A Text Book Of

PATHOPHYSIOLOGY FOR PHARMACISTS

As Per PCI Regulations

FIRST YEAR B. PHARM.

Semester - II

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Preface

Clinical role of pharmacists have been identified during last 9 years after establishment of regulations for Pharm. D in 2008 followed by establishment of Pharmacy practice regulations in 2015 by Pharmacy Council of India. The practice of Pharmacy needs some time to get strong footing in our country. During such time, subject like Pathophysiology need strong base by budding pharmacists.

Strong background of physiology is needed for understanding of Pathophysiology. Since a separate subject of Anatomy and Physiology is devoted in the degree curriculum, suggested by Pharmacy Council of India (PCI), the present book does not provide physiological background for the disease. Diseases as mentioned in the curriculum have been covered under the headings of etiology, signs and symptoms and complications. Since names of many diseases are new to the students of health profession/pharmacy, a separate section of appendix on definitions/diseases and syndromes/other related clinical terms are included in the book. Clinical details of the diseases which are relevant to health professionals/pharmacists are included only to the optimal extent. Many common abbreviations along with their full forms have been included as a section of appendix.

At national level, the subject is relatively new to the students of pharmacy. It is expected that the book will be welcomed by teachers and students of pharmacy. Still if there is any constructive criticism, it will be appreciated and considered while revising next edition of the book. We appeal to all the readers to forward their suggestions on the contents of the book.

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Syllabus

Unit I **10 Hours**

Basic Principles of Cell Injury and Adaptation:

Introduction, Definitions, Homeostasis, Components and types of feedback mechanisms, Causes of cellular injury, Pathogenesis (Cell membrane damage, Mitochondrial damage, Ribosome damage, Nuclear damage), Morphology of cell injury - Adaptive changes (Atrophy, Hypertrophy, Hyperplasia, Metaplasia, Dysplasia), Cell swelling, Intracellular accumulation, Calcification, Enzyme leakage and Cell death, acidosis and alkalosis, Electrolyte imbalance.

Basic Mechanism involved in the Process of Inflammation and Repair:

Introduction, Clinical signs of inflammation, Different types of inflammation, Mechanism of inflammation - Alteration in vascular permeability and blood flow, Migration of WBCs, mediators of inflammation, Basic principles of wound healing in the skin, Pathophysiology of Atherosclerosis.

Unit II **10 Hours**

Cardiovascular System:

Hypertension, Congestive heart failure, Ischemic heart disease (Angina, Myocardial infarction, Atherosclerosis and Arteriosclerosis)

Respiratory system: Asthma, Chronic obstructive airways diseases.

Renal system: Acute and Chronic Renal Failure.

Unit III **10 Hours**

Haematological Diseases:

Iron deficiency, Megaloblastic anemia (Vitamin B_{12} and folic acid), Sickle cell anemia, Thalasemia, Hereditary acquired anemia, Hemophilia.

Endocrine system: Diabetes, Thyroid diseases, Disorders of sex hormones.

Nervous system: Epilepsy, Parkinson's disease, Stroke, Psychiatric disorders: Depression, Schizophrenia and Alzheimer's disease.

Gastrointestinal system: Peptic Ulcer.

Unit IV **08 Hours**

Inflammatory bowel diseases, Jaundice, Hepatitis (A, B, C, D, E, F) Alcoholic liver disease.

Disease of Bones and Joints: Rheumatoid arthritis, Osteoporosis and Gout.

Principles of Cancer: Classification, etiology and pathogenesis of cancer.

Unit V **07 Hours**

Infectious diseases: Meningitis, Typhoid, Leprosy, Tuberculosis

Urinary tract infections.

Sexually transmitted diseases: AIDS, Syphilis, Gonorrhea.

