BASIC PRINCIPLES OF CELL INJURY AND ADAPTATION

For Class- B.Pharmacy 2nd Semester

Subject- Pathophysiology (BP204T)

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1.1 INTRODUCTION

Pathology is a scientific study of the nature of disease and its causes, processes, mechanism and effects are also called pathology.

If the cells fail to adapt under stress, they undergo certain changes leading to **Cell injury**. The affected cells may recover from the injury called **Reversible injury**; if cell may die, it is called **Irreversible injury.**

All forms of tissue injury start with molecular or structural alterations in cells. The normal cell undergoes modification in its structure and function in response to changes in demand and stress. Until these stresses become too severe the cell is to maintain a narrow range of structure and function so called- homeostasis. If the cell undergoes excessive physiological stresses or certain pathological stimuli, it can undergo adaptation. The principle cellular adaptation is atrophy, hypertrophy and hyperplasia. If the cell doesn't undergo adaptation or the cell adaptive capacity is exceeded, the cell in developing. The cell injury is reversible up to a certain level, but with severe or persistent stress the cell suffers irreversible injury and dies.

The relationship among adapted, reversible and irreversible cell injury can be seen in heart muscle. Myocardial fibers when subjected to increasing load, as in case of hypertension, the cell adapts and undergoes hypertrophy i.e. an increase in size and heart sufficiently pumps against the increased load structure.
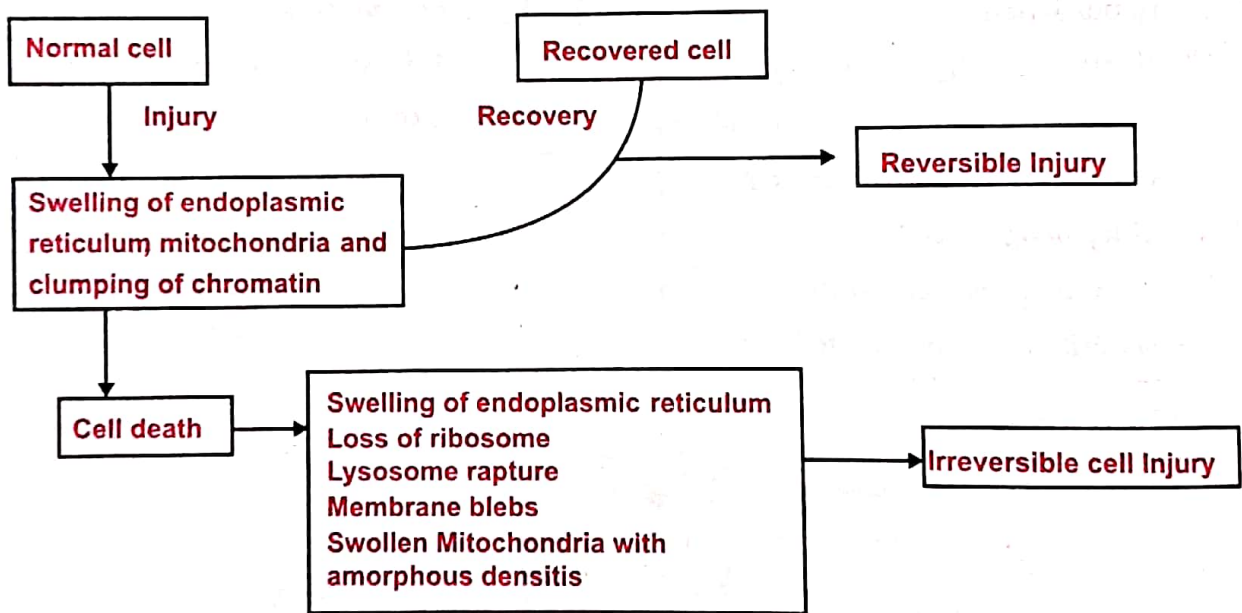
Fig. 1.1 Basic mechanism of reversible and irreversible Injury

The morphological pattern of cell death is coagulative necrosis caused by denaturation of cytoplasmic proteins and the breakdown of cell organelles. The cell death due to survival physiological and pathological processes is called *apoptosis*. The main cause is condensation and fragmentation. The mechanism by which apoptosis is induced to differ from that of necrosis.

Whether a specific stress, which induces adaptation or causes reversible or irreversible injury resulted in morphological changes, depends on many factors related to the cell only which are vulnerable, differentiation, blood supply nutrition and previous state of cell.

1.2 HOMEOSTASIS

The word *homeostasis* are derived from the Greek words *homeo*, or same, and *stasis*, or stable, and means remaining stable by remaining the same. Homeostasis is a process in which each of the body's biochemical or physiologic variables (body temperature; oxygen, sodium, calcium, glucose levels; and pH) was maintained within a narrow set point range. Negative feedback loops were used to sense and correct any deviations from the set point ranges for the variables, thereby supporting the survival of the individual, despite threats from the external or internal environments. Examples of homeostasis are:

Temperature regulation

Regulation of blood carbon dioxide level

Regulation of blood glucose level

Homeostasis typically involves negative feedback loops that counteract changes of various properties from their target values, known as **set points**. In contrast to negative feedback loops, positive feedback loops amplify their initiating stimuli, in other words, they move the system *away* from its starting state.

1.2.1 COMPONENTS AND TYPE OF FEED BACK SYSTEM

Three basic components are involved in every feedback loop:

Sensory Mechanism: The process of regulation first requires the body to be able to sense or identify the variable being controlled. If deviations from the normal set point range occur the sensor generates a signal from nerve impulse or hormone to transmit that information to the second component of the feedback loop.

Integrating or Control Center: When the control center receives input from a homeostatic sensor, that information is analyzed and integrated with input from other sensors, and then some specific action is initiated to maintain homeostasis. If significant deviation from the "set point" exists, then control center sends its own specialized signal to the third component of the control loop.

Effectors Mechanism: Effectors are organs such as muscles or glands that directly influence controlled physiological variables. The activities of effectors are ultimately regulated by feedback of information regarding their own effects on a controlled variable.

