to further tissue injury or inflammation.

Enzyme Leakage

- **Definition**: Occurs when damaged cells, particularly those undergoing necrosis, release intracellular enzymes into the extracellular space and eventually into the bloodstream.

Mechanism:

- When the plasma membrane is damaged due to injury or cell death, cellular enzymes leak out.
- These enzymes can be detected in blood tests and are used to diagnose tissue damage.

Causes:

- Mechanical trauma, toxins, ischemia.

Clinical Relevance:

- Measurement of specific enzymes in the blood (e.g., creatine kinase for myocardial infarction, alanine aminotransferase for liver injury) helps diagnose and monitor tissue damage.

Outcome:

- Indicator of cell injury or death, reflecting loss of membrane integrity.

Cell Death

Definition: Cell death can occur by two main processes: necrosis and apoptosis.

Forms:

A. Apoptosis

- Necrosis is uncontrolled cell death that occurs due to severe injury, often associated with inflammation.
- It is a pathological process in which cell membranes rupture, leading to the release of cellular contents that cause inflammation in the surrounding tissue.
- **Features**:
  - Cell shrinkage
  - Chromatin condensation
  - Nuclear fragmentation
  - Formation of apoptotic bodies
  - Phagocytosis by neighboring or immune cells
- **Outcome**: Typically, does not induce an inflammatory response.

B. Necrosis

- Apoptosis is a tightly regulated, programmed cell death that is often physiological and does not elicit an inflammatory response.
- It is crucial for tissue homeostasis, development, and the elimination of damaged cells.
- **Features**:
  - Cell swelling
  - Membrane rupture
  - Leakage of cellular contents
  - Inflammation in surrounding tissues
- **Subtypes**: Coagulative necrosis and other types with distinct morphological features.
- **Outcome**: Final consequence of irreversible cell injury.

Acidosis and Alkalosis

- Acidosis and alkalosis are conditions resulting from an imbalance in the body's acid-base homeostasis, affecting the pH level of the blood and other body fluids.
- The normal blood pH range is 7.35 to 7.45.
    - A pH **below 7.35** indicates **acidosis**,
    - A pH **above 7.45** indicates **alkalosis**.

Acidosis

- Acidosis occurs due to an excess of acidic substances (e.g., hydrogen ions) or a deficiency of alkaline substances (e.g., bicarbonate), leading to a decreased blood pH.

Types of Acidosis

A. Respiratory Acidosis

- **Cause**: Impaired gas exchange in the lungs resulting in carbon dioxide (CO2) accumulation.
- **Conditions**: Chronic obstructive pulmonary disease (COPD), severe pneumonia, acute respiratory distress syndrome (ARDS).
- **Mechanism**: Elevated CO2 levels increase carbonic acid concentration in the blood, lowering the pH.

B. Metabolic Acidosis

- **Cause**: Increase in non-respiratory acids or loss of bicarbonate.
- **Conditions**: Lactic acidosis (intense exercise), ketoacidosis (uncontrolled diabetes), kidney failure, ingestion of toxic substances, diarrhea, renal dysfunction.
- **Mechanism**: Accumulation of acids or loss of bicarbonate reduces blood pH.

Alkalosis

- Alkalosis occurs due to an excess of alkaline substances or a deficiency of acidic substances, leading to an increased blood pH.

Types of Alkalosis

A. Respiratory Alkalosis

- **Cause**: Hyperventilation leading to excessive CO2 elimination.
- **Conditions**: Anxiety, fever, pain, certain lung diseases.
- **Mechanism**: Decreased CO2 levels reduce carbonic acid concentration in the blood, raising the pH.

B. Metabolic Alkalosis

- **Cause**: Increase in bicarbonate levels or loss of non-respiratory acids.
- **Conditions**: Excessive vomiting (loss of gastric acid), ingestion of alkali substances, certain diuretic medications, endocrine disorders (e.g., primary hyperaldosteronism).

- **Mechanism**: Elevated bicarbonate levels or loss of acids increase blood pH.

