Pathophysiology(Unit-1)

B.Pharma 2nd semester

PATHOPHYSIOLOGY

UNIT-I

☆ Basic Principles of Cell Injury And Adaptation :-

The term pathophysiology comes from the Ancient Greek words pathos and phusiologia.

- Pathophysiology can be defined in simple words as a physiology of disease.
- pathophysiology is a medical discipline that focuses on the function and symptoms of diseased organs for purpose of diagnosis and treatment of disease.
- Pathophysiology involves some basic terms like.

(i.) Pathogens: pathogens are microbes (microscopic living organism) or other agents that cause disease.

(ii.) Pathogenesis: The pathogenesis means the progression or development of disease. ~~It helps~~ This involves number of events occur in response to attack of pathogens.

(iii.) Etiology: It is study of causes behind the behind the development of disease. It helps in diagnosis as well as proper treatment of disease.

iv. Epidemiology:- The Scientific study of factor which influence the frequency and distribution of infectious disease in Man.

v. Infection: Infection is the attack on host body tissue by pathogens and the reaction of host tissues to the pathogens and the toxins they produce.

vi. Disease: It is a response of body to the external factors and pathogens.

✱ Homeostasis:

- Homeostasis is the balance and stability that our body maintains to function properly.
- It's like an "Internal autopilot" that Constantly regulates different variables, such as body temperature, blood sugar Level, blood pressure and pH.
- When Something disturbs this balance, our body works to restore it and return to normality.
- For Example:- If we feel cold, our body increase heat production to warm us up.
- Homeostasis is essential for Maintaining our health and ensuring that our organs and System function Correctly.

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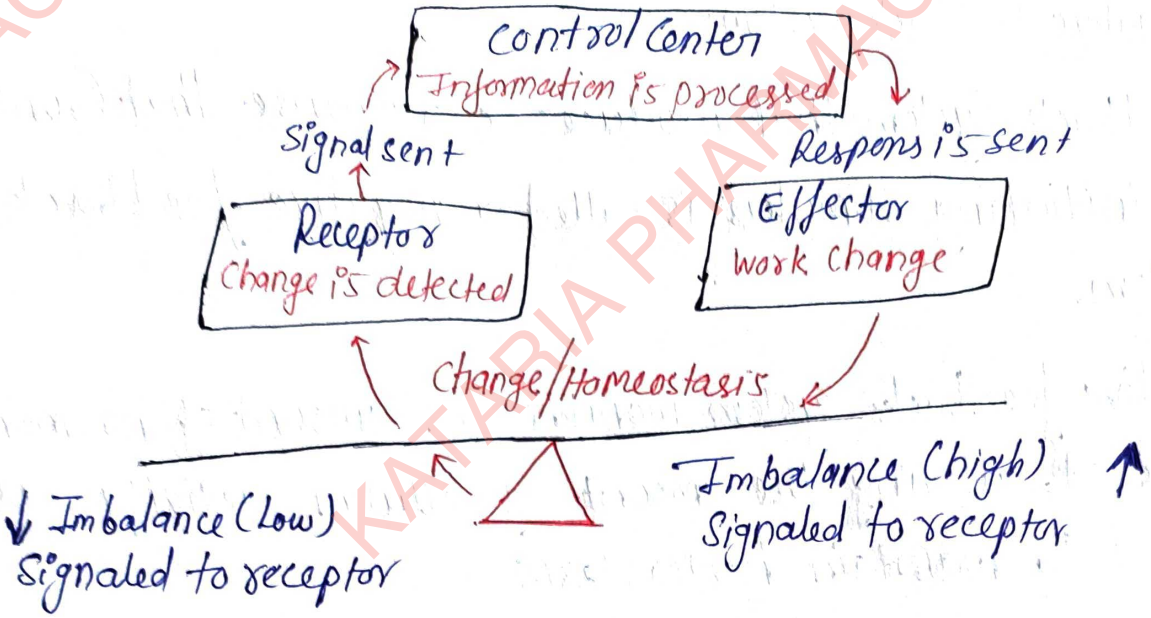
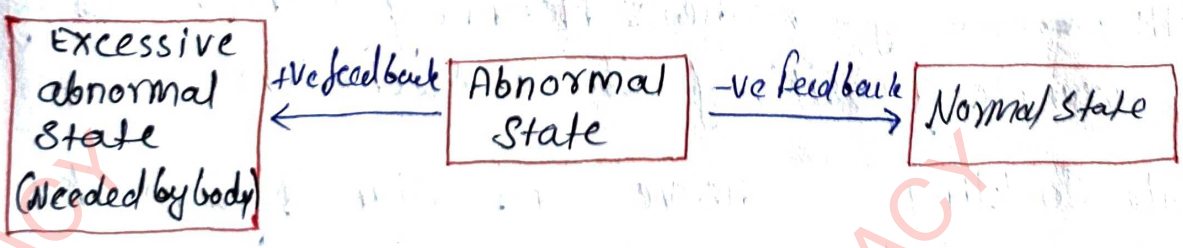


