

LECTURE NOTES

Undergraduate Nursing Students

Pathophysiology



**Ethiopia Public Health
Training Initiative**

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PREFACE

This pathophysiology lecture note will serve as a theoretical guideline for undergraduate nurse and other health sciences students.

Pathophysiology is the study of the disturbance of normal mechanical, physical, and biochemical functions, either caused by a disease, or resulting from a disease or abnormal syndrome or condition that may not qualify to be called a disease. An alternate definition is "the study of the biological and physical manifestations of disease as they correlate with the underlying abnormalities and physiological disturbances.

This lecture-note will provide a summarized basis for the students by expanding the student's knowledge in the sciences how alteration in structure (Anatomy) and function (Physiology) disrupt the human body as a whole. It is written for undergraduate students in nursing and other health oriented disciplines as prerequisite course for certain courses.

The understanding of disease process is continually being updated and clarified by research. In this text of pathophysiology, every attempt has been made to provide the most current available information in simplified and well-explained ways.



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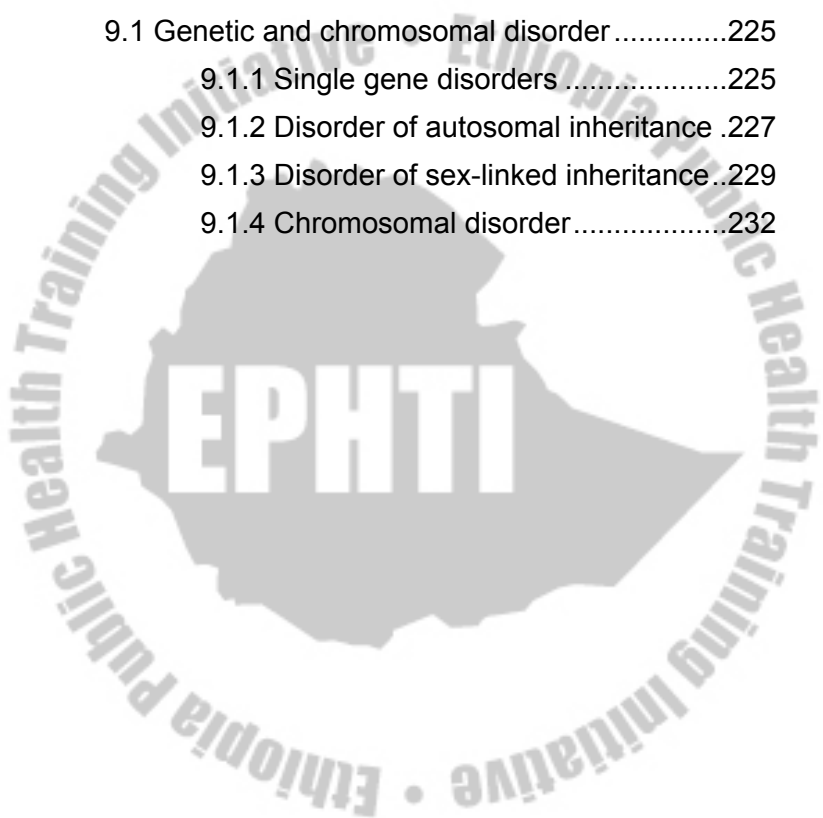
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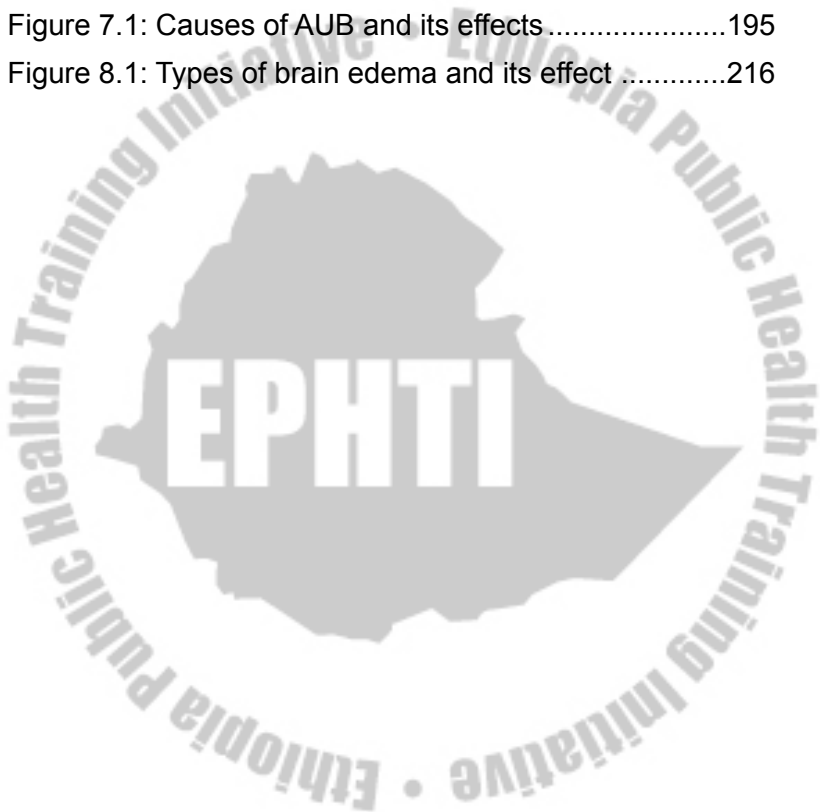
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LIST OF ABBREVIATIONS

ACTH	Adreno cortico trophic hormone
ADH	Anti diuretic hormone
AIDS	Acquired immuno deficiency syndrome
AMI	Acute myocardial infarction
ATP	Adenosine tri phosphate
AUB	Abnormal uterine bleeding
BBB	Blood brain barrier
BPH	Benign prostatic hyperplasia
CAH	Congenital adrenal hyperplasia
CHF	Congestive heart failure
CNS	Central Nervous System
COP	Cardiac out put
COP	Collid Osmotic Pressie
COPD	Chronic obstructive pulmonary disease
CSF	Cerebro spinal fluid
CT	Computed tomography
DI	Diabetes insipidus
DNA	Deoxyribonucluc acid
DUB	Dysfunctional uterine bleeding
EBV	Epstein bar virus
FSH	Follicle stimulating hormone
GH	Growth hormone
GIT	Gastro intestinal tract
GTD	Gestatimal Trombo Plastic Disease
HIV	Human immuno deficiency virus
HMD	Hyaline membrane disease

HPV	Human papiloma virus
HSV	Hepes simplex virus
HZV	Herpes zoster virus
ICP	Intra cranial pressure
IUCD	Intra uterine contraceptive device
LH	Leutenizing hormone
LHF	Left sided heart failure
MI	Myocardial Infarction
MRI	Magnetic resonance imaging
MPS	Mononuclear Phagocytic System
MSH	Melanocyte stimulating hormone
OIs	Opportunistic infections
PCP	Pnuemo cystic carnii pneumonia
PID	Pelvic inflammatory disease
PKU	Phenyl ketone uria
PMN	Poly morpho nuclear
PPD	Purified Protein Derivative
PUD	Peptic ulcer disease
RBC	Red blood cells
RES	Reticule Endothelial System
RHD	Rheumatic heart disease
RHF	Right sided heart failure
RNA	Ribonucleic acide
SIADH	Syndrome of inappropriate secretion of anti diuretic hormone
SLE	Systemic lupus erythematosus
STD	Sexually transmitted diseases
TH	Thyroid hormone
TLC	Total lymphocyte count

TSH	Thyroid stimulating hormone
UTI	Urinary tract infection
WBC	White blood cells



CHAPTER ONE

ALTERATIONS IN CELL FUNCTION AND GROWTH

Learning Objectives

At the end of this chapter the students will be able to:-

- Discuss neop-Define cellular adaptive changes
- Explain types of cellular adaptive changes.
- Discuss causes of cellular injury and cellular changes. lasia and abnormal cellular growth.
- Describe different types of neoplasms
- Discuss mechanisms of carcinogenesis

1.1 Cell injury and Cellular Adaptive Changes

The life cycle of a cell exists on continuum that includes normal activities and adaptation, injury or lethal changes. Adaptation is a normal life cycle adjustment like in growth during puberty; changes during pregnancy or aging and stressful life style produce physiologic changes that may lead to adaptation or disease.

The cell constantly makes adjustments to a changing, hostile environment to keep the organism functioning in normal steady state which is necessary to ensure the survival of the

Pathophysiology

organism. Prevention of disease by the body depends on the capacity of the affected cells to undergo self-repair and regeneration i.e. adaptive-changes.

- When cells are confronted to one of the following stimulus, they may undergo adaptive changes. The common stimuli are:-

a) Physical agents

- o Trauma, Burn, pressure, irradiation, etc

b) Chemical agents

- o Poisons, drugs, simple compounds, etc.

c) Micro organisms

- Bacteria
- Virus
- Fungus
- Parasites

d) Hypoxia

- Is the most common stimuli (cause)
- Is because of inadequate oxygen in the blood or decreased tissue

Perfusion.

e) Genetic defects

- Can affect cellular metabolism through inborn errors of metabolism or gross malformation

f) Nutritional imbalances

Pathophysiology

- Under nutrition or over nutrition causes cellular injury or changes.

g) Immunologic reaction

E.g. - Hypersensitivity reaction.

1.1.1 Types of cellular Adaptive-changes

- When cells are exposed to one of the above noxious-stimulus they will undergo one or more of the following types of adaptive changes:-
 - i. Increased concentrations of normal cellular constituents.
 - ii. Accumulate abnormal substances
 - iii. Change the cellular size or number or
 - iv. Undergo a lethal change.

1.1.2 Abnormal and normal accumulation of intracellular substances

Intracellular accumulations often result from environmental changes or an inability of the cell to process materials (substances) that cannot be metabolized by the cells. These substances may accumulate in the cytoplasm. As a result common changes include:-

- Cellular swelling

Pathophysiology

- Lipid accumulation (Fatty change process in the cytoplasm of cells).
- Glycogen depositions (Excess deposition of glycogen in organs).
- Calcification (precipitation of calcium in dead or Chronic inflammation area)
- Hyaline infiltration(characteristic alteration within cells or in the Extra-cellular spaces that appear as inclusion on stained histology).

1.1.3. Changes to cellular size or numbers

- Changes in size and numbers of the cells are usually as a result of response to adapt to harmful agents.
- The changes include:-

I) Atrophy

- Atrophy refers to a decrease in cell size.
- Causes: - Decreased work load (Disuse atrophy)
 - Loss of nerve supply
 - Decreased blood supply
 - Inadequate nutrition
 - Loss of hormonal stimulation
 - Eg. - Uterine atrophy after menopause.
- Physiologic Atrophy
 - Eg. - Loss of muscle bulk with ageing.

Pathophysiology

II) Dysplasia:-

- Dysplasia refers to the appearance of cells that have undergone some atypical changes in response to chronic irritation.
- It is not a true adaptive process in that it serves no specific functions.
- It is controlled reproduction of cells, but closely related to malignancy in that it may transform into uncontrolled, rapid reproduction.
- It is complete loss of normal architectural orientation of one cell with the next both in shape and size.
- Epithelial cells are common sites for dysplastic changes.

Eg: -Bronchial epithelium,

- Cervical epithelium, etc.

III) Hyperplasia:-

- It is defined as increase of tissue mass due to an increase in the number of cells.
- It occurs in cells that are under increased physiologic workload or stimulations. I.e. the cells are capable of dividing thus increasing their numbers.

Types of Hyperplasia

Pathophysiology

- a) Physiologic Hyperplasia: occurs when there hormonal stimulation
 - Occurs in puberty and pregnancy
- b) Compensatory-Hyperplasia
 - Occurs in organs that are capable of regenerating lost tissues.
 - Eg. When part of liver is destroyed.
- c) Pathologic Hyperplasia
 - Is seen in abnormal stimulation of organs with cells that are capable of regeneration.

E.g. Enlargement of Thyroid gland due to TSH from pituitary gland.

IV) Hypertrophy

- Is an increase in the size of individual cells, resulting in increased tissue mass with out an increase in the number of cells.
- It is usually response of a specific organ to an increased demand for work.

Example: - Enlargement of muscles in Athletes

V) Metaplasia

- Metaplasia is a reversible change in which one type of adult cell is replaced by another type.
- It is an adaptive substitution of one cell type more suitable to the hostile environment for another.

Pathophysiology

Eg. - Replacement of the normal columnar, ciliated goblet cells of the bronchial mucosa by Stratified squamous epithelial cells in chronic smokers.



Pathophysiology

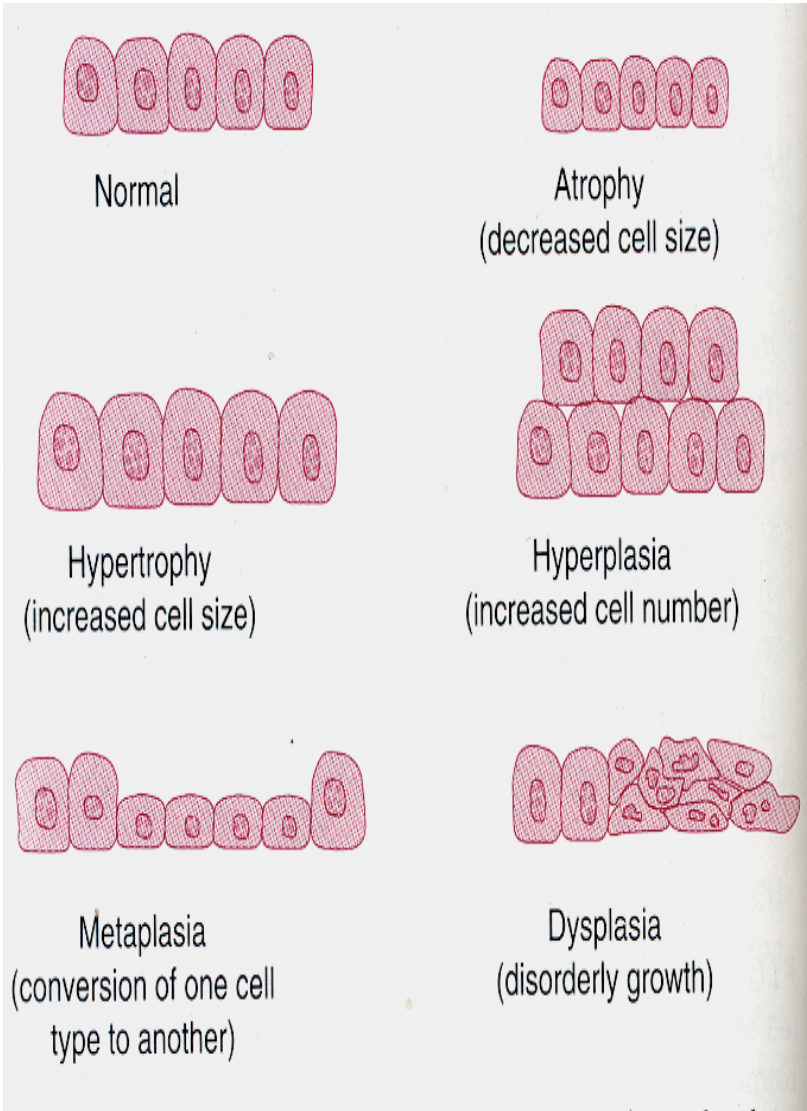


Figure 1.1 Types of cellular adaptive changes

1.1.4. CELLULAR INJURY AND LETHAL CHANGES

Pathophysiology

(Cell Death)

Cell injury can be sub lethal or lethal. Sub lethal injury alters functions with out causing cell death. The changes caused by this type of injury are potentially reversible if the injuring stimuli are removed.

Causes of cell injury:-

Causes of cell injury are the same causes of cellular adaptive changes as mentioned above.

Classification of cell injury:-

Cellular injury can be reversible or it may progress to irreversible change (Lethal change).

1. Reversible cell injury:-

Is cell injury which can be reversed when the stimulus or the cause of injury is removed.

Example

-Ischemia:

- Ischemia refers to a critical lack of blood supply to a localized area.
- It is reversible in that tissues are restored to normal function when oxygen is again supplied to them, but if late progress to ischemic infraction

Pathophysiology

- It usually occurs in the presence of atherosclerosis in the major arteries.
- The classic conditions resulting from ischemia is Angina pectoris.

2. Irreversible Cell injury

It is cellular injury that can not be corrected (reversed) after the stimulus or cause has been removed.

Example:-

a. Infarction:-

- Is localized area of tissue death due to lack of blood supply.
- It is also called Ischemic Necrosis.
- It is due to occlusion of blood vessels by thrombus or embolus. Septic Infarction is added when there is evidence of infection in the area.
- It is irreversible cellular death due to lack of blood supply, when ischemia is persistent or late.
 - Example:- Acute myocardial infarction (AMI)

b. Necrosis:-

Pathophysiology

- The term necrosis refers to cell or tissue death characterized by structural evidence of this death.
- The structural changes are mitochondrial swelling, rupture of cell membrane, shrinking of nucleus or fragmenting, and release of lysozomal-enzymes, etc.
- Based on the structural changes, Necrosis is classified in to two main classes:-

1. Coagulative-Necrosis

- Usually results from lack of blood supply to an area.
- The cell structure and its architectural outline is preserved, but the nucleus is lost (structureless necrosis)
- **Caseouse Necrosis:** - is a good example of structureless necrosis. It is common in tuberculosis and is characterized by central area of necrosis which is soft, friable and surrounded by an area with a cheesy, crumbly appearance.

2. Colliquative- Necrosis (liquefactive-Necrosis)

Pathophysiology

- It frequently occurs in brain tissues and results from break down of neurons by released lysosomal enzymes resulting in formation of pockets of liquid, debris and cyst like structures in the brain tissue.

Example:- Wet gangrene.

1.2. Neoplasm

1.2.1. Definition of terms:-

- **Neoplasm:** - New abnormal growth because of abnormal cellular- reproduction. It is synonymously used with tumor.
- **Aberrant cellular growth:-** An alteration in normal cell growth
- **Tumor:** - A growth of Neoplastic cells clustered together to form a mass. It can be benign or malignant.
- **Benign tumor:** - Is characterized by abnormal cell division but no metastasis or invasion of the surrounding tissues.
- **Malignant tumor:** - Abnormal cell division characterized by ability to invade locally, metastasize and reoccur. It is cancer cells.
- **Carcinogenesis:** - production or origination of cancer cells.

Pathophysiology

- **Sarcoma:** - Malignant growth from mesodermal tissues I.e. connective tissues, blood-vessels, organs, etc.
- **Metastasis:** - Ability to establish secondary tumor growth at a new location away from the primary tumor.
- **Carcinoma:** - Malignant growth originating in epithelial tissues

1.2.2. Benign and Malignant Neoplasia

- The capacity of undergoing mitosis is inherent in all cells. Mitosis is repressed or controlled until specific stimulation for growth occurs. Every time a normal cell passes through a cycle of division, the opportunity exists for it to become Neoplastic.
 - **N.B.** Cancer cells lack repression or lode control of Mitosis I.e. cancer cells are crazy cells.

1.2.3. Epidemiology

- Neoplastic-disease affects 1 in 4 persons in the world.
- Cancer can strike at any age but the chance increase with age.

Pathophysiology

- It is the leading cause of children death aged 3-14 years old.
- The three leading death producing cancer in men are cancer of the lung, colo-rectal and prostatic gland. For women the most common cancers are those of the breast, lung, and colorectal respectively.

1.2.4. Classifications of Neoplasms

- Neoplasms are classified according to their cells of origin and their behavior of growth as benign or malignant.

Table 1.1 A comparison of benign and malignant Neoplasms

Benign	Malignant
- Similar to cell of origin	- Dissimilar from cell of origin

Pathophysiology

- Edges move out word smoothly	- Edges move out ward irregularly.
- Compress locally	- Invade locally
- Slow growth rate	- Rapid to very rapid growth rate.
- Seldom Recur after removal by surgery	- Frequently recur after removal
- Necrosis and ulceration is uncommon	- Necrosis and ulceration common.
- Systemic effect is uncommon	- Systemic effect common.



1.2.5. Nomenclature of Neoplasms

- Naming of Neoplasia based on two main important features of the tumor. These are:-

A) Based on its Behavior of growth:-

i) **Benign**: - Add “oma” at the end for connective tissue origin tumors.

- Add “papiloma” for epithelial origin.
- Add “adenoma” for glandular origin.

ii) **Malignant**: – Add: - “sarcoma” at the end for malignant tumors of Connective tissues origin.

- Add “carcinoma” at the end for malignant tumors of epithelial origin.
- Add “adenocarcinoma” at the end for malignant tumors of glandular origin.

B) Based on cells of origin:-

- Neoplasms are named at their prefix by their cells of origin and their suffixes are added at the end to show whether they are benign or malignant.

Example: -

Behavior of growth

Cells of origin

Benign

Malignant

- Fatty cells

- Lipoma

- Liposarcoma

- Bone cells

- Osteoma

- Osteosarcoma

- Blood vessels

- Hemangioma

- Hemangiosarcoma

- Fibrous tissues

- Fibroma

- Fibrosarcoma

C) Exceptional Naming (Malignant Misnomers)

Pathophysiology

- There are some neoplasms that are named exceptionally to the above rules.

Examples:-

- **Hepatoma:** - malignant tumors of the liver cells. It is also called Hepato-cellular carcinoma
- **Hodgkin's disease:** - Malignant tumors of the lymphoid tissues.
- **Multiple myeloma:** - malignant tumors from the plasma cells.
- **Others:-** Leukemia, Ewing's sarcoma, etc.

1.2.6. Mechanisms of carcinogenesis

- There are large numbers of research done in the world to know the etiology of cancer but none of the theories that attempt to explain the peculiarities of the cancer cells have been completely successful. The following are some of the theories on carcinogenesis:

a. Genetic Instability:-

- The theory of somatic cell mutation supports the concept that mutational carcinogenic agents and heredity susceptibility can induce genetic abnormalities.

Pathophysiology

b. Carcinogens

- Carcinogens are those substances that are capable of inducing neoplastic growth. They are also called oncogenes. Some substances induce neoplastic growth at higher doses and exposure rates while others can be carcinogenic at lower doses and exposure rate.

The three commonly encountered carcinogens are:

1. Chemical carcinogens

- Many chemical agents are capable of causing Neoplasms in either humans or animals. Chemical carcinogens are grouped as:-

a. Polycyclic aromatic hydrocarbons:-

- They are common carcinogens; present in tobacco smoke or automobile exhaust, .Usually cause cancer of lips, oral-cavity, lungs, neck, pancreases,

b. Aromatic amines

- Commonly found in insecticides, certain foods and Naphthalene.

Pathophysiology

Usually related with cancer of the bladder.

c. Alkylating agents

- They can cause cancer when given in large dose. Are usually used as therapeutic agents. example:-
Nitrogen mustard
- Mustard gas

d. Others

- Like aflatoxines, nitrosamides, drugs, etc.

2. Physical carcinogenic agents

Ionizing radiation is a recognized cause of cellular mutations. Damage to DNA may be direct or indirect. A long latent period often exists between exposure and development of clinical disease.

- **Example**:-leukemia and skin cancers became very common long years later in Hiroshima and Nagasaki, Japan; after atomic bomb detonation.

3. Viral carcinogens (oncogenic viruses)

Viruses are thought to cause some human and Animals malignant neoplasms. Current evidence shows that viruses alter the genome of the

Pathophysiology

infected cells, which then alter the offspring of the host cells. Some of the oncogenic viruses are:-

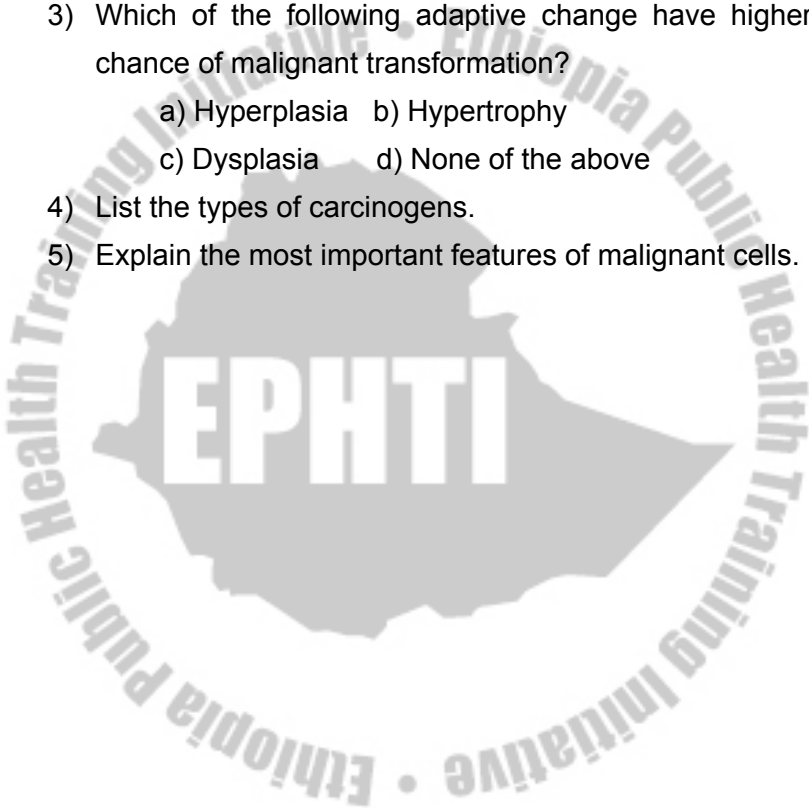
1. **EBV** (Epstein-Barr virus) → associated with Burkett's lymphoma.
2. **HPV** (Human-papilloma-virus) → associated with cervical cancer and skin-papilloma.