Symptoms and Complications

- Both acidosis and alkalosis can present with various symptoms, which depend on the severity and duration of the imbalance.
- Mild cases may be asymptomatic or cause non-specific symptoms, while severe cases can lead to:
  - Confusion
  - Muscle weakness
  - Seizures
  - Coma
  - Death

Treatment

Treatment

- Treatment involves addressing the underlying cause and correcting the acid-base imbalance.

Interventions include:

- Intravenous fluids
- Medications
- Oxygen therapy
- Other supportive measures as needed

Electrolyte Imbalance

- Electrolyte imbalances occur when the levels of essential electrolytes (minerals that carry an electric charge) in the body become too high or too low.
- Electrolytes play crucial roles in various physiological processes, including:
  - Maintaining fluid balance
  - Regulating nerve and muscle function
  - Maintaining proper pH levels
- Common electrolytes include:
  - **Sodium, Potassium, Calcium, Magnesium, Chloride, and Bicarbonate**

Causes of Electrolyte Imbalance

- Electrolyte imbalances can result from various factors, such as:

- Dehydration or overhydration
- Kidney dysfunction or renal failure
- Endocrine disorders (e.g., diabetes or adrenal insufficiency)
- Severe vomiting or diarrhea
- Certain medications (e.g., diuretics, corticosteroids, or chemotherapy drugs)
- Excessive intake or deficiency of specific electrolytes in the diet

Common Electrolyte Imbalances

1. **Hyponatremia (Low Sodium)**
   - **Causes**: Too much fluid intake, kidney problems, heart failure, some medications
   - **Symptoms**: Headache, tiredness, muscle weakness, seizures, coma (severe)
2. **Hypernatremia (High Sodium)**
   - **Causes**: Dehydration, too much salt, kidney issues
   - **Symptoms**: Thirst, confusion, muscle twitching, seizures
3. **Hypokalemia (Low Potassium)**
   - **Causes**: Vomiting, diarrhea, diuretics, certain endocrine issues
   - **Symptoms**: Muscle weakness, cramps, irregular heartbeats, paralysis (severe)
4. **Hyperkalemia (High Potassium)**
   - **Causes**: Kidney problems, too much potassium intake, some medications
   - **Symptoms**: Muscle weakness, heart palpitations, dangerous heart rhythms
5. **Hypocalcemia (Low Calcium)**
   - **Causes**: Vitamin D deficiency, kidney issues, certain medications
   - **Symptoms**: Muscle cramps, spasms, seizures, irregular heartbeats
6. **Hypercalcemia (High Calcium)**

- **Causes**: Overactive parathyroid gland, cancer, too much vitamin D
- **Symptoms**: Muscle weakness, constipation, kidney stones, confusion

Effects and Treatment

- Electrolyte imbalances can have significant effects on various body systems, particularly the **nervous** and **cardiovascular** systems.
- Mild imbalances may cause non-specific symptoms or be asymptomatic, while severe imbalances can lead to life-threatening complications.

Treatment typically involves:

- Identifying and addressing the underlying cause
- Administering appropriate interventions to restore normal electrolyte levels, such as:
  - **Intravenous (IV) fluids**
  - **Electrolyte supplementation** (e.g., sodium, potassium, calcium)
  - **Medications** to balance electrolyte levels (e.g., diuretics, potassium binders, or calcium supplements)

Basic mechanism involved in the process of inflammation and repair

Inflammation: Introduction, Clinical Signs, and Types

- Inflammation is the body's natural response to injury, infection, or harmful stimuli.
- It is a complex biological process involving the immune system's cells, blood vessels, and molecular mediators.

