A Text Book of

PATHOPHYSIOLOGY

(An Essential Guide for Pharmacy and Other Paramedical Courses)

As per PCI Regulations

B. Pharm. Sem. II

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Preface

Globally a pharmacist is a part of health care team and is therefore a health practitioner. Understanding mechanisms of disease enables him to design and implementation of clinical interventions which often prove effective in treatment of disease. Pathophysiology is an integrative science that draws concepts from many basic and clinical sciences, including Anatomy, Physiology, Biochemistry, Genetics, Cell and Molecular Biology, Pharmacology and Biophysics. The general theoretical framework of the subject Pathophysiology is based upon the theories and related concepts of adaptation and homeostasis. An orientation to disease as disordered physiology can enable a student to understand how and why the symptoms and signs of various conditions appear; the need to understand the mechanisms underlying the disease and its clinical manifestations, so that rational therapies can be devised.

Standard books on Pathophysiology to be taught in Pharmacy colleges, according to the syllabi prescribed by Pharmacy Council of India (PCI) and respective Universities in India were a long felt need. The vacuum created by the absence of such books has resulted in hardship to the teachers, students and to the examiners as well.

Textbook of Pathophysiology (As per PCI): An Essential Guide for Pharmacy and other Paramedical Courses is the first edition of the book. It emphasizes the etiopathogenesis of diseases and disorders. In preparing this book, author's aim has been, to satisfy the needs of the teachers and students of pharmacy colleges. Intended readers are not only pharmacy students but also medical and paramedical students. They will find the description of etiology, pathogenesis, pathology and pathophysiology of disorders along with clinical manifestation and treatment. Readers will definitely appreciate this book as a ready reference and refresher text. In particular, Pharmacy students will welcome the format and scope of the book as a means of learning pathophysiology. I am confident and sure that authors will find their endeavour fruitful as they have fulfilled the purpose and all what they expected and intended to accomplish by this book.

Outstanding features of book are:

- Detailed presentation of major disorders of all organ systems.
- Concise format, facilitating efficient use at all levels of pharmacy education.
- More than 50 major disorders and diseases are covered.
- Disease prevention and treatment information along with diagnosis.
- Organ system physiology elaborated for understanding physiologic process of diseases
- Glossary of key terms.

I earnestly ask for the co-operation of pharmacy teachers and students in suggesting improvements in contents and if any one feels the necessity of making omissions, corrections and verifications, it may be brought to authors notice so that the future edition may be made more perfect.

Prof. (Dr) Nitin B. Ghiware,
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Authors

Syllabus

UNIT I **10 Hours**

- Basic principles of Cell injury and Adaptation: Introduction, Definitions, Homeostasis, Components and Types of Feedback systems, 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, Intra cellular accumulation, Calcification, Enzyme leakage and Cell death, Acidosis & 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 WBC's, 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 (Vit 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 **8 Hours**

- Inflammatory Bowel Diseases, Jaundice, Hepatitis (A, B, C, D, E, G), Alcoholic liver disease.
- Disease of Bones and Joints: Rheumatoid arthritis, Osteoporosis and Gout
- Principles of Cancer: Classification, etiology and pathogenesis of cancer

Unit V **7 Hours**

- Infectious Diseases: Meningitis, Typhoid, Leprosy, Tuberculosis, Urinary tract infections
- Sexually Transmitted Diseases: AIDS, Syphilis, Gonorrhea

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Chapter...1

INTRODUCTION TO PATHOPHYSIOLOGY

1.1 INTRODUCTION

Pathophysiology is a modern integrative biomedical science founded on basic and clinical research concerned with the mechanisms responsible for the initiation, development, and treatment of pathological processes in humans and animals. There are two separate medical fields involved in pathophysiology. The first is physiology, the study of the body and its functions. The second is pathology, the study of disease and its impact on the body. When combined, pathophysiology means to know the way in which a disease progresses and to predict the next stage of a disease, which provides appropriate care to the patient.

Pathophysiology is 'the study of the changes of normal mechanical, physical and biochemical functions, either caused by a disease or resulting from an abnormal syndrome'. When something disrupts normal physiological processes, it enters the realm of pathophysiology. It looks at the specific malfunctioning that comes from or alternately causes disease. The study of pathology and the study of pathophysiology often involves substantial overlap in diseases and processes, but pathology emphasizes direct observations, while pathophysiology emphasizes quantifiable measurements. An example from the field of infectious disease would be the study of a toxin released by a bacterium, and what that toxin does to the body to cause harm, one possible result being sepsis. Another example is the study of the chemical changes that take place in body tissue due to inflammation. Following are important aspects among pathophysiology and related subjects.

Biology: Biology is a natural science. It is the study of life and living organisms, including their structure, function, growth, evolution, distribution and taxonomy. Pathological processes begin frequently at the cell level.

Anatomy and histology: Macro and micro structural properties of the human body are essential for understanding their pathology.

Biochemistry: Biochemistry is the branch of science that explores the chemical processes within and related to living organisms. It is a laboratory based science that brings together biology and chemistry. By using chemical knowledge and techniques, biochemists can understand and solve biological problems. Biochemical processes are changed under pathological condition.

Biophysics: Biophysical properties of cells, tissues and organs determine their structural and functional characteristics.

Physiology: It is the branch of biology dealing with the functions and activities of living organisms and their parts, including all physical and chemical processes. It is helpful to recognize pathologic functions.

Pathological anatomy: The ultrastructural and macro structural changes under pathological conditions help to understand functional changes and vice versa.

Microbiology and immunology: It helps to understand the mechanisms involved in development of disease caused mainly by pathogenic micro-organisms and disorders of immune system.

Etiology: Etiology is a branch of medical science dealing with the causes and origin of diseases.