Negative Feedback Control Systems

Negative Feedback Control Systems are inhibitory. They oppose a change by creating a response that is opposite in direction to the initial disturbance. They produce an action that is opposite to the change that activated the system. Negative feedback systems are responsible for maintaining a

constant internal environment. They keep variables from straying too far outside of their normal ranges.

Positive Feedback Control Systems

Positive Feedback Control Systems are stimulatory. It does not operate to help the body maintain a stable or homeostatic condition. It is often harmful or even disastrous, to survival. Instead of opposing a change in the internal environment and causing a "return to normal", positive feedback tends to amplify or reinforce the change that is reoccurring.

Temperature control is a negative feedback mechanism. Nerve cells relay information about body temperature to the hypothalamus. The hypothalamus then signals several effectors to return the body temperature to 37 degrees Celsius (the set point). The effectors may signal the sweat glands to cool the skin and stimulate vasodilation so the body can give off more heat.

If body temperature is below the set point, muscles shiver to generate heat and the constriction of the blood vessels helps the body retain heat. The hypothalamus can change the body's temperature set point, such as raising it during a fever to help fight an infection. Both internal and external events can induce negative feedback mechanisms.
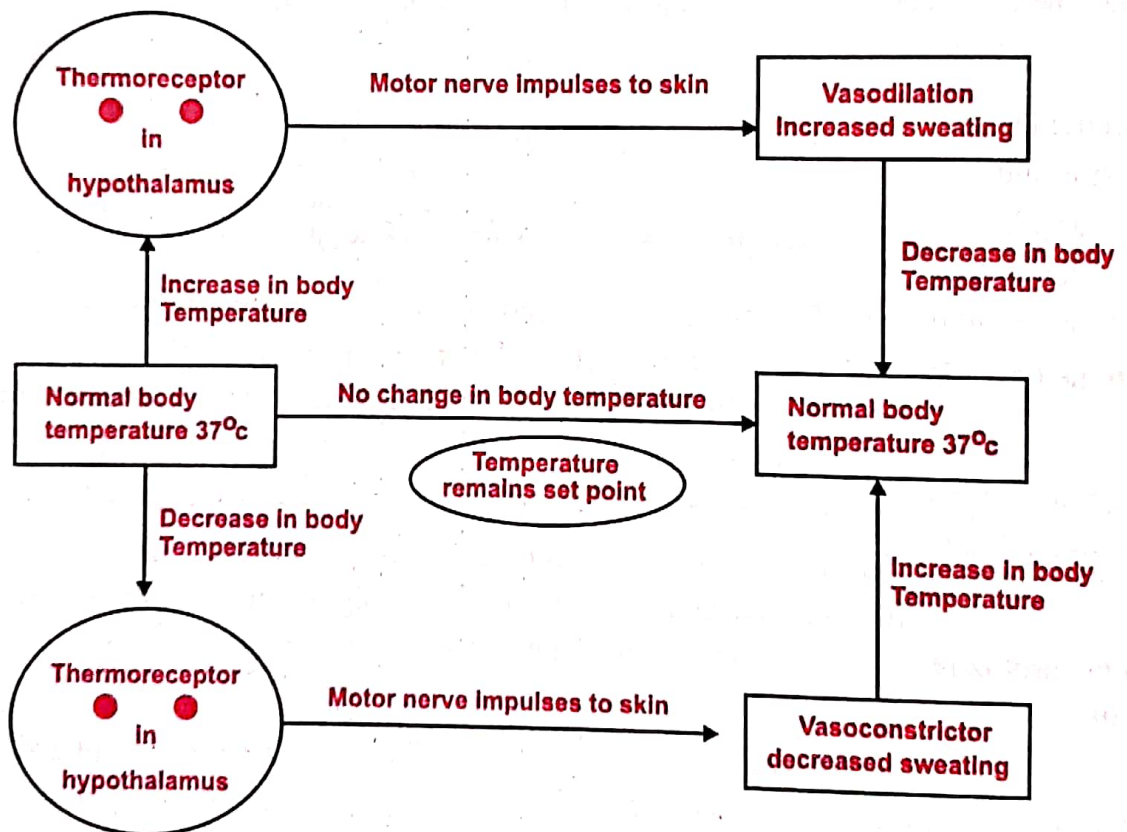
Fig. 1.2 Systematic representation of temperature regulation, negative feedback loops and positive feedback loops. If the body temperature is too high, a negative feedback loop will act to bring it back down towards the set point, or target value, of 98.6F/37 °C.

1.3 CAUSES OF CELL INJURY

Causes of cell injury are the stresses, which induce morphological changes in the cell from physical damage to gene defects, cause many metabolic diseases. The broad categories of various causes of cell injury and adaptation include: **(A)** Acquired and **(B)** Genetic causes. The acquired causes are: 1. Hypoxia and Ischemia 2. Chemical agents and drugs 3. Physical agents 4. Microbial agents 5. Immunologic agents 6. Nutritional imbalance 7. Aging. The genetic causes are defects in genes.

1.3.1 (A) Acquired causes

1. **Hypoxia and Ischemia:** Cells of different tissues essentially require oxygen to generate energy and perform metabolic function. It is due to reduced supply of blood when the arterial flow or the venous drainage is restricted by vascular disease or thrombi and inadequate oxygenation of the blood due to cardio-respiratory failure. Hypoxia is also due to loss of oxygen carrying capacity of the blood as seen in anemia or carbon monoxide poisoning where the production of a stable carbon monoxyhemoglobin block oxygen transport.

2. **Chemicals and drugs:** Chemical poisons, strong acids and alkali, environmental pollutants, insecticides and pesticides, oxygen at high concentration, hypertonic glucose and salts, alcohol and narcotic drugs and therapeutic administration of drugs are important causes of cellular adaptation, injury and death, the poisonous substances cause severe cell damage or even death to organisms. The mechanism of action is by acting on the vital function of cell such as membrane permeability, osmotic homeostasis, or in the functional capacity of the enzyme or cofactor.

3. **Physical agents:** Physical agents for cell injury are: Mechanical trauma (Road accident) Thermal trauma (Heat and cold), Electricity, Radiation and Rapid changes in atmosphere pressure all have a wide range of effects on the cell.