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Unit **1**

BASIC PRINCIPLES OF CELL INJURY AND ADAPTATION

♦ LEARNING OBJECTIVES ♦

At the completion of this unit, the student should be able to:

- Explain the cytoplasmic changes in reversible cell injury.
- Define and describe the nuclear changes in irreversible cell injury.
- Define apoptosis and give examples of its significance.
- List the most important causes of cell injury, and explain the role of oxygen radicals
- Describe outcomes of cell.
- Define and explain atrophy, hypertrophy and hyperplasia and give examples of each.
- Define and explain metaplasia and dysplasia and give appropriate examples of each.
- Explain why necrosis is not always visible when ischemia has caused sudden death. .
- Give a full account of the stereotyped processes of acute inflammation.
- Describe the acute phase reaction.
- Describe the role of mononuclear phagocytes in inflammation.
- Describe the alteration in vascular permeability and blood flow.

1.1 BASIC PRINCIPLES OF CELL INJURY AND ADAPTATION

1.1.1 Introduction

Pathophysiology is a convergence of pathology with physiology. Pathology is the medical discipline which describes conditions observed during a diseased state; while physiology is the boil ogical discipline which describes processes or mechanism operating within an organism in normal physiological conditions. Pathophysiology seeks to explain the physiological processes or mechanisms which are responsible for the observed pathological state.

Pathophysiology means the functional changes associated with or resulting from disease or injury. It can also be defined as functional changes which accompany a particular disease.

The subject of Pathophysiology has evolved with time. During 19^{th} century, germ theory was an important contribution to explain pathophysiology of infectious diseases. Anthrax was

identified to be caused by a microorganism. The disciplines like bacteriology and experimental pathology were established. In 1878, it was established that a number of diseases, differing clinically, anatomically, and in etiology can be produced experimentally by the injection of infected materials into animals. Germ theory of disease established cause-effect relationship identifiable by scientific investigation.

A first scientific laboratory was opened in US in 1878.

In the early part of 20th century, molecular basis of diseases, as related to infective organisms were established. Genetics and biochemistry were developed as disciplines. Around 1940, cell biology emerged as a new discipline filling the gap between cytology and biochemistry by applying new technology-ultra centrifuge and electron microscope- to identify and deconstruct cell structures, functions and mechanisms. The new science of cell and molecular biology was established. In 1953, molecular structure of DNA as a double helix was established.

In later part of 20th century, disease mechanisms were further comprehended based on understanding of immunology. In 1950s, researches on rheumatic fever, a complication of streptococcal infections, revealed that it was mediated by the host's own immune response. It was further identified that enzymes released by the innate immune cells i.e. macrophages degrade host tissue. Thus a combination of understanding in physiology, microbiology and immunology contributed greatly towards development of Pathophysiology.

Pathophysiology is a required area of study for nearly all health care professionals including medical, dental, physician assistant, occupational therapy, physical therapy, nurse practitioner, radiation therapists, pharmacists, nurses, radiologic science, chiropractic and paramedic programmes.

With time pharmacy practice is getting more clinically oriented. In such cases individuality of patient involving more than one concurrent disease is important. Choice of drug for the patient and adverse reactions to drugs is another important consideration. In view of this Pathophysiology of the disease including etiology, signs and symptoms and complications related to the disease are important.

Definitions:

Definitions of all clinically relevant terms related to Pathophysiology are compiled in the Appendix.

1.1.2 Homeostasis

Homeostasis is the property of a system within the body of a living organism in which a variable, such as concentration of a substance in solution, is actively regulated to remain very nearly constant. The word originates from two words: homeo and stasis. In Greek language homoios means similar and stasis means standing still. Thus the word indicates "staying the same". In human body there are internal and external variables operating at various points of

time. In spite of such variables, the body maintains a fairly constant environment due to mechanisms of homeostasis.

The concept of homeostasis was first described by a French physiologist Claude Bernard in 1865 and the word homeostasis was coined by American physiologist Walter Canon in 1926. Canon postulated that homeostasis was a process of synchronized adjustments in the internal environment resulting in the maintenance of specific physiological variables within defined parameters and that these parameters included blood pressure, temperature, pH and others; all with clearly defined normal ranges. Canon further postulated that threats to homeostasis might originate from the external environment like extremes of temperature or internal environment like infection. The threats can be physical, psychological or even emotional. Canon's work outlined that the maintenance of the internal physical and psychological balance, homeostasis, demands an internal network of communication, with sensors capable of identifying deviations from the acceptable ranges and effectors to return these deviations back within acceptable limits. He identified negative feed back systems and emphasized that the response to variables within the body would be same.