★Feedback System :-

Control Centers in the brain and other parts of the body Monitor and react to deviation from homeostasis using feedback Mechnism. Feedback System has two type.

(A) Negative feedback System
(B) Positive feed back System



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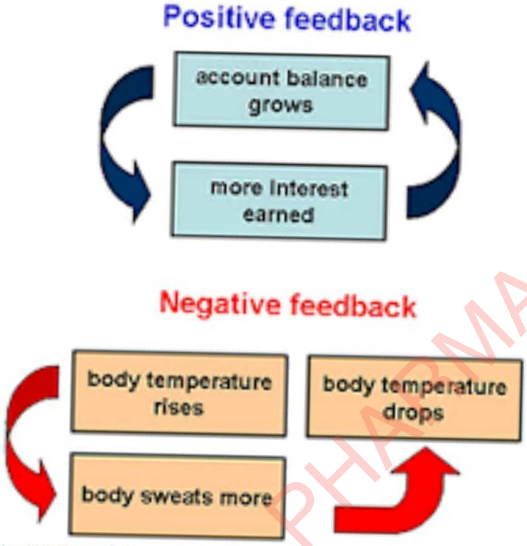
① Negative feedback System:-

A feedback System that produces a response that Counteracts the Initiating stimulus is Called a negative feedback System.

- Negative feedback System monitor the amount of hormones secreted, altering the amount of Cellular activity as needed to maintain homeostasis.



② positive feedback System:-

- It occur when the original effect of the Stimulus is enhanced by the output.
- The Conditions become extreame in this Mechnism.
- Milk Sereted by a Mother's Mammary gland is one of the example of positive feedback Mechnism.
- While Suckling, the nerve Sends Signals from the nipple to Stimulate the pituitary gland to Secrete prolactin.

- In turn, prolactin triggers the Mammary glands to secrete Milk.
- As the baby Suckles More Milk, More prolactin is Secreted and More Milk is produce.

☆ Causes of Cellular injury :-

Cell injury Can be defined as an alteration is cell structure or biochemical functioning.

or

It Can be define as a variety of Stresses a Cell bears as a result of changes in its internal and external environment

Causes of cell injury :-

There are numerous Causes for Cellular injury.

① Acquired Causes
② genetic Causes

① Acquired Causes :-

(i) Hypoxia / Ischemia : deficency of oxygen

(ii) physical agent : Road accident, Thermal trauma (heat, Cold) Electericity, Radiation

(iii) Chemical and drugs : Chemical poisons (cyanide, arsenic, Mercury Strond acid, alkalies, drug.

(iv) Infectious agent: rickettsiae, bacteria, fungi etc.

(v) Nutritional derangement: protein-Calorie deficiencies.

(vi) Psychologic factors: Mental stress, strain, anxiety, depression

(2) Genetic Causes:-

(i) Developmental defect (Morphogenic problems):-

Develop during fetal life. Some chemicals or drug induce teratogenic effects. These cause morphology change in embryonic development Eg. Thalidomide, Malformation.

(ii) Cytogenic effect:-

It includes change in number of chromosomes.

(iii) Single gene defect:-

It means the mutation in single gene. (DNA change)

(iv) Strong disease:-

Eg. Glucose-6-dehydrogenase deficency may cause hemolytic disease.