4. **Microbial agents:** Wide variety of microbes ranging such as bacteria, rickettsiae, viruses, fungi, protozoa, metals and other parasites affect the cell in various ways leading to cell death.

5. **Immunologic reactions:** The immune system works in the defense against biological agents, hence immune response reactions such as hypersensitivity reactions, anaphylactic reactions, autoimmune diseases may cause cell injury. Anaphylactic reactions to a foreign protein are a good example and reaction to endogenous self-antigens thought to be responsible for autoimmune diseases.

6. **Nutritional imbalance:** Nutritional deficiency causes cell death, A deficiency or an excess of nutrients may result in nutritional imbalances. Nutritional deficiency diseases may be due to overall deficiency of nutrients (starvation), protein calorie (Marasmus, Kwashiorkor), and minerals (anemia) or of trace elements. High fat diets are the cause of atherosclerosis and obesity.

7. **Aging:** the accumulation of injury caused by free radicals over the year may be responsible for cellular aging. Lipofucin a brownish-yellow granular intracellular pigments accumulates in a variety of tissues of heart, liver and brain as a function of age. The pigment represents complexes of lipids and protein that are derived from the oxidation of polyunsaturated lipids of subcellular membrane.

1.3.2 (B) Genetic causes

1. **Developmental defect:** (Errors in morphogenesis) Developmental defects are group of abnormalities during fatal life due to errors in morphogenesis.

2. **Cytogenic defects:** The chromosomal abnormalities are concerned abnormalities of chromosomes, it may be numerical or structural. The abnormalities occur due to increase or decrease in the numbers of the total chromosomes known as numerical abnormality. The abnormalities that occur due to changes in appearance of chromosomes is called structural abnormalities.

3. **Single-gene defects (Mendelian syndrome):** The defect follows classic mendelian patterns of inheritance and are called as Mendelian syndrome or disorder. It is due to mutation of a single gene.

4. **Disorders with multifactorial inheritation:** are the concern of multiple genes in combination with lifestyle and environmental factors. Conditions caused by many contributing factors are called complex or multifactorial disorders e.g. heart disease, diabetes, and obesity.

1.4 MECHANISM OF CELL INJURY (Pathogenesis)

Injury to cell may have many causes. The macromolecules, enzymes and organelles within the cell are so closely interdependent, hence it may not be possible to differentiate the primary target of Injury. With injurious agents the mechanism and location of cell injury are well defined. In such case oxygen plays a central role in the cell Injury. Lack of oxygen, which causes ischemia, is the cause of pathogenesis of cell injury. In partially reduced activated oxygen species such as Clostridium perfringens (anaerobic bacterial) have elaborate phospholipids, which attack phospholipids in cell membranes. These are called free radical species cause lipid oxidation and other deleterious effects on cell structure.
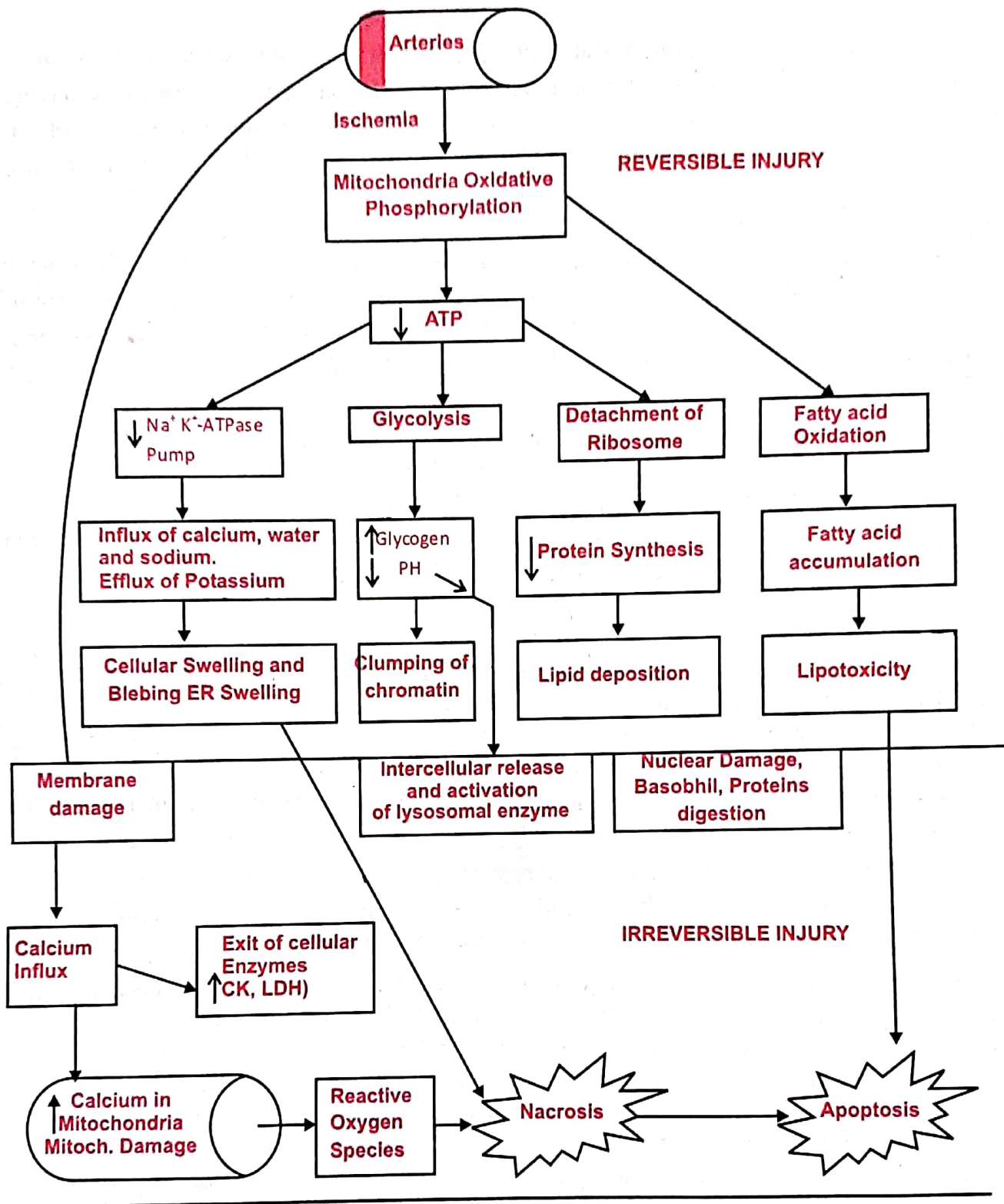
Fig. 1.3 A detail diagram reversible and irreversible ischemic cell injury. The ATP levels have a key role, ischemia can cause direct membrane damage, mitochondrial damage, ribosome damage and nuclear damage