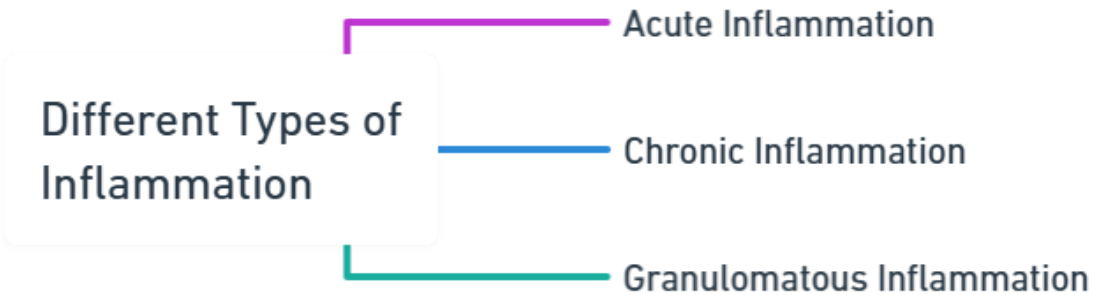
Primary Purposes of Inflammation:

- Eliminate the initial cause of cell injury
- Clear out damaged cells and tissues
- Establish a repair process
- While inflammation is essential for healing, chronic or excessive inflammation can contribute to various diseases, including:
    - Autoimmune disorders
    - Cardiovascular diseases
    - Cancer
- Understanding the types and signs of inflammation helps in diagnosing and treating various inflammatory conditions effectively.
- Proper management is crucial to prevent inflammation from contributing to chronic diseases.

Clinical Signs of Inflammation

- The classic signs of inflammation, also known as the five cardinal signs, are:
    - **Redness (Rubor)**: Increased blood flow to the affected area.
    - **Heat (Calor)**: Elevated temperature in the inflamed area due to increased blood flow.
    - **Swelling (Tumor)**: Accumulation of fluid in the tissues.
    - **Pain (Dolor)**: Release of chemicals that stimulate nerve endings.
    - **Loss of Function (Functio Laesa)**: Reduced function of the affected area due to pain and swelling.

Different Types of Inflammation



1. Acute Inflammation

- **Duration**: Short-term, lasting from a few hours to a few days.
- **Causes**: Infection, injury, or foreign bodies (e.g., splinters).
- **Characteristics**: Rapid onset, marked by the five cardinal signs. Involves the activation of immune cells like neutrophils.
- **Examples**: Cuts, burns, infections (e.g., bacterial, or viral).

2. Chronic Inflammation

- **Duration**: Long-term, lasting from weeks to years.
- **Causes**: Persistent infection, prolonged exposure to irritants (e.g., tobacco smoke), autoimmune diseases.
- **Characteristics**: Slow onset, less obvious symptoms. Involves different immune cells, such as macrophages and lymphocytes.
- **Examples**: Rheumatoid arthritis, inflammatory bowel disease, chronic infections (e.g., tuberculosis).

3. Granulomatous Inflammation

- **Duration**: Can be acute or chronic.
- **Causes**: Persistent pathogens (e.g., mycobacteria), foreign substances that the immune system cannot eradicate.
- **Characteristics**: Formation of granulomas, which are small nodules of immune cells that form around the foreign material.
- **Examples**: Tuberculosis, sarcoidosis, leprosy.

Mechanism of Inflammation

- Inflammation is a multi-step process involving changes in vascular permeability, blood flow, and the migration of white blood cells (WBCs) to the site of injury or infection.
- Understanding these mechanisms is crucial for developing treatments that can modulate the inflammatory response.

Key Mechanisms

A. Alteration in Vascular Permeability and Blood Flow

Vasodilation

- **Immediate Response**: After injury, local blood vessels dilate due to the release of chemical mediators like histamine and nitric oxide.
- **Effects**: Increased blood flow causes redness and heat in the affected area.

Increased Vascular Permeability

- **Endothelial Cell Contraction**: The cells lining the blood vessels contract, creating gaps that allow plasma proteins and leukocytes to exit the bloodstream.
- **Result**: Accumulation of fluid in tissues leads to swelling (edema).

Exudation

- **Fluid Movement**: The movement of fluid and plasma proteins into the tissue is called exudation.
- **Composition**: Contains immune cells, nutrients, and antibodies essential for fighting infection and repairing tissue.