The metabolic process of all living organisms can only take place in very specific physical and chemical environments. The best known homeostasis in human body is related to maintaining temperature, pH, osmolarity and concentrations of sodium, potassium, calcium, glucose, carbon dioxide and oxygen. Take the case of body temperature. Core body temperature is regulated by a homeostat, with sensors in hypothalamus of brain. The set point of the regulator is regularly reset. Body temperature in humans follows a circadian rhythm, with lowest temperatures occuring at night, and the highest in the afternoons. The temperature is 36.4°C from 2 a.m. to 6 a.m. and 37.5°C from 10 a.m. to 6 p.m. The regulator's set point is readjusted in adult women at the beginning of luteal phase of the menstrual cycle. The set point is again reset during infections to produce fever.

Homeostasis does not govern every activity in the body. Take the case of blood pressure in mammals. It is homeostatically controlled, and measured by stretch receptors in the walls of aortic arch and carotid sinuses. The sensors send messages via sensory nerves to the medulla oblongata of the brain indicating variation in blood pressure. Subsequently, the medulla oblongata sends messages through motor or efferent nerves to a variety of effector organs. One of the effector organs is the heart. Stimulation of heart rate leads to tachycardia while lowering of heart rate is called as bradycardia. Tachycardia or bradycardia may be set in when the blood pressure deviates below or above set points of 80-120 mm of mercury. Thus the heart rate, for which there is no sensor in the body, is not homeostatically controlled; however it is one of the effector responses to errors in arterial blood pressure. Another example is of rate of sweating. We sweat more in summer to maintain body temperature. Unlike this, we do not sweat in winter. We wear warm clothing to maintain body temperature.

Apart from the entities which are homeostatically controlled in the internal environment of the body, there are some variables which are neither homeostatically controlled nor involved in the operation of homeostasis. The blood urea concentration is an example. There are no sensors for urea. Blood urea is generated in liver during metabolism of amino acids of proteins. It is excreted by kidneys without active resorption or excretion by renal tubules. A high protein diet produces a high blood urea concentration. A poor protein diet with low blood plasma urea concentration leads to no secretion of urea in urine.

Homeostatic mechanisms:

There are two kinds of feed backs in a chain like event in human body. The mechanisms are called as negative feed back and positive feed back respectively. Take a case of chain reaction in which A is converted to B; B is converted to C; C to D and D to E. Quite often every change is controlled by activity of an enzyme. The rate of every enzymatic reaction can vary. The slowest reaction is termed as rate limiting step. If any of the intermediate from A to E is over produced, then higher concentration of the intermediate slows down the reaction leading to its generation. This is termed as negative feed back. Thus negative feed back limits higher production of an intermediate through a self controlling mechanism. Alternatively, if production of an intermediate is reduced below certain limits then related enzymes may be activated to restore level of the intermediate. This is called as positive feed back mechanism.

Control of arterial pressure involves pressure monitoring system, volume monitoring system, hormonal mechanisms, reflex regulation, autonomic control etc. Bradycardia due to higher blood pressure is an example of negative feed back mechanism. In a cascade of reactions in coagulation, activation of one clotting factor leading to activation of other factors promoting coagulation to limit blood loss is an example of positive feed back mechanism.

Operation of the feed back mechanisms involves three components:

- The sensor.
- The control center.
- The effector.

The sensor contains receptors which monitor change of the variable and provide sensory signal to the controlling center as soon as the change is detected. The carotid sinus and the aortic arch contain baro receptors in their valve to detect changes in blood pressure. They send signals to controlling center located in medullary oblongata.

The control centers are usually located in the Central Nervous System (CNS). Centers for blood pressure regulation are located in medulla oblongata and hypothalamus.

Effector is the target organ which carries out the demand of the control center to achieve an effective response. Blood vessels and heart are the effector organs related to blood pressure. Through bradycardia or tachycardia at heart and through vasodilation or vasoconstriction at blood vessels, they help in maintaining blood pressure.