Pathogenesis: Pathogenesis means the gradual development of a disease and the chain of events leading to disease in response to etiologic factor.

Clinical manifestations: These are the observable symptoms by which a disease may be diagnosed by a physician. Clinical presentations are the whole package of the disease process including epidemiology, history, physical examination and laboratory tests etc.

Need of pathophysiology study: It helps the health care professionals to find answers to important questions related to disease processes:

(a) What are the cause/causes of the disease, and why the disease is developing?

(b) What are the mechanisms responsible for disease onset, progression and recovery?

(c) What are the mechanisms responsible for development of symptoms and signs of disease?

It is important to understand the causes and mechanisms of the disease to find the way how to treat them safe and effectively.

In the clinical setting, pathologists, histotechnologists and cytotechnologist study tissues and cells to establish the cause of a disease. Physicians use that information to form a treatment plan.

Pathophysiology is a required area of study for nearly all healthcare professional school programs (medical, dental, physician assistant, occupational therapy, physical therapy, nurse practitioner, pharmacy, nursing, and paramedic programs) in the world.

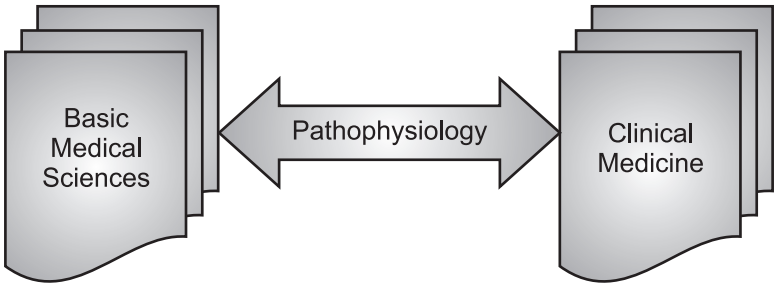


Fig. 1.1: Position of pathophysiology



UNIT I

Chapter...2

BASIC PRINCIPLES OF CELL INJURY AND ADAPTATION

2.1 INTRODUCTION TO HOMEOSTASIS

The concept of internal harmony was proposed by Claude Bernard in the 19th century, Walter Cannon coined the term homeostasis to describe the state of internal (Physiologic and psychological) balance or organization of function.

Homeostasis may be defined as "The maintenance of the internal conditions of body at equilibrium, despite changes in the external environment". For example, the core temperature of human body remains at about 37°C despite fluctuations in the surrounding temperature. Similarly, the blood glucose level remains normal despite carbohydrate rich diet. Stable internal conditions are important for the efficient functioning of enzymes.

2.2 ADAPTATION

Adaptation refers to process by which a system seeks to restore or maintain homeostasis. Adaptive mechanism may also be referred to as compensatory mechanisms, homeostatic mechanisms, control and regulatory mechanism. Although adaptation may be physiological, psychological, behavioural, in system's terminology adaptive mechanisms are examples of feedback to the system and may be represented by either negative or positive feedback loops.

a. Negative Feedback Loops:

Nearly, all physiologic adaptive responses are negative feedback loops. These processes act to restore homeostasis by inducing changes in the opposite direction of a force perturbing the system. For example, if injury with haemorrhage causes a decrease in blood pressure, sensors in blood vessels activate neural responses that causes increase in cardiac pumping and constriction of blood vessels. These changes cause an increase in blood pressure a change that negates the original disruption, completing the feedback loop and restoring the steady state. Other examples of Homeostasis are temperature control is vital to the maintenance of homeostasis within the body. Heat is sensed by thermo-regulators in both, the skin and the hypothalamus. The internal temperature is sensed by the hypothalamus, and external temperature is sensed by the skin. When the external temperature outside is too cold, messages are sent from the many thermo-receptors located within the skin, to the cerebellum leading to the hypothalamus.

The role of the cerebellum is to make the individual aware of feeling cold, which may cause voluntary behavioural changes such as putting on more layers of clothing or a coat.

Once the message is received by the hypothalamus, a series of reactions follow. The first of which is by the hypothalamus, which secretes thyroid releasing hormone (TRH). This hormone's target is the anterior lobe of the pituitary gland. When the TRH reaches its target, it releases Thyroid Stimulating Hormone (TSH) which enters the blood stream and stimulates thyroid gland to produce thyroxin. The role of thyroxin is to increase cellular metabolism in order to generate heat. This hormone also inhibits vasoconstriction, the process in which blood is diverted from the skin in order to conserve heat by keeping it deep within the body. Sweating is also reduced to keep the surface of the skin dry, thus preventing heat loss. In addition to all of these processes, the erector pilli muscles contract, causing the skin hairs to stand erect. This traps air between the hairs and the skin and creates a layer of insulation, therefore keeping the body warmer. In addition, the phenomenon of shivering is displayed and the bodies' metabolic rate is increased.

When the body temperature increases, messages are sent in the same way as if the body is cold to the hypothalamus. This causes an increase in the amount of sweating, this is releasing heat via water, and the water on the skin evaporates, cooling the body down. Vasodilatation is also apparent. In this instance, blood is diverted to the skin in order to loose heat. The erector pilli muscles relax, allowing the skin hairs to be lowered, and the bodies' metabolic rate is reduced. The reactions are different for each of the environmental states as the messages sent for each are different.