1.4.1 ISCHEMIC AND HYPOXIC INJURY

Cellular Injury: The term, ischemia, has been used to denote deficient blood supply to tissues due to obstruction of the arterial inflow. The disorders characterized by ischemia such as myocardial infarction, stroke, and peripheral vascular disease, continue to be among the most frequent causes of cell Injury or cell damage.

Cell damage: The effect of hypoxia is in the aerobic respiration cells involving the oxidation phosphorylation reactions in mitochondria. The generation of adenosine triphosphate (ATP) slows down or stops which may effect on many systems which causes failure of the active membrane sodium pump, this effects the accumulation of sodium intracellular and fusion of potassium out from the cell. Thus, it produces acute cellular swelling due to iso-osmotic gain of water. This stage is **reversible** if oxygen is restored.

If ischemia persists, the irreversible injury may be the result. It is associated with severe vacuolization of the mitochondria which includes cristate, extensive damage to plasma member, swelling of lysosome, and particularly massive calcium influx into cell, the cell leads to calcium deposits in mitochondrial matrix and efflux the cellular enzyme creatine kinases (CK) and lactate dehydrogenase; There is continued loss of proteins, essential coenzyme and ribonucleic acid from the hypermeable membranes. The cell reaches at stage to necrosis or cell death. This stage is called Irreversible Injury.

Nuclear damage: The decrease in cellular ATP and Increase in adenosine monophosphate (AMP) also stimulates the enzyme Phosphofructotokinase glycolysis in order to maintain the cells energy source by generating the ATP from glycogen. The glycogen gets rapidly depleted and hence causes histological changes. Glycolysis results in the accumulation of the lactic acid and inorganic phosphate from the hydrolysis of phosphate ester, it reduces the intercellular Ph and glycogen which results in clumping the chromatin. This stage is **reversible** if oxygen is restored.

If ischemia persists, the cell reaches at the next stage **irreversible injury.** The fall of PH leads to injury to the lysosomal membranes followed by leakage of their enzymes in to cytoplasm, activation of acid hydrolases and enzymatic digestion of cytoplasmic and nuclear components

Ribosome damage: This process also involves oxidative phosphorylation, decrease the ATP, the result detachment of ribosomes from the granular endoplasmic reticulum and dissociation of polysomes into monosomes decreased proteins synthesis , lipids deposition and lipotoxicity. This stage cell may recover the injury and is called reversible injury If hypoxia continues, it will lead to increased membrane permeability and diminished mitochondrial functions. This mitochondria will appear normal, slightly swollen or condensed, the endoplasmic reticulum is dilated and entire cell is markedly swollen, a stage arises called apoptosis Irreversible injury.

Mitochondrial Damage: Cell injury or damage occurs as a result of the initial ischemia. ATP levels and intracellular pH decreases as a result of anaerobic metabolism and lactate accumulation. As a consequence, ATPase-dependent ion transport mechanisms become dysfunctional, this stage is called **reversible Injury** if oxygen restored. If hypoxia continues which leads to contributing an increased intracellular and mitochondrial calcium levels (calcium overload), cell keeps swelling and rupture, and thus, there is cell death by necrotic, necroptotic, apoptotic, and autophagic mechanisms

1.4.2 FREE RADICAL MEDIATION OF CELL INJURY

Chemical species with unpaired or an odd number of electrons are called free radicals. In biological systems, the term free radicals mostly refer to reactive oxygen species (ROS) and are oxygen centered. Major ROS includes superoxide anion (O_2) hydrogen peroxide (H_2O_2), and hydroxyl radical (OH). Besides ROS, reactive nitrogen species (RNS), including nitric oxide (NO), peroxynitrite (NO_3), S-nitrosothiols also contribute to the generation of free radicals.

The radical are extremely unstable and react with inorganic membranes and nucleic acids in the cell. Free radical also initiates autocatalytic reactions where by the molecules with which they react are converted into free radical to start the chain of damage.