Following control systems are important for regulation of human body:

- Core body temperature
- Blood glucose
- Plasma ionised calcium
- Blood partial pressure of oxygen and carbon dioxide
- Blood oxygen content
- Arterial blood pressure
- Extra cellular sodium concentration
- Extra cellular potassium concentration
- Volume of body water
- Extra cellular fluid pH

As an illustration homeostasis of one parameter i.e. volume of body water is discussed below.

Homeostasis of volume of body water:

The volume of water in the body is measured by stretch receptors in the atria of heart. They are also indirectly sensed by measurement of the osmolality of plasma by the hypothalamus. Measurement of the plasma osmolality gives an indication of the water content of the body. It relies on the fact that water losses from the body through sweat, gut fluids in the form of fecal water and through vomitting/diarrhea and the exhaled air, are all hypotonic. It means that fluids like saliva, tears are less salty than plasma. Tears have almost the same salt content as that of extra cellular fluids while saliva is hypotonic with respect to plasma. Thus taste of saliva is not salty while tears are decidedly salty. Nearly all normal and abnormal losses of body water make extra cellular fluids hyper-osmolar. Conversely, excessive water intake dilutes the extra cellular fluids making it hypo-osmolar. Only after loss of water through urine body can become isotonic. Hence excessive water intake leads to frequent urination.

When the hypothalamus detects a hyper-osmolar extra cellular environment, it causes secretion of the hormone called antidiuretic hormone (ADH). For ADH, kidney is the effector organ. The effect of ADH on kidney tubules leads to reabsorption of water from distal convoluted tubules and collecting ducts, thus preventing further water loss. Simultaneously, hypothalamus stimulates thirst center in the brain to stimulate urge of drinking water. The caessation of urine flow prevents the hypovolemia and hypertonicity from getting worse. Thus drinking of water corrects the defect.

Hypo-osmolarity leads to very low plasma ADH levels. Low ADH results in inhibition of water reabsorption from kidney tubules, causing high volumes of very dilute urine to be excreted, thus getting rid of excess water in the body.

It is to be noted that urinary water loss, when the body water homeostat is intact, is a compensatory water loss, correcting excess of water in the body. Alternatively thirst reflex is an important second effector mechanism of the body water homeostat, correcting any water deficit in the body.

Stretching of the right atrium of the heart is a sign of excessive blood volume. It causes stretch receptors to secrete a hormone called as atrial natriuretic peptide (ANP) into blood. It causes kidneys to get rid of sodium along with water loss into urine. The net result is reducing volume of circulating blood.

Thus hypervolemia / hypovolemia are corrected by hormones like ADH / ANP. Water intake through thirst center or urination by kidney leads to homeostasis of volume of body water.

Homeostatic Breakdown:

Many diseases are the result of failure of one or more homeostat(s) in the body. The body water homeostat can be disrupted by inability to secrete ADH in response to even the normal body water losses via the exhaled air, the feces and sweating. On not receiving ADH signal, the kidneys produce huge unchanging volumes of very dilute urine, causing dehydration and even death.

Another example is of type I diabetes mellitus. In this case blood glucose homeostat ceases to function due to destruction of beta cells of pancreas. This means that the glucose sensor is absent and the effector pathway of insulin level in blood remains unchanged. The blood glucose concentration rises to very high levels, while the body's proteins are degraded into amino acids and are used for generating energy via gluconeogenesis. If untreated, the condition can be fatal.

1.1.3 Components and Types of Feedback Mechanisms

There are two types of feedbacks: positive feedback and negative feedback.

1. Positive Feedback:

It is a process that occurs in a feedback loop in which the effects of a small disturbance on a system include an increase in the magnitude of perturbation. An example of two products **A** and **B** can be cited here. In case of positive feedback **A** produces more of **B** which in turn produces more of **A.** positive feedback enhances or amplifies an effect by it having an influence on the process which gave rise to it.

Several examples of positive feedback can be cited in physiology.

- The onset of contractions in childbirth, known as the Ferguson reflex. When a contraction occurs, the hormone oxytocin causes a nerve stimulus, which further stimulates the hypothalamus to produce more oxytocin, which increases uterine contractions. This results in contractions increasing in amplitude and frequency.