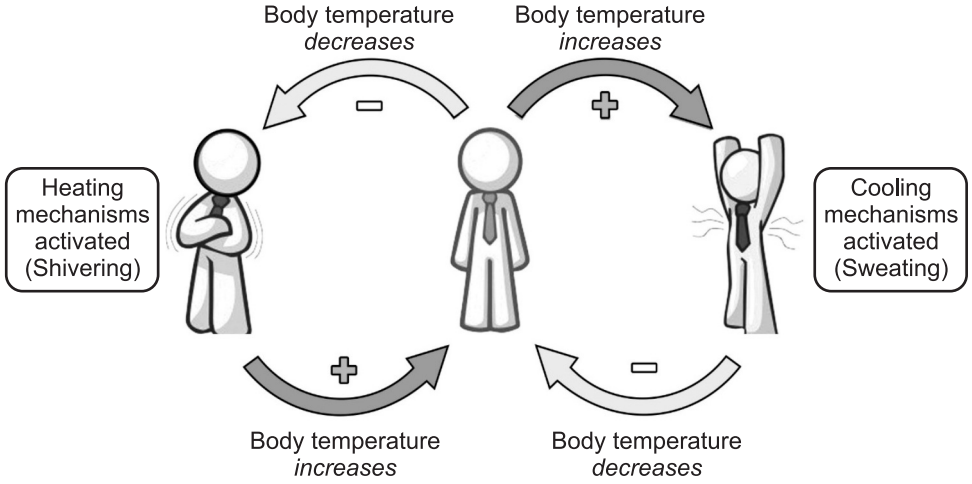


Fig. 2.1 : Homeostasis of temperature by negative feedback loop

Water balance is another very important aspect of homeostasis, which needs to be controlled within narrow limits. The control of water balance is conducted using the following series of events. The osmoreceptors located within the hypothalamus detect the condition of fluid balance within the body. If the fluid balance is too low, then the hypothalamus will act to bring the level back, by keeping more water

within the body. If the concentration of water within the body is too high, then the hypothalamus will react to excrete more water from the body. In the event of the hypothalamus sensing a change in fluid balance, messages are sent to the cerebellum, from where a feeling of thirst is produced. This is only when there is not enough water within the body. In addition, the hypothalamus sends a message also to the posterior pituitary gland to induce the secretion of ADH. The action of the ADH in this instance is to increase the permeability of the collecting duct of the kidney and increase the amount of water which is reabsorbed into the body.

Blood glucose is another contributing factor to homeostasis. The blood glucose concentration in the blood is vital to the functioning of cells within the body and is controlled by a number of internal structures and external influence (food and drink). If too much glucose is present within the blood, then specific receptors located within the pancreas detect this. These receptors then send messages to the cerebellum, feelings of satiety (feeling full) are induced, and therefore the individual's intake of food is decreased. Messages are also sent to the islets of Langerhans for the production of insulin to commence. Once insulin is produced, it is secreted into the capillary circulation and eventually into the systemic blood stream. The insulin has many effects, mainly consisting of increasing the intake of glucose by all the cells of the body. This action uses up surplus glucose and brings back a stable equilibrium. The insulin also aids in the conversion of glucose into a substance called glycogen in the liver, thus lowering the level of glucose in the blood and restoring equilibrium.

On the other hand, if there is not enough glucose in the bloodstream, then the very same receptors, which are located in the pancreas, detect the change. Once again, a message is sent to the cerebellum, which brings around feelings of hunger, therefore increases the consumption of food and drink. Messages are also sent to cells in the islets of Langerhans to start the production of glucagon. This glucagon is released by the islets of Langerhans into the capillary circulation. In turn, the systemic blood stream stimulates the liver to convert stored glycogen into glucose. In addition, the liver is stimulated also to start the conversion of amino acids into glucose, therefore the levels of glucose in the bloodstream rise and equilibrium is achieved.

Homeostasis is also heavily involved with the control of the respiratory rate. In the norm, individuals are not conscious of their respiration. This is because the act of respiration is involuntary. Respiration is under involuntary control through an area of the brain termed as the medulla. Within the medulla is an area known as the breathing centre. The breathing centre is composed into sections, allowing each to tackle an alternate aspect to respiration. Both the dorsal and the lateral areas assist with inspiration and provide stimulation for respiration. In addition, the ventral area increases both the depth and rate of respiration. The centre is linked with the intercostal nerves and the phrenic nerves, leading to the diaphragm. These routes provide a method of communication between the thorax, the respiratory system, and the medulla.

The medulla is chief in maintaining a constant rate of respiration and

depth. However, both external and internal stimuli can alter the rate of respiration, making it higher or lower than the norm. The main influence to this is the level of carbon dioxide in the blood stream. If the concentration of carbon dioxide in the blood stream increases, then chemo-receptors located within both aortic and carotid bodies become aroused. Medulla receives sensory impulses from chemoreceptors, and integrated impulses are send to the intercostal muscles and the diaphragm through phrenic and intercostal nerves. This causes them to contract and relax more quickly and therefore increase the breathing rate, in order to introduce more oxygen to the blood stream and bring back equilibrium of both oxygen and carbon dioxide levels in the blood stream. This process is an example of negative feedback.

As for the control of the breathing rate, the medulla also controls the heart rate. The set process for the regulation of the heart rate is rather complex and is as follows. As an individual exercises, special receptors located within the muscles send impulses to the medulla. Once these messages are received, the medulla secretes epinephrine and norepinephrine. The combination of these two chemicals proceed through pathways within the nervous system until they reach the Sino-atrial node, located within the myocardium. It acts like a pacemaker, controlling its electrical activity. These chemicals arouse the Sino-atrial node, making it produce more electrical energy, thus making the heart rate increase.

On the other hand, when exercise is ceased, the muscles send additional impulses to the medulla which responds by secreting the hormone acetylcholine. This hormone decreases the heart rate by slowing down the electrical impulses from the Sino-atrial node and therefore, decreases the heart rate. In addition, the medulla can also recognize other factors which cause an increase in heart rate. These include emotional stress. In this instance, the medulla also takes information from the thalamus, which informs the medulla of the stressor. This is with the addition of information received from the nervous system. The combination of the two would enable the best response possible to be triggered. Homeostatic processes are controlled by negative feedback and hence these systems occur more commonly within the body.

b. Positive Feedback Loops:

The response to disruptive forces is in the same direction as the force; thus tending to increase the instability of the system. Positive feedback loops are almost always maladaptive or harmful and are often termed vicious cycles, downward spirals, or decompensation states.