(v) Disorder with Multifactorial inheritance:-

- occur due to both genetic as well as environmental factors.

Eg. Colours of hair, eyes, height.

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Pathogenesis of Cell injury :-

pathogenesis is the process by which a disease or disorder develops. It can include factors which contribute not only to the onset of the disease or disorder, but also to its progression and maintenance.

- The word comes from Greek word "pathos" means "suffering disease" and "genesis" means "Creation".

① Cell Membrane damage :-

persistent Ischaemia and hypoxia result in irreversible changes in structure and function of the cell i.e Cell death

- The pathogenesis of cell injury involves certain events like damage of Cell Membrane (Cell membrane disruption, Cytoskeletal damage etc), mitochondrial damage (appearance of vacuoles, deposition of Calcium salts etc), ribosomal damage, nuclear damage.

② Mitochondrial damage :-

- Mitochondria - Suppliers of energy in the form of ~~energy~~ ATP
- Damage by increased Cytosolic Calcium, ROS, oxygen deprivation.
- 2 major Consequence of damage
  - failure of oxidative phosphorylation and progressive depletion of ATP culminating in necrosis of the cell

- Increased permeability of the mitochondrial membrane resulting in leakage of protein into cytosol and death by apoptosis.

③ Ribosome damage:-

- Damage to ribosomes can lead to disease which termed as Ribosomopathy.
- Ribosomopathies are caused by alteration in the structure or functioned of ribosomes.
- Name of some these disease are listed below.

① Diamond-blakfan anemia:-
It is characterized normocytic or macrocytic anemia (Low RBC counts) with decreased erythroid progenitor cells in the bone marrow.

② Dyskeratosis Congenital:-
The entity was classically defined by the abnormal skin pigmentation, nail dystrophy is abnormal changes in the shape, colour, texture, and growth of the fingernails or toenails.

③ Shwachman-Diamond Syndrome:-
It is characterized by bone marrow dysfunction, skeletal abnormalities and short stature.

④ Nuclear damage :-

DNA or nucleoproteins are damaged by activated lysosomal enzymes such as proteases and endonucle.

- Irreversible damage to nucleus can be in 3 forms.

(i) Pyknosis - Condensation and clumping of nucleus
(ii) Karyorrhexis - nuclear fragmentation
(iii) Karyolysis - dissolution of nucleus.

★ Morphology of cell injury :-

- Morphology is the study of form, shape or structure.
- Cell injury refers to a variety of structural and functional changes that occur in cells when they are exposed to harmful stimuli.
- The morphological changes seen in injured cells can be reversible or irreversible, depending on the severity and duration of the insult.

Adaptive Changes :-

- In order to survive and maintain the normal steady state "Homeostasis". the cells adjust themselves with the changing environment depending on the physiological needs, which is termed as Physiological adaptation.

- The physiological and pathological adaptation are brought about by the following two processes:-

1. By increasing their number (i.e hyperplasia), or by increasing or decreasing their size (i.e hypertrophy and atrophy, respectively).
2. By changing the pathway of phenotypic differentiation of cells, i.e Metaplasia and dysplasia.

- Adaptive Cellular responses include the following Mechnism:

1. An alteration in the receptor binding on the Cell Surface.
2. An alteration in the Signalling Mechnism for protein Synthesis.
3. Introduction of new proteins

① Atrophy:-

- Atropy is the term to describe a reduction in the cell size.
- Though the function of such cells may be reduced, yet they do not die.
- poor nutrition, reduced blood Supply, loss of innervation, decrease in physical work, loss of endocrine stimulation and ageing result in atophy.

② Hypertrophy :-

- Hypertrophy is the term used to describe an increase in the Cell size.

This occurs due to an increase in the number of organelles and the amount of structural protein.

- As the size of cells increase, the organ size also increase
- Sometimes, hypertrophy may occur along with hyperplasia (↑ in number of cells), thus resulting in enlargement of the organ.
- Hypertrophy is divided in two types.

1. Physiologic hypertrophy :- The best example of this hypertrophy and hyperplasia is enlarged size of uterus during pragnancy.

2. Pathologic hypertrophy :- Some examples of disease associated with pathological hypertrophy are hypertrophy of Cardiac, smooth and skeletal Muscles.