The radical are imitated within the cells due to absorption of radiant energy.e. Ultraviolet light X-rays or in the reduction reaction that occurs during normal physiology processes or may be derived from enzymatic metabolism of exogenous chemicals.
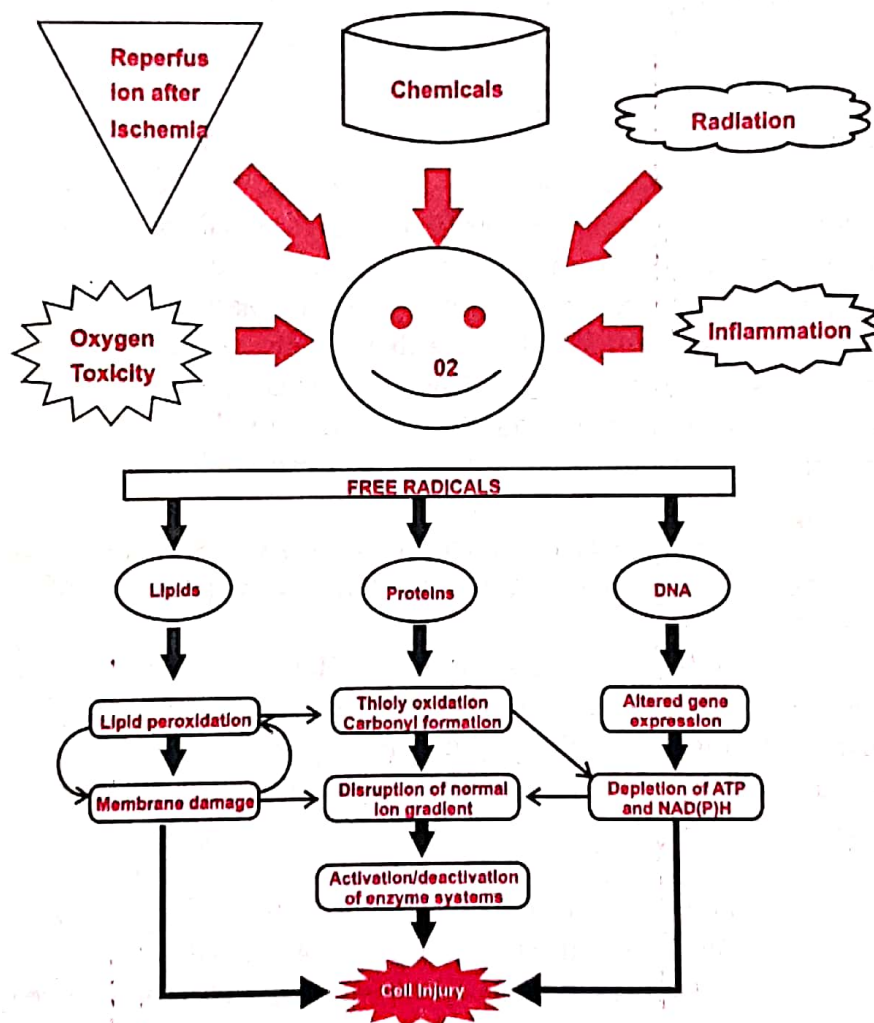

Fig. 1.4 Schematic representation of formation the free radicals and action of free radicals on lipids, proteins and DNA. Free radicals acts in a nonspecific manner with proteins membrane lipids and nucleic acids which cause cell injury by various mechanisms.

1.5. MORPHOLOGY OF CELL INJURY

The cell is a highly-structured complex of molecules and organelles that are arranged to fulfil routine metabolic housekeeping functions and the specialised functions that make one cell different from another. In order to carry out these functions the cell has energy needs and some transport mechanisms to facilitate the import of metabolites and the export of waste products. Injury to a cell results in relative disruption to one or more of these structures or functions. Certain injurious agents (radiation, certain chemicals, viruses, and some bacterial and fungal toxins) these stimuli which bring changes in cellular morphology can be divided into three patterns:

1. Pattern of active cell injury i.e. reversible and irreversible leading to necrosis or apoptosis.
2. Sub cellular alteration that occurs mainly as response to more chronic or persistent injurious stimuli.
3. Intercellular accumulation of a number of substance i.e. lipids, carbohydrates, proteins which is a result of derangements in cell metabolism or excessive storage.
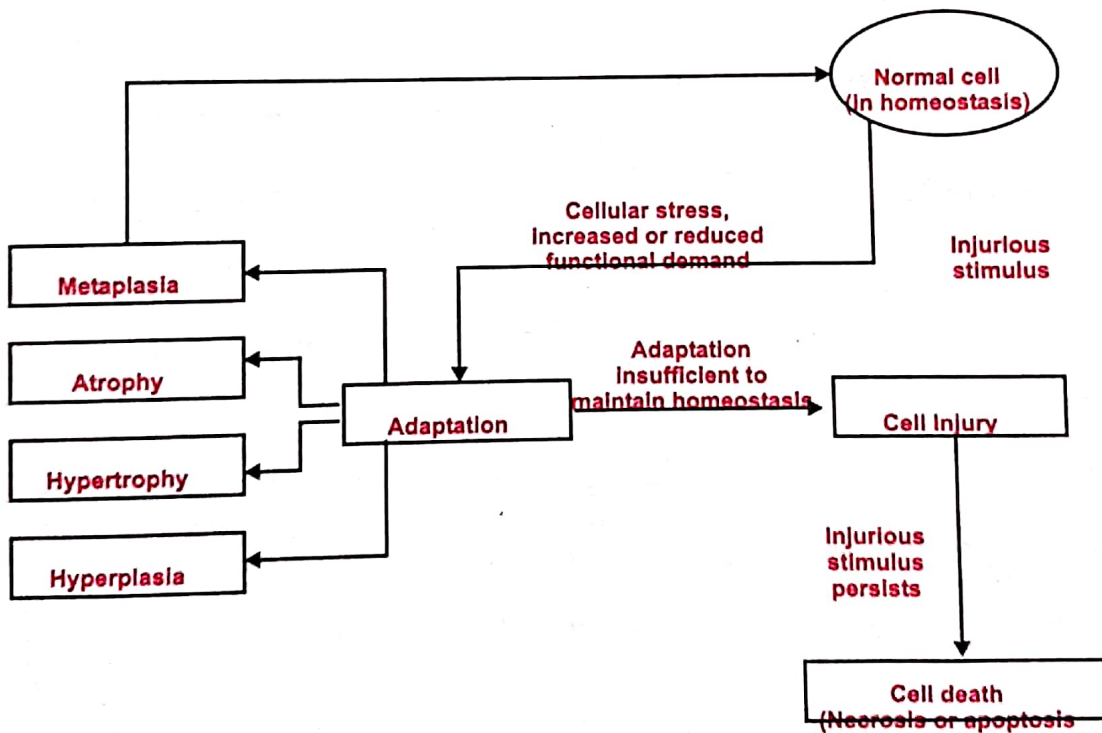
Fig. 1.5 Morphological of cell injury *cell injury.* The end result may be total recovery, permanent impairment and death.

1.6 CELLULAR ADAPTIVE CHANGES

Cell must undergo adaptation even under normal conditions to overcome changes in its environment. These physiological adaptations are due to the response to normal stimulation by hormones or endogenous chemical substances, for example enlargement of breast and induction of lactation in pregnancy. The pathological adaptations may undergo the same mechanism but provide the cell with ability to adapt to their environment in order to escape the injury.

Thus the cellular adaptations are the state, which is intermediate between normal or unstressed injured cells.