4. Other Factors in carcinogenesis

Epidemiologic studies have revealed other factors in the occurrence of neoplasms besides chemical, physical and viral-carcinogens. Some of these factors are dietary habits, sexuality, and other personal habits like smoking, alcohol consumption etc.

Review Questions

- 1) List the types of cellular adaptive changes.
- 2) Discuss the common stimuli for cellular changes?
- 3) Which of the following adaptive change have higher chance of malignant transformation?
 - a) Hyperplasia
 - b) Hypertrophy
 - c) Dysplasia
 - d) None of the above
- 4) List the types of carcinogens.
- 5) Explain the most important features of malignant cells.



CHAPTER –TWO

ALTERATIONS IN BODY DEFENSE

Learning Objectives

At the end of this chapter the students will be able to:-

- Discuss the different types of body defense mechanisms
- Describe Pathophysiologic events of inflammations.
- List local and systemic manifestations of inflammations
- Describe the pathophysiology of resolution (healing) process of Inflammations.
- Compare and contrast pathophysiology of wound healing and fracture Healing.
- Discuss common examples of both acute and chronic inflammatory Conditions.
- Discuss HIV/AIDS and its pathophysiology

2.1. Body Defense Mechanisms against Injury

Pathophysiology

To protect against injury and infection, the body has various defense mechanisms. These defense mechanisms are:-

- 2.1.1) The skin and mucous membranes
- 2.1.2) The mononuclear phagocyte system
- 3) The inflammatory response and
- 2.1.4) The immune system

2.1.1. The skin and mucous membranes

The skin and mucous membranes are the first line of defense mechanisms. They serve as a mechanical barrier for protection of the body against different injurious agents. Break in these barriers give pave for way of injurious agents.

2.1.2. Mononuclear Phagocyte System

The mononuclear phagocyte system (MPS) consists of monocytes and macrophages and their precursor cells. In the past, the MPS system was called the reticuloendothelial system (RES). However, it is not a body system with distinctly defined tissues and organs. Rather, it consists of phagocytic cells located in various tissues and organs (see Table 2.1). The phagocytic cells are either fixed or free (mobile). The macrophages of the liver, spleen, bone marrow, lungs, lymph nodes, and nervous system (microglial cells) are fixed phagocytes. The monocytes (in blood) and the macrophages found in connective tissue, termed histolytic, are mobile, or wandering, phagocytes.

Pathophysiology

Monocytes and macrophages originate in the bone marrow. Monocytes spend a few days in the blood and then enter tissues and change into macrophages. Tissue macrophages are larger and more phagocytic than monocytes.

The functions of the macrophage system include recognition and phagocytosis of foreign material such as microorganisms, removal of old or damaged cells from circulation, and participation in the immune system.

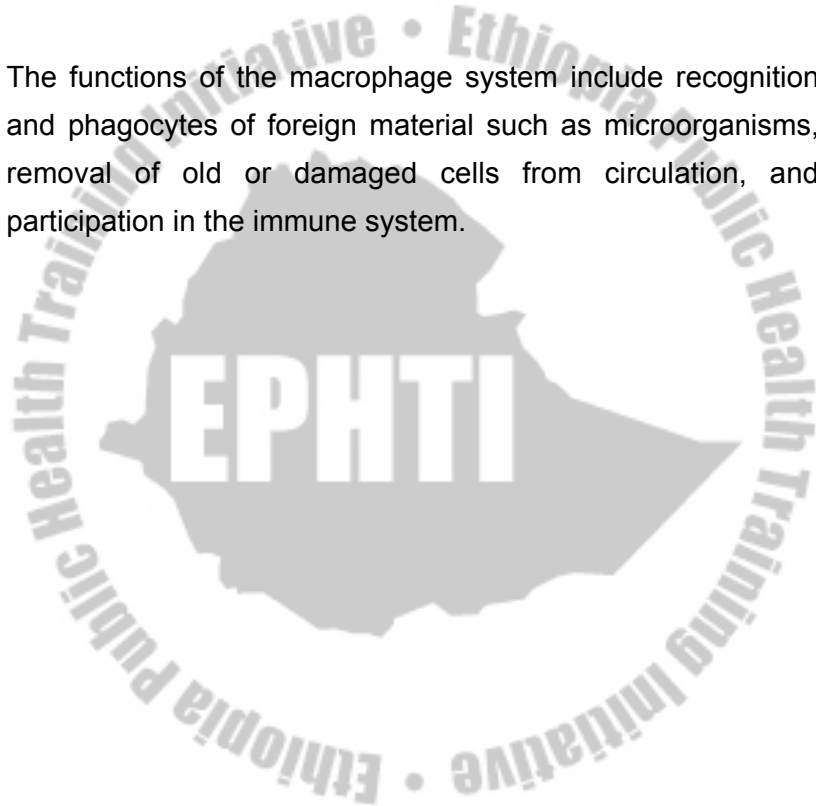


Table-2.1 Location and Name of Macrophages

LOCATION	NAME
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Pathophysiology

Connective Tissue	Histiocytes
Liver	Kupffer Cells
Lung	Alveolar Macrophages
Spleen	Free and Fixed macrophages
Bone Marrow	Fixed Macrophages
Lymph Nodes	Free and Fixed macrophages
Bone Tissue	Osteoclasts
Central Nervous System	Microglial Cells
Peritoneal Cavity	Peritoneal Macrophages
Pleural Cavity	Pleural Macrophages
Skin	Histiocyte, Langerhans' Cells
Synovium	Type A Cells

2.1.3. INFLAMMATORY RESPONSE

The inflammatory response is a sequential reaction to cell injury. It neutralizes and dilutes the inflammatory agent, removes necrotic materials, and establishes an environment suitable for healing and repair. The term *inflammation* is often but incorrectly used as a synonym for the term *infection*.

Pathophysiology

Inflammation is always present with infection, but infection is not always present with inflammation. However, a person who is neutropenic may not be able to mount an inflammatory response. An infection involves invasion of tissues or cells by microorganisms such as bacteria, fungi, and viruses. In contrast, inflammation can also be caused by nonliving agents such as heat, radiation, trauma, and allergens.

The mechanism of inflammation is basically the same regardless of the injuring agent. The intensity of the response depends on the extent and severity of injury and on the reactive capacity of the injured person. The inflammatory response can be divided in to:-

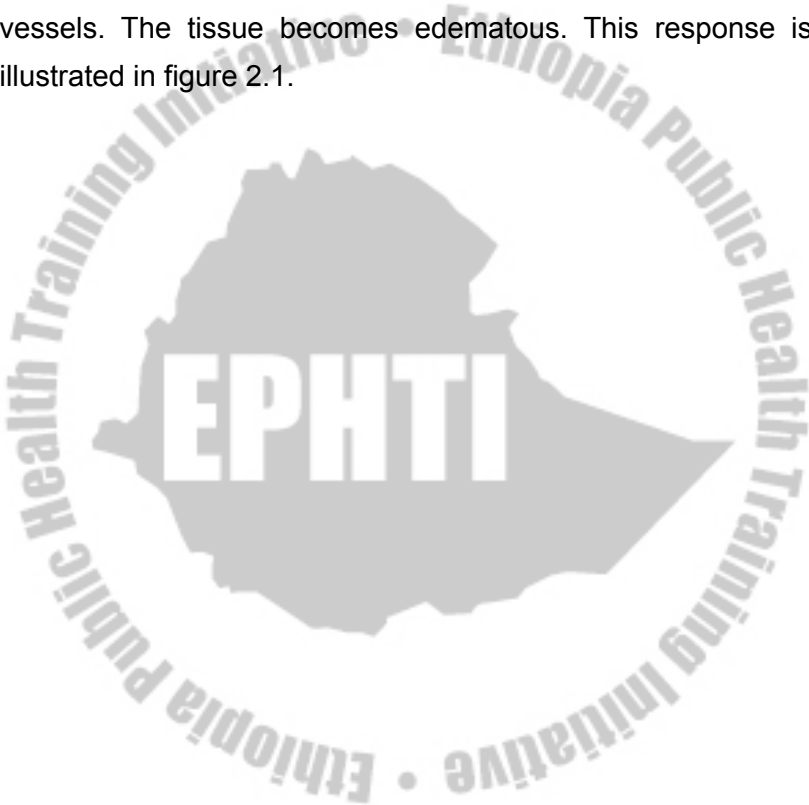
- 1) Vascular response,**
- 2) Cellular response,**
- 3) Formation of exudates**
- 4) Healing.**

1) VASCULAR RESPONSE

After cell injury, arterioles in the area briefly undergo transient vasoconstriction. After release of histamine and other chemicals by the injured cells, the vessels dilate. This vasodilatation results in hyperemia (increased blood flow in the area), which raise filtration pressure. Vasodilatation and chemical mediators cause endothelial cell retraction, which

Pathophysiology

increases capillary permeability. Movement of fluid from capillaries into tissue spaces is thus facilitated. Initially composed of serous fluid, this inflammatory exudates later contains plasma proteins, Primarily albumin. The proteins exert oncotic pressure that further draws fluid from blood vessels. The tissue becomes edematous. This response is illustrated in figure 2.1.



Pathophysiology

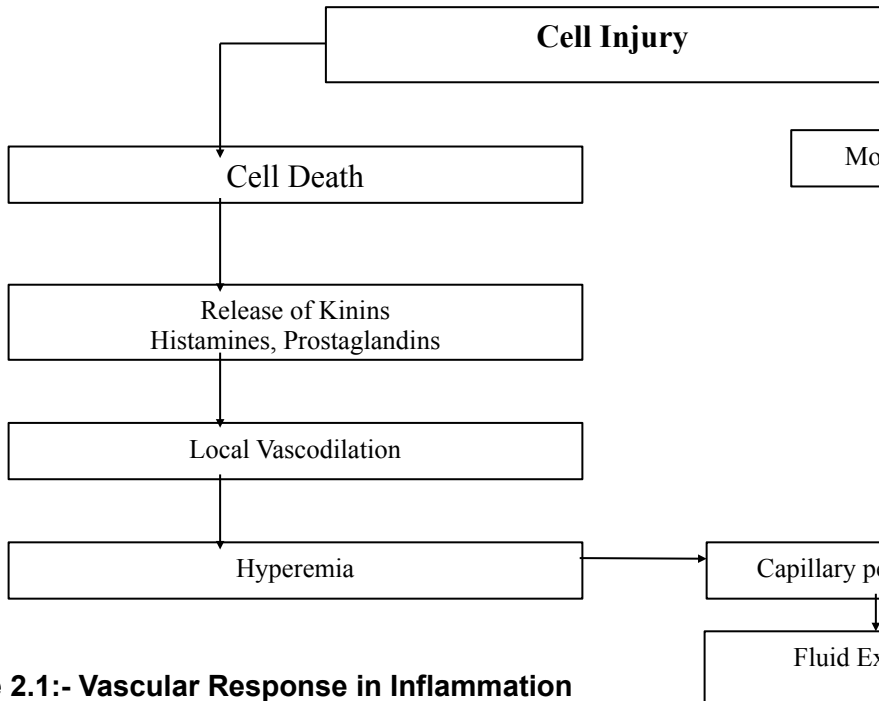


Figure 2.1:- Vascular Response in Inflammation

2)THE CELLULAR RESPONSE

This is characterized by extravasations of leucocytes from the lumen into interstitial tissue followed by phagocytosis.

- **Extravasations** involve the following sequence of events: -
 - a) Margination
 - b) Transmigration across the endothelium to interstitial tissue (also called diapedesis).
 - c) Migration in the interstitial tissues towards a chemotactic stimulus called Chemotaxis.

a) Margination of leukocytes

- It is the adherence of leukocytes to the endothelial cells lining. Mainly to the post Capillary venules.

b) Transmigration of leukocytes

- This is the movement of leukocytes by extending pseudopodia through the vascular wall by a process called **diapedesis**.
- Leukocytes escape from venules and small veins but only occasionally from capillaries.

c) Chemotaxis

- It is a unidirectional leukocyte attraction within tissue space guided by the presence of bacteria and cellular debris.
- All granulocytes, monocytes and to a lesser extent lymphocytes respond to chemotactic stimuli.

d) Phagocytosis

Pathophysiology

- Once the cell has reached to the site of injurious agent (in interstitial tissue) phagocytosis ensues.
- Phagocytic cells include polymorphonuclear leukocytes (particularly neutrophils), monocytes and tissue macrophages.
- Phagocytosis involves three distinct but interrelated steps:-
 - 1. Recognition and attachment** of the particle to be ingested by the leukocytes:
 - Phagocytosis is enhanced if the material to be phagocytosed is coated with certain plasma proteins called opsonins.
 - 2. Engulfment**
 - As a result of fusion between the phagosome and lysosome, a phagolysosome is formed and the engulfed particle is exposed to the degradative lysosomal enzymes
 - 3. Killing or degradation**
 - The ultimate step in phagocytosis of bacteria (any foreign body) is killing and degradation.

There are two forms of bacterial killing methods:

- a. Oxygen independent mechanism:

Pathophysiology

- It is mediated by lysosomal enzymes (the primary and secondary granules) of polymorphonuclear leukocytes.
- b. Oxygen dependent killing of microbes:
- This is microbial killing by the generation of oxygen metabolites such as super oxide, H_2O_2 , HO^- , etc.

Chemical mediators of inflammation

- Chemical mediators originate either from the plasma or from cells (neutrophils, macrophages, lymphocytes, basophiles, mast cells and platelets).
- Some of the chemical mediators of inflammation include histamine, serotonin, lysosomal enzymes, prostaglandins, leukotriens, activated oxygen species, nitric oxide, cytokines,
- Mediators of the inflammatory response are presented in (see table2.2

Table 2.2. Mediators of Inflammation

MEDIATION	SOURCE	MECHANISM OF ACTION
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Pathophysiology

Histamine	Stored in granules of basophils, mast cells, platelets	Causes vasodilation & increased vascular permeability by stimulating contraction of endothelial
Serotonin	Stored in platelets, mast cells, enterochromaffin cells of GI tract Produced from precursors	and creating widened gap between cells Causes increased vasodilation and increased vascular permeability by stimulating endothelial class
K i n i n s (bradykinin)	factor kininogen as a result of activation of Hageman factors (XII) of clotting system	and creating widened gap between cells; stimulates smooth muscle contraction Causes contraction of smooth muscle and dilation of blood vessels; result in stimulation of pain Stimulate histamine release;
C o m p l e m e n t Components (C3a, C4a, C5a)	Anaphylaxis agents generated from complement pathway activation Produced from activation of the clotting system	stimulate chemotaxis Increases vascular permeability; stimulate chemotaxis from neutrophils and monocytes
Fibrinopeptides	Produced from Arachidonic acid	PGE ₁ AND PGE ₂ cause vasodilation; LTB ₄ stimulate chemotaxis
Prostaglandins	a n d	

3) EXUDATES FORMATION

Exudates consist of fluid and leukocytes that move from the circulation to the site of injury. The nature and quantity of exudates depend on the type and severity of the injury and the tissues involved (see Table 2.3).

Table-2.3 TYPES OF INFLMMATIORY EXUDATE

TYPE	DESCRIPTIN	EXAMPLES
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Pathophysiology

Serous	<p>Serous exudates result from outpouring of fluid that has low cell and protein content; it is seen in early stages of inflammation or when injury is mild</p>	Skin blisters, pleural effusion
Catarrhal	<p>Catarrhal exudates are found in tissues where cells produce mucus. Mucus production is accelerated by inflammatory response.</p>	Runny nose associated with URTI
Fibrinous	<p>Fibrinous exudates occur with increasing vascular permeability and fibrinogen leakage into tissue spaces. Excessive amount of fibrin coating tissue surfaces may cause them to adhere.</p>	Furuncle(boil), abscess, cellulites (diffuse inflammation in connective tissue)
Hemorrhagic	<p>Hemorrhagic exudates result from rupture or necrosis of blood vessel walls; it consists of RBCs that escape into tissue.</p>	Hematoma

Clinical Manifestations of inflammations

Pathophysiology

The clinical manifestations of inflammation can be classified as

- i. Local response to inflammation includes the manifestations of redness, heat, pain, swelling, and loss of function (see table 2.4).
- ii. Systemic response to inflammations

Table 2.4 LOCAL MANIFESTATIONS OF INFLAMMATION

MANIFESTATIONS	CAUSE
1) Redness (rubor)	Hyperemia from vasodilatation
2) Heat (color)	Increased metabolism at inflammatory site
3) Pain (dolor)	Change in PH; Change in ionic concentration; nerve stimulation by chemicals (e.g. histamine, prostaglandins); pressure from fluid exudates
4) Swelling (tumor)	Fluid shift to interstitial spaces; fluid exudates accumulation
5) Loss of function (function laesa)	Swelling and pain

➤ **Systemic manifestations of inflammation:-**

Include leukocytosis with a shift to the left, malaise, nausea and anorexia, Increased pulse and respiratory rate, and fever.

- **Leukoctosis** results from the increased release of leukocytes from the bone marrow. An increase in the circulating number of one or more types of leukocytes may be found. Inflammatory responses are accompanied by the vaguely defined constitutional symptoms of malaise, nausea, anorexia, and fatigue. The causes of these systemic changes are poorly understood but are probably due to complement activation and the release of cytokines (soluble factors secreted by WBCs that act as intercellular messengers) from stimulated WBCs. Three of these cytokines, interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF), are important in causing the constitutional manifestations of inflammation, as well as inducing the production of fever. An increase in pulse and respiration follows the rise in metabolism as a result of an increase in body temperature.

- **Fever**

Pathophysiology

- The onset of fever is triggered by the release of cytokines. The most potent of these cytokines are IL-1, IL-6, and TNF (released from mononuclear phagocytic cells).
- These cytokines cause fever by their ability to initiate metabolic changes in the temperature-regulating center. The synthesis of prostaglandin E2 (PGE2) is the most critical metabolic change. PGE2 acts directly to increase the thermostatic set point. The hypothalamus then activates the sympathetic branch of the autonomic nervous system to stimulate increased muscle tone and shivering and decreased perspiration and blood flow to the periphery. Epinephrine released from the adrenal medulla increases the metabolic rate. The net result is fever.
- With the physiologic thermostat fixed at a higher-than-normal temperature, the rate of heat production is increased until the body temperature reaches the new set point. As the set point is raised, the hypothalamus signals and increases in heat production and conservation to raise the body temperature to the new level. At this point the individual feels chilled and shivers. The shivering response is the body's method of

Pathophysiology

raising the body's temperature until the new set point is attained. This seeming paradox is dramatic: the body is hot yet an individual piles on blankets and may go to bed to go warm. When the circulating body temperature reaches the set point of the core body temperature, the chills and warmth-seeking behavior cease.

The classifications of febrile response

- The febrile response is classified into four stages:
Prodromal, chill, flush and defervescence.

(See Table2.5)

Pathophysiology

Table-2.5 STAGES OF THE FEBRILE RESPONSES

STAGE	CHARACTERISTICS
• Prodromal	• Nonspecific complaints such as mild headache, fatigue, general malaise, and muscle aches
• Chill	• Cutaneous vasoconstriction, “goose pimples,” pale skin; feeling of being cold; generalized shaking chill; shivering causing body to reach new temperature set by control center in hypothalamus
• Flush	• Sensation of warmth throughout body; cutaneous vasodilatation; warming and flushing of the skin
• Defervescence	• Sweating; decrease in body temperature

The released cytokines and the fever they trigger activate the body's defense mechanisms. Beneficial aspects of fever include increased killing of microorganisms, increased phagocytes by neutrophils, and increased proliferation of T cells. Higher body temperature may also enhance the activity of interferon, body's natural virus-fighting substance.

Types of Inflammation

Pathophysiology

The basic types of inflammation are acute, sub- acute, and chronic.

In acute inflammation the healing occurs in 3 to 3 weeks and usually leaves no residual damage. Neutrophils are the predominate cell type at the site of inflammation.

A sub acute inflammation has the features of the acute process but lasts longer. For example, infective endocarditic is a smoldering infection with acute inflammation, but it persists throughout weeks or months.

Chronic Inflammation lasts for weeks, months, or even years. The injurious agent persists or repeatedly injures tissue. The predominate cell types at the site of inflammation are lymphocytes and macrophages. Chronic inflammatory process are debilitating and can be devastating. The prolongation and chronicity of any inflammation may be the result of an alteration in the immune response.

4) HEALING PROCESS

The final phase of the inflammatory response is healing. Healing includes the two major components of regeneration and repair. **Regeneration** is the replacement of lost cells and tissues with cells of the same type. **Repair** is healing as a result of lost cells being replaced by connective tissue of different origin. Repair is the more common type of healing and usually results in scar formation.

Pathophysiology

Example of healing processes:-

A) Wound Healing

B) Fracture Healing

A) Wound Healing

Wound healing follows also either Regeneration or Repair by scar.

- **Regeneration**

The ability of cells to regenerate depends on the cell types (see Table). Labile cells, such cells of the skin, lymphoid organs, bone marrow, and mucous membranes of the GI, urinary, and reproductive tracts, divide constantly. Injury to these organs is followed by rapid regeneration.

Stable cells retain their ability to regenerate but do so only if the organism is injured. Examples of stable cells are liver, pancreas, kidney, and bone cells.

Permanent cells do not regenerate: Examples of these cells are neurons of the CNS and cardiac muscle cells. Damage to CNS neurons or heart muscle can lead to permanent loss. Healing will occur by repair with scar tissue.

Table-2.6. REGENERATION ABILITY OF DIFFERENT TYPES OF TISSUES

TISSUE TYPE	REGENERATIVE ABILITY
-------------	----------------------

Pathophysiology

<ul style="list-style-type: none">• Epithelial Skin, linings of blood vessels, mucous membranes• Connective Tissue<ul style="list-style-type: none">BoneCartilageTendons & LigamentsBlood• Muscle<ul style="list-style-type: none">SmoothCardiacSkeletal	<ul style="list-style-type: none">• Cells readily divide and regenerate• Active tissue heals rapidly• Regeneration possible but slow• Regeneration possible but slow• Cell actively regenerate• Regeneration usually possible (particularly in GI tract)• Damaged muscle replaced by connective tissue• Connective tissue replaces severely damaged muscle; some regeneration in moderately damaged muscle occurs
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Pathophysiology

Repair is a more complex process than regeneration. Most injuries heal by connective tissue repair. Repair healing occurs by primary, secondary, or tertiary intention.

Primary Intention

Primary intention healing takes place when wound margins are nearly approximated, such as in a surgical incision or paper cut. A continuum of processes is associated with primary healing (see Table 2.7). These processes include three phases.

Table-2.7. Phases In Primary Intention Healing

PHASE	ACTIVITY
<ul style="list-style-type: none">Initial (3 to 5 days)	Approximation of incision edges; migration of epithelial cells; clot serving as meshwork for starting
<ul style="list-style-type: none">Granulation (5 days to 4 weeks)	capillary growth Migration of fibroblasts; secretion of collagen; abundance of capillary buds;
<ul style="list-style-type: none">Maturation Phase & Scar Contraction (7 days to several months)	fragility of wound Remodeling of collagen; strengthening of scar

Secondary Intention

Wounds that occur from trauma, ulceration, and infection and having large amounts of exudates and wide irregular wound margins with extensive tissue loss may not have edges that can approximated. The inflammatory reaction may be greater than in primary healing. This results in more debris, and exudates. The debris may have to be cleaned away (derided) before healing can take place.

In some instances a primary lesion may become infected, creating additional inflammation. The wound may reopen, and healing by secondary intention takes place.

The process of healing by secondary intention is essential as primary healing. The major differences are the greeter defect and the gaping wound adages. Healing and granulation takes place form the edges inward and from the bottom of the wound upward until the defect is filled. There is more granulation tissue and the result is much larger scar.