These states can lead to death if not interrupted by treatment. In advanced shock, for example, the increased rate and pumping force of the heart eventually increase the demand of the heart muscle for oxygenated blood. The gap between oxygen supply and demand widens, and cardiac failure results. Positive feedback systems generally control infrequent conditions such as ovulation, childbirth and blood clotting.

Two positive feedback mechanisms control release of oxytocin:

- **Uterine contractions during childbirth:** When contractions start, oxytocin is released which stimulates more contractions and more oxytocin is released,

hence contractions increase in intensity and frequency. Production and release of oxytocin stops after the baby is delivered.

- **Secretion of breast milk:** The stimulation of a baby sucking its mother's breast leads to secretion of oxytocin into the mother's blood, which leads to milk being available to the baby via the breast. The mother's production and release of oxytocin ceases when the baby stops feeding.

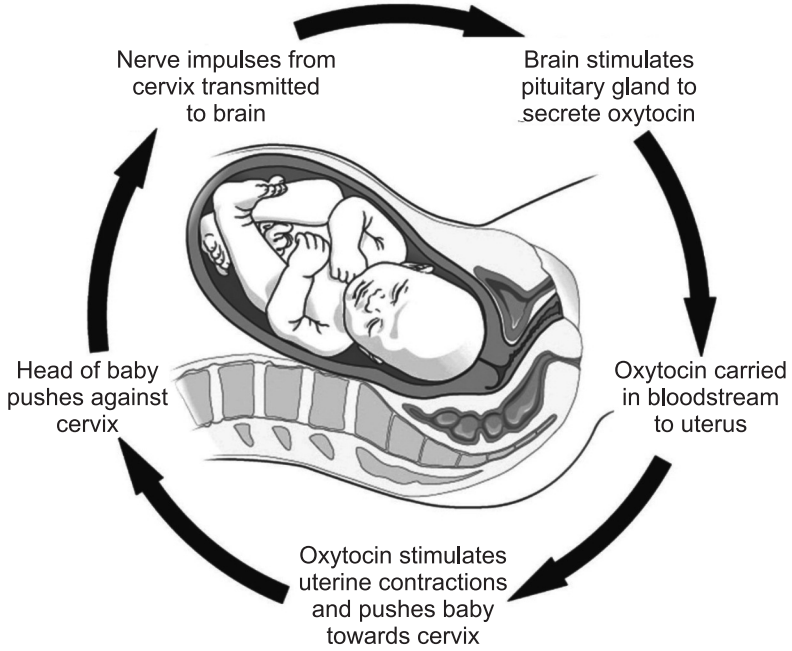


Fig. 2.2 : Uterine contractions during childbirth by positive feedback mechanism

Table 2.1 : Example for Negative and Positive feedback mechanism

Negative Feedback mechanism	Positive Feedback mechanism
Thermoregulation: If body temperature changes, mechanisms are induced to restore normal levels.	**Childbirth:** Stretching of uterine walls cause contractions that further stretch the walls (this continues until birth occurs).
Blood sugar regulation: Insulin lowers blood glucose when levels are high; glucagon raises blood glucose when levels are low.	**Lactation:** The child feeding stimulates milk production which causes further feeding (continues until baby stops feeding).
Osmoregulation: ADH is secreted to retain water when dehydrated and its release is inhibited when the body is hydrated.	**Ovulation:** The dominant follicle releases oestrogen which stimulates LH and FSH release to promote further follicular growth.
Sex Hormones: The synthesis and release of sex hormones is regulated by negative feedback mechanism.	**Blood clotting:** Platelets release clotting factors which cause more platelets to aggregate at the site of injury.

2.3 CELL INJURY

Cell injury is the common denominator in almost all diseases. It is defined as 'an alteration in cell structure or biochemical functioning, resulting from some stress that exceeds the ability of the cell to compensate through normal physiologic adaptive mechanisms'. Cell injury results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents or suffer from intrinsic abnormalities. Different injurious stimuli affect many metabolic pathways and cellular organelles. Injury may progress through a reversible stage and culminate in cell death.

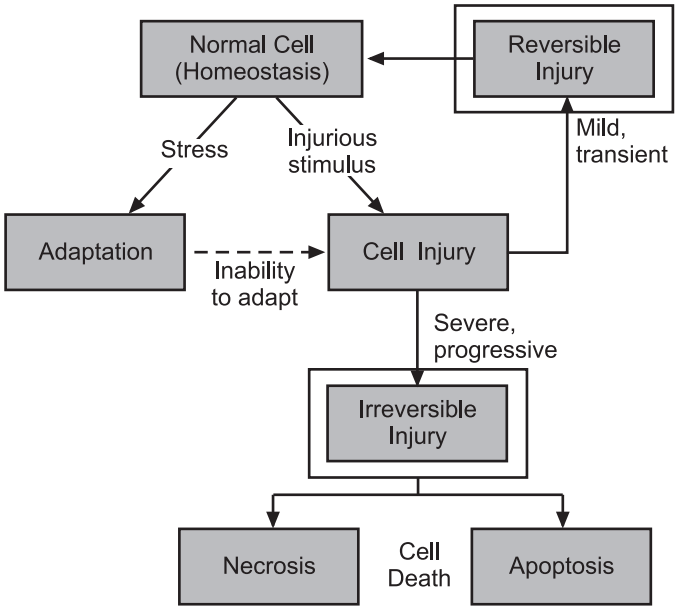


Fig. 2.3 : Cell injury

a. Reversible cell injury: In early stages or mild forms of injury the functional and morphologic changes are reversible if the damaging stimulus is removed. At this stage, although there may be significant structural and functional abnormalities, the injury has typically not progress to severe membrane damage and nuclear dissolution.