The cell adaptations are many, some involve up or down regulations on specific cellular receptor which involves in the metabolism of certain components. (1) For example regulation of cell surface receptors involved in uptake and degradation of low density lipo-proteins (LDL) (2) the other are induction of new proteins synthesis by target cells such as heart stock or stress shock proteins which protects cells from some form of injury

The other adaptation involves the cell from producing one type of proteins to another or overproduction of one proteins of one protein. In such case where the cell is produced, various types of collagens and extracellular matrix,the proteins can be seen in chronic inflammation and fibrosis.

The common adaptive responses are atrophy (decreased cell size), hypertrophy (increased cell size), hyperplasia (increased cell number), metaplasia (conversion of one cell type to another), and dysplasia (disorderly growth). Each of these changes is potentially reversible when the cellular stress is relieved..

1.6.1 ATROPHY

Atrophy is a decrease or becoming smaller in cell size, loss of cell substance is named atrophy. If atrophy takes place in an enough number of an organ's cells, the complete organ gets smaller or

becomes atrophic. Atrophy can affect any organ, but it is most commonly found in the heart, skeletal muscle, the brain, and secondary sex organs. Atrophy can be classified as *physiologic* or *pathologic*.

Atrophy
(decreased cell size)

Normal
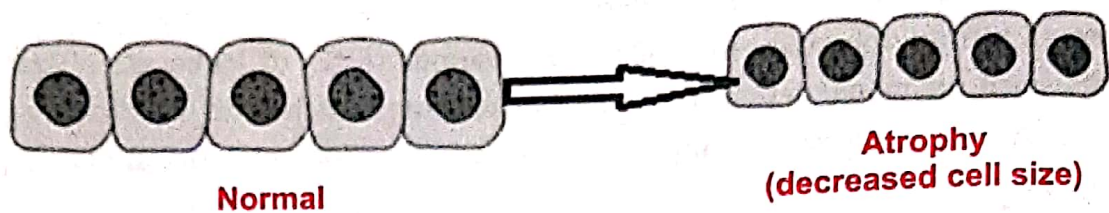
Fig 1.9. The adaptive cellular response of atrophy

Physiologic atrophy takes place with early development. For example, the thymus gland undergoes physiologic atrophy during childhood. Pathologic atrophy takes place as an outcome of decrease in blood supply, nutrition, hormonal stimulation, workload and pressure. The effect of beings made without motion in bed for a going on for a long time exhibit a type of skeletal muscle atrophy called disuse atrophy. Atrophy getting old ages the brain cells to become atrophic and endocrine-dependent organs, such as the gonads, to get smaller as hormonal stimulation decreases. If atrophy is caused by normal physiologic conditions or by pathologic conditions, atrophic cells exhibit the same basic changes.

Some of these stimuli are physiological whereas others are pathogenic. The cellular changes are identical in both cases and the cell shrinks to a small size. Wherever the survival is possible, it affects mitochondria and myofilaments and less on edoplasmic reticulam. The mechanisms probably include decreased protein synthesis, increased protein catabolism, or both. *Up-regulation of proteasom*e which cause atrophy.

Hormones such as insulin, thyroid glucocorticoids and prostaglandin influence such as protein synthesis. For example a slight increase in protein degradation over a long period result in atrophy as it occurs in muscular dystrophies.

In some cases atrophy as a result of chronic malnutrition is often accompanied by a "self-eating" process called *autophagy* inducing **autophagic vacuoles.** Some of the cell debris within autophagic vacuoles resists digestion and remains as membrane bound residual bodies, which remains in cytoplasm as sarcophagi. Examples of such residual bodies are present in sufficient number, which imparts a brown discolors to the tissue (Brown atrophy).

1.6.2 HYPERTROPHY

Hypertrophy is an increase in the size of cells, which leads to increase in organ size. Hypertrophy is due to increased functional demand or by specific hormonal stimulation, which may occur during physiological and pathogenic conditions.

Normal → **Hypertrophy (Increased cell size)**
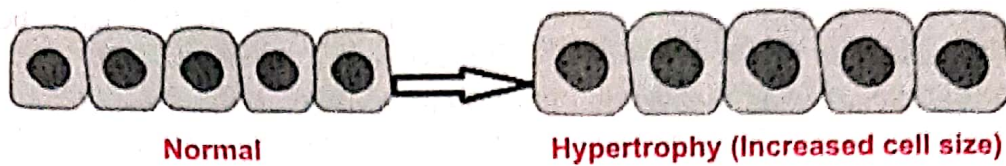
Fig. 1.10 The adaptive cellular response of hypertrophy

For example in the physiological growth of uterus during pregnancy, which involves both hypertrophy and hyperplasia. The cellular hypertrophy is stimulated by estrogen receptor, which allows its interaction with nucleus DNA resulting in increased synthesis of smooth muscle proteins and increase in cell size of the uterus. Thus this physiological hypertrophy is due to hormonal stimulations.

Hypertrophy is an adaption response which is also due to enlargement of muscles. The cells of the heart and kidneys are particularly responsive to enlarge. The striated muscle cells of both the heart and skeletal muscles are capable of hypertrophy. Physiologic hypertrophy in skeletal muscle occurs in response to heavy work. Enlargement of the heart is caused by dilation of the cardiac chambers, is short-lived, and is followed by increased synthesis of cardiac muscle proteins, allowing muscle fibers to do more work. The nucleus also is hypertrophic and exhibits increased synthesis of deoxyribonucleic acid (DNA). The increase in cell size is associated with an increased accumulation of protein in the cellular components (plasma membrane, endoplasmic reticulum, myofilaments, mitochondria) and does not allow an increase in the amount of cellular fluid. With time passing by cardiac hypertrophy is characterized by extracellular matrix remodeling and increased growth of adult myocytes. The myocytes progressively increase in size and reach a limit beyond which no further hypertrophy can occur.

The more the number of myofilament undergoes an increased workload with an increase in level of metabolic activity per unit of volume of the cell does not differ in comparison to normal cell.

Proteins synthesis in heart is by two mechanisms of hypertrophys:

1. The mechanical stretch through stretch receptor which triggers RNA synthesis leads to proteins production.

2. Activation of alpha-adrenergic receptor on the surface of myocytes alter gene expression for certain contractile protein.