Tertiary intention

Tertiary intention (delayed primary intention) healing occurs with delayed suturing of a wound in which two layers of

Pathophysiology

granulation tissue are suture together. This occurs when a contaminated wound is left open and sutured closed after the infection is controlled. It also occurs when a primary wound becomes infected, is opened, is allowed to graduate, and is then sutured. Tertiary intention usually results in a larger and deeper scar than primary or secondary intention.

B. Bone Healings

- Bone healing occurs in a similar manner with soft tissue healing, but it is however more complex and takes longer time. Although the exact mechanism is controversial; the following five stages are identified:-

1) Stage of Hematoma Formation:-

- Occurs during the first 48-72 hours following fracture.
- Develops as blood leaks from torn vessels into the bone fragments and clotting factors in the injured area remain to initiate the formation of fibrin mesh work, which serves as frame work for in growth of fibroblast and new capillaries. Granulation tissue eventually invade and replace the clots.

2) Stage of Cellular Proliferation:-

- Three layers of bone (periosteum, endosteum, and medullary canal) are involved in the roliferation.

Pathophysiology

- During this process the osteoblast multiply and differentiate into fibrocartilagenous callus; softer and more flexible than callus.
- The collar edge on either side of the fracture eventually unit to form a bridge, which connects the bone, fragments.

3) Stage of Callus Formation:-

- During the early stage of callus formation, the fracture become sticky as osteoblast continue to move in and through the fibrin bridge to help keep it firm. Then bone calcifies as mineral salt deposit to form true callus in 3-4 weeks time.

4) Stage of Ossification:-

- It involves the final lying down of bone.
- This is the stage at which fracture has been bridged and is firmly united.
- Mature bone replaces the callus and excess callus is gradually resorbed and appear united on X-ray.
- Cast can be removed safely at this stage.

5) Stage of Remodeling and Consolidation: -

- It involves resorption of the excess bony callus that develops within the marrow space and encircle the extended aspect of fracture site.

Pathophysiology

N.B: - Function usually returns after six months after union, and complete function may take longer time.

Factors Affecting Fracture Healings

- Factors that determine degree of fracture healing are classified as local factors and those factors specific to the patients: -

1) Local Factors: -

- Nature of injury
 - Edematous.
 - Displacement.
- Degree of bridge formation in the healing.
- Amount of bone loss
- Type of bone injury
 - Cancellous bone heals faster
 - Cortical bone heals slowly.
- Degree of immobilization achieved.
- Local infection
 - Retard healing.
- Local malignancy
- Bone necrosis
 - Prevents blood flow to the site.

2) Individual Factors: -

- Age:-younger –healing is faster.
- Older –healing is slower.

Pathophysiology

- Poor nutrition
- Debilitating diseases: – Diabetes
 - Rheumatoid Arthritis
- Coagulation disorders.
- Circulatory problems.

Common Example of Acute inflammatory Conditions

PNEUMONIA

- **Definition:** -

- Microbial invasion of the lung parenchyma evoking exudative solidification (consolidation) of the lung tissues.

- **Etiology:** -

Pneumonia can be caused by bacteria, viruses, fungi, parasites or chemicals.

- **Classification:** -

- Based on etiologic agents: -

- **Bacterial:** - pneumococcal, staphylococcal, mycoplasma, etc.
- **Viral:** - influenza, respiratory syncythial virus etc
- **Fungal:** -Histolasopasma captulatum, aspergilla fumigates, etc
- **Parasitic:** -PCP (Pneumocystic carini pneumonia),
- **Chemicals:-**Gastric Aspirate,

Pathophysiology

- Based on the gross anatomic distribution of the disease:-

- **Broncho pneumonia** and
- **Lobar pneumonia**

N.B:- The best classification is etiologic based, however; anatomic classification is also commonly utilized.

- **PATHOPHYSIOLOGY:-**

Each day the respiratory airways and alveoli are exposed to more than 10,000liters of air containing hazardous dusts, chemicals and microorganisms. The fate of the inhaled particles depends on their sizes. The normal lung is free from bacteria, and there are potent defense mechanisms that clear or destroy any bacteria inhaled with air. Some of the defense mechanisms are:-

- **Nasal clearance-**
Sneezing, or blowing.

- **Tracheo-bronchial clearance**

Mucocilliary action that is eventually expectorated or swallowed.

- **Alveolar clearance**
 - Bacteria or solid particles deposited in alveoli are phagocytosed by alveolar macrophages. The macrophages are propelled to oropharynx and swallowed. Alternatively particle lidden macrophages

Pathophysiology

move through interstitial spaces and reenter the bronchioles or enter the lymphatic capillaries.

N.B:-Pneumonia can result whenever; these defenses mechanisms are impaired or whenever, the resistance of the host in general is lowered. Factors that affect the resistance in general include chronic diseases, immunologic deficiencies, and treatment with immunosuppressive agents and unusual virulent infections.

- The Clearance mechanisms can be interfered by many factors including: -
 - ✓ **Loss or suppression of cough reflex**, as a result of:-
 - Coma
 - Anesthesia
 - Neuromuscular disorders
 - Drugs or chest pain (this may lead to aspiration of gastric Content).
 - ✓ **Injury of mucocilliary apparatus:-**
 - Owing to cigarette smoke.
 - Inhalation of hot or corrosive gases,
 - Viral diseases

Pathophysiology

- ✓ **Interference with phagocytic or bactericidal action of alveolar macrophages: -**

- Alcohol
- Tobacco smoke
- Anoxia

- **Morphology of lobar pneumonia**

Pneumococci and Klebsiella mainly cause lobar pneumonia and lobar pneumonia is characterized by four stages: -

1. Stages of Acute Congestion: - lasts - 2 days.

- ✓ The lung feels dark and firm. The alveoli are filled with eosinophilic edema, containing many gram-positive diplococcal and PMNs

2. Stages of Red Hepatization: - lasts 2nd to 4th day.

- ✓ Lung is dry, firm, red and granular. The pleural surface is grey-white and friable.
- ✓ The capillaries are engorged, filled with fibrin exudates, RBC and numerous neutrophils.

3. Stages of Grey Hepatization - lasts 4th - 8th day.

- ✓ Cut surface is dry, granular and grey. Alveoli contain fibrins, dead and live neutrophils and occasionally

Pathophysiology

degenerating erythrocytes (hemolysis RBCS)

4. Stages of Resolution - after 8th day.

- ✓ Migration of macrophages from the alveolar space into the exudate, which latter liquefied by fibrinolytic system. Complete resolution and aeration takes 1-3 weeks, but pleural adhesion between the two layers usually persists.

N.B: -These classic stages (phases) of lobar pneumonia are now infrequent owing to effective antibiotic therapy that prevents the development of full blown lobar consolidations.

Common Examples of Chronic Inflammatory Conditions

A. TUBERCULOSIS: -

Is prototype example of granulomatous inflammation.

Tuberculosis infects one third of world population and kills about three million people yearly and it is the single most important infectious disease.

Etiology:

Pathophysiology

Mycobacterium tuberculosis and *Mycobacterium bovis* are the regular infecting rod shaped, acid and alcohol fast, strict aerobic, non spore forming organism with waxy coat. It has a slow generation time (4-6 weeks) to obtain a colony of mycobacterium tuberculosis. *M. tuberculosis* is transmitted by inhalation of infective droplets coughed or sneezed into the air by a patient with tuberculosis; however, *M. bovis* is transmitted by milk from infected cows. *M. avium* and *M. intracellulare* cause disseminated infection.

Pathophysiology

- **Primary infection:** -
 - Primary phase of *M. tuberculosis* infection begins with inhalation of the mycobacterium most often in the lower segment and middle lobes of the lung. It is phagocytosed by alveolar macrophages and transported by these cells to hilar lymph nodes. Naïve macrophages are unable to kill the mycobacterium, which multiply and lyses the host cell, infect other macrophages and sometimes disseminate through blood to other parts of the lung and elsewhere in the body (called disseminated tuberculosis).

Pathophysiology

- After few weeks T-cell mediated immunity is demonstrable by PPD reaction. First the CD4 T cells interaction with macrophages secretes interferons which activate macrophages to kill intracellular mycobacterium through reactive nitrogen intermediates, including NO, NO₂, HNO₃.
- Second CD 8+ suppressor T-cells lyses macrophages infected with mycobacterium through a FAS - independent, granular dependent reaction and kill mycobacterium.
- Third CD4 -CD8 (double negative) T-cell lyses macrophages in a FAS dependent manner without killing mycobacteria. Lyses of these macrophages results in the formation of caseating granuloma and direct toxicity to the mycobacteria may contribute to the necrotic caseous centers.
- The primary infection of sub -pleural lesion, the intervening macrophage reactions with in accompanying lymphangitis and the hilar lymph nodes,

Pathophysiology

caseous lesions is called **primary complex** (often called a **Ghon focus**).

Fate of primary complex (Ghon focus) include:-

I. Fibrosis and calcifications: -

- The response T-cell mediated immune induces hypersensitivity to the organisms and controls 95% of primary infection. This is associated with progressive fibrosis and calcification of persistent caseous debris. Moreover, most bacilli are, but few remain viable for years till the persons immune response fails.

- However if the infected person is immunologically immature, as in a young child or immunocompromized as in AIDS patients, the course of this primary infection is quite different. Such persons lack the capacity to coordinate integrated hypersensitivity and cell-mediated immune responses to the organism and thus often lack the capacity to contain the infection. Granulomas are poorly formed or not

Pathophysiology

formed at all, and infection progresses at the primary site in the lung, the regional lymph nodes or at multiple sites of disseminations. This process produces progressive primary tuberculosis.

II. Progressive primary tuberculosis pneumonia: -

- Commonly seen in children less than five years of age but it occurs in adults as mentioned in those with suppressed or defective immunity.

III. Pleural effusion: -

- Sub pleural focus may discharge bacilli or antigen into the pleural cavity resulting in the development of **pleural effusion**. It is common in adolescent infected with *M. tuberculosis* for the first time.

Hilar or mediastinal groups of lymph nodes may be enlarged with caseous necrosis that may result in:-

- Obstruction of the bronchus by the enlarged lymph-nodes leading to lobar collapse.
- The caseous hilar lymph node may penetrate the bronchial wall and resulting in rupture of the wall with pouring of caseous materials into the bronchus hence, tuberculosis broncho-pneumonia ensues.

Pathophysiology

- The caseous materials may be disseminated to other parts of the body via blood streams called Miliary tuberculosis.

N.B- Tuberculosis can affect almost all part of the body, Except the Enamel of the teeth.

B. LEPROSY: -

Definitions

- Leprosy or Hansen disease is a slowly progressive infection caused by *Mycobacterium leprae* affecting the skin and peripheral nerves and resulting in deformity, loss of sensation and ulceration. Though *M. leprae* is in most part contained in the skin, the disease is transmitted from person to person through aerosols from lesions in upper respiratory tract.

Pathophysiology

- The bacillus is acid fast obligate intracellular organism that does not grow in culture and it grows best at 32-34 degree centigrade of the temperature of human skin. Like *M. tuberculosis*, *M. leprae* secretes no toxins but its virulence is based on properties of its cell wall. The bacillus produce potentially destructive granulomas or by interference with the metabolism of cells and thereby

Pathophysiology

macrophages, disseminate through the blood but grows only relatively on cool tissues of the skin and extremities.

- Dissemination based on host immune response. Leprosy is a bipolar disease. Two forms of the disease occur depending on whether the host mounts a T-cell mediated immune response (**tuberculoid leprosy**) or is anergic (**lepromatous leprosy**). The polar forms are relatively stable but **the borderline** form is unstable without treatment. It may deteriorate to lepromatous leprosy. Patients with tuberculoid leprosy form granuloma with few surviving bacteria (**paucibaccillary disease**). The 48 hours lepromin skin test is strongly positive CD4 + type 1 helper T-cell secrete IL-2 and there are also few CD8+ lymphocytes.
- In contrast patients with lepromatous leprosy lack T-cell mediated immunity, are anergic to lepromin and have diffuse lesions (globi containing foamy macrophages, stuffed with large numbers of mycobacteria (**multibacillary disease**))
- Lepromatous leprosy lesions lack CD4+ type I T-cell at their margins but in stead contain

Pathophysiology

many CD8+ suppressor T-cell in a diffuse pattern. The CD8+ suppressor T-cell secrete IL-10 which inhibits helper T-cells and may mediate the anergy seen in lepromatous leprosy. This CD8 suppressor T-cell also secretes IL-4 which indicates antibody production by B-cell.

- Antibody production is not important in lepromatous leprosy and rather the formation of antigen antibody complexes in lepromatous leprosy leads to erythema-nodosum *regionosum*, a life threatening vasculitis, and glomerulonephritis.

N.B:- Because of the different parasite filled lesions lepromatous leprosy is more infectious than those with tuberculoid leprosy.

4. IMMUNOLOGICAL DEFENSE MECHANISM

Introduction

Immunopathology is the study of diseases, which have or appear to have an immunologic basis. The immune system is a two-edged sword on one hand, **immunodeficiency states** render humans easy prey to infections and possibly tumors; on the other hand, **a hyperactive immune system** may cause fatal disease.

2.1.4. A) Hypersensitivity Reactions

Definition

- ✓ Hypersensitivity reactions refer to exaggerated response of immune system to an antigen (foreign body).
- ✓ The antigen that elicits the response is called an allergen.
- ✓ The purpose of the immune response is to protect against invasion by foreign organisms, but they often lead to tissue damage. Thus, an immune response that results in tissue injury is broadly referred to as a **hypersensitivity reaction**.

Classification: -

- Hypersensitivity reactions can be divided into 4 types depending on the mechanism of immune recognition involved and on the inflammatory mediator system recited, which is **Gell and Combs classification**.
- Types - I, II, and III depend upon the interaction of antibody with the target, whereas, in type IV reactions recognition is achieved by antigen receptors on T-cells.

1) Type-I (Immediate Hypersensitivity Reaction)

Pathophysiology

- It affects those people who are susceptible to the disease genetically.
- Susceptibility to allergy is inherited and may result from excessive IgE-production.
- Pathophysiology
 - The immune response is activated when antigen binds to IgE antibodies attached to the surface of mast cells
 - Mast cells are found in connective tissue, skin, and mucus membranes.
 - The reaction proceeds when the IgE molecule specific for a particular antigen become cross-linked on the surface of mast cell and triggers the release of intracellular granules.
 - The granules contain histamine and other chemotactic substances.
 - Histamine causes peripheral vasodilatation and an increased vascular permeability, resulting in local vascular congestion and edema.
 - Histamine also cause bronchospasm often associated with allergic reaction.

Example: - Bronchial asthma, Allergic rhinitis, contact dermatitis

2) Type-II (Cytotoxic Hypersensitivity)

Pathophysiology

- In type-II hypersensitivity response, a circulating antibody, usually an IgG reacts with an antigen on the surface of a cell.
- The antigen could be a normal component of the membrane. It also may be a foreign antigen, such as a pharmacological agent, that adheres to the surface of the host's own cells.
- **Example:** - Autoimmune hemolytic anemia
 - Erythroblastosis fetalis
 - Drug- induced hemolysis

3) Type-III (Immune complex disease)

- Immune complex disease results in the formation of antigen-antibody complexes that activate a variety of serum factors especially complement.
- This results in precipitation of complexes in vulnerable areas, leading to inflammatory process in intravascular, synovial, endocardial and other membranes of the vulnerable organs.
- The antigen-antibody complexes accumulate in the circulation and if not cleared, the complex lodge in the tissue, where they initiate inflammatory reaction that leads to tissue destruction.

4. Type-IV (Cell- Mediated Hypersensitivity)

Pathophysiology

- Type-IV response is the result of specifically sensitized T-lymphocytes.
- Activation causes a delayed-type response.

Delayed Hypersensitivity

- It is due to the specific interaction of T-cells with antigen. The T-cells reacts with the antigen and release lymphokines that draws macrophages in to the area and elicit inflammatory reaction locally.
- The tuberculin response is the best example of the delayed hypersensitivity response and is used to determine whether a person has been sensitized to the disease. Reddening and indurations of the site begins with in 12-72hours

- Example

✓ **Contact Dermatitis**

- A common allergic skin reaction
- It is a T-cell response with a delayed reaction
- It occurs on contact with certain common household chemicals, cosmetics and plant toxins.
- The area becomes red and indurated, and vesicles begin to appear. The lymphocytes and macrophages infiltrate the area and react against the epidermal cells.

Pathophysiology

✓ **Transplant or Graft Rejection**

- Rejection of tissues and transplanted organs involves several of the hypersensitivity response.
- Rejection is defined as the process by which the immune system of the host recognizes, develops sensitivity to, and attempts to eliminate the antigenic differences of the donor organ.
- It is a complex reaction that involves both cell-mediated and humoral responses. Cytotoxic T-lymphocytes may either attack grafted tissues directly or secrete chemotactic cytokines that activate macrophages for tissue destruction.
- Humoral response involves formation of antibodies that circulate. The antibodies cause graft tissue destruction as they become more sensitized.

2.1.4. B) Immunodeficiency diseases

Definition:-

The term immunodeficiency covers a group of disorders in which defects result in impaired resistance to microbial infections.

Classifications

Pathophysiology

Deficiencies of specific immune response are divided into primary and secondary types.

1. Primary immunodeficiency diseases:-

Are those disorders which usually manifest in early childhood and there is a good evidence that the disease is genetically determined. Primary immunodeficiency diseases which are almost always genetically determined are further divided into:-

- Deficiencies of antibody (B - cells).
- Deficiency of cell mediated (T-cells) immunity.
- Combined T-cells and B-cells Deficiency (Severe combined immunodeficiency disease)
- Complement factor deficiency.

2) Secondary immunodeficiency diseases

- Secondary immunodeficiency is defined as deterioration in previously strong immune status.
- The causes are usually secondary to systemic conditions like:-
 - Diabetic mellitus
 - Renal failure
 - Liver failure
 - Poor nutrition
 - Cancers
 - Broad spectrum antibiotics

Pathophysiology

- Prolonged steroid therapy
- Human Immunodeficiency Virus (HIV/AIDS)

Human Immunodeficiency Virus (HIV/AIDS)

- **HIV-pathogenesis and Natural course of the Disease**

- **HIV-Virology**

- The virus HIV is a retrovirus, which belongs to a class Lent virus
- Is a single stranded RNA virus, which later transcribed to double stranded DNA by reverse transcriptase enzyme.
- Integrates into the host genome.
- Has high potential for genetic diversity.
- It can lie dormant with in a cell for many years, especially in resting (memory) CD4+ lymphocytes.

HIV-types

- HIV-1: - world wide pandemic (currently about 40million people).
- HIV-2: -Isolated in west Africa
 - Causes AIDS much more slowly than HIV-, but otherwise clinically similar.

Structures of HIV

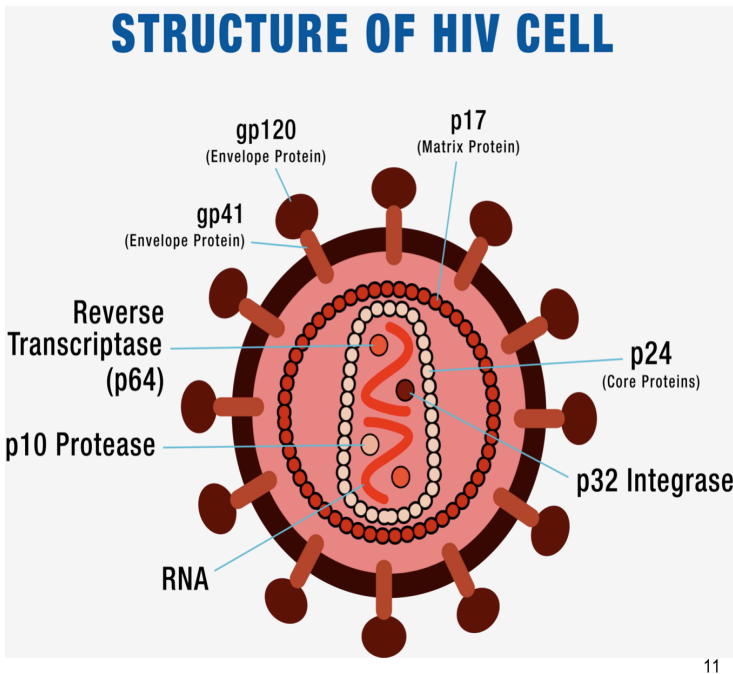
- HIV has two parts: -

a) The viral-Envelope: -

- The outer covering of the virus.
- Contains different types of glycoprotein like gp-120 and gp-41 on the envelopes, which helps for binding of the virus into the host target cells.

b) The viral –core (Nucleus)

- Located centrally and contains: -
 - Single stranded RNA.
 - Enzymes like:- Reverse transcriptase
 - Integrase
 - Protease.
 - Core proteins like P24.



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Figure-2.2 Structure of HIV

How HIV Enters cells

- Once the virus is inoculated into the body by different routes, the viral gp-120 envelope protein binds to CD4-molecules of the target cells:-
 - CD4- molecules are found on T-cells, macrophages, and Microglial cells.
 - Binding to CD4 is not sufficient for entry, the V3 loop of gp-120 envelope protein should bind to the co-Receptors of the target cells:-

Pathophysiology

- CC R5-Receptor → found on macrophages.
- CXCR4-Receptor → found on T-lymphocytes.

➤ Fusion

- Binding of the virus to the co-receptors results in fusion of viral envelope with cell membrane of the target cells (Macrophages and T-lymphocytes)
- Fusion is followed by release of viral core into the host cell cytoplasm by uncoating its envelope.

➤ Transcription

After the core enters to the host-cytoplasm, the enzyme Reverse transcriptase begins to transcribe the single stranded RNA into double stranded DNA. It occurs in the first 24 hours.

➤ Integration

The Integrase - enzyme integrate the double stranded DNA in to the host DNA. Then the viral genetic material synthesizes its own proteins for replication using the host machinery (genetic material).It occurs in the 72-hours after exposure to the virus.

➤ Assembly

The newly synthesized viral proteins are assembled in to virions by protease enzyme.

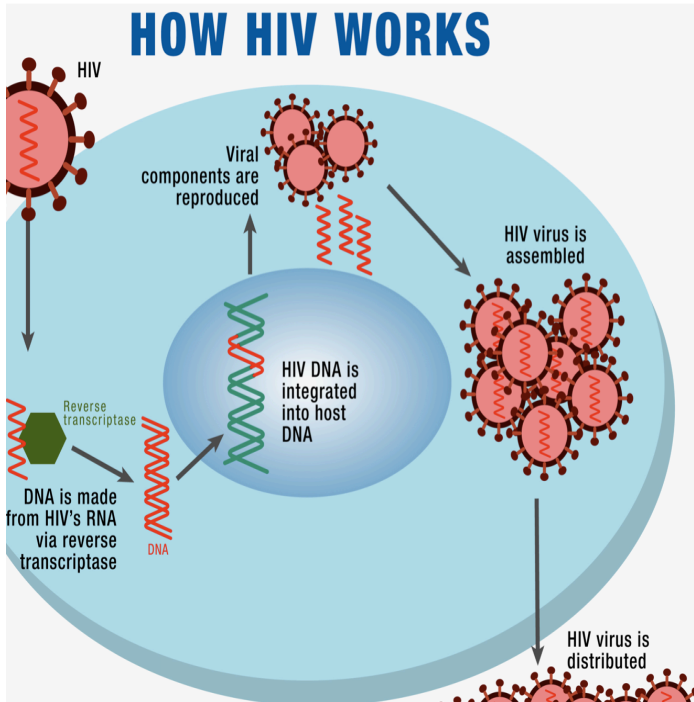
➤ Budding

Pathophysiology

The assembled virions buds it self by taking cell membrane as an envelope then released in to the circulation.

➤ **Viral-Dissemination**

The released virus in to the circulation disseminate to all tissue of the body by binding into macrophages and T-lymphocytes.



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Figure-2.3 Mechanism of HIV Entry and replication in the target cells

Viral-host Dynamics

- About 10-billion virions are produced daily.
- Average life-span of an HIV-virion in plasma is ~ 6hours.
- Average life-span of an HIV-infected CD4 lymphocyte is 1.6days.

Pathophysiology

- HIV can lie dormant within a cell for many years, especially in resting (memory) CD4 cells.

General principles of Immune Dysfunction in HIV

- All elements of immune systems are affected
- Advanced stages of HIV are associated with substantial disruption of lymphoid tissue:
 - Impaired ability to mount immune response to new antigen
 - Impaired ability to maintain memory response
 - Loss of containment of HIV-replication
 - Susceptibility to opportunistic infections.