B. Migration of White Blood Cells (WBCs)

Margination

- **Peripheral Movement**: Slowed blood flow causes WBCs, especially neutrophils, to move to the vessel walls (marginate).

Rolling and Adhesion

- **Interaction with Endothelium**: WBCs roll along and adhere to the endothelial surface via adhesion molecules (e.g., integrins on WBCs and selectins on endothelial cells).
- **Enhancement by Mediators**: Cytokines and other mediators enhance this adhesion process.

Transmigration (Diapedesis)

- **Crossing the Vessel Wall**: WBCs extend pseudopods between endothelial cells, squeezing through gaps to enter surrounding tissue.

Chemotaxis

- **Directed Movement**: WBCs migrate toward the injury site, guided by chemical signals like chemokines and components of the complement system.

Phagocytosis

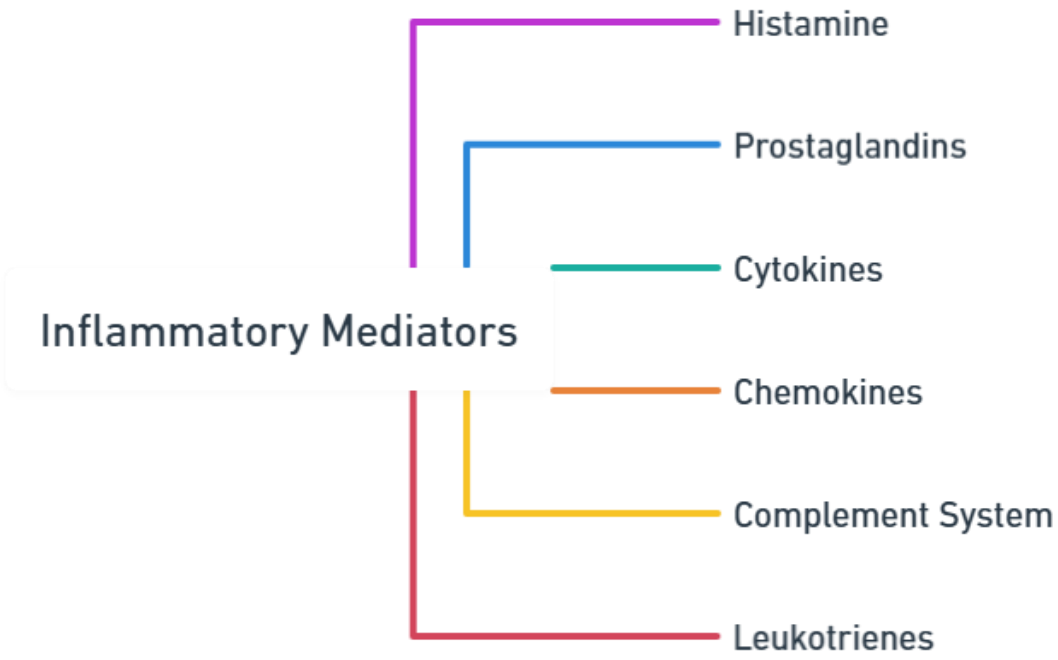
- **Engulfing Pathogens**: Neutrophils and macrophages engulf and digest pathogens, debris, and dead cells.
- **Recognition**: Targets are recognized through receptors that bind to opsonins (e.g., antibodies, complement proteins) coating the pathogens.

Mediators of Inflammation

- Inflammation is regulated by various chemical mediators that orchestrate the inflammatory response.
- These mediators can be derived from cells or plasma, and have different roles in initiating and sustaining inflammation.

- Mediators of inflammation are substances that play key roles in initiating and regulating inflammatory responses.

Main Types of Inflammatory Mediators



1. Histamine

- **Source**: Released by mast cells and basophils.
- **Function**: Increases vascular permeability and causes vasodilation, leading to redness and swelling.

2. Prostaglandins

- **Type**: Lipid compounds.
- **Function**: Intensify inflammation by promoting vasodilation, fever, and pain.

3. Cytokines

- **Examples**: Interleukins and Tumor Necrosis Factor (TNF).
- **Function**: Proteins that modulate the immune response and regulate inflammation.