Whatever may be the mechanism of hypertrophy, the hypertrophy may reach to a limit beyond which enlargement by muscle mass is no longer compensated for increased burden and results in cardiac failure. At this stage number of degenerative changes occurs in myocardial fibers, which gets lysed resulting in loss of myofibrillar contractile elements.

The limiting factors for continuous hypertrophy and the cause of regressive changes are due to diminish oxidative capabilities of mitochondrion or to alteration in proteins synthesis and degradation.

1.6.3 HYPERPLASIA

Hyperplasia is an increase in the number of cells resulting from an increased rate of cellular division. The cell growth is increased due to multistep process involving the production of growth factors, which stimulate the remaining cells to synthesize new cell components and, ultimately, to divide. Hyperplasia and hypertrophy are closely related and often develop simultaneously in tissue. Both hyperplasia and hypertrophy take place if the cells are capable of synthesizing DNA.

Normal   Hyperplasia (Increased cell number)
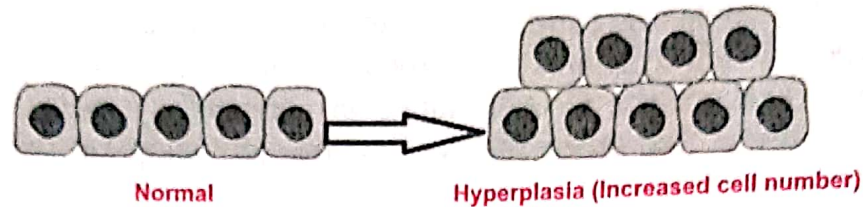
Fig. 1.11 The adaptive cellular responses of hyperplasia

Cardiac and skeletal muscle cells have no capacity for hyperplastic growth and thus usually undergo only hypertrophy.

Hyperplasia can be physiologic or pathological: Physiology hyperplasia is divided into

(1) Hormonal hyperplasia seen in proliferation of the epithelium of the female breast at puberty and during pregnancy

(2) Compensatory hyperplasia i.e. hyperplasia occurs·

Compensatory hyperplasia is an adaptive mechanism that enables certain organs to regenerate. For example when a portion of tissue is removed, mitotic activity in the remaining liver cells begins as early 12 hours after hypertrophy resulting the liver to attain its normal weight and after that the mitoses ceases. The stimuli for cell proliferation are polypeptide growth factors and hormones, which are produced by remaining hepatic cell. The various specific factors that appear to be involved in liver regenerating are transforming growth factor **hepatocyte growth factor (HGF),** is a mediator in vitro of liver regeneration. In addition, other in vitro growth factors and cytokines (cell-signaling proteins) that increase hepatic cell regeneration includes transforming growth factor-alpha (TGF-α), epidermal growth factor (EGF), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).

Hormonal hyperplasia most from of pathological hyperplasia is due to excessive hormonal stimulation and its effect on growth factor on targeted cells. A type of hormonal induced abnormal hyperplasia develops some time in endometrium. After a normal menstrual period there is a rapid burst of increased activities in endometrium, which is potentiated by pituitary hormones and ovarian estrogens and progesterone. If the normal level of estrogen and progesterone is disturbed and there is an increase in estrogen level which will result in hyperplasia.

Hyperplasia is also an important response of increase of connective tissue cell in wound healing in which proliferating fibroblast and blood vessels are stimulated by growth factor, which aids in repair.

Hypertrophy and hyperplasia are two distinct processes. They occur together and may be triggered by the same mechanism. Estrogen induced growth in uterus causing increase DNA

synthesis and enlargement of smooth muscle and epithelium. Both processes are imitated by binding of estrogen to a receptor complex in the cytoplasm of target cells.

In some instances the dividing cell such as renal epithelial cells undergo hypertrophy but not hyperplasia. Growth inhibitors such as TTGF-a may be involved. The cells which are not undergoing division causes hypertrophy only. Nuclei in such cells have much higher DNA content then normal myocardial cells, because there is a cell arrest in the G2 phase of the cell cycle without undergoing mitosis.

1.6.4 METAPLASIA

Metaplasia is the reversible replacement of one adult cell by another, sometimes less differentiated, cell type. Metaplasia is best seen in the form of squamous change that occurs in respiratory tract in the habitual cigarette smoke. The normal columnar ciliated epithelial cells of trachea and bronchi are replaced mainly by striated squamous epithelial cells.

Normal

Metaplasia
(Conversion of one cell
type to another)
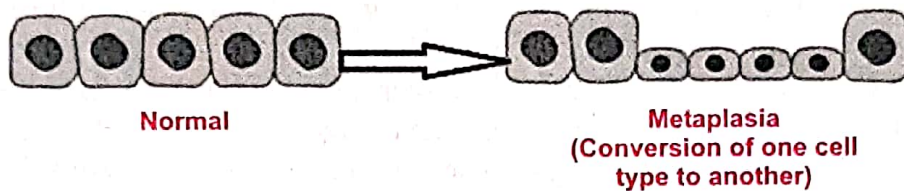
1.12 The adaptive cellular response of metaplasia

Stone in the excretory ducts of the salivary gland, pancreas or bile ducts may cause replacement of The normal secretary columnar epithelium. A deficiency of vitamin A induced aquamous metaplasia in the respiratory epithelium. In all the instance the rugged stratified squamous epithelium will able to survive under these circumstances where as more fragile specialized epithelium may extinct. Metaplasia may also occurs in mesenchymal cells but may not occurs be a adaptive response. The fibroblasts may become transformed to osteoblasts or chondroblasts to produce bone or cartilage which is not seen in normal cases. For example bone is occasionally formed from soft tissue particularly in foci of injury and this process represents a form divergent differentiation.