- Another example is the process of blood clotting. When the tissue is injured, it releases specific chemicals which activate platelets in the blood. An activated platelet further releases chemicals to activate more platelets. This causes a rapid cascade and the formation of a blood clot.
- In case of excitation-contraction coupling of the heart, an increase in intracellular calcium ions of the cardiac myocyte is detected by ryanodine receptors in the membrane of sarcoplasmic reticulum which transport calcium out into the cytosol in a positive feedback physiological response.

2. Negative Feedback:

It occurs when some function of the output of a system, process, or mechanism is fed back in a manner that tends to reduce the fluctuations in the output, whether caused by changes in the input or by other disturbances. In biological systems, qualitatively different influences can oppose each other.

Some biological systems exhibit negative feedback. Hormonal control is one of the examples.

- Most endocrine hormones are controlled by a physiologic negative feedback inhibition loop, such as the glucocorticoids secreted by the adrenal cortex. The hypothalamus secretes corticotrophin-releasing hormone (CRH), which directs the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). In turn, ACTH directs the adrenal cortex to secrete glucocorticocoids, like cortisol. Glucocorticoids not only perform their respective functions throughout the body but also negatively affect the release of further stimulating secretions of both the hypothalamus and the pituitary gland, effectively reducing the output of glucocorticoids once a sufficient amount has been released. (See Fig. 1.1).

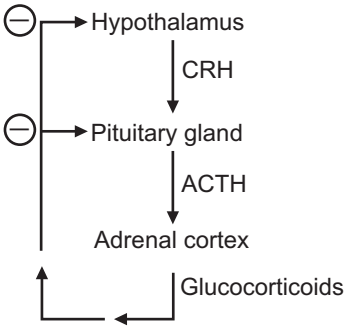


Fig. 1.1: Control of endocrine hormones by Negative feedback

The disruption of feedback loops can lead to undesirable results: in case of blood glucose levels, if negative feedback fails, the glucose level in the blood may begin to rise dramatically, thus resulting in diabetes.

Both positive feedback and negative feedback together contribute significantly in maintaining self-organization within biological systems.

1.1.4 Causes of Cellular Injury

Cell damage can occur as a result of an adverse stimulus which disrupts the normal homeostasis of affected cells. The causes can be physical, chemical, infectious, biological, nutritional or immunological. Cell damage can be reversible or irreversible. Depending on the extent of injury, the cellular response may be adaptive and wherever possible, homeostasis is restored. If severity of the injury exceeds the ability of the cell to repair itself then the cell dies. Cell death is relative to both the length of exposure to a harmful stimulus and also severity of the damage.

Pathogenesis: (Cell Membrane Damage, Mitochondrial Damage, Ribosomal Damage, Nuclear Damage)

The pathogenesis of a disease is the biological mechanism(s) that leads to the diseased state. It also describes the origin and development of the disease, whether it is acute, chronic or recurrent. The term originates from a Greek word: pathos means disease and genesis means creation.

Types of pathogenesis include microbial infection, inflammation, malignancy and tissue breakdown. Thus bacterial pathogenesis is the mechanism by which a bacterium like salmonella can cause diarrhoea.

Most diseases are caused by multiple processes; e.g. certain cancers like lymphoma originate from dysfunction of immune system.

The pathogenic mechanisms of a disease are set in motion by the underlying causes. If the causes are controlled, the disease can be prevented. Often, a potential cause is identified by epidemiological observations before a pathological link can be identified between the cause and the disease.

Cell Membrane Damage:

Cell membrane diseases are life-threatening disorders which are genetic in nature. They usually work against proteins in the body which are important for ion channels and various receptors within the membrane. These diseases operate either by disrupting the normal functions of the cells or by simply affecting the cell membrane. Many of these disorders contain other components.

Following are some of the important disorders related to cell membrane:

- **Hyaline membrane disease:** It is commonly associated with pre-term infants. It affects the lungs at the time of birth causing respiratory distress. As a result, lungs require abnormal levels of oxygen and carbon dioxide exchange after birth.
- **Alzheimer's disease:** The oxidative stress caused by Alzheimer's disease in the brain results in phospholipid alterations. These alterations disrupt functions of the brain cells.