4. Chemokines

- **Type**: A subset of cytokines.
- **Function**: Attract white blood cells to sites of infection or injury (chemotaxis).

5. Complement System

- **Description**: A series of plasma proteins.
- **Function**: Enhances the ability of antibodies and phagocytic cells to clear microbes and damaged cells.

6. Leukotrienes

- **Type**: Lipid compounds.

- **Function**: Mediate allergic and inflammatory responses by increasing vascular permeability and attracting leukocytes.

Basic principles of wound healing in the skin

- The basic principles of wound healing in the skin involve a series of biological events aimed at repairing damaged tissue and restoring skin integrity.

Phases of Wound Healing

- The repair of wounds in the skin occurs in four major overlapping phases:

1. Hemostasis (Immediate)

- Timing: Seconds to minutes after injury
- Goal: Stop bleeding
- Blood vessels constrict (vasoconstriction)
- Platelets aggregate and adhere to exposed collagen
- Formation of a fibrin clot (via coagulation cascade)
- Clot serves as a temporary matrix and releases growth factors (e.g., PDGF, TGF-β)

2. Inflammation (First 24-72 hours)

- Vasodilation follows hemostasis
- Influx of neutrophils (first 24–48 hours): clear microbes and dead tissue via phagocytosis
- Macrophages appear after ~48 hours: key to orchestrating further healing by:
  - Phagocytosis
  - Secretion of cytokines (IL-1, TNF-α)
  - Release of growth factors (VEGF, PDGF, TGF-β) for angiogenesis and fibroblast activation

Note: This phase is critical to set the stage for repair.

3. Proliferation (Days 3–10)

- Involves the creation of new tissue. Key events:

A. Fibroblast Proliferation

- Fibroblasts migrate into the wound, stimulated by PDGF, FGF, and TGF-β
- Produce collagen (mainly Type III initially) and extracellular matrix (ECM) components

B. Angiogenesis (Neovascularization)

- Formation of new capillaries from existing vessels

- Driven by **VEGF**, **FGF**, **angiopoietins**
- Ensures oxygen and nutrient delivery to healing tissue

C. Granulation Tissue Formation

- Granulation tissue = new connective tissue + capillaries + fibroblasts
- Appears as red, soft, and granular
- Replaces the clot and acts as a scaffold for epithelial cells

D. Re-epithelialization

- Keratinocytes from wound edges proliferate and migrate across the wound bed
- Stimulated by **EGF**, **TGF-α**

E. ECM Synthesis

- Fibronectin, hyaluronic acid, proteoglycans form early ECM
- Later replaced by stronger collagen matrix

4. Maturation and Remodeling (From day 7 up to months)

- Type III collagen is replaced by Type I collagen
- Collagen is cross-linked and aligned along tension lines to increase tensile strength
- Capillary density decreases (regression of unnecessary vessels)
- Final result: fibrous scar tissue
- Note:
  - Tensile strength increases gradually but never reaches 100% of original tissue
  - ~70–80% at maximum (after several months)

Types of Wound Healing

1. Healing by First Intention (Primary Union)

- Occurs in clean, uninfected surgical wounds with closely apposed edges (e.g., sutured wounds)
  - Minimal tissue loss
  - Minimal granulation tissue and scarring
  - Epithelial regeneration predominates
- Timeline:
  - 24 hrs: Neutrophils and epithelial coverage begins
  - 48–96 hrs: Macrophages dominate; collagen synthesis begins
  - Day 5: Peak neovascularization; Type III collagen abundant

- 2nd week: Reduced inflammation; collagen remodeling
- 1 month: Scar formed

2. Healing by Second Intention (Secondary Union)

- Occurs in large wounds, ulcers, or abscesses where wound edges are not approximated
  - Extensive tissue loss
  - Greater inflammation, more granulation tissue
  - Wound contraction occurs via myofibroblasts
  - Larger scar forms

3. Healing by Third Intention (Delayed Primary Closure)

- Contaminated wounds initially left open to allow infection control
- Later closed surgically
- Healing is between primary and secondary intention in terms of scarring and granulation

Factors Influencing Wound Healing

Wound healing can be positively or negatively influenced by various local and systemic factors.