b. Irreversible cell injury (Cell death): Because of cell death with continuing damage, the injury becomes irreversible, at which time the cell cannot recover and it dies. There are two types of cell death, necrosis and apoptosis which differ in their morphology, mechanisms, and roles in disease and physiology. When damage to membranes is severe, enzymes leak out of lysosomes, enter the cytoplasm, and digest the cell, resulting in necrosis. Cellular contents also leak out through the damaged plasma membrane and elicit a host reaction (inflammation). Necrosis is the major pathway of cell death in many commonly encountered injuries, such as those resulting

from ischemia, exposure to toxins, various infections and trauma. When a cell is deprived of growth factors or the cell's DNA or proteins are damaged beyond repair, the cell kills itself by another type of death, called apoptosis, which is characterized by nuclear dissolution without complete loss of membrane integrity. Apoptosis is an active, energy dependent, tightly regulated type of cell death that is seen in some specific situations. Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with pathologic cell injury.

i. Necrosis: Necrosis is one of the basic patterns of irreversible cell injury and death. Necrosis has long been considered the "unregulated" pattern of cell injury and death, representing a messy end to a damaged cell that consequently causes a potent inflammatory response.

ii. Apoptosis: This is a pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die by activating enzymes capable of degrading the cell's own nuclear DNA, nuclear and cytoplasmic proteins. Fragments of the apoptotic cells then break off; giving the appearance that is responsible for the name (apoptosis, "falling off"). The plasma membrane of the apoptotic cell remains intact, but the membrane is altered in such a way that the cell and its fragments become avid targets for phagocytes. The dead cell is rapidly cleared before its contents have leaked out, and therefore cell death by this pathway does not elicit an inflammatory reaction in the host. Thus, apoptosis differs from necrosis, which is characterized by loss of membrane integrity, enzymatic digestion of cells, leakage of cellular contents, and frequently a host reaction. However, apoptosis and necrosis sometimes coexist, and apoptosis induced by some pathologic stimuli may progress to necrosis.

Table 2.2 : Difference between Necrosis and Apoptosis

	Necrosis	Apoptosis
Stimuli	Hypoxia, Toxins	Physiologic and Pathologic.
Histology	Cellular swelling, coagulation, necrosis, disruption of organelles.	Single cells, Chromatin condensation, apoptic bodies.
DNA breakdown	Random diffuse.	Internucleosomal.
Mechanism	ATP depletion, membrane injury, free radical damage.	Gene activation, endonuclease.
Tissue reaction	Inflammation.	No inflammation, phagocytosis of apoptotic bodies.

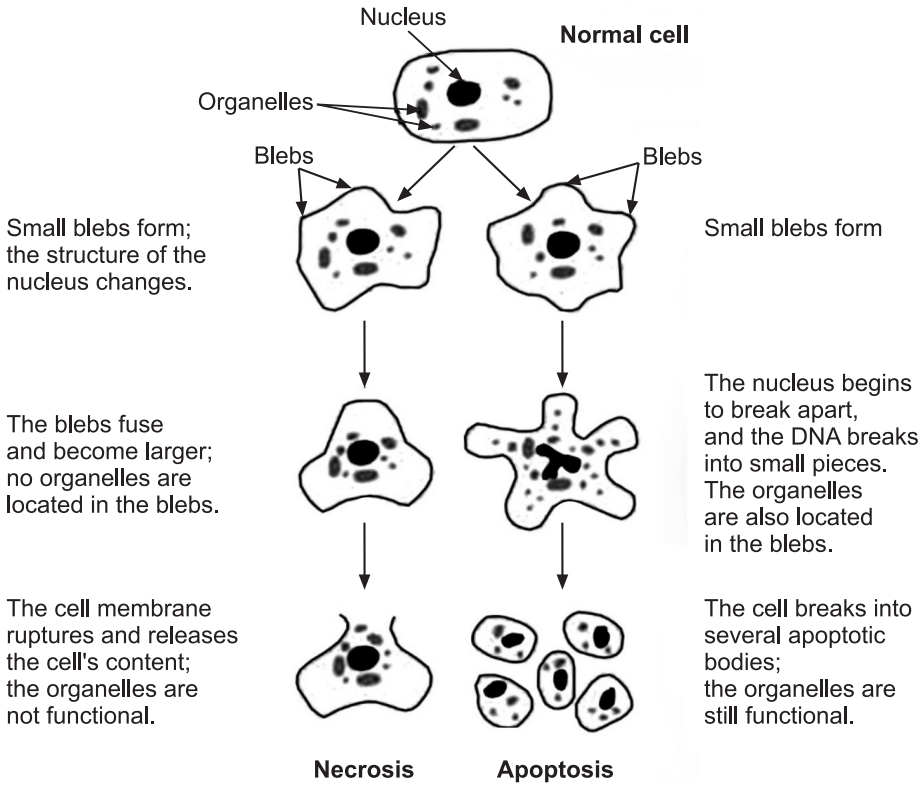


Fig. 2.4 : Mechanisms of necrosis and apoptosis

2.3.1 Etiology of Cell Injury

Cell injury is a sequence of events that occur if the limits of adaptive capability are exceeded or no adaptive response is possible. This can be due to physical, chemical, infectious, biological, immunological factors and nutritional cellular abnormalities.