Mechanisms of CD4 Depletion and Dysfunction

- **Direct**
 - Elimination of HIV-infected cells by virus – specific immune responses
 - Loss of plasma membrane integrity because of viral budding.
 - Interference with cellular RNA Processing.

- **Indirect**
 - ✓ **Syncytium formation:-**

Pathophysiology

- Uninfected cells may bind in to HIV-infected cells due to viral gp-120.
- This results in fusion of the cell membranes and subsequent syncytium formation
- These syncytiums are highly unstable, and die quickly.
- ✓ **Apoptosis:-**
 - Condensation of HIV-infected cells then cleared by phagocytosis
- ✓ **Autoimmunity:-**
 - Autoimmune destruction may happen due to disturbance in immune-system dis-regulatory mechanisms.

Consequence of cell-Mediated Immune Dysfunction (CD4-Depletion)

- Inability to respond to intra cellular infections and Malignancy.

This results in opportunistic infections and neoplasms. The common opportunistic organisms are:-

- **Bacteria**
 - Mycobacterium
 - Salmonella
 - Legionella
- **Parasites**
 - Leishmania

Pathophysiology

- Toxoplasmosis
- Cryptosporidium, microsporidium, etc

➤ **Virus**

- Herpes simplex virus (HSV)
- Varicella- zoster virus (VZV)
- JC virus
- EBV- related lymphoma

Natural History of HIV infection

Modes of infection

- sexual transmission at genital or colonic mucosa
 - Blood transfusion
 - Mother to child
 - Accidental occupational exposure
- Once the virus is inoculated to the host body by one of the above modes; viral entry to the target cells occurs then the individual passes through the following three courses of the disease:-
- **Stage of primary HIV-infection**
 - **Stage of latency**
 - **Stage of AIDS**

Stage of primary HIV-infection

- The period immediately after infection characterized by high level of viremia (> 1million) for a duration of a few weeks.
- Associated with a transient fall in CD4.
- Nearly half of patients experience infectious mononucleosis like symptoms (fever, rash, swollen lymph glands)
- Primary infection resolves as body mounts HIV-specific adaptive immune response: - That is cell-mediated response (CTL) followed by humoral immune system

Pathophysiology

stimulation clears acute viremia and then the patient enters “stage of clinical latency”.

Stage of clinical latency

- During this stage the virus is already cleared by the immune system and hide it self inside the target cells (CD4+-cells) and other tissues like the brain, lymph nodes and body fluids,
- The patient is clinically symptom free but the virus keeps on replication in side those tissues. So, this is just clinical latency but not virological latency.
- Immunological tests are positive and the person is also potentially infectious.

Stage of AIDS

- AIDS develops as HIV slowly destroys CD4-cells over years of infection.
- As the CD4-count drops, infections takes “Opportunity” of this weakened immune system, resulting in opportunistic infections (OI)
- When an individual’s immune system is damaged to the extent that these OIS Occur, the individual is said to have AIDS.

Review Questions

Pathophysiology

- 1) Define different types of body defense mechanism
- 2) What are the common types of phagocytes based on their site?
- 3) List the systemic and local manifestations of acute inflammations.
- 4) What are the two types of healing mechanisms of inflammatory process?
- 5) List the pathophysiologic events of inflammatory process.
- 6) Lists the Pathophysiologic mechanisms of fracture healing.
- 7) Discuss the mechanism of delayed hyper sensitivity reactions
- 8) Discuss the mechanisms of HIV-entry and immune invasions.
- 9) What Pathophysiologic changes happen in acute HIV – infection phase?
- 10) List stages of the febrile response febrile response

CHAPTER THREE

ALTERATIONS IN OXYGENATION OF TISSUES

Learning Objectives

At the end of this chapter the students will be able to:-

- Identify common causes of poor tissue oxygenations.
- Discuss congestive heart failure.
- Describe pathophysiology of restrictive lung diseases.
- Describe pathophysiology of obstructive lung diseases.
- Differentiate acute and chronic obstructive pulmonary diseases
- Discuss pathophysiology of occlusive diseases of the blood vessels.

Introduction

All tissues in our body need persistent and adequate amount of oxygen for normal metabolic activities. Poor tissue oxygenation can result from several causes.

The common causes are:

- Congestive heart failure (CHF)
- Lung diseases
- Vascular occlusions (thrombosis)
- Air poisoning (carbon monoxide),
- Anemia
- Shock

3.1 Congestive Heart Failure (CHF)

3.1.1. Definition

- Heart failure refers to a constellation of signs and symptoms that result from the heart's inability to pump enough blood to meet the body's metabolic demands.
- The pump itself is impaired and unable to supply adequate blood to meet the cellular needs.

3.1.2. Causes of CHF

The causes of CHF are classified into two major classes as **underlying causes** and **precipitating (Secondary) causes**.

I. Underlying causes

Pathophysiology

- It is the main pathological lesion that is responsible for the heart not to pump adequately.

-These include: -

- **Myocardial lesions**
 - Cardiomyopathy
 - Myocarditis
 - Myocardial infarction
- **Valvular & Endocardial lesions**
 - Endocarditis
 - Congenital valvular- heart disease
 - RHD (Rheumatic Heart Disease)
- **Pericardial – lesions**
 - Pericarditis
 - Cardiac-tamponade

II. Precipitating (secondary) causes.

Normally in the absence of precipitating factors or causes, an individual heart with those underlying lesions tries to compensate by making multiple pathophysiologic changes. But when the precipitating causes come to the picture the individual heart goes in to full- blown clinical signs and symptoms of CHF. The precipitating causes are abbreviated by a phrase “heart-fails”.

- **H** = Hypertension
- **E** = Infective Endocarditis

Pathophysiology

- **A** = Anemia
- **R** = Rheumatic –fever (Recurrence)
- **T** = Thyrotoxicosis
- **F** = Fetus (pregnancy)
- **A** = Arrhythmias
- **I** = Infections
- **L** = Lung problems (pathologies)
- **S** = Stress, salts, etc.

3.1.3. Pathophysiology of Heart Failure

- The onset of heart failure may be acute or insidious. It is often associated with systolic or diastolic over loading and with myocardial weakness. As the physiologic stress on the heart muscle reaches a critical level, the contractility of the muscle is reduced and cardiac output declines, but venous input to the ventricle remains the same or becomes increased which is responsible for cardiac – over load.
- When cardiac output is decreased; the body undergoes alteration to compensate for the failure. There are two types of **compensatory-mechanisms** for congestive-heart failure:-

I. Systemic compensatory mechanisms

- A. Reflex increase in sympathetic activity.

Pathophysiology

- B. Release of rennin from the kidneys.
- C. Anaerobic metabolism by affected tissues.
- D. Increased extraction of oxygen by the peripheral cells.

II. Cardiac compensatory mechanisms

a. Myocardial dilatation: -

In acute or short-term mechanisms, as the end-diastolic fiber length increases, the ventricular muscle responds with dilatation and increased force of contraction (**Starling's law**)

Example:- Acute myocardial infarction results in ventricular –dilatations.

b. Myocardial Hypertrophy

In long-term mechanisms, ventricular hypertrophy increases the ability of the heart muscle to contract and push its volume into the circulation.

Example:- Hypertension results in ventricular hypertrophy, which maintains pumping blood for several years against increased after-load.

A) Sympathetic response to heart Failure:-

A decrease in cardiac output results in decreased blood pressure, which causes a reflex stimulation of sympathetic nervous system (SNS). The SNS causes increased force and

Pathophysiology

rate of myocardial contraction. It also causes vasoconstriction of arterioles throughout the body. These effects temporarily prolong the patient's life. But in the long run, it facilitates the progress of **pumping failure** (cause **cardiac decompositions**).

B) Renin Angiotensin Aldosterone system:-

- It constantly works to maintain fluid volume and blood pressure through the following cascades:-

- Decreased perfusion of tissues.



- Release of **Renin** from juxtaglomerular cells of the kidney.



- Formation of **Angiotensin- I** (formed from Angiotensinogen in the liver by the action of renin)



- Formation of **Angiotensin –II** (by enzyme reaction in the pulmonary-capillary bed)

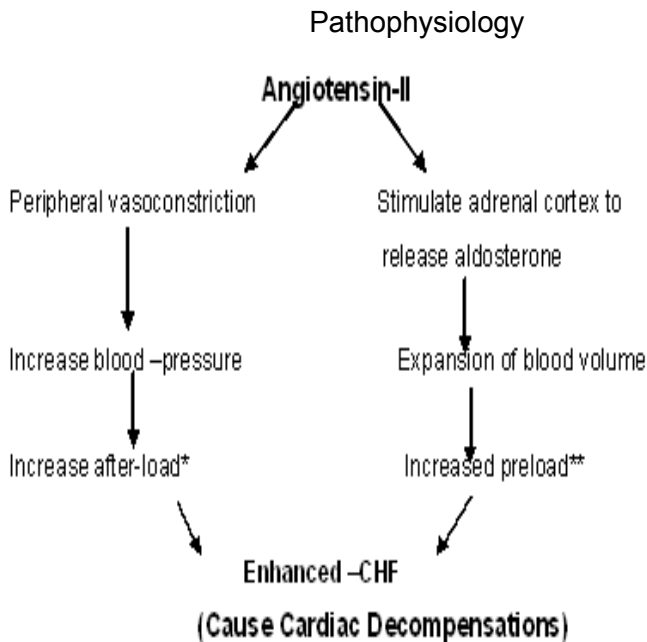


Figure 3.1 Effects of angiotensin-II in congestive heart failure

NB. * After load- the arterial pressure against which the ventricles must contract.

**** Preload-** It is the pressure during filling of the ventricles or tension on myocardium due to congestion.

C) Anaerobic Metabolism

- When cells do not receive adequate blood or oxygen, metabolism decreases and alternative methods are used to produce energy. The major alternative method is anaerobic production of ATP, which results in formation of **lactic acid** as a bi-product.

Pathophysiology

- Even if the formed ATP by this mechanism could prolong the life of the tissues, the accumulation of the metabolic bi-product (lactic acidosis) inhibits myocardial contractility, which facilitates the pumping failure.

D) Oxygen extraction from RBCS

- Oxygen extraction from RBCS to the tissue increases when the circulation is inadequate and the perfusion is diminished.
- Normally, about 30% of oxygen is extracted from RBCS by the peripheral tissues, but greater amounts can be extracted during periods of poor perfusion.

➤ **Subsequent effects of compensatory mechanisms**

All of the compensatory mechanisms described above may preserve the life of the individual but they usually aggravate the underlying conditions:-

- **Sympathetic Responses:** - Preserve life by increasing blood flow to brain and heart. But increases the cardiac work load by increasing after load (vasoconstriction)
- **Renin- Angiotensin-Aldosterone system:** - Maintain blood volume and pressure to life initially, but the aldosterone effect results in increase pre-load (fluid-over load) on the heart.

Pathophysiology

Also increased after-load due to vasoconstriction effect of Angiotensin-II.

- **Anaerobic metabolism:** - This also preserves life by forming ATP. But its metabolic bi-product; lactic acid accumulation results in depression of the myocardial contractility.
- **Myocardial Hyper trophy and myocardial Dilatation:** - Increase oxygen demand by the myocardium. Put more stress on the already failed heart.

3.1.4. Classification of Heart-Failure

- ✓ -Based on clinical manifestations heart failure has been classified into two:-
 - I) **Left-sided Heart Failure:** - Forward or low out put syndrome dominate.
 - II) **Right-sided Heart Failure:-** The congestive phenomenon dominates.

Pathophysiology

- ✓ But, in reality both features are present in heart failure just as both left-sided and right-sided because the heart and lungs are interconnected; what affects one side of the heart eventually affects the other.

I. Left Heart Failure (LHF)

- ✓ -Left heart failure occurs when the output of the left ventricle is less than the total volume of blood received from the right side of the heart through the pulmonary circulation. As a result, the pulmonary circuit becomes congested with blood that cannot be moved forward and the systemic blood pressure falls.

Causes

- Myocardial infraction (MI) commonest cause
- Systemic Hypertension
- Aortic stenosis or insufficiency
- Cardiomyopathy
- Mitral stenosis and insufficiency; also causes symptoms of LHF

Pathophysiology of LHF

- **Back word effects of LHF**
 - Because the left ventricle cannot pump out all of its blood; blood dams back to the left atrium into the four pulmonary veins and pulmonary

Pathophysiology

capillary bed (PCB). As the volume of blood in the lungs increases, the pulmonary vessels are congested and fluid starts to pass in to the interstitial spaces and alveoli to cause **pulmonary-edema**. Some times, acute pulmonary edema may occur which is a life-threatening condition by impairing gas exchange.

- These phenomena are congestive phenomena of LHF that result from the volume over load of the left ventricle. They are called the backward effects of LHF.
- **Forward Effects of LHF**
- The left ventricle also cannot pump its normal stroke volume out to the aorta. Thus, the systemic blood pressure decreases. This decrease is sensed by baro-receptors that cause a reflex stimulation of sympathetic nervous system (SNS), which results in increased heart rate and peripheral vasoconstriction.
 - Decreased cardiac out-put cause decreased tissue perfusions, which stimulate the **RAA-system** as a compensatory mechanism. Angiotensin-II correct blood pressure by Vasoconstriction, while aldosterone increases blood

Pathophysiology

volume by sodium retention. These are called the forward effects of LHF.

Signs and symptoms of LHF

- **Dyspnea**
 - The earliest manifestation
 - Is because of fluid accumulation in the lung interstitial space which impairs gas exchange, so that respiratory rate increased to compensate.
 - Is on exercise first then at rest on late stage.
- **Orthopnea**
 - In ability to breathe in supine position
 - Is because of lung congestion due to decreased gravity effect resulting in increased venous return while on supine positions.
- **Paroxysmal nocturnal dyspnea**
 - Is onset of acute episodes of dyspnea at night.
 - The cause is unknown; but thought to be due to improved cardiac Performance at night during decumbency.
 - The increased venous return results in pulmonary congestion which causes acute pulmonary edema.
- **Cardiac Asthma**

Pathophysiology

- Refers to wheezing due to bronchospasm induced by heart failure.
 - The bronchioles may react to the increased fluid in the alveoli, Constrict and produce characteristic wheezing.
- **Pulmonary-edema**
 - Is an acute, life-threatening condition that usually results from back ward effect of LHF.

Pathophysiology

II) Right Heart Failure (RHF)

- ✓ Right heart failure occurs when the output of the right ventricle is less than the input from systemic venous circulation. As the result, the systemic venous circuit is congested and the out put to the lungs decreased.

Causes

- LHF because of back ward effect of LHF which causes pulmonary vascular congestion (hypertension)
- Chronic obstructive lung disease (corpulmonale)
- Pulmonary embolism
- Right ventricular infarction.
- Congenital heart disease.

Pathophysiology of RHF

- **Back ward or congestive effects of RHF**
 - In RHF, the right ventricle cannot pump all of its contents forward so blood dams back from the right ventricle to the right atrium causing an increased pressure in systemic venous circuit. This results in congestion of organs like liver and spleen with peripheral edema due to oozing of fluid.

- **The Forward effects of RHF**

Pathophysiology

- The right ventricle also cannot maintain its output to the lung. This results in a decreased pulmonary circulation and decreased return to the left side of the heart.
- These forward effects of RHF cause all of the forward effects of LHF.

Signs and symptoms of RHF

- Pitting, dependant edema: - on the foot ,on the sacrum, etc
- Hepato splenomegally (enlarged spleen & liver) because of congestion.
- Respiratory distress: - because of acute pulmonary congestion.
- Neck veins distension: - because of congestions of the veins.
- Anasarca (generalized body swelling) occurs in severe form of RHF.

3.2 Obstructive Diseases of blood vessels

Pathophysiology

- Obstructive diseases of the arteries or veins are common causes of alteration in tissue oxygenation.
- The causes of vascular obstruction are broad but in this portion emphasis is given only to vascular obstruction due to coagulation disorders (i.e. Thrombo-embolism and infarction)
- Thrombo-embolisms can be :-
 - A. Venous-Thrombosis
 - B. Arterial-Thrombosis
 - C. Mural –Thrombosis

A. Venous Thrombosis

- Clotting in the wall of the vein is called venous thrombosis. Normally, the wall of the veins are lined by a membrane called endothelium which has a protective ability for platelet aggregation by repelling (pushing) the adherence of platelet to the wall of the veins.
- The three precipitating factors for venous thrombosis are:-

1. Lesions of the endothelium

- Lesions or inflammation of the endothelium results in loss of

Pathophysiology

protective capacity of endothelium to aggregation of platelet, and platelet aggregate on the lesion sites to enhance thrombus formation

2. Relative stasis of venous blood flow

- A slowed flow of blood in the venous blood stream is associated with platelet aggregation. Example: - prolonged immobilization.

3. Hypercoagulability of Blood

- Increased blood viscosity or thickness; increase coagulability of the blood.
- Increase in blood viscosity can result from:-
 - Dehydration, polycythemia (increased RBCs), etc.

Pathophysiology

- Once the thrombi are formed the fates of the thrombus are:-

I. Embolization: -

- Is a sudden proximal propagation after detachment from the original thrombus organizing sites.

Pathophysiology

- Emboli can be small or large and tend to be lodge in the vessels of pulmonary circulation.

II. Organizations and permanent occlusion of the lumen:-

- This occurs in small vessels or narrow lumens.
- Compensated by collateral formations.

III. Partial fibrosis and partial lyses

This is due to the effect of naturally occurring fibrinolysins in the blood which results in involution of the thrombus leading to recanalization.

B. Arterial thrombosis

- Clotting in the wall of the arteries is called arterial-thrombosis
- Atherosclerosis and endothelial injuries are predisposing factors for arterial thrombosis.

C. Mural thrombosis

- Clotting in the wall of the heart or valves are called mural thrombosis.
- The common predisposing factors are endocardial lesions, valvular lesion and blood stasis.
- Embolism to distal organs are common like to:-

-Brain → Stroke

3.3 Lung Diseases

Introduction

- To live is to breathe!
- Between a newborn's first breath and last expiration is a lifetime of respiration.
- Breathing is the only bodily function that occurs automatically and can be controlled voluntarily as well. It is the only bodily functions that immediately interact with unfriendly environment. Irritants, gases, and microorganisms especially constantly attack the lungs. Consequently, the respiratory apparatus has developed an elaborate defense system to protect itself and body from these inhalants. It is when the defense systems are weak that lung diseases ensue.
- The main function of the lungs is to take oxygen from the air and deliver it across the alveolar capillary membrane to the hemoglobin, which carries it to the tissue and also to expel carbon dioxide in to the environmental air.
- But some times this normal vital function of the lungs can be impaired due to lung diseases, which results in alteration in tissue oxygenation. Lung

Pathophysiology

diseases are generally classified into two main categories.

3.2.1. Restrictive lung disease, and

3.2.2. Obstructive pulmonary disease.

3.3.1 Restrictive lung disease

- ✓ Restrictive pulmonary disease is an abnormal condition that causes a decrease in total lung capacity (TLC) and vital capacity. It involves difficulty in the inspiratory phase of respiration. To make it clear, common causes of restrictive lung diseases and their pathophysiology of disease are classified based on their anatomical site as follows: -

Pathophysiology

Causes

Pathophysiology

a) Brain cause

- ❖ Respiratory center depression - Direct depression of the respiratory center in the medulla
 - Narcotic toxicity
 - Central nervous system lesions
 - Head injury, etc.

b) Chest wall abnormalities

- ❖ Thoracic deformity - Deformity of chest compress lung tissues and limits thoracic excursion.
 - Kyphoscoliosis
 - Pectus excavatum
 - Pigeon chest deformity
- ❖ Traumatic chest wall instability - The instable rib pulls area in and causes pressure on parenchyma during inspiration which increase work of breathing.
 - Filial chest (Fracture of groups of ribs leads to Unstable chest wall)
- ❖ Neuromuscular disorders - Paralysis of intercostal muscles, diaphragm and

Pathophysiology

- Guillain-Barre syndrome a c c e s s o r y muscles result in difficulty of inspiration.

(Acute toxic polyneuritis)

- Duchene muscular dystrophy

C) Pleural disorders

- Accumulation of

fluid, air, blood or pus in the

- Pleural effusion pleural-cavity

 results in limitation of lung

(Accumulation of fluid) e x p a n s i o n

during inspiration or may cause lung

- Pneumothorax collapse if it is

 massive

(Accumulation of air)

- Hemothorax

(Accumulation pus)

- Empyema (Accumulation of puss)

- Pleural thickening (due to fibrosis)

d) Disorders of lung parenchyma

- All of these

conditions affect the lung tissues and

- Lung fibrosis result in

 reduced compliance and reduced lung

- Pneumonia function. Thus

 they are restrictive lung diseases.

Pathophysiology

- Atelectasis
- Pulmonary tuberculosis
- Pulmonary edema, Hyaline membrane disease (HMD),
etc.

N.B:- Some of the common restrictive disorders of the lung parenchyma are discussed briefly as follow.

Pathophysiology

3.3.1.1. Atelectasis

- Atelectasis is a very common, acute, restrictive disease that involves the collapse of previously expanded lung tissue or incomplete expansion at birth. It is usually described as a shrunken, airless state of the alveoli.

Causes

There are two major types of atelectasis based on causes: -

I) Compression Atelectasis

- It is alveolar collapse produced by such condition as compression from the out side, like in the case of: -
 - Pneumothorax
 - Pleural effusion and
 - Tumors in the thorax

II) Absorption Atelectasis

- It is alveolar collapse when secretions, pus, or mucosal edema in the bronchi and bronchioles obstruct these airways and prevent the movement of air into the alveoli.
- Stasis of secretion in the air way provide excellent medium for bacterial growth and results in stasis pneumonia
- Atelectasis is a common postoperative complication due to retained secretions. After surgery, the patients

Pathophysiology

cough response is decreased due to pain and medications. This results in stasis of secretions and then alveolar-collapse will occur.

Clinical-features: -

- Depends on the amount of Atelectasis (mild or severe atelectasis)

• **Mild case:** - Asymptomatic

• **Severe-case:** - Dyspnea

- Cough

- Fever

- May progress to broncho- pneumonia

3.3.1.2. Pneumonia

- It is inflammation of the lung parenchyma.
- It is one of the common causes of restrictive lung disease and occurs either when the host resistance is defective or due to high virulence of the organism or both.

➤ **Pathophysiologic changes on the lung**

- When the lung parenchyma is inflamed by one of the inflammatory cells and exudative fluids accumulate in the lung tissues, which result in solidification of the spongy elastic lung to form what we call **consolidation**. When this happens, the lung loses its normal compliance or expansion capacity on

Pathophysiology

inspiratory phase and that is termed as restrictive lung disease. *See detail about pneumonia in chapter 2.*

3.3.1.3. Pulmonary Edema

Introduction

- The pulmonary vascular system has a great capacity to accommodate blood up to three times its normal volume. But at a critical pressure point fluid moves across the alveolar capillary line, and **pulmonary edema** occurs. Pulmonary edema is simply an accumulation of fluid in the tissues (interstitium and alveoli of the lungs).
- **Hydrostatic** and **osmotic pressures** are the major forces that affect movement of fluid across the capillary membrane. The normal hydrostatic pressure in the pulmonary capillary is 7 to 10 mmHg. And the plasma oncotic pressure is about 25 mmHg. Therefore, the alveoli tend to stay “dry”, since the oncotic pressure opposes fluid movement into the interstitium and alveoli.
- For pulmonary edema to occur the hydrostatic pressure in the pulmonary bed must increase to

Pathophysiology

25 to 30 mmHg when capillary permeability is normal and the alveolar system is intact.

Causes of pulmonary Edema

- **Left sided Heart failure (LHF)**
 - The most common cause of pulmonary edema.
 - It is due to backward effect of LHF (discussed previously)
- **Acute inflammations (Increased capillary permeability)**
 - Any form of acute inflammation in the lung results in increased capillary permeability due to vasodilatation .As a result, plasma fluid escapes easily to the alveoli and interstitium.
 - Can be due to:
 - Poisoning gas inhalation
 - Aspiration of gastric juices
 - Microorganisms, etc
- **Fluid volume overload**
 - Excessive volume overload can occur due to I.V.fluid rehydration or massive transfusion of blood.
 - May also result in brain edema as well.