Local Factors

1. Infection

- Most important cause of delayed healing
- Prolongs inflammation
- Increases tissue injury
- Leads to more granulation tissue and fibrosis

2. Blood Supply and Oxygenation

- Adequate perfusion is essential
- Hypoxia impairs fibroblast function, collagen synthesis, and leukocyte activity
- Examples:
  - Diabetes mellitus (microvascular disease)
  - Atherosclerosis

3. Foreign Bodies

- Examples: sutures, splinters, dirt
- Prolong inflammation

- Act as nidus for infection

4. Mechanical Stress / Tension

- Repeated trauma or movement disrupts the wound
- Prevents proper re-epithelialization

5. Size and Location of the Wound

- Larger wounds heal more slowly
- Wounds in poorly vascularized areas (e.g., lower limb in diabetics) heal slowly

6. Type of Tissue

- Regenerative capacity varies by tissue type:
  - **High regeneration:** Skin, liver
  - **Poor regeneration:** Cardiac and nervous tissue (healing mainly by scarring)

Systemic Factors

1. Nutritional Status

- Protein deficiency → impaired collagen synthesis and cell proliferation
- Vitamin C deficiency (scurvy) → defective collagen hydroxylation → poor wound strength
- Zinc → cofactor for DNA synthesis and cell proliferation
- Iron and copper → essential for collagen cross-linking

2. Age

- Healing is slower in the elderly due to:
  - Reduced cell proliferation
  - Decreased angiogenesis
  - Presence of co-morbidities

3. Diabetes Mellitus

- Poor perfusion (microvascular disease)
- Increased susceptibility to infection
- Impaired leukocyte function
- Impaired fibroblast activity

4. Immunosuppression

- Causes: steroids, immunosuppressive drugs
- Leads to decreased inflammatory response
- Steroids specifically:

- Inhibit TGF-β
- Reduce fibroblast activity
- Impair angiogenesis

5. Chronic Diseases

- Conditions such as anemia, uremia, cancer, systemic infections impair healing

6. Medications

- NSAIDs and glucocorticoids delay healing by:
  - Inhibiting prostaglandin synthesis
  - Reducing inflammation and fibroblast migration

7. Smoking and Alcohol Use

- Nicotine → vasoconstriction → poor perfusion
- Carbon monoxide → reduces oxygen delivery
- Alcohol → impairs immune and fibroblast function

Complications of Wound Healing

A. Deficient Healing

- **Wound dehiscence**: reopening of wound
- **Ulceration**: poor perfusion or chronic pressure

B. Excessive Healing

- **Hypertrophic scar**: raised scar, confined to original wound
- **Keloid**: excessive collagen beyond wound borders; more common in darker-skinned individuals

C. Exuberant Granulation (Proud Flesh)

- Excess granulation tissue prevents re-epithelialization

D. Contractures

- Excessive wound contraction → deformities (e.g., in burns)

Pathophysiology of Atherosclerosis

- Atherosclerosis is a chronic disease characterized by the buildup of lipids, inflammatory cells, and fibrous elements in large arteries.
- This process leads to the hardening and narrowing of arterial walls, which can result in serious cardiovascular events.