③ Hyperplasia :-

Hyperplasia is the term used to describe an increase in cell number.

- If the cell replicate excessively, hyperplasia may occur.

Hyperplasia Can also be either physiologic or pathologic.

(ii) physiologic hyperplasia :-

proliferation of the glandular epithelium of female breast during puberity and pregnancy is the best example of this type of hyperplasia.

(iii) pathologic hyperplasia :-

This mostly occurs when the hormones and growth factor are stimulated significantly. For example of a proliferation endometrial activity occurs after a normal menstural period.

- The common causes of pathologic hyperplasia are:
  - prolonged irritation e.g. fibrosis / Nodules in hands.
  - Nutritional disorder e.g. Iodine deficiency
  - Infections e.g. chicken pox
  - Endocrine disorder e.g. prostate hyperplasia.

(4) Metaplasia :-

- Metaplasia is the term used to described a reversible change in the cells (or tissues).
- metaplasia is characterised by replacement of one type of cells (or tissue) by another type e.g columnar epithelial cells convert into squamos epithelial cells.
- Through the basic structure of both is the same, yet their functional capacity is altered.

Metaplasia is caused by following conditions:

1) prolonged irritation e.g gall stone cause metaplasia of columnar cells to stratified squamos epithelial cells in gall bladder wall.
2. Endocrine disturbances e.g Columnar epithelium of prostate change into squamos epithelial.
3. Injections e.g pulmonary adenomatosis.

(5) Dysplasia:

- Dysplasia is a term used to describe disordered cellular development.
- Usually occurs along with metaplasia and hyperplasia, thus is also known as atypical hyperplasia.

- Most common example of dysplastic changes are seen in the uterine cervix and respiratory tract

* Cell Swelling :-

Cell Swelling, also known as Cellular edema occurs when Cells increase in volume due to an accumulation of wate

This phenomenon can happen under various pathological Condition.

Causes :-

- Osmotic imbalance : when the balance of Solute inside and outside the cell is disrupted, water may enter the cell to balance osmotic pressure.
- Hypoxia/Ischemia : Lack of oxygen can impair Cellular respiration and ATP production, leading to dysfunctior ion pumps, causing water influx.
- Toxins : Some toxins can damage Cellular membranes or ion channels leading to water uptake.
- Infection : Certain viral or bacterial infection can alter cell permeability.

Detection :-

Microscopy : Swollen Cells often appear enlarged with clear vacuolated Cytoplasm under the Microscope.

Biomakers :- Elevated levels of intra - cellular enzyme in the blood can indicate cell membrane damage and swelling.

☆ Intracellular Accumulation :-

- Various Substance get accumulated in abnormal amount within the cell cytoplasm or nucleus, that can disrupt its normal function and potentially lead to cellular injury or death.

- These accumulations can result from various metabolic processes, environmental expouses and pathological conditions.

Type of Intracellular accumulation :-

① Lipid :-

- Steatosis (fatty change) :- Accumulation of triglycerides within cells. commonly seen in the liver due to alcoholism obesity, and diabetes.
- Cholesterol and Cholestrol Esters :- Deposits in Machrophages and smooth muscles cells in atherosclerosis.

② proteins

- Misfolded proteins: Accumulation of misfolded protein can result in disease such as Alzheimer's disease and parkinson's disease,
- Excessive normal protein :- overproduction or decreased breakdown can lead to intracellular accumulation, seen in conditions like nephrotic syndrom

③ ~~pro~~ Glycogen :-

- Glycogen storage Disease :- Genetic disorder such as pompe disease and McArdle disease result in defective glycoger Metabolism and its accumulation in various tissue.
- Diabetes Mellitus :- Excess glucose Can lead to increase intracellular glycogen stores in various Cells especially hepatocytes.

④ Pigments :-

- Melanin :- Accumulation Can occur in Conditions like Addison's disease.

⑤ Other Substance :-

- Calcium: Dystrophic Calcification in necrotic tissue or Metastatic Calcification due to hyperCalcemia
- Water: Cellular edema as a result of osmotic imbalance or Cell injury.