Pathophysiology

- **Post head Injury**
 - Due to sympathetic nervous system stimulation, resulting in deviation of blood to heart and lungs so that pulmonary edema may occur in patients with head injury.
- **Decreased colloid osmotic pressure**
 - Due to hypo-albuminemia from:
 - Liver diseases
 - Kidney diseases
 - Wasting diseases (Malnutrition)
- **Drug-induced injury**
 - Some drugs may cause alveolocapillary injury, which causes increase in alveolocapillary permeability.
 - The drugs are:
 - Antibiotics (some)
 - Hydrochlorothiazide
 - Heroin
 - Oxygen toxicity – it is commonly encountered
- **High altitude**
 - Mechanism unknown
 - Diffuse pulmonary edema

Clinical Features

Pathophysiology

The clinical features of pulmonary edema are directly attributable to its pathophysiology: -

- Mild- pulmonary edema
 - Develops slowly
 - Major symptoms are wheezing, dyspnea and dry cough
- Severe pulmonary edema
 - Dyspnea
 - Orthopnea: - dyspnea on supine position due to increased blood flow to the lung.
 - Wheezing
 - Productive cough of frothy sputum:- (some times blood stickled sputum because of ruptured capillaries due to high pressures).
 - Increased elastic work of breathing due to lung stiffening and loss of compliance as the amount of interstitial fluid increases
 - Rales: - bubbling sounds heard when the lung is filled by fluid.

3.3.1.4. Pulmonary Fibrosis

- Pulmonary fibrosis is a chronic restrictive condition that involves diffuse fibrosis of the lung tissue and results in severe loss of compliance with lung stiffness.

Causes

Pathophysiology

– Occupational exposure to substances such as coal dusts.

- Pulmonary tuberculosis
- Idiopathic (unknown causes)

3.3.1.5. Idiopathic respiratory distress syndrome of the newborn (Hyaline membrane disease /HMD/)

- Hyaline membrane disease (HMD) of the newborn is the most clearly understood abnormality that involves surfactant deficiency.
- The surfactant layer develops late in fetal life, at above the 28th to 32nd week. Infants born before the 28th weeks are at greater risk of developing HMD.

Pathophysiology

- Normally in a matured new born the alveoli are kept patent and protected from collapse by a chemical that fills the alveolar mucosa called **surfactant**. Surfactant is produced by the alveolar mucosa itself. But, when it is deficient like in premature babies the alveolar mucosal wall adheres and ensue collapse. Then the newborn starts to manifest all symptoms of restrictive lung diseases.

Clinical features

Pathophysiology

- Dyspnea from the first moment of life and
- Shallow respiration
- Lower ribs retraction
- Grunting
- Cyanosis (bluish discoloration of the body)

3.3.2. Obstructive Pulmonary Diseases

- In general, obstructive pulmonary conditions obstruct airflow within the lungs, leading to less resistance to inspiration and more resistance to expiration. This results in prolongation of the expiratory phase of respiration. Expiratory phase is more compromised since expiration is a passive process, while inspiration is assisted by accessory muscles of the respiration and it is less compromised.
- Obstructive pulmonary diseases are classified into **two classes** based on durations as: -

3.3.2.1. A) Acute obstructive Airway Disease

3.3.2.2. B) Chronic obstructive pulmonary Disease (COPD)

3.3.2. Acute obstructive Airway Disease

- The classification of an acute obstructive airway disease is dependent on the episodic nature of the condition.
- The two major entities in this classification are: -

Pathophysiology

- I) Acute Bronchitis; and
- II) Bronchial Asthma.

N.B. - In both cases, the obstruction is intermittent and reversible unlike in COPD.

I) Acute Bronchitis

- It is a common condition caused by infection and inhalants that result in inflammation of the mucosal lining of the tracheobronchial tree.

Causes

- **Viruses:** - Influenza viruses
 - Adenoviruses
 - Rhinoviruses
- **Bacterial:** - Mycoplasma pneumoniae
- **Inhalants:** - Smokes

Pathophysiology of Acute Bronchitis

Inflammation of **the tracheobronchial Mucosa**

↓

Results in **increased mucus secretion**, bronchial swelling, and dysfunction of the cilia.

↓

Leads to **increased resistance to expiratory airflow**, usually resulting in some air trapping on expiration.

Pathophysiology

It is manifested as follows: - _____

- Expiratory wheezing
- Cough productive of mucoid sputum
- Bacteria may be superimposed on the viral bronchitis.

II) Bronchial –Asthma

Definitions

- Asthma is an episodic, acute airway obstruction that results from stimuli that would not elicit such a response in healthy individuals.
- The person with asthma has a tendency toward bronchospasm as a response to a variety of stimuli.

Pathophysiology

- The common characteristics of all asthmatic reactions are **hyper-responsiveness** and an **inflammatory response** in the airways.

Causes

The causes of asthma are divided into two: -

a) Extrinsic (Allergic) Asthma

- ✓ Allergic asthma usually affects the child or young teenagers who frequently relate family history of allergy, hives, rashes, and eczema.
- ✓ It is usually self-limited and frequently precipitated by exposure to a specific antigen.
- ✓ Common allergens are:
 - Mite found in house dust.
 - Seasonal asthma (pollen allergy) etc.
- ✓ Extrinsic asthma decrease in frequency and severity as the child get older.
- ✓ And less likely to remit in adult hood.

b) Intrinsic- Asthma: -

- ✓ Intrinsic asthma usually affects adults, who did not have asthma or allergy prior to middle adult hood.
- ✓ No family history of asthma or allergy.
- ✓ Attacks are often related to infection of the respiratory tract or to exercise, emotions and other factors may also play a role.

Pathophysiology

Pathophysiology of Bronchial Asthma

- The pathophysiology of bronchial asthma attack is related to the release of chemical mediators in an **IgE- mast cell** interaction.

When the antigen enters the air ways



IgE are produced against the antigens



Then, the **IgE** binds or interacts with mast cells, so that the mast cells are ruptured to release chemical mediators like **histamine** and others.



Release of these chemical mediators results in:-

1. Bronchospasm, which involves rhythmic squeezing of the airway.
2. Production of abnormally large amount of thick mucus, and
3. Inflammatory response, including increased capillary permeability and mucosal edema.



NARROWING OF THE AIRWAYS



- ✓ Difficulty of expiratory phase of respiration

Pathophysiology

- ✓ Retention of expired air in the alveoli & lung hyper inflation.

Clinical Manifestations

- The signs and symptoms of asthmatic attack are closely related to the status of the airways.
- The manifestations are variable and unpredictable.
- Bronchospasm and accumulation of mucus plugs or edema results in Obstruction of the airways; and air trapping (due to expiratory flow resistance)
- Then the patients start to manifest with: -
 - Hyper inflated alveoli (lungs)
(Due to retained air)
 - Expiratory wheezing (Noisy sound on expiration created when air pass through a narrowed air way)
 - Diaphragmatic flattening: - due to pressure created by hyper inflated alveoli and as the result, diaphragmatic function is limited as a major organ of respiration.
 - Fatigue: - due to increased work of breathing.
(Labored breathing)

Pathophysiology

- Thick, sticky sputum: - due to increased sputum production and dehydration.
- Anxiety (panic): - due to hypoxia or air hunger.
- Tachycardia: - to compensate for the hypoxia etc.

N.B. Once the attack has subsided and underlying precipitators have been cleared or treated, the lung usually return to normal. I.e. it **is reversible condition!!**

3.3.2.2. Chronic Obstructive Pulmonary Diseases (COPD)

- Chronic obstructive pulmonary disease (COPD) is one of the commonest causes of morbidity and mortality worldwide
- The prevalence increase with age
- COPD is similar to asthma in that expiratory airflow is obstructed and exacerbations and remissions are common.
- COPD differs from acute obstructive lung diseases in that lung tissues do not return to normal between exacerbations or attacks in

Pathophysiology

chronic conditions. I, e. pulmonary damage is progressive process.

(Irreversible lung damage)

Causes of COPD

- i) Accumulation of secretion
 - A) Chronic Bronchitis
 - B) Bronchiectasis
 - C) Cystic fibrosis
- ii) Anatomical causes
 - D) Emphysema

A) Chronic Bronchitis

Definition

- ✓ Chronic bronchitis is defined when a person has a productive cough on most days for at least 3 consecutive months in 2 successive years.
- ✓ Continued bronchial inflammation and progressive increase in productive cough and dyspnea not attributable to specific cause.
- ✓ Usually, the inflammation and cough are responses of the bronchial mucosa to chronic irritation from cigarette smoking, atmospheric pollution or infection.

Pathophysiology

Pathophysiology

- Chronic irritation by cigarette smoking, atmospheric pollution, or infection

↓

- This results in chronic inflammatory process in the bronchial mucosa with vasodilation, congestion, edema and infiltrated by lymphocytes, macrophages, PMN cells.

|

- These lead to thickening and rigidity of bronchial mucosa with excessive secretion plus narrowing of the passageways first for maximal expiration then to inspiratory air flow.
- **The final outcomes of chronic bronchitis are:**
 1. Increased airway resistance with or without emphysematous changes.
 2. Right heart failure (cor pulmonale)
 3. Dysplasia of the respiratory epithelial cells, which may undergo malignant changes.

Clinical Features

- Cough productive of copious sputum: - due to excessive secretion from bronchial mucosa.
- Cyanosis: - Bluish discoloration of the body due to hypoxia.

- They are called “**Blue**

bloaters”

Pathophysiology

- ❑ Mild degree of hyperinflation: - due to retained expiratory air when it pass through narrow air way.
- ❑ Right side Heart failure (**corpulmonare**): - due to effect of chronic hypoxia, pulmonary artery hypertension occurs. This increase after load to the right ventricle that lead to RHF. With different symptoms of RHF.

B) Bronchiectasis

Definition

- ✓ Bronchiectasis is a chronic disease of the bronchi and bronchioles, characterized by irreversible dilatation of the bronchial tree and associated with chronic infection and inflammation of these passageways.

Pathophysiology of Bronchiectasis

- ✓ It is usually preceded by bronchopneumonia that causes the bronchial mucosa to be replaced by fibrous scar tissue. This process

Pathophysiology

leads to destruction of the bronchi and permanent dilatation of bronchi and bronchioles, which allows the affected area to be targets for chronic smoldering infections.

- ✓ It usually affects the lower lobes due to gravity effects and stasis.

Clinical features

- ✓ The disease is usually initiated by infection of the affected bronchi or areas
- ✓ Symptoms of infection are common.
- ✓ Increased volume of mucopurulent sputum and occasionally blood stickled during the acute exacerbation phase.

C) Cystic Fibrosis

Definition

- ✓ It is a hereditary disorder in which large quantities of viscous material are secreted.

Pathophysiology

- ✓ It affects the sweat glands, pancreas and mucus secreting glands of the bronchi and small intestine
- ✓ Not common in Ethiopia

D) Pulmonary Emphysema

Definition

- ✓ Emphysema is a permanent, abnormal enlargement of the acinus (Portion of the lung distal to terminal bronchiole) with associated destructive changes.
- ✓ It is usually classified with chronic bronchitis because of simultaneous occurrence of the two conditions
- ✓ In anatomic terms, emphysema involves portion of the lung distal to terminal bronchioles (acinus) where gas exchange takes place.

Etiology

- ✓ The exact cause of emphysema is unknown but most cases are related to: -
 - Smoking
 - Infection
 - Air pollution

Pathophysiology

- Deficiency of α - antitrypsin enzyme.

Pathophysiology of Pulmonary Emphysema

- ✓ Emphysema is due to many separate injuries that occur over a long time when the lung is exposed to one of the above causes.
- ✓ The elastin and fiber network of the alveoli and airways are broken down the alveoli enlarge and many of their walls are destroyed.
- ✓ Alveolar destruction also undermines the support structure for the airways, making them more vulnerable to expiratory collapse.
- ✓ Destruction of elastin and fibers results in loss of elastic recoil of lung, so that

Pathophysiology

air trapping occurs and the resultant alveolar hyperinflation causes compression of the bronchi and bronchioles, which also precipitate expiratory collapse of the airways.

Clinical manifestation

- The onset is insidious
- It may overlap with those of chronic bronchitis
- Dyspnea early on exertion later at rest
- Hyper-inflated lung due to air trapping causes **barrel chest** (Increased anteroposterior chest diameter)

Review Questions

- 1.What are common causes of poor in tissue oxygenations.
- 2.Discuss the compensatory mechanisms of congestive heart failure.
- 3.Discus the difference between the pathophysiology of LHF & RHF.
- 4.What does cardiac Decompensation mean?
- 5.Discuss causes and pathophysiology of restrictive lung diseases.
- 6.How does pneumonia cause restrictive lung disease?
- 7.Discuss pathophysiologic changes of bronchial asthma.
- 8.What is the difference between acute obstructive lung disease and chronic chronic obstructive lung diseases?
- 9.Discus the pathophysiologic mechanisms of venous thrombosis.

CHAPTER FOUR

ALTERATION IN DISTRIBUTION OF BODY FLUID

Learning Objectives:-

At the end of this chapter the students will be able to:-

- Explain physiologic mechanisms of regulation of interstitial fluid.
- Describe pathophysiologic mechanism of edema formations.
- Discuss effects and classifications of edema.
- Describe pathophysiology of Nephrotic syndrome.
- Explain pathophysiology and clinical feature of cirrhosis.

4.1. Regulation of interstitial fluid volume

Introduction

- Exchange of fluid between the vascular compartment and the interstitial spaces occurs at the capillary level. The capillary filtration pressure pushes fluid out of the capillaries and colloidal osmotic pressure exerted by the plasma proteins and pulls fluid back into the capillaries. Albumin which is the smallest and most abundant of plasma proteins, provide the major osmotic force for the return of fluid to vascular compartments.
- Normally slightly more fluid leaves the capillary bed than can be reabsorbed. This excess fluid is returned to the circulation by way of lymphatic-channel.

4.2. Edema

- Refers to excess interstitial fluid in the tissues
- It is not a disease but rather the manifestation of altered physiological function.

4.2.1. Mechanisms of Edema formation

Pathophysiology

- There are four major mechanisms of edema formation.
 - I. Increased capillary pressure
 - II. Decreased colloidal osmotic pressure
 - III. Increased capillary permeability
 - IV. Obstruction of lymphatic flow.

I. increased capillary pressure

- Edema develops when an increase in capillary pressure causes excess movements of fluid from the capillary bed into the interstitial space.

The common causes of increased capillary hydrostatic pressures are:-

- **Congestive heart failure**
 - **Right side heart failure:** - increased capillary hydrostatic pressure due to increased systemic venous pressure with increased blood volume.
 - **Left side heart failure:** - leads to increase in pulmonary capillary pressure (PCP). When the PCP exceeds 25mmHg, pulmonary edema can occur.
- **Renal Failure**

Pathophysiology

- Renal failure results in edema by increasing capillary pressure due to salt and water retention which results in vascular congestion.
- **Liver cirrhosis with portal hypertension:-**
 - Portal veins hypertension can occur when there is venous obstruction like in the case of cirrhosis, per portal fibrosis, etc. so that capillary hydrostatic pressure of the portal vein increases resulting in ascites (fluid in abdominal cavity).
- **Venous obstruction**
 - Localized edema occurs when there is venous obstruction like in the case of phlebothrombosis (thrombus formation in the vein).
- **Increased gravitational forces:** - Increased gravitational force occurs in long standing Leg Edema.

II. Decreased Colloid Osmotic Pressure (COP)

- Plasma proteins exert the osmotic force that is needed to move fluid back into the capillary from tissue space. Edema develops when plasma protein level become inadequate because of abnormal loss or inadequate productions.
 - When fluid moves to the interstitial space vascular volume decrease, as a result, the kidney responds by secreting rennin-angiotensin aldosterone hormones that cause salt and water retention to worsen the edema.
- **Hypoproteinemia**:-causes decreased colloid osmotic pressure and results from:-
- ✚ **Malnutrition**: - example – Edema in kwashiorkor.
 - ✚ **Liver failure**:-Decreased albumin synthesis by the liver.
 - ✚ **Protein loss**:-in burn excess loss of protein occurs when large area of skin is injured or destroyed.
 - ✚ **Protein losing enteropathy**:-is a protein malabsorption syndrome, which results in protein loss with stool.
 - ✚ **Nephrotic syndrome**: loss of large amount of protein through urine, when the glomerular capillaries become permeable to plasma proteins.

III. Increased capillary permeability

- Direct damage to blood vessels, such as with trauma and burns, may cause increased permeability of the endothelial junctions.
- Localized edema may occur in response to an allergen, such as a bee sting.
- Inflammation causes vasodilatation, which leads to accumulation of fluids in the affected area.

IV. Obstruction of the Lymphatics

- Osmotically active plasma proteins and other large particles rely on the lymphatic for movements back into the circulatory system from interstitial space.
- When lymph flow is obstructed → lymph edema occurs.
- The edema is usually localized.
- Common causes of lymphatic obstruction are:-
 - Surgical removal of lymph nodes for cancer
 - Radiation therapy
 - Malignant metastasis
 - Inflammations

Pathophysiology

- Filariasis (parasitic infection of the lymph vessels)

4.2.2. Effect of Edema.

- Effects of edema depend largely on its location.
- Edema of brain and lung → causes acute life threatening condition
- Edema of face → may limit opening of eye lid
- Edema of foot and others → create problem in obtaining proper fitting shoes and clothing.
- Edematous tissues generally are more susceptible to injury and development of ischemic tissue damage.

Example: - Pressure sores.

4.2.3. Classification of Edema

- There are three types of fluid collection in the tissues

a. Pitting edema

- When accumulation of interstitial fluid exceeds the capacities of tissue gel, the tissue water is mobile; I.e. It can be translocated with pressure exerted by finger. An indentation remains after the finger has been removed.

b. Non pitting Edema

Pathophysiology

- Is a condition in which several proteins have accumulated in the tissue space and coagulated.
- Often the area is firm and discolored with progression to stasis dermatitis.
- Is usually seen in lymphatic obstruction, venous thrombosis, or following local trauma.

c. Accumulation of fluid in the serous cavities

- The potential spaces are closely linked with lymphatic drainage system.
- Obstruction to lymph flow → Fluid accumulation.
- Inflammatory process → accumulation of exudative fluid due to vasodilatation in the potential spaces.

➤ **Examples**

- Pleural effusion:- accumulation of fluid in pleural cavity
- Ascites: - accumulation of fluid in the peritoneal cavity.
- Pericardial effusion: - accumulation of fluid in the pericardium.

4.3. Nephrotic syndrome:-

4.3.1. Definition: -

Pathophysiology

- Nephrotic syndrome is not a specific glomerular disease, but a constellation of clinical findings that result from increased glomerular permeability to protein.

4.3.2. Features of Nephrotic syndrome

- Massive proteinuria (daily loss of 3.5 gm or more)
- Hypoalbuminemia (less than 3gm/dl)
- Generalized edema — due to decreased **COP**.
- Hyper-lipidemia

➤ Generalized edema

- It is usually the first manifestation and can be so severe as to be incapacitating.
- It results from a decreased colloidal osmotic pressure that accompanies the loss of plasma protein.
- Other factors like increased salt and water retention may also play a role in edema formation.

➤ Hyperlipidemia

- It is characterized by elevated serum level of both triglycerides and cholesterol
- It is due to compensatory increase in albumin synthesis by the liver; which serves as stimulant for synthesis of low-density lipoproteins.
- The patients are at higher risk of developing atherosclerosis, due to high level of low – density lipoproteins.

Pathophysiology

➤ **Hypoalbuminemia**

- Usually less than 3gm/dl.
- It is due to proteinuria.
 - Massive proteinuria:-
- It is the core pathophysiologic problem in nephrotic syndrome.
- Together with proteinuria, there is also loss of the following components in urine:-
 - Loss of Immunoglobulin → makes them susceptible to infections
 - Loss of low molecular coagulation factors like factor IX, X XI, XII prothrombin, plasminogen, and antitrypsin creates imbalance in coagulation factors __, makes them susceptible for thrombosis.

4.3.3. Causes of Nephrotic syndrome

- There are two types of Nephrotic syndrome based on the causes:-

I) Secondary glomerular disease:-

- It is common in adults
- Usually due to systemic diseases like
 - Diabetic mellitus or
 - Systemic lupus erythematosus (SLE)

II) Primary glomerular diseases

- This type almost always occurs in children under 15 years old.
- The primary glomerular lesions are
 - a) Minimal change disease
 - b) Focal sclerosis
 - c) Membranous glomerulopathy
 - d) Membranoproliferative glomerulonephritis

4.4. Cirrhosis of the liver

Pathophysiology

4.4.1. Definition

- Cirrhosis is a general term for a condition that destroys the normal architecture of the liver lobules.
- It has the following important structural features:-
 - a. Destruction of liver parenchyma
 - b. Separation of the lobules by fibrous tissues
 - c. Formation of structurally abnormal nodules, and
 - d. Abnormal vascular architecture

4.4.2 classifications of cirrhosis

1. Cirrhosis is classified according to its causative agents and resultant pathologic configurations as :-
 - a. Biliary cirrhosis
 - b. post necrotic cirrhosis
 - c. Alcoholic cirrhosis

a) Biliary cirrhosis

Pathophysiology

- It is due to an intra hepatic block that obstructs the excretion of bile or it may occur secondary to obstruction of the bile ducts.
- The obstruction in one area of biliary passage results in bile stasis; that causes injury and scarring around the hepatocytes with evidence of fibrosis.

b) Post necrotic cirrhosis

- It follows massive liver necrosis and involves the destruction of lobules and even lobes of the liver.
- It may occur after hepatitis or after exposure to hepatotoxins such as certain drugs.

C. Alcoholic cirrhosis

- The most common cause of cirrhosis is excessive alcohol consumption
- At least 75% of alcohol related deaths are attributed to cirrhosis.

➤ **Stages in developments of alcoholic cirrhosis**

1. Stage of fatty change

- Excessive accumulation of fat with in liver cells causes liver enlargement
- Alcohols replace fat as a fuel for liver metabolism and impair mitochondrial ability to oxidize fat.
- Don't usually produce symptoms

Pathophysiology

- It is reversible once the alcohol intake has been discontinued.

2. Stage of Alcoholic Hepatitis

- It is an intermediate stage between fatty changes and cirrhosis
- It is characterized by inflammation and necrosis of liver cells, thus is always serious and some times fatal.
- The necrotic lesions are generally patchy but may involve entire lobe.
- The stage is characterized by hepatic tenderness, paler, anorexia, nausea, jaundice, ascites and liver failure. Some patients may be asymptomatic.

3. Stage of cirrhosis

- Cirrhosis is the direct result of liver injury caused by fatty liver and alcoholic hepatitis.
- The normal liver structure is replaced by bands of fibrous tissue with areas of regenerating cells.
- As the disease progress liver shrinks.

4.4.3. Clinical Manifestations of cirrhosis

-The Manifestations of cirrhosis are variable, ranging from asymptomatic Hepatomegally to hepatic failure.

- **Early manifestations:-** right upper quadrant pain
 - Sensation of fullness
- **Late manifestation:-**
 - The late manifestations are related to **portal hypertension** and **liver cell failure(Hepatocellular failure)**
 - **Portal Hypertension:-**
 - The fibrotic bands cause narrowing of the portal vein to cause portal hypertension
 - It is followed by back ward congestion of all tributaries of portal veins.

▪Example:-

- Esophageal veins congestion called **Esophageal varices**
- **Ascites:-**accumulation of fluid in abdominal cavity due to increased hydrostatic pressure.
- **Splenic enlargement:** - due to congestion by blood.

Pathophysiology

- **Hepatocellular failure** results in:-
 - Decreased production of bile.
 - Decreased plasma protein (Hypoalbuminemia)
 - Decreased blood clotting factors.
 - 1. Accumulation of metabolic bi-products and toxins like bilirubin, ammonia and other substances in the circulation since the liver loses its detoxification capacity. This is one of the reasons for hepatic coma to occur.

Review Questions:-

1. Discuss the mechanisms of regulation of interstitial fluid.
2. List the mechanisms of edema formation.
3. What does colloidal osmotic pressure mean?
4. What are the effects of edema on our body?
5. List causes of increased capillary permeability.
6. Discuss the mechanism of edema formation in nephrotic syndrome and liver Cirrhosis

CHAPTER FIVE

ALTERATION IN GIT FUNCTION

Learning objectives

At the end of this chapter the students will be able to:-

- Discuss back ground information about peptic ulcer diseases (PUD).
- Explain predisposing factors and pathogenesis of PUD.
- List clinical manifestations and complications of PUD.
- Describe causes and Pathophysiologic changes of intestinal obstructions

5.1. Peptic Ulcers Diseases (PUD)

Introduction

- ✓ Peptic ulcer disease represents a break in the continuity of the gastrointestinal tract mucosal layer.
- ✓ It is commonly categorized into two as gastric and duodenal peptic ulcer diseases.
- ✓ Gastric and duodenal peptic ulcers with their remissions and exacerbations represent a chronic health problem.
- ✓ Duodenal ulcers are 5 to 10x more common than gastric ulcer.
- ✓ Ulcers in duodenum occur at any age and are frequently seen in early adult hood. While Gastric

Pathophysiology

ulcers tend to affect the old age group with peak incidence in the 6th- 7th decade.