A) Acquired cause:

Acquired causes of cell injury are further categorized as:

(a) Oxygen deprivation (Hypoxia)
(b) Physical agents
(c) Chemical agents and drugs
(d) Microbial agents
(e) Immunologic agents
(f) Nutritional derangement
(g) Psychological factors
(h) Idiopathic agents

(a) Oxygen deprivation: Hypoxia is a deficiency of oxygen, which causes cell injury by reducing aerobic oxidative respiration. Hypoxia is an extremely important and common cause of cell injury and cell death. Causes of hypoxia include reduced blood flow (ischemia), inadequate oxygenation of the blood due to cardiorespiratory failure, and decreased oxygen-carrying capacity of the blood, as in anemia or carbon monoxide poisoning (producing a stable carbon monoxyhemoglobin that blocks oxygen carriage) or after severe blood loss. Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die. For example, if an artery is narrowed, the tissue supplied by that vessel may initially shrink in size

(atrophy), whereas more severe or sudden hypoxia induces injury and cell death.

(b) Physical agents for cell injury: Mechanical trauma (e.g., Road accident), Thermal trauma (e.g., Heat and cold), Electricity, Radiation (e.g., U.V. radiation), Rapid changes in atmosphere pressure.

(c) Chemicals and Drugs: The list of chemicals that may produce cell injury defines compilation. Simple chemicals such as glucose or salt in hypertonic concentrations may cause cell injury directly or by deranging electrolyte balance in cells. Even oxygen at high concentrations is toxic. Trace amounts of poisons, such as arsenic, cyanide or mercuric salts, may damage sufficient number of cells within minutes or hours to cause death. Other potentially injurious substances are our daily companions: environmental and air pollutants, insecticides, and herbicides; industrial and occupational hazards, such as carbon monoxide and asbestos; recreational drugs such as alcohol; and the ever-increasing variety of therapeutic drugs.

(d) Microbial agents: Injuries by microbes include infection caused by bacteria, rickettsiae, viruses, fungi, protozoa and other parasites.

(e) Immunological Agents: The immune system serves an essential function in defence against infectious pathogens, but immune reactions may also cause cell injury. Injurious reactions to endogenous self-antigens are responsible for several autoimmune diseases. Immune reactions to many external agents, such as viruses and environmental substances, are also important causes of cell and tissue injury. Example: Hypersensitivity reactions, anaphylactic reactions, autoimmune diseases.

(f) Nutritional derangement: A deficiency or an excess of nutrients may results in nutritional imbalances. Nutritional deficiency diseases may be due to overall deficiency of nutrients (starvation), protein calorie (Marasmus, Kwashiorkor), and minerals (Anaemia) or of trace elements. Nutritional excess is a problem of society which results from obesity, in atherosclerosis, heart diseases and hypertension.

(g) Psychological factors: There are number of specific biochemical or morphological changes in common acquired mental diseases due to mental stress, strain, anxiety, overwork and frustration. Problems of drug addiction, alcoholism and smoking results in various diseases such as liver damage, chronic bronchitis, lung cancer, peptic ulcer, hypertension, ischemic heart diseases etc.

(h) Idiopathic factor: The causative factor of cell injury is unknown.

B) Genetic cause:

In western countries, genetic defects constitute about 50% total mortality in infancy and childhood, while in developing and under developing countries 95% of infant mortality occurs. Genetic cases are such as, Developmental defect (Errors in morphogenesis), cytogenic defects (chromosomal abnormalities), Single-gene defects (Mendelian syndrome), Storage diseases (Inborn Errors of metabolism), Disorders with multifactorial inheritation.

2.3.2 Pathogenesis of Cell Injury

Cell damage can be reversible or irreversible. Depending on the extent of injury, the cellular response may be adaptive and homeostasis is maintained. Cell death occurs when the severity of the injury (Stress) exceeds the cell's ability to repair itself. Cell death is relative to both the length of exposure to a harmful stimulus and the severity of the damage caused. Cell death may occur by severe cell swelling or cell rupture, denaturation and coagulation of cytoplasmic proteins and breakdown of cell organelles (necrosis) or internally controlled cell death, chromatin condensation and fragmentation (apoptosis). Now, we have discussed the causes of cell injury and necrosis and their morphologic and functional correlates, we next consider in more detail the molecular basis of cell injury, and then illustrate the important principles with a few selected examples of common types of injuries. The biochemical mechanisms linking any given injury with the resulting cellular and tissue manifestations are complex, interconnected, and tightly interwoven with many intracellular metabolic pathways. It is therefore often difficult to pinpoint specific molecular alterations caused by a particular insult.

The cellular response to injurious stimuli depends on the type of injury, its duration, and its severity. Thus, low doses of toxins or a brief duration of ischemia may lead to reversible cell injury, whereas larger toxin doses or longer ischemic intervals may result in irreversible injury and cell death. The consequences of an injurious stimulus depend on the type, status, adaptability, and genetic makeup of the injured cell. The same injury has vastly different outcomes depending on the cell type; thus, striated skeletal muscle in the leg accommodates complete ischemia for 2 to 3 hours without irreversible injury, whereas cardiac muscle dies after only 20 to 30 minutes. The nutritional (or hormonal) status can also be important; clearly, a glycogen-replete hepatocyte will tolerate ischemia much better than one that has just burned its last glucose molecule. Genetically determined diversity in metabolic pathways can also be important. For instance, when exposed to the same dose of a toxin, individuals who inherit variants in genes encoding cytochrome P-450 may catabolize the toxin at different rates, leading to different outcomes. Much effort is now directed toward understanding the role of genetic polymorphisms in responses to drugs and toxins and in disease susceptibility.

Cell injury results from functional and biochemical abnormalities in one or more of several essential cellular components. The most important targets of injurious stimuli are:

- Mitochondria, the sites of ATP generation;
- Cell membranes, on which the ionic and osmotic homeostasis of the cell and its organelles depends;
- Protein synthesis;
- The cytoskeleton; and
- The genetic apparatus of the cell.