Mechnisms of Accumulation :-

① Increased production or intake :-

- overproduction of substance like lipid in metabolic syndromes.
- Excessive intake of substances eg iron from repated blood transfusion leading to hemosiderosis.

② Decreased Degradation or Excreation:-
- Defective enzymatic pathway as seen in genetic Storage disease.
- Impaired excreation pathways leading to accumulation within Cells.

Example of disease Associated with Intracellular Accumulation

1. Fatty Liver Disease: Accumulation of triglycerides in hepatocytes due to metabolic Syndrome or alcohol abuse.
2. Alzheimer's disease: Accumulation of beta-amyloid plaques and tau protein tangles.
3. Atherosclerosis: cholesterol accumulation in arterial walls leading to plaque formation.
4. Hemochromatosis: excessive iron accumulation in organs leading to tissue damage.

Management and treatment:-
→ Managing Conditions like diabetes, obesity or hyperLipidemia
→ Dietary and lifestyle changes
→ Medication use to enhance Metabolism or excreation of accumulated substance.

☆ Calcification :-

Calcification refers to the abnormal deposition of Calcium salts in tissue as well as trace amount of other Mineral (like Magnesium and iron).

- Calcification Can be of the following two types :

1. Dystrophic Calcification :-

- occurs in necrotic or damaged tissues.
- Normal serum Calcium Levels.
- Common in atherosclerotic plaques, tuberculous Lymph nodes, and areas of chronic inflammation.

2. Metastatic Calcification :-

- occurs in normal tissues due to elevated serum Calcium Levels (hypercalcemia).
- Common Sites include kidney lungs, stomach and blood vessels.
- Causes of hypercalcemia include hyperparathyroidism, chronic renal failure, and Certain cancers.

Clinical example :-

- Atherosclerosis : Calcification of arterial plaques.
- Chronic kidney Disease : Metastatic Calcification due to secondry hyperparathyroidism.
- Tuberculosis : Dystrophic calcification in granulomas.

Diagnosis :-

- Imaging: X-rays, CT scans, and Ultrasounds can detect Calcified areas.
- Histology: Staining techniques used to visualize Calcium deposit in tissue sample.

Management :-

- Treating Underlying Conditions: Managing hypercalcemia or inflammation.
- Medications: phosphate binders in chronic kidney disease bisphosphonates for hypercalcemia
- Surgical Removal: In Cases of Symptomatic Calcifications like kidney stones.

★ Enzyme Leakage :-

Enzyme Leakage refers to the release of intracellular enzymes into the extracellular space or into the blood stream. often indicative of cell damage or lysis.

Causes :-

1. Cell injury :-
   - Mechnical Damage: physical trauma or injury to tissue Can Cause Cell rupture
   - Chemical injury: exposure to toxins or harmful chemicals Can disrupt Cell membranes.

2. Pathological Conditions:-

- Ischemia and hypoxia: Reduced blood flow or oxygen supply can damage cell membrain Membranes, leading to enzyme release.
- Inflammation: Inflammatory processes can cause cell lysis and enzyme leakage.
- Infection: viral or bacterial infections can lead to cell destruction and enzyme release.

3. Apoptosis and Necrosis :-

- Apoptosis: programmed cell death, while usually controlled can still lead to some enzyme release.
- Necrosis: uncontrolled cell death result in significant enzyme leakage.

Common Enzymes Involved:-

- Lactate Dehydrogenase (LDH)
- Aspartate Aminotransferase (AST) and Alanine Aminotransfer
- Creatine kinase (CK)
- Amylase and lipase

Diagnosis:-

- measuring enzyme level in blood can help diagnose and monitor various condition.

* Management and treatment:-

1. Addressing the Underlying Cause:-

- Treatment focuses on managing the underlying cause of cell injury or disease (e.g treating infections, reducing ischemia).

2. Monitoring:-

Regular monitoring of enzyme levels can help assess the progression of disease and the effectiveness of treatment.

☆ Acidosis :-

Acidosis (pH below 7.35) is a condition involving accumulation of acid which causes the body fluid pH to become more acidic compaired to the normal pH of 7.4. A reduce pH means increase in acidosis.