- ✓ Both types of ulcer affect men 3 to 4 times compared to women.
- ✓ Peptic ulcers can occur in any area of GI tract that is exposed to acid-pepsin secretions.

- **Common sites are:-**

1. Ulceration in esophagus caused by reflux of gastric secretions
2. In stomach and duodenum: - the common sites.
3. In Meckel's diverticulum that contain misplaced gastric tissue.

Predisposing factors for PUD: -

- Peptic ulcer represents a break in the continuity of the mucosal layer. The following conditions are some of incriminated predisposing factors for development of GI mucosal ulceration: -
 - A. Increased level of mucosal aggressive factors (Increased acid and pepsin production)

OR

Pathophysiology

- B. Inability of the mucosal barrier to resist the destructive action of the gastric secretions (enzymes & acids).

N.B:-It is more likely that both of the above factors contribute to the development of peptic ulcer diseases.

A. Increased acid and pepsin production

- Increased pepsin-production and HCl production is influenced by several factors like neural and hormonal stimulation.

➤ **For Example: -**

□ **The hormone gastrin: -**

- This is produced in the antrum of stomach, is potent stimulus for HCl production. Also gastrin hormone has been attributed to the following actions: -

1. Increasing number of acid and pepsin producing cells in stomach
2. Increased sensitivity of parietal cells to food and other stimuli like → alcohol, caffeine, etc increases HCl production.
3. Excessive vagal stimulation → stimulates HCl production.
4. Impaired inhibition of gastric secretions as food moves in to intestine.

□ **Neural stimulations: -**

Pathophysiology

- Normally gastric secretion is inhibited as food moves in to the intestinal lumen. This reflex inhibition of gastric secretions may be impaired in certain type of ulcers known as **Cushing's ulcer (stress ulcer)**: -which occur in association with severe brain injury, severe burn or neurosurgery. (By causing increased central stimulation of vagus nerve, severe brain injury and neurosurgery resulting in unresponsiveness to the reflex mechanisms that normally control gastric secretions).

B. Inability of the mucosal Barrier to Resist Gastric Secretions

- The defense of the mucosal surface depends on an adequate blood flow and intact mucosal barriers. This is suitable to hydrogen ion.
 - Basic abnormality in person with gastric-peptic ulcer is an increased permeability of the epithelial layer of the stomach to hydrogen ion.
- **The following conditions affect mucosal barrier integrity: -**
- ✓ Chronically diseased mucosal membrane is unable to secrete sufficient mucus to form an effective barrier

Pathophysiology

- ✓ Reflux of bile from intestine to stomach has been implicated in peptic ulcer.
- ✓ Also numbers of drugs are recognized as a “**barrier- breaker**” both aspirin and alcohol are known to damage this barrier.
- ✓ Anxiety and stress → sympathetic stimulation inhibition of glands (Brunner’s gland) that is important to produce mucus secretions.
- ✓ Identification of a gram-negative, S-shaped bacterium called *helicobacter pylori*. Which colonize the mucus secreting epithelial cells of stomach and duodenum and digest the protective mucus secreting membranes.

Clinical Manifestations and complications of PUD

- The clinical manifestation of uncomplicated peptic ulcer focus on discomfort and pain. Pain, which is described, as waning, gnawing or crampy like, is usually rhythmic and frequently occurs when the stomach is empty. The Pain is usually over small area near the mid-line in the epigastrium and may radiate below the costal margins in to back or rarely to the right shoulder.
- Food or antacids relieve the pain.
- A peptic ulcer can affect one or all layers of the stomach or duodenum. An ulcer may penetrate only

Pathophysiology

the mucosal surface or it may extend in to the smooth muscle layer.

- Spontaneous remissions and exacerbations are common. Healing of muscularis layer involving replacement with scar regeneration is often less than perfect in which repeated episodes of ulceration occur.

- **Complications of peptic ulcer includes:**
 - **Hemorrhage:** - results from erosions of the mucosa.
 - Cause upper GI-bleeding (Hematemesis & melana)
 - **Perforation hemorrhage:** - is from granulation tissue or from erosion of an ulcer in to an artery or vein
 - **Obstruction:** -is caused by edema, spasm or formations of scar tissue interfere with free passage of gastric contents through the pylorus or adjacent area. Epigastric fullness, heaviness after meal with severe case of obstruction vomiting of undigested food. The presence of an over night gastric residual of 50ml of undigested food indicates severe obstruction.
 - **Perforation:** - occurs when an ulcer erodes through all the layers of the stomach or duodenal wall.

Pathophysiology

- With perforation, GI-contents enter the peritoneum and cause peritonitis or perforated adjacent structures such as pancreas.
- Sudden onset of severe epigastric pain that radiates to back, restlessness, inadequate pain relief from eating foods or taking antacids in persons with long standing history of PUD may signify penetration.

5.2 Intestinal obstruction

- **Definitions:** -
 - An impairment of movement of intestinal content in cephalocaudal direction.
- **Causes**
 - The cause of intestinal obstruction could be categorized under two headings: -
 1. Mechanical (dynamic) causes.
 2. Reflex paralytic (adynamic) causes.

Mechanical obstruction

Classifications

- **Extrinsic factor:** -
 - Adhesions of peritoneum
 - Hernias

Pathophysiology

- Volvulus (Twisting of the bowel lumen)
- **Intrinsic factors**, which encroach on the patency of the bowel.
 - Telescoping of the bowel (intussusceptions)
 - Fecal impaction
 - Stricture of the bowel
 - Tumors
 - Ascariasis bolus

Types of mechanical obstructions: -

- There are 3-types of Mechanical obstruction
 - Simple → No alteration in blood flow
 - Strangulated → there is obliteration in blood flow
 - Closed → when bowel is obstructed in both ends.

Pathophysiology

Reflex paralytic (adynamic) Obstructions

- Usually affects small bowel since the ileum has the narrowest lumen and is the most prone site to obstruction.
- Paralytic ileus is seen most commonly following abdominal surgery or trauma.
- It occurs early in the course of peritonitis and can result from chemical irritation caused by bile, bacterial toxins, electrolyte imbalance (hypokalemia) & vascular insufficiency.

Pathophysiology of Intestinal Obstruction

Obstruction of the intestinal lumen



Loss of fluid and electrolytes to the area with gas accumulation in the intestinal lumen proximal to the obstructed part leads to distension of the proximal lumen



Results in dehydrations and hypovolemic shock. The mechanisms of dehydrations in intestinal obstructions are:-

1. Intestinal obstruction interferes with reabsorption of 7 to 8 liters of electrolyte rich extra cellular fluid in small bowel.
2. Lost in the vomitus of 7 liters to 8 liters which represent about half of the extra cellular fluid volume of an average adult can occur in 24hours or less following acute intestinal obstruction.
3. The patient can not drink fluids.



If untreated, the distention resulting from bowel obstruction tends to perpetuate itself by causing atony of the bowel & further distension is aggravated by the accumulation of gases.



Pathophysiology

About 70% of these gases are estimated to be due to swallowed air. As distension moves proximally involving additional segments of bowel.

The increased pressure within the intestinal lumen compromise mucosal blood flow → necrosis/ exudation of the bowel → eventually strangulation, gangrenous change and ultimate **perforation of bowel** with bacterial over growth → Release of endotoxin & bacterimia → SEPSIS.

Clinical Manifestations of Intestinal Obstructions

The manifestation of intestinal obstruction depends on the degree of obstruction and its duration. With acute obstruction the onset is usually sudden and dramatic but with chronic one onset is more gradual. **The cardinal symptoms** of intestinal obstruction are:

1. Pain: - which is colicky, especially with mechanical obstruction. It is due to increased peristalsis as the intestine attempts to move the content forward.
- Also there is increased bowel sound.
2. Absolute constipation: - failure to pass faeces and flatus.

Pathophysiology

3. Abdominal distention: - due to gases accumulations and atonia of the Smooth muscles in the intestinal lumen
4. Vomiting: - leads to fluid and electrolyte imbalance.
 - The vomitus may contain feculent matter (offensive).

● **Signs of Gangrenous Changes or Strangulations:-**

If an acute intestinal obstruction left untreated for long duration, usually above 72 hours, strangulations and gangrenous change is the rule. The following are clinical signs of gangrenous changes:-

- The patient becomes weak and prostrated.
- Development of fever
- Tachycardia
- Absence of peristalsis (bowel sound)
- Increased abdominal tenderness.

N.B: - with development of strangulations mortality rate is increased by 25%.

Reviews Questions

Pathophysiology

1. What are the two important predisposing factors for development of PUD?
2. List the causes of intestinal obstructions.
3. What are the most important Pathophysiologic effects of intestinal obstructions?

CHAPTER SIX

ALTERATIONS IN ENDOCRINE FUNCTIONS

Learning objectives

At the end of this chapter the students will be able to:

- Describe primary and secondary endocrine disorders
- List effects of excessive secretion of growth hormone on different organs/systems
- Discuss the clinical features of follicle stimulating hormone and luteinizing hormones
- Describe diabetes insipidus
- Compare and contrast the hypo and hyper state of thyroid function.
- Describe the pathophysiology of graves' disease.
- Discuss the pathophysiology of cushing's syndrome

6.1 Review of the endocrine system

Hormones

Hormones are generally thought of as chemical messengers that are transported in body fluids.

Structural classification

Hormones have diverse structures ranging from single modified amino acids (epinephrine and thyroxine), poly peptides (growth hormone and insulin), and glycoproteins (follicle-stimulating hormone and luteinizing hormone) to lipids (steroid hormones such as cortisol).

Function

Hormones do not initiate reactions; rather they are modulators of body and cellular responses. Hormones can produce either a generalized or a localized effect. For example, thyrotropin acts selectively on the thyroid gland, where as epinephrine affects the function of many body systems.

Synthesis

Protein and peptide hormones are synthesized in the rough endoplasmic reticulum and stored in granules or vesicles within the cytoplasm of the cell until secretion is required. The lipid-soluble steroid hormones are released as they are synthesized (smooth endoplasmic reticulum).

Transport

Pathophysiology

Hormones are delivered from cells of the endocrine gland to target cells:

1. Blood-borne delivery
2. Neurocrine
3. Neuroendocrine
4. Paracrine

Metabolism

Hormones secreted by endocrine cells must be continuously inactivated to prevent their accumulation. Both intracellular and extra cellular mechanisms participate in the termination of hormone function. Some hormones are enzymatically inactivated at receptor sites where they exert their action.

Rate of reaction

Hormones react at different rates. The neurotransmitters, such as epinephrine, have a reaction time of milliseconds. Thyroid hormone, on the other hand, requires days for its effect or occur.

Mechanisms of action

Hormones exert their action by binding to specific receptor sites located on the surface of the target cells. The function of these receptors is to recognize a specific hormone and translate the hormonal signal into a cellular response.

Control of hormone levels

Hypothalamic – pituitary regulation

Because the integration of body function relies on input from both the nervous system and the endocrine system, it seems logical that input from the nervous system would participate in the regulation of hormone levels. In this respect, the hypothalamus and the pituitary (hypophysis) act as an integrative link between the central nervous system and the many endocrine mediated functions of the body.

Feedback mechanisms

The level of many of the hormones in the body is regulated by negative feedback mechanisms.

6.2 General aspects of altered endocrine function

Most endocrine disorders fall into one of four categories:

- 1) Too little hormone (hyposecretion);
- 2) Hypersecretion;
- 3) Reduced response of the target cells (hyporesponsiveness); and
- 4) Hyperresponsiveness.

It can also be seen in two ways:

- Hypofunction and hyper function

Pathophysiology

Hypofunction of an endocrine gland can occur for a variety of reasons.

Causes – congenital defects

- Distraction of the gland
- Aging
- Gland atrophy
- Receptor defects
- Biologically inactive hormone

- **Hyperfunction** is generally associated with excessive hormone production

This can result from:-

- Excessive stimulation and hyperplasia of the endocrine gland
- Hormone – producing tumor of the gland

6.2.1 Primary and secondary disorders

Endocrine disorders can generally be divided into two groups- primary or secondary. Primary defects in endocrine function originate within the target gland responsible for producing the hormone.

In secondary disorders of endocrine function, the target gland is essentially normal, but its function is altered by defective levels of stimulating hormones or releasing factors from the hypothalamic – pituitary system.

Diagnostic methods

Pathophysiology

There are a number of techniques for assessing endocrine function and hormone levels.

- Effect of a hormone on body function
e.g. blood glucose reflects insulin level.
- Radio immunoassay

6.3 Alterations in endocrine control of growth and metabolism

Growth hormone (GH)

Growth hormone, also called somatotropin, is a 191-amino-acid polypeptide hormone synthesized and secreted by special cells in the anterior pituitary referred to as somatotropes and stimulates the liver to produce insulin-like growth factor -1(IGF-1) also known as somatomedin c.

Effects of GH

- Linear bone growth & cartilages
- Growth of visceral organs
- Growth of endocrine organs
- Growth of skeletal and cardiac muscles
- Development of skin and connective tissue

Pathophysiology

Aside from its effects on growth, GH facilitates the rate of protein synthesis by all of the cells of the body; it enhances fatty acid mobilization and increases the utilization of fatty acids for fuel; and it maintains or increases blood glucose for fuel.

GH is, in summary, an anabolic hormone, promotes protein synthesis and free fatty acids. Growth hormone is stimulated by hypoglycemia, fasting, starvation, increased blood levels of amino acids and stress conditions.

Growth hormone is inhibited by increased glucose levels, free fatty acid release, cortisol, and obesity.

6.4 Disorders of the anterior pituitary gland

6.4.1 Growth hormone excess

Normally IGF-1 signals the anterior pituitary to reduce GH production. Overproduction of GH is almost always caused by a benign pituitary tumor (adenoma). The pituitary tumor secretes GH despite elevated IGF-1 levels, leading to the unwanted growth of bones and other soft tissues:

Overproduction of GH also causes elevation of blood glucose through insulin antagonism. Prolonged glucose levels associated with an elevation in GH leads to glucose intolerance.

Pathophysiology

In children, the excessive secretion of GH results in gigantism. When the onset of GH excess occurs before closure of the epiphyses, the long bones are still capable of longitudinal growth. The excessive growth seen is usually proportional. These children may grow as tall as 240 cm and weigh more than 136kg.

In adults, excessive secretion of GH results in acromegaly. Acromegaly is characterized by an overgrowth of the bones and soft tissues. Since the problem develops after epiphyseal closure in adults, the bones are unable to grow longer. Instead, the bones increase in thickness and width. Acromegaly is relatively rare.

Pathophysiology

Clinical manifestations

Manifestations of acromegaly begin gradually, usually in the 20s and 30s.

Individuals experience enlargement of the hands and feet. The fingertips develop a tufted or clubbed –like appearance. The enlargement of the bones and cartilage may cause symptoms that range from mild joint pain to deforming, crippling arthritis. Changes in physical appearance occur, with thickening and enlargement of bony and soft tissues on the face and head. Enlargement of the mandible causes the jaw to jut forward. The paranasal and frontal sinuses enlarge, as does the bony tissue of the forehead. Enlargement of soft tissue around the eyes, nose, and mouth results in a coarsening of facial features. Enlargement of the tongue results in speech difficulties.

Sleep apnea may also occur and is related to upper airway narrowing and obstruction resulting from increased amounts of pharyngeal soft tissues.

The skin becomes thick, leathery, and oily.

Women may develop menstrual disturbances.

Individuals with acromegaly are more likely to develop polyps in the colon and colon cancer.

Pathophysiology

The enlarged pituitary tumor gland can exert pressure on surrounding structures within the brain, leading to visual disturbances and headaches.

Because GH mobilizes stored fat for energy, it increases free fatty acid levels in the blood and predisposes the patient to atherosclerosis. The hormone also antagonizes the action of the insulin and causes hyperglycemia.

Left untreated, acromegaly can lead to a number of changes in the body. Effects on the cardiovascular system include cardiomegaly, left ventricular hypertrophy, angina pectoris and hypertension. Other systems that undergo change include the respiratory, gastrointestinal, genitourinary, musculoskeletal, and nervous systems.

Diagnostic studies

- History
- Physical examination
- Plasma IGF-1, IGF binding protein-3 levels
- GH response to an oral glucose challenge
- MRI- pituitary tumor
- CT

Management includes surgical (hypophsectomy), radiation and drug therapies.

Excesses of other tropic hormones

An excess of tropic hormones and the over production of a single anterior pituitary hormone usually produces a syndrome related to hormone excess from the target organ. For example, if adrenocorticotrophic hormone (ACTH) is increased, cushing's disease results; if thyroid-stimulating hormone (TSH) levels are excessive, hyperthyroidism develops.

Prolactinomas (prolactin- secreting adenomas) are the most frequently occurring pituitary tumor. Common manifestations experienced by women with prolactinomas include galactorrhea, a dysfunction (anovulatory, infertility), menstrual dysfunction (oligomenorrhea or amenorrhea), decreased libido, and hirsutism. In men, impotence and decreased libido and sperm density may result.

The affected patient may also experience headaches and visual problems. The visual problems are secondary to pressure on the optic chiasm.

Since prolactinomas do not typically progress in size, drug (Dopamine agonist) therapy is usually the first-line treatment.

6.4.2 Hypofunction of the pituitary gland

Pathophysiology

Hypopituitarism: is a rare disorder that involves a decrease in one or more of the pituitary hormones. A deficiency of only one pituitary hormone is referred to as selective hypopituitarism. Total failure of the pituitary gland results in deficiency of all pituitary hormones—a condition referred to as panhypopituitarism. The most common hormone deficiencies associated with hypopituitarism involve GH and gonadotropins (eg. LH,FSH)

The most common cause of pituitary hypofunction is a pituitary tumor. Autoimmune disorders, infections, pituitary infarction (Sheehan syndrome), or destruction of the pituitary gland (as a result of trauma, radiation and surgical procedures)also can cause hypopituitarism. Sheehan syndrome is a postpartum condition of pituitary necrosis and hypopituitarism that occurs after circulatory collapse from uterine hemorrhaging.

Clinical manifestation

Common symptoms associated with a space –occupying lesion include head aches, visual changes, anosmia and seizures.

GH

Adults with GH deficiency often have subtle nonspecific clinical findings. They have truncal and decreased muscle mass causing reduced strength, decreased energy, and exercise capability; Depressed mood as well.

Pathophysiology

Children with idiopathic growth hormone releasing factor have adequate somatotropes, whereas children with pituitary tumors or agenesis of the pituitary lack somatotropes. Child with GH deficiency have short stature, proportion of weight to height is normal retarded bone and tooth development & delayed sexual maturity.

FSH and LH

FSH and LH deficiencies in the adult women are first manifested as menstrual irregularities, diminished libido, and changes in secondary sex characteristics (eg decreased breast size). Men with FSH and LH deficiencies experience testicular atrophy, diminished sperm atogenesis, loss of libido, impotence, and decreased facial hair and muscle mass.

ACTH

A deficiency of ACTH and cortisone often produces a nonspecific clinical picture. Signs and symptoms may include weakness, fatigue, headache, dry and pale skin, and diminished axillary and pubic hair. Individuals may have postural hypotension, fasting hypoglycemia, diminished tolerance for stress, and poor resistance to infection.

TH

Pathophysiology

The clinical presentation of an individual with thyroid hormone deficiency associated with hypopituitary is similar with primary hypothyroidism, common symptoms include cold intolerance, constipation, fatigue, lethargy and weight gain.

Diagnostic studies

- In addition to history and physical examination
 - Radiologic tests: MRI and CT
 - Direct and indirect determination of pituitary hormones

Management

- Surgery or radiation for tumor removal
- Life long hormone replacement

6.5 Disorders associated with antidiuretic hormone (ADH)

Secretion

The two primary conditions associated with ADH secretion are a result of either over production or underproduction of ADH. Over production of ADH results in a condition known as syndrome of inappropriate antidiuretic hormone (SIADH). Underproduction of ADH results in a condition referred to as diabetes insipidus (DI).

ADH, also referred to as arginine vasopressin (AVP), is synthesized in the hypothalamus and then transported and

Pathophysiology

stored in the posterior pituitary gland. It plays a major role in the regulation of water balance and osmolarity.

6.5.1 Syndrome of inappropriate antidiuretic hormone (SIADH)

SIADH results from an abnormal production or sustained secretion of ADH and is characterized by fluid retention, serum hypo osmolality, dilutional hyponatremia, hypochloremia, concentrated urine in the presence of normal or increased intravascular volume, and normal renal function. This syndrome occurs more commonly in older adults.

Clinical manifestations

Excess ADH increases the permeability of the distal tubule and collecting duct, which leads to the reabsorption of water into the circulation. Consequently, extra cellular fluid volume expands, plasma osmolality declines, the glomerular filtration rate increases, and sodium levels decline (dilutional hyponatremia). Hyponatremia causes muscle cramps and weakness. Initially, thirst, dyspnea on exertion, fatigue, and dulled sensorium may be evident. The patient with SIADH will experience low urinary output and increased body weight. As the serum sodium level falls, manifestations become more severe and include vomiting, abdominal cramps, muscle twitching, and seizures. As plasma osmolality and serum sodium levels continue to decline, cerebral edema may occur,

Pathophysiology

leading to lethargy, anorexia, confusion, headache, seizures, and coma.

Diagnostic studies

Simultaneous measurements of urine and serum osmolality.

Diabetes insipidus (DI)

Diabetes insipidus is associated with a deficiency of production or secretion of ADH or a decreased renal response to ADH. The decrease in ADH results in fluid and electrolyte imbalances caused by increased urinary output and increased plasma osmolality.

There are several classifications of diabetes insipidus. Central DI (also known as neurogenic DI) occurs when any organic lesion of the hypothalamus, infundibular stem, or posterior pituitary interferes with ADH synthesis, transport, or release. Nephrogenic DI describes a condition in which there is adequate ADH, but there is a decreased response to ADH in the kidney. Lithium is one of the most common causes of drug-induced nephrogenic DI. Hypokalemia and hypercalcemia may also lead to nephrogenic DI.

Psychogenic DI, a less common condition is associated with excessive water intake. This can be caused by a structural

Pathophysiology

lesion in the thirst center or may be caused by psychiatric problems.

•

Clinical manifestations

DI is characterized by increased thirst (polydipsia) and increased urination (polyuria). The primary characteristic of DI is the excretion of large quantities of urine (5-20 L per day) with a very low specific gravity (< 1.005) and urine osmolality of $< 100 \text{ mosm/kg}$ ($< 100 \text{ mmol/kg}$). Serum osmolality is elevated as a result of hypernatremia due to pure water loss in the kidney. Most patients compensate for fluid loss by drinking large amounts of water so that serum osmolality is normal or only moderately elevated. The patient may be fatigued from nocturia and may experience generalized weakness.

6.6 Alteration in thyroid function

An alteration in thyroid function can represent either a hypo functional or hyper functional state. The manifestations of these two altered states are summarized below.

Table 6.1 Manifestations of hypothyroid and hyperthyroid states

Pathophysiology

Level of organization	Hypo state	Hyper state
Basal metabolic rate	Decreased	Increased
Sensitivity to catecholamines	Decreased	Increased
General features	Myxedematous features keep voice impaired growth (child	Exophthalmos lid lag decreased blinking
Blood cholesterol levels general behavior	Increased mental retardation (Infant) Mental & physical sluggishness somnolence	Restlessness, irritability anxiety hyperkinesia wakefulness
Cardiovascular function	Decreased cardiac output Brady cardia	Increased cardiac out put tachycardia and palpitations
Gastro intestinal function	Constipation decreased appetite	Diarrhea increased appetite
Respiratory function	Hypoventilation	Dyspnea
Muscle tone and reflexes	Decreased	Increased, with tremor and fibrillatory twitching
Temperature tolerance	Cold intolerance	Heat intolerance

Pathophysiology

Skin and hair	Decreased sweating and dry skin and hair	Increased sweating and thin and silky skin and hair
Weight	Gain	Loss

Disorders of the thyroid may represent a congenital defect in thyroid development or they may develop later in life, with a gradual or a sudden onset. Goiter is an increase in the size of the thyroid gland. It can occur in hypothyroid, euthyroid, and hyperthyroid states. Goiters may be diffuse, involving the entire gland without evidence of nodularity, or they may contain nodules. Diffuse goiters usually become nodular. Goiters may be toxic, producing signs of extreme hyperthyroidism, or thyrotoxicosis, or they may be nontoxic. Diffuse nontoxic and multinodular goiters are the result of compensatory hypertrophy and hyperplasia of follicular epithelium secondary to some derangement that impairs thyroid hormone output. The degree of thyroid enlargement is usually proportional to the extent and duration of thyroid deficiency. The increased thyroid mass usually achieves a normal, or euthyroid, state eventually. Multinodular goiters produce the largest thyroid enlargements and are often associated with thyrotoxicosis. When sufficiently enlarged they

Pathophysiology

may compress the esophagus and trachea, causing difficulty in swallowing, a choking sensation, & respiratory stridor. Such lesions may also compress the superior vena cava, producing distention of the veins of the neck and upper extremities, edema of the eyelids and conjunctiva, and syncope with coughing.