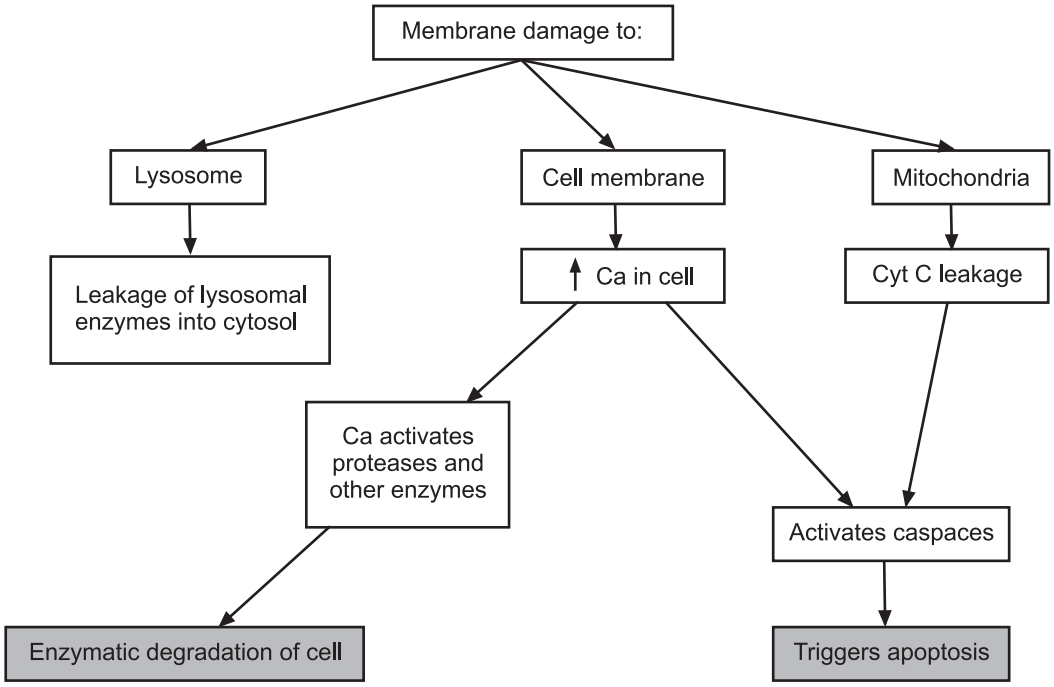


Fig. 2.5 : Pathogenesis of cell injury

A) Mechanism of Reversible Cell Injury: As the name implies, this occurs if extreme stress persists and the cell is unable to adapt to overcome the stress. Reversible cell injury results in cellular and morphological changes that can still be reversed if the stress is eventually removed. There are three mechanisms by which reversible cell injury may occur.

- Depleted resources of ATP in the cell owing to decreased levels of Oxidative Phosphorylation.
- Hydropic cellular swelling, a phenomenon caused by changes in ion concentrations and water influx.
- Organelles within the cell show minute alterations.

a) ATP depletion: ATP depletion and decreased ATP synthesis are frequently associated with both hypoxic and chemical (toxic) injury. High-energy phosphate in the form of ATP is required for many synthetic and degradative processes within the cell. These include membrane transport, protein synthesis, lipogenesis, and the deacylation-reacylation reactions necessary for phospholipid turnover. Depletion of ATP to 5% to 10% of normal levels has widespread effects on many critical cellular systems. The activity of the plasma membrane energy-dependent sodium pump is reduced. Failure of this active transport system, due to diminished ATP concentration and enhanced ATPase activity, causes sodium to accumulate intracellularly and potassium to diffuse out of the cell. The net gain of solute is accompanied by isosmotic gain of water, causing cell swelling, and dilation of the endoplasmic reticulum and cellular energy metabolism is altered. If the supply of oxygen to cells is reduced, as in ischemia, oxidative phosphorylation ceases and cells rely on glycolysis for energy production.

This switch to anaerobic metabolism is controlled by energy pathway metabolites acting on glycolytic enzymes.

The decrease in cellular ATP and associated increase in adenosine monophosphate stimulate phosphofructo-kinase and phosphorylase activities. These result in an increased rate of anaerobic glycolysis designed to maintain the cell's energy sources by generating ATP through metabolism of glucose derived from glycogen. As a consequence, glycogen stores are rapidly depleted.

Glycolysis results in the accumulation of lactic acid and inorganic phosphates from the hydrolysis of phosphate esters. This reduces the intracellular pH, resulting in decreased activity of many cellular enzymes.

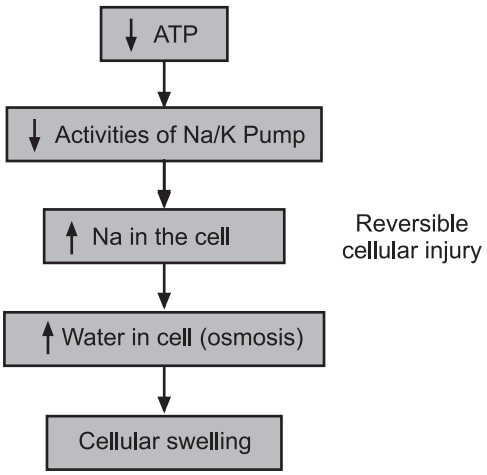


Fig. 2.6 : Mechanism of cellular swelling due to depletion of ATP synthesis

b) Damage to Mitochondria: Mitochondria are the cell's suppliers of life-sustaining energy in the form of ATP, but they are also critical players in cell injury and death. Mitochondria can be damaged by increase of cytosolic Ca^{2+}, reactive oxygen species, and oxygen deprivation, and so they are sensitive to virtually all types of injurious stimuli, including hypoxia and toxins.