Types of Acidosis :-

① Metabolic acidosis :-

occurs when there is an excess production or reduced excretion of non-volatile acids or a loss of bicarbonat

- Causes:

- Increase Acid production: Lactic acidosis (due to Sever hypoxia), ketoacidosis (in unconhrolled diabetes), ingestion of toxins (e.g methanol, ethylene glycol).

- Decreased Acid Excreation:-
  Renal failure
- Bicarbonate Loss:-
  Diarrhea or renal tubular acidosis.

(2) Respiratory Acidosis:-

Results from an accumulation of Carbon dioxide (CO_2) due to impaired Lung function.

Causes :-

- Hypoventilation: due to chronic obstructive pulmonary disease (COPD), severe asthma, drug overdose, neuromuscular disorder.

Symptoms:-

- General: Fatigue, confusion, headache
- Severe Cases: Shortness of breath, lethargy, decreased consciousness, coma.

Treatment:-

~~1. Metabolic Acidosis:-~~

1. Address underlying Cause:
   - Metabolic Acidosis: Treat conditions like diabetes, renal failure or toxins ingestion.

- Respiratory Acidosis:- Improve ventilation (e.g through bronchodilators, mechnical ventilation) and address underlying respiratory disorder.

2. Supportive Measures:-

- IV Bicarbonate: In Severe metabolic acidosis to neutralize excess acid.
- Oxygen therapy: In respiratory acidosis to improve oxygenation.

☆ Alkalosis:-

Alkalosis (pH above 7.45) is a condition involving accumulation of base which causes the body fluid pH to become less acidic compared to the normal pH of 7.4. An increased pH means decrease in acidity.

Type of Alkalosis:-

① Metabolic Alkalosis:-
occurs when there is an excessive loss of hydrogen ions (H^+) or a gain in bicarbonate (HCO_3^-)

Causes:-

- Loss of hydrogen ions: vomiting, Nasogastric Suctioning
- Excessive bicarbonate intake: Ingestion of bicarbonate-containing antacid.

- Diuretic use: Loss of potassium and hydrogen ions.
- Hyperaldosteronism: Increased renal H^+ excretion.

(2) Respiratory Alkalosis :-

Results from an excessive Loss of Carbondioxide (CO_2) due to hyperventilation.

Causes :-

- Hyperventilation: Anxiety, panic attacks, fever pain, mechnical Ventilation.
- Hypoxia: high altitudes, pulmonary disease.
- CNS Disorder :- stroke, meningitis

Symptoms of Alkalosis :-

General: irritability, muscle twitching, Muscle cramps, tingling or numbness in the extremities.

severe Cases: Seizures, tetany, arrhythmias and Coma.

Diagnosis :-

- Arterial blood gas Analysis: measures pH, partial pressure of Carbon dioxide and bicarbonate
- serum Electrolytes: To assess chloride, potassium and bicarbonate levels.

☆ Treatment :-

① Address underlying Causes :-

- Metabolic Alkalosis : Treat conditions like vomiting, diuretic use, or hormone imbalances.
- Respiratory Alkalosis : Reduce hyperventilation (e.g Using paper bags for anxiety-induced hyperventilation) and address underlying respiratory conditions.

② Supportive Measures :-

- Electrolyte replacement : potassium and ~~chlo~~ chloride supplementation.
- Intravenous fluids : Isotonic saline to correct volume depletion and promote renal bicarbonate excreation.

☆ Electrolyte Imbalance :-

The electrolytes present in blood are having a fixed Level. Changes in the amount of these electrolytes lead to the electrolyte imbalances.

- Normal Levels of Some important electrolytes are given below:

- Calcium: 4.5-5.5 mEq/L
- Chloride: 97-107 mEq/L
- potassium: 3.5-5.3 MEq/L
- Megnesium: 1.5-2.5 mEq/L
- Sodium: 136-145 mEq/L

- The level of an electrolyte in the blood Can become too Low or too high, leading to an imbalance.
- Important electrolytes are lost in sweat during exercise, including sodium and potassium.

→ The Concentration Can also be affected by rapid Loss of fluids, Such as after a bout of diarrhea or vomiting.

→ These electrolytes must be replaced to maintain healthy Levels.

→ The kidney and Several hormones regulate the Concentratio of each electrolyte.