- **Cystic fibrosis:** It is a disease which brings about an excessive production of fluid in the lungs due to a defective calcium-ion channel. This channel contains a protein which is important to the cell membrane of lungs. The channel controls the quantum of fluids and mucus in lungs. When the channel mutate leading to alteration in proteins, it causes the mucus to build up in the lungs, creating difficulty in breathing.
- **Duchenne muscular dystrophy:** This disease affects dystrophin in the muscle cell. Dystrophin allows the muscle cell wall to connect with the intracellular section. In absence of dystrophin, the cell membrane is incapable of repairing itself, destroying it and causing muscular dystrophy.

Mitochondrial Damage:

A mitochondrion is developed from about 3000 genes. Mitochondrial DNA encodes just 37 of these genes; the remaining genes are encoded in the cell nucleus and the resultant proteins are transported to mitochondria. Only about 3% of the genes (100 out of 3000) are allocated for making ATP. Nearly, 97% (2900 out of 3000) are involved with other functions tied to the sepcialised duties of the differentiated cell in which it resides. These non-ATP related functions are intimately involved with most of the major metabolic pathways used by a cell to build, breakdown and recycle its molecular building blocks.

Mitochondrial damage can lead to diseases which are together termed as mitochondrial diseases. Mitochondria are found in every cell of the human body except sperm and red blood cells. Mitochondria convert the energy of food molecules into ATP; therefore they are called as power houses of cells.

Sometimes mitochondrial diseases are caused by mutations in the mitochondrial DNA. At other times they are caused by mutations in genes of the nuclear DNA whose gene products are imported into the mitochondria (mitochondrial proteins) as well as acquired mitochondrial conditions. Often mitochondrial diseases are inherited.

Symptoms of mitochondrial diseases include poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, neurological problems, autonomic dysfunction and dementia. As a rule, mitochondrial diseases are worse when the defective mitochondria are present in the muscles, cerebrum or nerves; because these cells use more energy than most other cells in the body.

Following are the examples of mitochondrial diseases:

- Mitochondrial myopathy.
- Diabetes mellitus and deafness (DAD).
- Leber's hereditary optic neuropathy (LHON): visual loss beginning in young adulthood.

- Leigh syndrome: sub-acute sclerosing encephalopathy.
- Neuropathy, ataxia, retinitis pigmentosa and ptosis (NARP): a type of dementia.
- Myoneurogenic gastrointestinal encephalopathy (MNGIE): a type of neuropathy.
- Myoclonic Epilepsy with Ragged Red Fibres (MERRF): short stratured, hearing loss, lactic acidosis and exercise intolerance.
- Mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke- like symptoms (MELAS).
- Mitochondrial neurogastrointestinal encephalomyopathy (MNE).

Ribosomal Damage:

Damage to ribosomes can lead to diseases which are termed as ribosomopathy. Ribosomopathies are caused by alterations in the structure or function of ribosomal component proteins or rRNA genes, or other genes whose products are involved in ribosome biogenesis.

Ribosomes are essential for protein synthesis in all living organisms. They contain a scaffold of ribosomal RNA (rRNA) on which an extensive variety of ribosomal proteins (RP) are arrayed. Ribosomopathies can arise from abnormalities of either rRNA or various RPs.

Abnormal ribosome biogenesis is linked to several human genetic diseases. Names of some of these diseases are listed below. Details including which chromosomes areaffected, genotype, phenotype, protein and the site of disruption are known for these diseases.

- Diamond-Blackfan anemia.
- Dyskeratosis congenital.
- Shwachman-Diamond syndrome.
- 5q-myelodysplastic syndrome.
- Treacher Collins syndrome.
- Cartilage-hair hypoplasia.
- North American Indian childhood cirrhosis.
- Isolated congenital esplenia.
- Bowen-conradi syndrome.
- Cancer.

Nuclear Damage:

Following diseases are caused by damage to the cell nucleus:

- **Cornella de Lange Syndrome:** It is a rare genetic disorder present from birth. It causes range of physical, cognitive and medical challenges and affects both sexes equally. Some of the important symptoms of the disease are as follows:
  - ✓ Low birth weight
  - ✓ Delayed growth and small stature
  - ✓ Developmental delay