There are two major consequences of mitochondrial damage:

- Mitochondrial damage often results in the formation of a high-conductance channel in the mitochondrial membrane, called the mitochondrial permeability transition pores. The opening of this channel leads to the loss of mitochondrial membrane potential and pH changes, resulting in failure of oxidative phosphorylation and progressive depletion of ATP, culminating in necrosis of the cell.
- The mitochondria also contain several proteins that are capable of activating apoptotic pathways, including cytochrome C (the major protein involved in electron transport). Increased permeability of the mitochondrial membrane may result in leakage of these proteins into the cytosol and death by apoptosis. Thus, cytochrome C plays a key dual role in cell survival and

death. In its normal location inside mitochondria, it is essential for energy generation and the life of the cell, but when mitochondria are damaged so severely that cytochrome C leaks out, it signals cells to die.

c) Influx of Calcium: Failure of the Ca^{2+} pump leads to influx of Ca^{2+}, with damaging effects on numerous cellular components. With prolonged or worsening depletion of ATP, structural disruption of the protein synthetic apparatus occurs, manifested as detachment of ribosomes from the rough endoplasmic reticulum and dissociation of polysomes into monosomes, with a consequent reduction in protein synthesis. Ultimately, there is irreversible damage to mitochondrial and lysosomal membranes, and the cell undergoes necrosis.

In cells deprived of oxygen or glucose, proteins may become misfolded, and misfolded proteins trigger a cellular reaction called the unfolded protein response that may lead to cell injury and even death. A protein misfolding is also seen in cells exposed to stress, such as heat, and when proteins are damaged by enzymes and free radicals.

1. **Defects in membrane permeability:** Early loss of selective membrane permeability leading ultimately to overt membrane damage is a consistent feature of most forms of cell injury. The plasma membrane can be damaged by ischemia, various microbial toxins, lytic complement components, and a variety of physical and chemical agents. Several biochemical mechanisms may contribute to membrane damage.
2. **Decreased phospholipid synthesis:** The production of phospholipids in cells may be reduced whenever there is a fall in ATP levels, leading to decreased energy dependent enzymatic activities. The reduced phospholipid synthesis may affect all cellular membranes including the mitochondria themselves, thus exacerbating the loss of ATP.
3. **Increased phospholipid break-down:** Severe cell injury is associated with increased degradation of membrane phospholipids, probably due to activation of endogenous phospholipases by increased levels of cytosolic Ca^{2+}.
4. **ROS:** Oxygen-free radicals cause injury to cell membranes by lipid peroxidation, discussed earlier.
5. **Cytoskeletal abnormalities:** Cytoskeletal filaments serve as anchors connecting the plasma membrane to the cell interior. Activation of proteases by increased cytosolic Ca^{2+} may cause damage to elements of the cytoskeleton.
6. **Lipid breakdown products:** These include unesterified free fatty acids, acyl carnitine, and lysophospholipids, catabolic products that are known to accumulate in injured cells as a result of phospholipid degradation. They have a detergent effect on membranes. They also either insert into the lipid bilayer of the membrane or exchange with membrane phospholipids, potentially causing changes in permeability and electrophysiologic alterations. The most important sites of membrane damage during cell injury are the mitochondrial

membrane, the plasma membrane and membranes of lysosomes.

7. **Mitochondrial membrane damage:** As discussed above, damage to mitochondrial membranes results in decreased production of ATP, culminating in necrosis, and release of proteins that trigger apoptotic death.
8. **Plasma membrane damage:** Plasma membrane damage leads to loss of osmotic balance and influx of fluids and ions, as well as loss of cellular contents. The cells may also leak metabolites that are vital for the reconstitution of ATP, thus further depleting energy stores.
9. **Injury to lysosomal membranes:** Injury to lysosomal membranes results in leakage of their enzymes into the cytoplasm and activation of the acid hydrolases in the acidic intracellular pH of the injured (e.g., ischemic) cell. Lysosomes contain RNAases, DNAases, Proteases, Glucosidases, and other enzymes. Activation of these enzymes leads to enzymatic digestion of cell components, and the cells die by necrosis.
10. **Damage to DNA and proteins:** Cells have mechanisms that repair damage to DNA, but if this damage is too severe to be corrected (e.g., after radiation injury or oxidative stress), the cell initiates its suicide program and dies by apoptosis. A similar reaction is triggered by improperly folded proteins, which may be the result of inherited mutations or external triggers such as free radicals. Since these mechanisms of cell injury typically cause apoptosis.
11. **Reduced protein synthesis:** As a result of continued hypoxia, membranes of endoplasmic reticulum and Golgi apparatus swell up. Ribosomes are detached from granular endoplasmic reticulum and polysomes are degraded to monosomes, thus dispersing ribosomes in the cytoplasm and inactivating their function. Similarly reduced protein synthesis occurs in Golgi apparatus. Up to this point, withdrawal of acute stress that resulted in reversible cell injury can restore the cell to normal state.

B) Mechanism of Irreversible Cell Injury: The long term decrease in oxygenated blood supply results in irreversible damage of the cellular structure and functions. The sequence of the reversible cell injury continues and reach into irreversible cell damage (cell death). In irreversible cell injury, the inability of the cell to reverse mitochondrial and plasma membrane dysfunction on reperfusion or reoxygenation. Beside this there is further reduction in ATP continued depletion to proteins, reduced intracellular pH and leakage of lysosomal enzymes into the cytoplasm. These biochemical changes alter the normal functions of cell which are described as follows:

1. **Mitochondrial damage:** As a result of continued decrease in oxygenated blood supply, irreversible cell damage occurs and on reperfusion with injured cell, excess intracellular calcium collects in the mitochondria disabling its function. Morphologically, mitochondrial changes are vacuoles in the mitochondria and deposition of amorphous calcium salts in the mitochondrial matrix.