- Low Levels of electrolytes Can also effect overall health.
- The most Common imbalances are of Sodium and potassium.

Symptoms of electrolyte imbalance :-

A harmful Concentration of magnesium, sodium, potassium or Calcium Can provide one or more of the following Symptom

- Irregular heartbeat
- Weakness.
- Bone disorder
- Change in blood pressure
- Muscle spasm
- Seizures.

Causes :-

There are many Causes for an electrolyte imbalance.

- kidney disease
- Loss of body fluid from prolonged vomiting, diarrhea, Sweating or high fever.
- Inadequate diet and lack of vitamins from food.
- Severe dehydration.
- Congestive heart failure.
- Cancer treatment
- Some drugs, such as diuretics (Furosemide or bumetanid
- Hormonal and endocrine disorder.

☆ Basic Mechnism Involved in the process of inflammation and repair :-

☆ Inflammation :-

Inflammation is a defensive response to the injury or infection, which induces physiological changes to control tissue damage and to remove the pathogenic infections.

Types of inflammation :-

① Acute inflammation :-

- Short-term response lasting from a few hours to a few days.
- Characterized by redness, heat, swelling, pain, and loss of functions.
- Commonly seen in injuries like cuts, bruises, or infections like colds.

② Chronic inflammation :-

- Long-term response that can last for months or years.
- May result from persistent infections, autoimmune disease, prolonged exposure to irritants, or chronic conditions like obesity.
- Can lead to tissue damage and contribute to various diseases such as arthritis, heart disease, and cancer.

Causes of Inflammation :-

The following agent are responsible for the Causation of inflammation:

- Physical Agents : e.g Heat, Cold, radiation, and Mechnical trauma
- Chemical Agents: e.g organic and Inorganic Chemicals.
- Immunological Agent: e.g immunological agent like Cell-Mediated and antigen-antibody reaction.
- Biological Agent: e.g viral, bacterial, and fungal infection and Microbial toxins.

Clinical Sign of Inflammation :-

Clinical Signs of Inflammation include:

1. Rubor (Redness): It denotes redness at the Site of Inflammation, resulting from the dilation of vessels, which Leads to an Increase In the blood flow.
2. Tumour (Swelling): It denots Swelling at the Site of inflammation resulting from the Collection of exudates at the inflamed Site.
3. Calor (Heat): It denots ~~pain~~ Slightly elevated temperature at the site of Inflammation, resulting from the dilation of vessels which increase the blood flow.
4. Dolor (pain) :- It denotes pain at the site of inflammation, resulting from the Compression of nerve by the Swelling

in addition to the release of chemical ~~medication~~ Mediators (direct effect) in response to inflammatory process.

✱ Process of inflammation:-

Inflammation is a Complex biological response to harmful Stimuli such as pathogens, damaged Cells, or irritants.

① Initiation:-

- **Recognition of the Stimulus:-**
  - Pathogen-associated Molecular patterns (PAMPs) and damage associated Molecular patterns (DAMPs) are recognized by pattern recognition receptors (PRRs) or Immune Cells.
- **Release of inflammatory Mediator:**
  Immune Cells such as macrophages, dendritic Cells, and Mast Cells release Cytokines (e.g TNFα, IL-1, IL-6) Chemokines, histamines and prostaglandins.

② Vascular changes:-

- **Vasodilation:-**
  Mediators like histamine and nitric oxide Cause blood vesseles to dilate, Increase blood flow to the area, resulting in redness and heat.
- **Increased Vascular permeability:-**
  Mediators Such as bradykinin and Leukotriens Increase the permeability of blood vessels, allowing proteins and Immune Cells to enter the tissue, Causing Swelling (edema).

③ Cellular Response :-

- Leukocyte Recruitment and activation :-
  chemokines attract Leukocytes (neutrophils, monocytes) to the site of injury. These cells adhere to the endothelial and migrate through the vessels wall into the tissue.
- phagocytosis and pathogen clearance :-
  Neutrophils and macrophages engulf and destroy pathogens and ~~debr~~ debris.