6.6.1 Hypothyroidism

Hypothyroidism can occur as a congenital or as an acquired defect. The absence of thyroid function at birth is called cretinism. When the condition occurs later in life it is called myxedema.

Congenital hypothyroidism

Congenital hypothyroidism is perhaps one of the most common causes of preventable mental retardation. Hypothyroidism in the infant may result from a congenital lack of the thyroid gland or from abnormal biosynthesis of thyroid hormone or deficient TSH secretion. With congenital lack of the thyroid gland, the infant usually appears normal and functions normally at birth since hormones have been supplied in utero by the mother. Thyroid hormone is essential for normal brain development and growth, almost half of which occurs during the first six months of life. If untreated, congenital hypothyroidism causes mental retardation and impairment of growth. Long-term studies show that closely

Pathophysiology

monitored thyroxine supplementation begin in the first six weeks of life results in normal intelligence. However, if treatment is delayed to between three months and seven months, 85% of these infants will have definite retardation. Fortunately, neonatal screening tests have been instituted to detect congenital hypothyroidism during early infancy in developed countries. In this test, a drop of blood is taken from the infant's heel and analyzed for T4 and TSH.

Myxedema (acquired hypothyroidism)

When hypothyroidism occurs in older children or adults it is called myxedema. The term myxedema caused by an accumulation of a hydrophilic mucopolysaccharide substance in the connective tissues throughout the body. The hypothyroid state may be mild, with only a few signs and symptoms, or it may progress to a life-threatening condition or dysfunction of the thyroid gland (primary hypothyroidism) or as a secondary disorder caused by impaired hypothalamic or pituitary function.

Primary hypothyroidism may result from thyroidectomy (surgical removal) or ablation of the gland with radiation. Certain goitrogenic agents, such as lithium carbonate (used in the treatment of manic-depressive states) and the antithyroid drugs propylthiouracil and methimazole in continuous dosage, can block hormone synthesis and produce hypothyroidism

Pathophysiology

with goiter. Large amounts of iodine can also block thyroid hormone production and cause goiter, particularly in persons with autoimmune thyroid disease.

Probably the most common cause of hypothyroidism is Hashimoto's thyroiditis, an autoimmune disorder in which the thyroid gland may be totally destroyed by an immunologic process. It is the major cause goiter and hypothyroidism in children.

Hashimoto's thyroiditis is predominantly a disease of women. The course of the disease varies. At the onset only a goiter may be present. In time, hypothyroidism usually become evident. Although the disorder generally causes hypothyroidism, a hyperthyroid state may develop mid course in the disease. The transient hyperthyroid state is due to leakage of preformed thyroid hormone from damaged cells of the gland.

Myxedema affects almost all of the organ systems in the body. The manifestations of the disorder are largely related to two factors.

1. The hypometabolic state resulting from thyroid hormone deficiency and
2. Myxedematous involvement of body tissues.

Pathophysiology

Although the myxedema is most obvious in the face and other superficial parts, it also affects many of the body organs and is responsible for many of the manifestations of the hypothyroid state.

The hypometabolic state associated with myxedema is characterized by a gradual onset of weakness and fatigue, a tendency to gain weight despite a loss in appetite, and cold intolerance. As the condition progresses, the skin becomes dry and rough and acquires a pale yellowish cast, which is due primarily to carotene deposition, and the hair becomes coarse and brittle. There is loss of the lateral one-third of the eyebrows. Gastrointestinal motility is decreased, giving rise to constipation, flatulence, and abdominal distention. Nervous system involvement is manifested in mental dullness, lethargy, and impaired memory.

As a result of fluid accumulation, the face takes on a characteristic puffy look, especially around the eyes. The tongue is enlarged, and the voice is hoarse and husky. Myxedematous fluid can collect in the interstitial spaces of almost any organ system. Pericardial or pleural effusion may develop. Mucopolysaccharide deposits in the heart cause generalized cardiac dilatation, bradycardia, and other signs of altered cardiac function.

Diagnosis

- Low serum T4
- Low resin T3
- Elevated TSH
- Antithyroid test- if hashimoto's is suspected
- TRH stimulation test in secondary hypothyroidism

Myxedematous coma

Myxedematous coma is a life-threatening end-stage expression of hypothyroidism. It is characterized by coma, hypothermia, cardiovascular collapse, hypoventilation, and severe metabolic disorders that include hyponatremia, hypoglycemia, and lactic acidosis. It occurs most often in the elderly and is seldom seen in persons under age 50. The fact that it occurs more frequently in winter months suggests that cold exposure may be a precipitating factor. The severely hypothyroid person is unable to metabolize sedatives, analgesics, and anesthetic drugs, and these agents may precipitate coma.

6.6.2 Hyperthyroidism

Hyperthyroidism, or thyrotoxicosis, results from excessive delivery of thyroid hormone to the peripheral tissue. It is seen most frequently in women 20 to 40 years of age. It is commonly associated with hyperplasia of the thyroid gland,

Pathophysiology

multinodular goiter, and adenoma of the thyroid. Occasionally it develops as the result of the ingestion an overdose of thyroid hormone. When the condition is accompanied by exophthalmos and goiter, it is called graves' disease. Thyroid crisis, or storm, is an acutely exaggerated manifestation of the hyperthyroid state.

Many of the manifestations of hyperthyroidism are related to the increase in oxygen consumption and increased utilization of metabolic fuels associated with the hyper metabolic state as well as the increase in sympathetic nervous system activity that occurs. The fact that many of the signs and symptoms of hyperthyroidism resemble those of excessive sympathetic activity suggests that the thyroid hormone may heighten the sensitivity of the body to the catecholamines or that thyroid hormone itself may act as a pseudo catecholamine. With the hypermetabolic state, there are frequent complaints of nervousness, irritability, and fatigability. Weight loss is common despite a good appetite. Other manifestations include tachycardia, palpitations, shortness of breath, excessive sweating, and heat intolerance. The person appears restless and has a fine muscle tremor. Even in persons without exophthalmos there is an abnormal retraction of the eyelids and infrequent blinking and patients appear to be staring. The hair and skin are usually thin and have a silky

Pathophysiology

appearance. Hyperthyroidism can be treated by surgical, radioactive iodine or the use of drugs.

Graves' disease

Graves' disease is a state of hyperthyroidism, goiter, and exophthalmos. The cause of graves' disease and the development of the exophthalmos, which results from edema and cellular infiltration of the orbital structures and muscle, is poorly understood. Current evidence suggest that it is an immune disorder characterized by abnormal stimulation of the thyroid gland by thyroid – stimulating antibodies that act through the normal TSH receptors. The exophthalmos is thought to result from an exophthalmos-producing factor whose action is enhanced by anti bodies. The ophthalmopathy of Graves' disease can cause severe eye problems, including paralysis of the extraocular muscles, involvement of the optic nerve with some visual loss, and corneal ulceration since the lid do not close over the protruding eyeball.

Thyroid storm

Thyroid storm (crisis) is an extreme and life threatening form of thyrotoxicosis.

It is often precipitated by stress, such as infection, by diabetic ketoacidosis, by physical or emotional trauma, or by manipulation of a hyperactive thyroid gland during thyroidectomy. Thyroid storm is manifested by a very high

Pathophysiology

fever, extreme cardiovascular effects and severe central nervous system effects. The mortality rate is high. Thyroid storm requires rapid diagnosis and implementation of treatment.

6.7 Disorders of Adrenal cortical function

6.7.1 Congenital adrenal hyperplasia (adrenogenital syndrome)

Congenital adrenal hyperplasia (CAH) describes a congenital disorder caused by an autosomal recessive trait in which a deficiency exists in any of the five enzymes. It is a defect in the synthesis of cortex that results in increased levels of ACTH and adrenal hyperplasia. The increased levels of ACTH over stimulate the pathways of steroid hormone production, particularly those involving the production of adrenal androgens. Mineralocorticoids may be produced in excessive or insufficient amount, depending on the precise enzyme deficiency. Both males and females are affected. Males are seldom diagnosed at birth, unless they have enlarged genitalia or lose salt and manifest adrenal crisis; in female infants, an increase in androgens is responsible for creating the virilization syndrome of ambiguous genitalia.

6.7.2 Adrenal insufficiency

There are two forms of adrenal insufficiency: primary and secondary. Primary adrenal insufficiency, or Addison's

Pathophysiology

disease, is due to the destruction of the adrenal gland. Secondary adrenal insufficiency is due to a disorder of the HPA system.

Primary adrenal insufficiency (Addison's disease)

Addison's disease is a relatively rare disorder in which all the layers of the adrenal cortex are destroyed. Most often the underlying problem is idiopathic adrenal atrophy, which probably has an autoimmune basis.

Addison's disease is a chronic metabolic disorder that requires lifetime hormone replacement therapy. The adrenal cortex has a large reserve capacity, and the manifestations of adrenal insufficiency do not usually become apparent until about 90% of the gland has been destroyed. These manifestations are primarily related to:

- hyperpigmentation resulting from elevated ACTH levels
- mineralocorticoid deficiency and
- glucocorticoid deficiency

Hyperpigmentation in Addison's disease, ACTH levels are elevated in response to the fall in cortisol. It is important to note that the amino acid sequence of ACTH is strikingly similar to that of melanocyte stimulating hormone (MSH): thus, hyperpigmentation is seen in about 98% of persons with Addison's disease and is helpful in distinguishing the primary

Pathophysiology

and secondary forms. This hyperpigmentation becomes more pronounced during periods of stress.

Mineralocorticoid deficiency: mineral corticoid deficiency caused increased urinary losses of sodium, chloride, and water along with decreased excretion of potassium. The result is hyponatremia, loss of extra cellular fluid, decreased cardiac out put, and hyper caemia. There may be an abnormal appetite for salt. Orthostatic hypotension is common. Dehydration, weakness, and fatigue are often present as early symptoms. If loss of sodium and water is extreme cardiovascular collapse and shock will ensue.

Glucocorticoid deficiency: Because of a lack of glucocorticoids, the patient has poor tolerance to stress. This deficiency causes hypoglycemia, lethargy, weakness, fever, and gastrointestinal symptoms such as anorexia, nausea, vomiting and weight loss.

Secondary adrenal insufficiency

Secondary adrenal insufficiency can occur as a result of hypopituitarism or because the pituitary gland has been surgically removed. However, a far more common cause than either of these is the rapid withdrawal of glucocorticoids that have been administered therapeutically. These drugs

Pathophysiology

suppress the HPA system, with resulting adrenal cortical atrophy and lack of cortisol.

Acute adrenal crisis

Acute adrenal crisis is a life –threatening situation of Addison's disease is the underlying problem, exposure to even a minor illness or stress can precipitate nausea, vomiting, muscular weakness, hypotension, dehydration, and vascular collapse. The onset of adrenal crisis may be sudden, or it may progress over a period of several days. The symptoms may also occur suddenly in children with salt-losing forms of the adrenogenital syndrome. Massive bilateral adrenal hemorrhage cause an acute fulminating form of adrenal insufficiency. Hemorrhage can be caused by meningococcal septicemia (called Waterhouse-Friderichsen syndrome), adrenal trauma, anticoagulant therapy, adrenal vein thrombosis, or adrenal metastases. Adrenal insufficiency is treated with replacement glucocorticoid therapy.

6.7.3. Glucocorticoid hormone excess

(Cushing's syndrome)

Cushing's syndrome is characterized by a chronic elevation in glucocorticoid (and adrenal androgen) hormones. Because the condition is more frequently caused by increased ACTH production, the mineral corticoids are usually not involved in the syndrome.

Pathophysiology

Cushing's syndrome can result from either overproduction of hormones by the body or long term therapy with one of the potent pharmacologic preparations of glucocorticoids (iatrogenic Cushing's syndrome). Three important forms of Cushing's syndrome result from excessive glucocorticoid production by the body. One is a pituitary form, which results from excessive production of ACTH by a tumor of the disease cases, and since this form of the disease was the one originally described by Cushing, it is called Cushing's Disease.

The other forms of excess glucocorticoid levels are referred to as Cushing's Syndrome. The second form is the adrenal form, caused by an adrenal tumor. The third is the ectopic Cushing's, due to an ACTH-producing tumor such as occurs in some bronchogenic cancers.

The major manifestations of Cushing's Syndrome represent an exaggeration of the normal effects of cortisol. Altered fat metabolism causes a peculiar deposition of fat characterized by a protruding abdomen; subclavicular fat pads or "buffalo hump" on the back; and a round, plethoric "moon face." There is muscle weakness, and the extremities are thin because of protein breakdown and muscle wasting. In advanced cases, the skin over the forearms and legs becomes thin, having the appearance of parchment. Purple striae (stretch marks), from

Pathophysiology

stretching of the catabolically weakened skin and subcutaneous tissues, are distributed on the abdomen and hips. Osteoporosis results from destruction of bone proteins and alterations in calcium metabolism. With osteoporosis there may be back pain and rib & vertebral fractures.

As calcium is mobilized from bone, renal calculi may develop. Derangements in glucose metabolism are found in some 90% of patients, with clinically overt diabetes mellitus occurring in about 20%. The gluco corticoids possess mineralocorticoid properties; this causes hypercalcemia as a result of excessive potassium excretion & hypertension resulting from sodium retention. Inflammatory and immune responses are inhibited, resulting in increased susceptibility to infection. Cortisol increases gastric secretion, and this may provoke gastric ulceration and bleeding.

An accompanying increase in androgen level causes hirsutism, mild acne, and menstrual irregularities in women. Excessive levels of the gluco corticoids may give rise to extreme emotional lability.

The treatment of Cushing's Syndrome, whether by surgery, irradiation, or drugs, is largely determined by the etiology.

Review questions

- List the organ/system which are affected by excess secretion of growth hormone.
- Discuss the Pathophysiology of diabetes insipidus.
- Compare and contrast the hypo and hyper state of thyroid function.
- Discuss the Pathophysiology of Cushing's Syndrome.

CHAPTER SEVEN

ALTERATION IN GENITOURINARY FUNCTION

Learning Objectives

At the end of this Chapter the students will be able to:

- Explain pathophysiology of abnormal Uterine Bleeding (AUB).
- Discuss pathophysiology of Dysfunctional Uterine Bleeding (DUB).
- Describe pathophysiology of pelvic inflammatory Diseases (PID)
- Explain Pathophysiologic effects of obstructive uropathy
- Discuss pathophysiology of Benign prostatic hyperplasia (BPH).
- Describe pathophysiology of renal stone

7.1. Abnormal Uterine Bleeding (AUB)

Pathophysiology

- Any form of bleeding from reproductive tract other than the normal menstrual bleeding is called abnormal uterine bleeding (AUB).
- The normal menstrual bleeding is because of regular shedding (sloughing) of the endometrial wall when the serum estrogen and progesterone level are low.
- The normal menstrual bleeding is characterized by:-
 - Bleeding lasting for about 5 days.
 - The blood should be non-clotted blood.
 - The amount of blood loss in average is about 30 to 150ml.
 - The bleeding is every 21 to 35 days and in average every 28days.
- Any form of bleeding from genital tract other than the above normal characteristic of menstrual bleeding is called abnormal uterine bleeding (AUB)
- Abnormal uterine bleeding is usually symptom of some underlying disease process rather than a disease entity by itself.

7.1.1. The Different patterns of AUB

Pathophysiology

- **Menorrhagia** (hyper menorrhoea): - Excessive menstrual blood flow (More than 150 ml per menses).
- **Metrorrhagia** (Intermenstrual bleeding): - Bleeding between period-Irregular menses
- **Polymenorrhoea**:- Abnormally frequent menstrual bleeding (Usually before 21 days).
- **Oligomenorrhoea**:- Abnormally infrequent menstrual bleeding (Usually beyond 35 days)
- **Amenorrhoea**: - Absence of menstrual bleeding for three consecutive cycles.
- **Perimenopausal bleeding**: - Irregular bleeding before menopause.
- **Postmenopausal bleeding**: - Bleeding that occurs one or more years after menopause.

7.1.2. Causes of AUB

- There are many causes of AUB, and are classified in to four classes:-

a. Complications of pregnancy

- Abortions
- Ectopic pregnancy (pregnancy out side the uterus)
- GTD (gestational trophoblastic diseases)

b. Organic Lesions

- Benign lesions of genital tracts:-
 - Vaginal tumors
 - Cervical polyps

Pathophysiology

- Cervicitis
- Endometrial polyp
- Myoma.
- Malignant lesions
 - Vaginal cancer
 - Cervical cancer
 - Endometrial cancer

c. Constitutional Disease

- Bleeding disorders (like platelet abnormality & coagulation factor defect)
 - Hypertension.

d. True dysfunctional uterine bleeding (DUB)

- It is uterine bleeding associated with endocrine dysfunction.

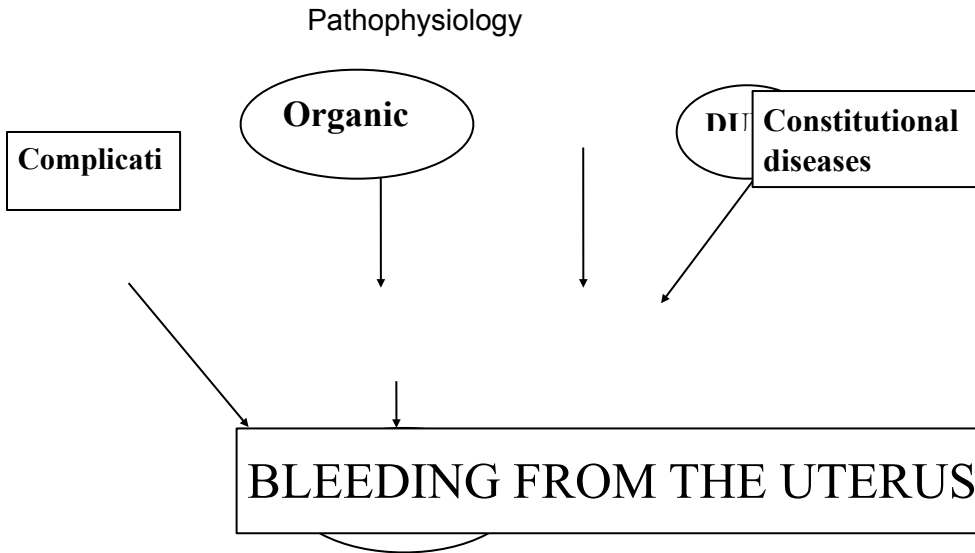


Figure: 7.1 Causes of AUB and its effects

Pathophysiology

Dysfunctional Uterine Bleeding (DUB)

- The term dysfunctional uterine bleeding refers to abnormal bleeding that is as the result of endocrine dysfunction.
- Fifty percent of DUB occurs in women over age of 40 years (perimenopausal) and 20% occurs in adolescent under 20 years.
- It is often associated with absence of ovulation (persistent unovulatory period)
- When there is no ovulation, there is no corpus luteum formation, this result in inadequate production of progesterone.
- Deficiency or absence of progesterone in the circulation results in absence of secretory changes in the endometrium. The endometrium becomes hyperplastic due to the effect of estrogen alone.
- As estrogen levels decrease from degenerating follicles, with drawl bleeding occurs.
- Psychogenic uterine bleeding may be included in DUB. Emotions also may directly affect the uterine blood vessels and produce bleeding. Emotional disturbance may stimulate hypothalamus and has resultant influence on gonadotrophic hormones.

7.2. Pelvic Inflammatory Disease (PID)

Pathophysiology

▪Definition

-Pelvic inflammatory disease (PID) is defined as any infection of upper reproductive tract (above the inner cervical-os). I.e. it includes:-

- Endometritis:- inflammation of the endometrium
- Endoparametritis:- inflammation of parametrial structures.
- Salpingitis: - inflammation of fallopian tubes.
- Oophoritis: - inflammation of the ovaries.
- Pelvic peritonitis (abscess):- inflammation of the pelvic peritoneum and puss collections.

▪Causes (Etiology)

-Etiologies of PID are categorized into four classes:-

a) Post STD –PID

-These are caused by ascending serious bacterial infection

acquired through sexual intercourse.

- Included: -

- Gonorrhoea
- Chlamydia trachomatis

b) Post abortal PID

- ✓ Post abortal PID is due to ascending normal floras of the vagina following opening of the cervical os.

Pathophysiology

Normally, the upper genital tracts are sterile and bacteria can not ascend easily due to the effect of tightly closed cervix and thick cervical secretions.

- ✓ When cervix is opened for abortion, this will pave the way for the normal floras of the vagina to ascend.
- ✓ The risk increases with criminal abortion.
- ✓ Organisms: - Polymicrobial (all normal floras)
-Both aerobic and anaerobes.

c) Post partal – PID

- ✓ Post partal PID takes place following delivery.
- ✓ The mechanism is the same with post abortal PID; it is due to ascending normal flora from vagina to the sterile upper genital tract following cervical dilatation in delivery.
- ✓ The risk increase with prolonged duration of labor and operative deliveries
- ✓ Organism: - Polymicrobials (Normal floras of vagina)

- Aerobic organism,

and

- Anaerobic organism.

d) Post Intrauterine Devices (IUDS) - PID

- Insertion of IUDs also gives a chance for bacteria to ascend to the upper genital tract.

▪**Clinical Features of PID**

-Triads of PID are: -

- Fever with chills and rigor (>38 degree centigrade)
- Severe pelvic pain (sudden onset)
- Heavy, purulent, offensive vaginal discharge

-Specific Histories: -

- History of sexually transmitted disease
- History of abortion or pelvic surgery
- History of delivery
- History of IUCDS-uses

7.3. Obstructions in urinary tract (Obstructive Uropathy)

Obstructive disorders may cause considerable renal dysfunction, including hemorrhage, renal failure, if they are left untreated.

Normally urine is formed by the nephrones in the renal parenchyma, then collected in the renal pelvic to flow through the ureter and reaches urinary bladder.

When the bladder becomes full, urethral sphincters are opened then urine passes through urethra to be voided out. Any form of obstacle to urinary flow can cause obstructive uropathy.

Pathophysiology

Causes: -

- There are many causes of urinary flow obstruction; but the principal obstructive conditions are: -
 - a) Benign prostatic Hyperplasia (BPH)
 - b) Renal calculi
 - c) Renal tumors
 - d) Urethral strictures; etc.

a) Benign prostatic Hyperplasia (BPH)

- Benign prostatic hyperplasia affects the majority of men over 50 years old.
- The prostatic size increase due to hyperplastic proliferation of glandular and cell tissues
- Normally, the prostate gland weights 20gm, surrounds the urethra, and consists of four lobes.
- By age 70years, the prostate may weigh from 60 gm as much as 200gm.

Pathogenesis

- The cause of BPH is unknown but it is believed to result from an imbalance between serum testosterone and estrogen level that occur with advancing age.
- As age increase the level of both testosterone and estrogen decreases, but the rate of estrogen reduction is rapid than testosterone reduction; and the testosterone level is

Pathophysiology

elevated relative to estrogen level, which stimulate hyperplastic growth of prostatic gland.

Clinical Features

- Acute urinary retention
 - Symptoms of prostatism (frequency, urgency, dribbling, dysuria, etc)
 - Chronic retention → over flow incontinence, and renal insufficiency.

b) Renal calculi (stone disease)

- Calculi can form in various areas of the renal system.
- Crystallization in the renal pelvis is called nephrolithiasis
- Urolithiasis refers to stone any where in the urinary tract.

Etiology: - Not clearly known

- It is common in hot environmental condition. The proposed etiologies are: -

•Urinary stasis → the excreted material will be saturated.

Due to obstruction

•Infection → disturbs the PH of urine → crystallization of particles → stone

•Lack of inhibitors for stone formation:-Normally there are inhibitors for stone formation in urine, decreased or lack of inhibitors cause stone.

Pathophysiology

Types of Renal calculi

Table 7.1 Types of renal stones based on its chemical compositions

Calcium oxalate	Triple phosphate	Urate stone	Cystine stone
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Pathophysiology

<ul style="list-style-type: none"> -They are irregular with sharp projection -Radio-opaque -Cause bleeding (hematuria) 	<ul style="list-style-type: none"> -Formed by ammonium, magnesium and calcium phosphate (struvite) -Grows in infected alkaline urine -Tends to be very large (stag horn) -Dirty, radio-opaque 	<ul style="list-style-type: none"> - multiple - hard, smooth - Radio-lucent 	<ul style="list-style-type: none"> -Congenital error of metabolism -Cystinuria -contain sulfur. -Radio-opaque
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Clinical Features

- Symptoms are variable
- Silent calculi may cause no symptoms but progressive destruction of the renal parenchyma.
- Bilateral stones may cause uremia (renal failure) due to obstruction.
- Pain (75%) located in renal angle
- Hematuria (bloody urine).
- Repeated urinary tract infection (UTI)

C) Renal Tumors

- Renal tumors are not common.