1. **Endothelial Injury**
   - **Cause**: Damage to the endothelial cells lining arterial walls due to factors like hypertension, smoking, or high cholesterol.
   - **Effect**: Increased permeability of the endothelium, allowing lipids to enter the arterial wall.
2. **Lipid Accumulation**
   - **LDL Infiltration**: Low-density lipoprotein (LDL) particles penetrate the damaged endothelium and accumulate in the intima (inner arterial layer).
3. **Inflammatory Response**
   - **Oxidation of LDL**: Accumulated LDL becomes oxidized, triggering an inflammatory reaction.
   - **Monocyte Migration**: Monocytes adhere to the endothelium, migrate into the intima, and differentiate into macrophages.
4. **Foam Cell Formation**
   - **Engulfing Oxidized LDL**: Macrophages ingest oxidized LDL, transforming into foam cells.
   - **Fatty Streaks**: Aggregation of foam cells forms fatty streaks, the earliest visible atherosclerotic lesions.
5. **Fibrous Plaque Formation**
   - **Smooth Muscle Cell Migration**: Smooth muscle cells move from the media (middle arterial layer) to the intima.
   - **Extracellular Matrix Production**: These cells proliferate and secrete collagen and other matrix components, forming a fibrous cap over the lipid core.
6. **Plaque Progression**
   - **Growth**: The plaque enlarges, narrowing the arterial lumen and impeding blood flow.
   - **Calcification**: Over time, plaques may harden due to calcium deposition.
7. **Plaque Rupture and Thrombosis**
   - **Instability**: Thin fibrous caps are prone to rupture.
   - **Thrombus Formation**: Rupture exposes underlying tissues, leading to blood clot formation that can further obstruct the artery or cause embolism.

Clinical Manifestations

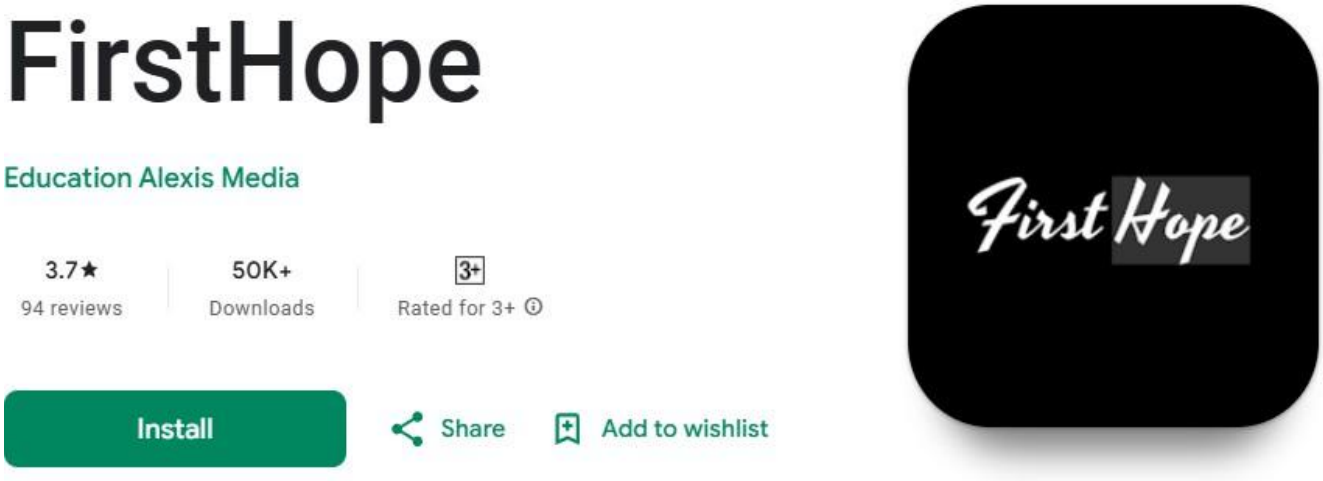
- **Coronary Artery Disease**: Leading to angina or heart attacks.
- **Stroke**: Due to impaired blood flow to the brain.
- **Peripheral Artery Disease**: Causing pain and mobility issues in limbs.

Key Risk Factors

- **Hyperlipidemia**: High LDL and low HDL cholesterol levels.
- **Hypertension**: Elevated blood pressure damages arterial walls.
- **Smoking**: Causes oxidative stress and endothelial injury.
- **Diabetes**: Leads to endothelial dysfunction and promotes inflammation.
- **Obesity and Sedentary Lifestyle**: Contribute to unfavourable lipid profiles and hypertension.
- **Genetic Predisposition**: Family history increases risk.

First Hope

Easy Short Notes Designed to Help You Score Better



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