④ Resolution and Repair :-

- Termination of the Inflammatory Response :-
  - Anti-Inflammatory Cytokines (e.g IL-10, TGF-β) and lipid mediator (e.g resolvins, protectins) help to resolve inflammation.
  - Apoptosis of immune cells and clearance of dead cells by macrophages occurs.
- Tissue Repair :-
  - Fibroblasts produce extracellular Matrix Components to rebuild tissue.
  - New blood vessels from through ~~to~~ angiogenesis, and epithelial cells proliferate to restore the integrity of the tissue.

* Mediators of inflammation :-

Factor that mediate the process of inflammation are known as endogenous mediators of increase vascular permeability or permeability factors.

- There are various endogenous Compounds which Can increase vascular permeability. (pain, fever, vasodilation)
- Substance that act as chemical mediators of inflammation Can either be released from the cells or from the plasma.

Following are the chemical mediators of accute inflammation

1] Cell-derived Mediator :-

- Vasoactive amines : Histamine, 5-hydroxytryptamine
- Arachidonic acid metabolite : eicosonoids
- Lysosomal Components: neutrophils, monocytes
- platelet activating factor: basophils or mast Cells.
- Cytokines : IL-1, TNF-α, TNF-β, IF-γ, chemokines.
- Nitric oxide and oxygen metabolites.

(2) plasma-Derived Mediators :-

- The kinin System : Bradykinin
- The Clotting System : Fibrin and fibrinopeptides
- The fibrinolytic System : plasmin
- The Complement System : Anaphylatoxins.

☆ Principle of wound healing in skin :-

Wound healing in the skin is a complex and dynamic process that involves multiple overlaping phases: Homeostasis, inflammation, ~~proli~~ proliferation and remodeling.

① Homeostasis (Immediate) :-

- Vasoconstriction : Blood vessels constrict to reduce bleeding
- platelet aggregation : platelets form a temporary plug.
- Clot formation : Coagulation cascade form a fibrin clot to stabilize the plug.

② Inflammation (Hours to Day) :-

- Vasodilation : Increased blood flow to wound.
- Immune response : Neutrophils and macrophase clean the wound and release growth factor.

③ proliferation (Day to weeks) :-

- Angiogenesis : Formation of new blood vessels.
- Fibroplasia : ~~Fibroplasia~~ Fibroblasts produce Collagen and extracellular matrix.
- Granulation Tissue : New tissue forms, rich in Capaillaries and fibroblasts.

④ Remodeling (weeks to Month) :-

- Collegen Remodeling : Type III Collegen is replaced by Stronger Type I Collagen.

- Wound Contraction: myofibroblasts pull wound edge together.

key Factor Affecting Wound healing :-

- Age: Healing Slows with age.
- Nutrition: Adequate nutrients, especially protein and vit.
- Oxygenation: Essential for cellular functions and energy production.
- Infection: Can delay healing by prolonging inflammation.
- Chronic Disease: Condition like diabetes impair healing.
- Medications: Some like Corticosteroids, can inhibit healing.

Pathophysiology of Atherosclerosis :-

Atherosclerosis is a chronic, progressive disease characterized by the accumulation of lipids, inflammatory cells, and fibrosis fibrous elements within the arterial walls.

Initiation and progression :-

1. Endothelial injury and Dysfunction :-
   - Initial injury to the endothelial cells lining the arteries can be caused by factors like hypertension, hyperlipidemia, smoking and diabetes.

- This injury leads to increased permeability of the endothelial and allows low-density lipoprotein (LDL) Cholestrol to infiltrate the arterial wall.

② Lipid Accumulation :-

- LDL Cholestrol accumulates in the intima (inner layer of the artery.
- LDL Undergoes oxidation, becoming oxidized LDL, which is highly atherogenic.

③ Inflammatory Response :-

oxidized LDL triggers an inflammatory response, attracting monocyte to the site of endothelial injury.

- Monocyte migrate into the inner layer, differentiate into macrophages, and ingest oxLDL, transforming into foam cell.

② plaque Development :-

- Fibrous Cap formation.
- plaque Growth and Complications.

③ plaque Rupture and thrombosis.

- This exposure leads to platelet aggregation and thrombs
- This exposure leads to acute clinical event Such as myocardial infraction (Heart attak), Stock, depending on the affected artery.