Pathophysiology

- Tumors of the renal system can cause damage to the renal parenchyma whether they are benign or malignant.

Classification

➤ **Benign Renal Tumors**

- Not very common
- Includes: – Adenoma of renal parenchyma
 - Papilloma of renal parenchyma
 - Lipoma, etc
- Hematuria and dull pain in the flank are common complaints.

➤ **Malignant renal tumors**

- Include: - wilms tumor: - it occurs in children
 - Renal cell carcinoma: - it occurs in adults
- Clinical features
 - Pain and hematuria are the earliest symptoms.
 - Symptoms of metastatic disease occurs more frequently such as Varicocele and hypertension.

d) Urethral strictures

- **Definition**: - urethral stricture is defined as narrowing of the urethral lumen due to fibrous band formation.
- **Cause**
 - Congenital urethral structures:- from birth
 - Post STD urethral stricture:-
 - It is due to sexually transmitted diseases.

Pathophysiology

- It occurs 10-15 years after gonorrheal or chlamydial urethritis
- It is because of healing of the inflammatory process by formation of excess fibrous bands.
- Post procedural urethral stricture:-
 - It occurs following urologic procedural like catheterizations. Minor trauma to the urethral mucosa may heal by forming strictures years after the procedure.
- **Clinical features**
 - Acute or chronic urinary retentions.
 - Urine stasis and back-flow of urine: - Results in hydronephrosis and Renal- failure
 - Symptoms of renal-failure (uremia).

Pathophysiologic Effects of Obstructive Uropathy

Obstruction to urinary path way (flow)



Stasis of urine and back flow ⇒ Bacterial over growth (pyelonephritis)

Pathophysiology



Hydronephrosis



Mechanical compression and distension of the renal pelvis. ⇒ **RENAL FAILURE**



Review Questions

1. What is abnormal uterine bleeding?
2. List the causes of AUB?
3. List the mechanisms of pelvic inflammatory diseases.

Pathophysiology

4. What are the Pathophysiologic effects of obstructive uropathy?
5. List the causes of Obstructive uropathy.

CHAPTER EIGHT ALTERATION IN NEURONAL FUNCTION, INTRA CRANIAL MASS EFFECT AND MENINGITIS

Learning objectives

At the end of this chapter the students will be able to:

- Discuss Pathophysiology of increased intracranial pressure
- Explain causes of increased intracranial pressure (ICP).
- List manifestations of increased intracranial pressure
- Mention complications of increased ICP
- Describe types and pathophysiologic effects of head injury.
- List types of intracranial infections.

8.1. Alteration in cerebral volume and pressure (ICP)

Introduction

- Intracranial pressure (ICP) is a pressure in the cranial cavity.
- Cranial cavity contains blood vessels, brain tissue, and CSF within the rigid confines of non-expandable skull.

Pathophysiology

- The normal intracranial pressure is 50 – 200mm H₂O (4-15 mmHg).
- Small increase in one component can be compensated in decrease in volume of one or both of other components of the cranial cavity.
- Normal fluctuation in intracranial pressure occurs with respiratory movement and activities of daily living such as straining, coughing and sneezing.
- An abnormal variation in intracranial volume with subsequent change in ICP can be caused by a volume change in any of the three intracranial components.

Example:

- An increase in tissue volume results from brain tumors, brain edema, or bleeding into brain tissue.
- An increase in blood volume develops when there is vasodilatation of cerebral vessels or obstruction of venous out flow.
- Excess production, decreased absorption, or obstructed circulation of CSF affords the potential for an increase in CSF component.
- Brain tumors → change in volume occurs slowly.
- But from head injury → change in volume develops rapidly.

8.1.1. Compensatory Mechanisms for Increased ICP:-

- CSF and blood volumes: – are capable of compensating increased ICP.
- CSF production is constant but reabsorption can vary for adjustment (by pressure difference between CSF in subarachnoid space and blood in dural sinuses). Because changes in ICP produce an increase in CSF pressure with out increasing dural sinus pressure reabsorption of CSF will increase.
- The impact of increase in blood, brain tissue or CSF volume on ICP varies among individuals and depends on the amount of increase that occurs, the effectiveness of **compensation mechanisms** and cerebral elasticity and plasticity.
 - Blood vessels: – elastic component.
 - Brain tissues: - plastic component.
 - CSF: - Reabsorption.
- ❖ When the CSF and blood can no longer compensate for increased volume and the excess space in the cranial cavity is filled, the ICP rises sharply and may result in **cerebral hypoxia** or **brain shift**.
- ❖ When the pressure in the cranial cavity approaches or exceeds the mean systemic arterial pressure, tissue

Pathophysiology

perfusion becomes inadequate, cellular hypoxia results and if maintained, neuronal death may occur.

- ❖ The highly specialized cortical neurons are the most sensitive to oxygen deficits → decreased in level of consciousness is one of the earliest and most reliable sign of increased ICP.
- ❖ The increased cellular hypoxia leads to general neurological deterioration. The level of consciousness may deteriorate from alertness through confusion, lethargy, obtundation, stupor, and coma.

- ❖ One of the late reflexes seen with marked increased in ICP is CNS ischemic response; which is triggered by ischemia of vasomotor centre in brain stem. Neurons in vasomotor centre respond directly to ischemia by producing a marked increase in mean arterial blood pressure. Some times up to 270mmHg is accompanied by widening of pulse pressure and a reflex slowing of the heart rate. These triads of signs some times called the **Cushing reflex** is important but late indicator of increased ICP.

8.1.2 Manifestations of Increased ICP

- Indirectly the following clinical features can serve as physiologic parameters to assess raised ICP:-

Pathophysiology

- Cushing Reflex: -
 - Raised Blood Pressure
 - Slow Pulse Rate
 - Widening of pulse pressure.
- Pupillary response alteration, and
- Change in level of consciousness that change with increase in ICP.
- Projectile vomiting.
- Severe global head ache.

Hydrocephalus

● Definition: -

- One form of increased volume in the cranial cavity is hydrocephalus, which is defined as an abnormal increase in CSF volume within any part or all of the ventricular system.

● Causes: -

- **Decreased absorption of CSF:** -
 - Decreased absorption of CSF can be caused by two Mechanisms: -
 - 1) Block in CSF path way to arachnoids villi (None communicating hydrocephalus)

Common causes are:-

-Congenital malformations

Pathophysiology

- Infections, and
- Tumors

2) Failure of Villi to transfer CSF to Venous System (Communicating hydrocephalus)

➤ **Over production of CSF: -**

- Adenoma of choroid plexus can cause an over production of CSF.
- It is less common than decreased absorption.

● **Clinical manifestations of Hydrocephalus: -**

- The signs of ICP elevation are associated with age of onset, type of hydrocephalus, and extent of pressure rise.
 - In infant and children: — head enlargement
 - In adults:— no head enlargement
- symptom depends on whether it appears rapidly or slowly.
 - Rapidly: - increased ICP
 - Slowly: - less apt to develop increased ICP

Cerebral edema (Brain swelling)

● **Definition: -**

An increase in brain tissue volume secondary to abnormal fluid accumulations.

● **Types of Brain Edema:-**

Pathophysiology

There are two types of brain edema:-

a) Vasogenic Brain Edema:-

- Increased extra cellular fluid that surrounds brain cells.
- Occurs in conditions like: - Brain tumors
 - Prolonged ischemia
 - Infectious process (meningitis)
 - Impaired function of Blood Brain

Barrier (BBB) – following injury.

- Occurs in the white mater of the brain.
- Can displace cerebral hemisphere (**Herniation**)

b) Cytotoxic Brain Edema:-

- Actual swelling of brain cells them selves.
- Neurons, glial cells and endothelial cells swell.
- Results from hypo osmotic state from water intoxication.
- Occurs in both white and gray mater.

Pathophysiology

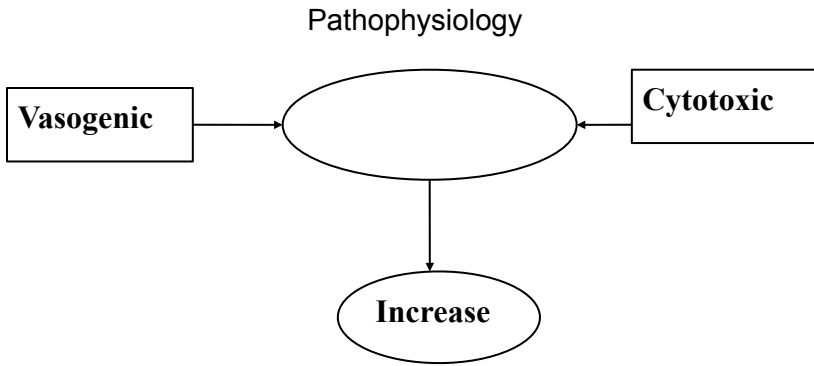


Figure 8.1 types of brain edema and its effect

Pathophysiology

● **Clinical Features of Brain Edema:-**

- The manifestations depend on the brain's compensatory mechanisms and the extent of the swelling.
- May cause: - Herniation
- Change in mental status (stupor, coma)

Brain Herniation

● **Definition:-**

Displacement of brain tissue under the tough dural folds of falx cerebri, tentorium cerebri towards the less dense area.

● **Classifications: -**

There are two broad categories of herniation:-

1. Supratentorial Herniation.
2. Infratentorial Herniation

➤ Supratentorial Herniation

There are three subtypes based on sites.

➤ Infratentorial herniation :-

Results from increased pressure in the brain compartment and often progress rapidly. Cause death because it is likely to involve the lower brain stem centre that control vital function.

8.2 Head injury

-There are three major components of head injury:-

- Scalp injury
- Skull fracture, and
- Brain injury

● Skull Fracture

-One of the most serious types of direct head injury is skull fracture

- Simple linear skull fracture:— break in continuity of the bone.
- Depressed skull fracture:--- When bone fragments are imbedded into brain tissues.
- Basilar skull fracture: -fracture of base of the skull and may be associated with: – Leakage of CSF from nose (rhino rhea)
 - Leakage of CSF from ear (Otto rhea)
 - Laceration of vessels of durra leads to intracranial bleeding.

● Brain Injuries

Injury to the brain parenchyma:- There are two types of brain injury:-

- a) Primary Head injury
- b) Secondary Head injury

a) Primary Head Injury: -

Pathophysiology

- ✓ Primary head injury → in which damage is due to the impact.
- ✓ Includes Concussion and contusions.

- **Concussion:** -

Momentary interruptions of brain function with or without loss of consciousness. Recover within 24 hours. Headache, irritability, insomnia, poor concentration could persist for months.

(Post concussion syndrome)

- **Contusion:** -

In severe head injury; there is cerebral contusion, tearing and shearing of brain structures which may lead to neurological deficits like hemiplegia. Injuries to the blood vessels cause accumulations of blood in the cranial cavity.

N.B:- Since brain floats freely in the CSF, bouncing of brain in this closed confined rigid skull results in concussion or contusion called Coup and counter coup injury.

- **Coup:** - injury on the side of impact (below site of impact).
- **Counter coup:** - injury in opposite side of the impact.

b) Secondary brain injuries

Pathophysiology

- It is brain injury that develops subsequently after the impact has gone.
- The causes are: -
 - Intracranial hematoma
 - Brain Edema, and
 - Infections

● Intracranial Hematoma

- Is bleeding in the cranial cavity.
- There are four common types based on the site of bleeding:-
 - **Epidural hematoma:-** bleeding outside dura
 - **Subdural hematoma:-** bleeding below dura
 - **Subarachnoidal hematoma:-** bleeding below the arachnoids matter.
 - **Intraparenchymal hematoma:-** bleeding inside the brain tissues.

N.B: - The final consequence of intracranial bleeding is formation of intracranial Space occupying mass effect, which is manifested by sign and symptom of raised intracranial pressure (ICP).

● Infections:-

Pathophysiology

- Intra cranial infection one of a common and fatal condition.
- It may occur following head injury or spontaneously.
- There are two types of intracranial infections:-
 - a) Meningitis: - infection of Meninges
 - b) Encephalitis: - infection of brain parenchyma.

a) Meningitis:-

- **Definition:**-Inflammation of pia mater, sub-arachnoids mater & space.

Caused by infection, but chemicals could also cause.

- **Classifications:** -

- Acute meningitis.
- Sub acute meningitis.
- Chronic meningitis.

❖ Acute Meningitis

- Causes

- Acute pyogenic Meningitis: –bacterial
 - Streptococcus pneumonia.
 - Neisseria meningitides
 - *H. influenzae*- in children below 5 years old.
- Acute lymphocytic Meningitis – viral
 - Coxsackie virus

Pathophysiology

- Mumps virus
- Epstein Bar virus (EBV)
- Herpes simplex type- II virus (HSV-II)

➤ **Risk factors for Meningitis**

- Head trauma: - basal skull bone fracture
- Upper respiratory tract infection: -
 - Otitis Media,
 - Sinusitis,
 - Mastoditis,
- Neurosurgery
- Systemic sepsis,
- Immune compromised host.

➤ **Most common symptoms and signs: -**

- Fever, chills: - due to release of inflammatory mediators and endotoxins.
- Headache: - due to raised ICP as the result of inflamed Meninges.
- Photophobia: - due to raised ICP
- Nausea & vomiting: - due to raised ICP
- Neck pain & neck stiffness
- Positive Meningeal signs:-

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- Kernig's sign –resistance to extension of leg while the patient is lying with the hip flexed at right angle.
- Brudzinski sign: when forcible flexion of the neck results in flexion of hip and knee.

N.B – The path physiologic mechanisms of these signs are due to stretching of inflamed meninges, which results in pain upon performing the maneuvers.

Review Questions

1. What is the normal expected value of intracranial pressure?

Pathophysiology

2. What are the three components of the intracranial cavity?
3. What are the manifestations of raised ICP?
4. Mention the compensatory mechanisms of increased ICP.
5. List the types of head injury & their features.
6. What are the predisposing factors for meningitis?

CHAPTER NINE

GENETIC DISORDERS

Learning Objective

At the end of this chapter students will be able to:

- Describe genetic and chromosomal disorders
- Differentiate dominant and recessive disorders
- List autosomal and sex- linked disorders
- Describe disorders of sex- linked inheritance
- Discuss chromosomal disorders

9.1 Genetic and Chromosomal Disorders

Genetic disorders represent changes (or mutations) in gene function or changes in chromosomal structure. A genetic disorder can involve a single gene trait or it can involve a polygenic trait.

The effects of an abnormal genetic trait may present at birth or may not become apparent until later in life.

9.1.1 Single gene Disorders

Single gene disorders may dominant or recessive, and genes located on the non sex chromosomes (Autosomal genes) or those located on the sex chromosomes may be affected. Disorders of the Y, or male, chromosome are extremely rare.

Some disorders of Single- gene inheritance

Autosomal dominant

- Achondroplasia
- Adult polycystic kidney disease
- Huntington's chorea
- Hyper cholestrerolemia
- Marfan's syndrome
- Multiple neurofibromatosis
- Osteogenesis imperfecta
- Spherocytosis
- Von willebrand's disease

Autosomal Recessive

- Color blindness
- Cystic fibrosis
- Glycogen storage diseases
- Oculocutaneous albinism
- Phenylketonuria(PKU)
- Renal glycosuria
- Sickle cell disease
- Tay- sachs diseases
- Wilson's disease

X- Linked recessive

- Bruton- type agammaglobulinemia
- Classic hemophilia

Pathophysiology

- Duchenne- type muscular dystrophy

9.1.2 Disorders of Autosomal Inheritance

The autosomes are represented on 22 homologous pairs of chromosomes. The autosomes on each chromosome are arranged in strict order, with each gene occupying a specific location or locus, and in pairs, with one maternal and one paternal member. The two members of a gene pair are called alleles. If both members of a gene pair are identical then the person is homozygous for the locus; if the members are different, then the person is heterozygous. Any gene-determined characteristic is a trait. Eg If the trait is only expressed in the heterozygote, it is said to be dominant and if it is only expressed in the homozygote, it is recessive.

In autosomal dominant disorders, a single mutant allele from an affected parent is transmitted to an offspring regardless of sex. The unaffected relatives of the parent or unaffected siblings of the offspring do not transmit the disorder. The affected individual has a 50% chance of transmitting the disorder to each offspring. Autosomal dominant disorders are characterized by reduced penetrance and variable expressivity, and age of onset that is later in life (eg. Huntington's chorea), and a mutant gene that tends to involve a structural or a regulatory protein. Although there is a 50%

Pathophysiology

chance of inheriting a dominant genetic disorder, there can be wide variation in gene expression.

Autosomal recessive disorders are manifested when both members of the gene pair are mutant alleles. In this case, both parents may be unaffected but are carriers of the defective gene. Autosomal recessive disorders affect both sexes. The occurrence risk in each pregnancy is one in four for an affected child, two in four for a carrier child, and one in four for a normal (non carrier, unaffected) homozygous child. With autosomal recessive disorders, the expression of the gene tends to be more uniform than with autosomal dominant disorders; the age of onset is frequently early in life, and in many cases enzyme proteins are affected by the mutation.

9.1.3 Disorders of Sex- Linked Inheritance

Sex- linked inheritance is almost always associated with the X, or female, chromosome and is predominantly recessive. The common pattern of inheritance is one in which an unaffected mother carries one normal and one mutant allele on the x chromosome. This means that she will have a 50% chance of being carriers of the mutant gene. When the affected male procreates, he will transmit the defect to all of his daughters, who will then become carriers of the mutant gene. Since the genes of the Y chromosome are unaffected, the affected male will not transmit the defect to any of his sons and they will not be carriers or transmit the disorder to their children.

Many single gene disorders result in inborn errors of metabolism. These biochemical defects involve the formation of abnormal structural proteins, abnormal biochemical mediators or enzymes, or abnormal membrane bound transport system or receptor proteins.

Structural protein defects are usually manifested as autosomal dominant disorders. An example is marfan's syndrome, it is a disorder of the connective tissues that is manifested by changes in the skeleton, the eyes, and the cardiovascular system. Characteristics of the skeletal defects are a long thin body hyperextensive joints, arachnodactyly (spider fingers), and scoliosis. Defects of the eye include the upward

Pathophysiology

displacement of the lens and the potential for retinal detachment. Involvement of connective tissue in the cardiovascular system may lead to mitral valve disease and a tendency for development of a dissecting aortic aneurysm. Abraham Lincoln's extremely long legs and the unequal lengths of his thumbs suggest that he may have been mildly affected by Marfan's syndrome. Both Abraham Lincoln and a distant male cousin, who was diagnosed as having Marfan's syndrome, are descendants of Mordecai Lincoln II. Although Mordecai almost certainly had the gene for Marfan's syndrome, he showed no signs of the disorder, probably because in him the gene had low expressivity.

Primary enzyme defects are usually autosomal recessive. These enzyme defects may result in any of the following:

1. Deficiency of a metabolic end product
2. Production of harmful intermediates/ toxic by products of metabolism or
3. Accumulation of destructive substances within the cell.

In albinism, the basic biochemical defect is the absence or non-functioning of the enzyme tyrosinase. This enzyme is necessary for the production of melanin, the pigment that gives skin its color. Phenylketonuria (PKU) is another genetically inherited primary enzyme defect. In this disorder, there is a deficiency of phenylalanine hydroxylase, the

Pathophysiology

enzyme needed for conversion of phenylalanine to tyrosine, and as a result of this deficiency, toxic levels of phenylalanine accumulate in the blood. Like other inborn errors of metabolism, PKU is inherited as a recessive trait and is manifested only in the homozygote. Infants with the disorder are treated with a special diet that restricts phenylalanine intake.

Taysachs disease is caused by an accumulation of ganglioside GM₂ (a glycolipid) in body tissues due to an enzyme deficiency (hexosaminidase AO_x) resulting in gangliosidosis. It is inherited as an autosomal recessive disorder. Infants with Taysachs appear normal at birth but begin to manifest neurologic signs at about 6 months of age. These neuralgic manifestations eventually lead to muscle flaccidity, dementia, and finally death at about 2 to 3 years of age.

9.1.4 Chromosome Disorders

Pathophysiology

Chromosome disorders involve a change in chromosome number or structure that results in damage to sensitive genetic mechanism or in reproductive disorders.

I. Alterations In Chromosome Duplication

Mosaicism is the presence in one individual of two or more cell lines characterized by distinctive karyotypes. This defect results from an accident during chromosomal duplication

II. Alterations in Chromosome Number

A change in chromosome number is called aneuploidy. Among the causes of aneuploidy are failure of separation of the chromosomes during or genesis or spermatogenesis. This can occur in either the autosomes or the sex chromosomes and is called nondisjunction. Nondisjunction gives rise to germ cells that have an even number of chromosomes (22 or 24). The products of conception that are formed from this even number of chromosomes will have an uneven number of chromosomes, either 45 or 47. Monosomy refers to the presence of only one member of a chromosome pair. The defects associated with monosomy of the autosomes are severe and usually cause abortion.

Monosomy of the X chromosome (45, X/O), or Turner's syndrome causes less severe defects. Polysomy, or the presence of more than two chromosome to a set, occurs when

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a germ cell containing more than 23 chromosomes is involved in conception. This defect has been described for both the autosomes and the sex chromosomes. Trisomies of chromosomes 8, 13, and 21 are the more common forms of polysomy of the autosomes. There are several forms of polysomy of the sex chromosomes in which one or more extra X or Y chromosomes are present.

Trisomy 21 (Down's syndrome) is the most common form of chromosome disorder. It has an incidence of 1 in 800 births. The condition is usually accompanied by moderately severe mental retardation.

The risk of having a baby with down's syndrome is greater in women who are 35 years of age or older at the time of delivery.

The physical features of a child with Down's syndrome are distinctive, and therefore the condition is usually apparent at birth. These features include a small and rather square head. There is upward slanting of the eyes, small and malformed ears, an open mouth, and a large and protruding tongue. The child's hands are usually short and stubby with fingers that curl inward, and there is usually only a single palmar (simian) crease. There are often accompanying congenital heart

Pathophysiology

defects of particular concern is the much greater risk that these children have for the development of acute leukemia.

Monosomy X (Turner's syndrome)

Turner's syndrome describes a monosomy of the X chromosome (45, X/o) with gonadal agenesis, or absence of the ovaries. There are variations in the syndrome, with abnormalities ranging from essentially none to webbing of the neck with redundant skin folds, non pitting edema of the neck with redundant skin folds, non pitting edema of the hands and feet, and congenital heart defects (particularly coarctation of the aorta). Characteristically, the female with Turner's syndrome is short in stature, but her body proportions are normal. She does not menstruate and shows no signs of secondary sex characteristics. Administration of estrogen may cause the secondary sexual characteristics to develop. The infertility associated with turner's syndrome can not be reversed.

Poly somey X (Klinefelter's syndrome)

Klinefelter's syndrome is characterized by an x- chromatin-positive (47,x/x/y) male and is associated with testicular dysgenesis. In rare cases, there may be more than one extra

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X chromosome for example, 47x/x//x/y. The condition may not be detected in the newborn. The infant usually has normal male genitalia, with a small penis and small, firm testicles. Hypogonadism during puberty usually leads to a tall stature with abnormal body proportions in which the lower part of the body is longer than the upper part. Later in life, the body build may become heavy with a female distribution of sub-cetaceous fat and variable degrees of breast enlargement. There may be deficient secondary male sex characteristics. There may be sexually dysfunction, along with complete infertility and potency. Replacement hormone therapy with testosterone is used to treat the disorder.

III. Alterations in chromosome Structure

Aberrations in chromosome structure occur when there is a break in one or more of the chromosomes followed by rearrangement or deletion of the chromosome parts. Among the factors believed to cause chromosome breakage are the following:

1. Exposure to radiation sources, such as X- rays
- 2 Influence of certain chemicals
- 3 Extreme changes in the cellular environments and
- 4 Viral infections

Pathophysiology

A number of patterns of chromosome breakage and rearrangement can occur. There can be a deletion of the broken portion of the chromosome.

Review Questions

1. Give two examples of autosomal dominant disorders.
2. Compare and contrast the autosomal and sex- linked disorders.
3. Describe taysachs disease.
4. List the conditions as a result of primary enzyme defects.
5. Describe the pathophysiology of one among the disorders of primary enzyme defects.

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