1.6.5 DYSPLASIA

Dysplasia occurs when abnormal changes in the size, shape, and organization of adult cells which is related to hyperplasia and is often called atypical hyperplasia.
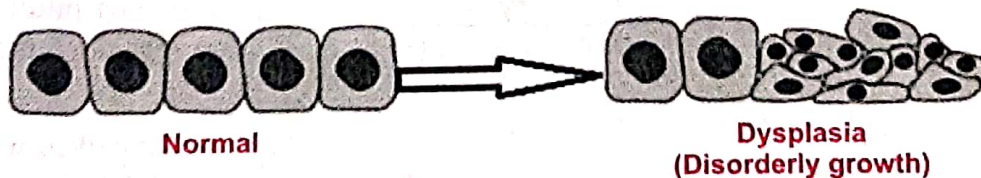

Normal

Dysplasia
(Disorderly growth)

Fig. 1.13 The adaptive cellular response of dysplasia

It is not consider a true adaptive process however; frequently changes are encountered in epithelial tissue of the cervix and respiratory tract. These changes are strongly associated with common neoplastic growths and often are found adjacent to cancerous cells. Dysplasia is often categories as mild, moderate, or severe; and also recommendations to use either "low grade" or "high grade.

1.7 CELLULAR SWELLING

Cellular swelling applicable to accumulation of water, or hydropic swelling, is the first manifestation of most forms of reversible cell injury. Hydropic swelling results from abnormal function of the sodium-potassium (Na^+-K^+) pumps that normally maintain ionic equilibrium of the cell. In this stage cell membrane is swell and the channels become closed, the Na^+-K^+ pump unable to exchange the ions results in accumulation of sodium ions within the cell, creating an osmotic gradient for water entry. Because Na^+-K^+ pump function is dependent on the presence of cellular ATP, any injury that results in insufficient energy production also will result in hydropic swelling. Hydropic swelling is characterized by a large, pale cytoplasm, dilated endoplasmic reticulum, and swollen mitochondria. With severe hydropic swelling, the endoplasmic reticulum may rupture and form large water-filled vacuoles. Generalized swelling in the cells of a particular organ will increase in size and weight of organ. The swelling of cell is reversible
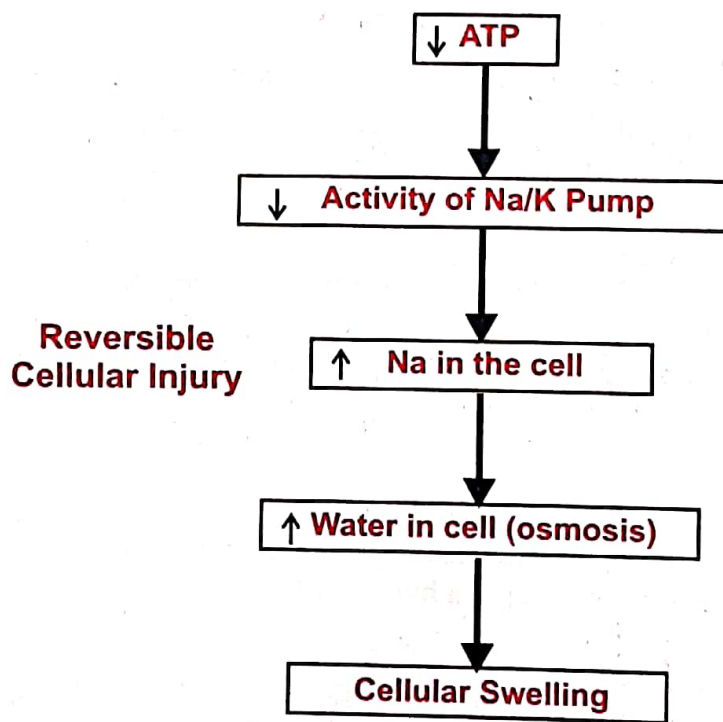

Fig 1.14 Mechanism of cellular swelling.

The ultrastructural changes of reversible cell injury include: (1). Plasma membrane alterations, blabbing, blunting, distortion of microvilli (2). Loosening of intercellular attachments (3). Creation of myelin figures (4). Mitochondrial changes, mitochondrial swelling, mitochondrial rarefaction, the appearance of small Phospholipid-rich amorphous densities (5) Deletion of the

endoplasmic reticulum: detachment, disaggregation of polysomes nuclear alterations, disaggregation of granular and fibrillar elements. If these changes arises in the cell, the cell undergos swelling.

1.8 INTRACELLULAR ACCUMULATIONS

The normal cells accumulate abnormal amount of substance either for temporary or permanently which may be harmful to the cell and may cause injury. These accumulations are either in cytoplasm or it is more frequently within lysosomes. The process of intracellular accumulation can be divided into three general types

1. Due to the production of normal endogenous substances at normal or increased rate but their metabolism is not adequate at the rate; the best example is fatty changes in liver.

2. The accumulation of endogenous substances because they are not metabolized due to lack of enzymes that block the specific metallic pathway. If the enzyme deficiency in genetically inborn the error in metabolism leads to storage diseases.

3. Abnormal exogenous substances is deposited and accumulation due to lack of enzymatic machinery to degrade the substances or the ability to transport to the other sites. Accumulation of carbon particles and non metabolized chemicals like silca particles are an example to be quoted here.

Lipids (a) Fatty change: The fatty changes means the abnormal accumulation of fats within parenchyma cells,which appear as fats vacuoles within cell, resulted in increase in interacellular lipids, which causes non lethal injury. Fatty changes are seen in liver which is the organ involved in fat metabolism. This may also occur in heart, kidney and other organs. The mechanism of fatty changes can be seen in alchol users because Fatty change is most often seen in liver and heart but it may occur in other organs also. The mechanism of fatty changes can be seen in alcohol users because alcohol is hepatotoxic which alters mitochondrion and microsomal functions. Increased free fatty synthesis diminished triglyceride utilization, decreases fatty acid oxidation , block lipoproteins excreation and enhances the peripheral lipolysis, which causes increased delivered and enhanced uptake of free fatty acid in alcohol induced fatty liver. Other causes of fatty liver includes proteins malnutrition, diabetic mellitus, obesity and hepatotoxins. The significance of fatty changes depends on cause and severity of accumulation. If it is mild it has no effect on cellular function, but in severe cases it may impair cellular function. If some vital interacellular changes occur it is irreversible but otherwise it is reversible (as in tetra choloride posinoing) where death of cell occurs without undergoing dry fatty changes.

Fatty change is most often seen in the liver and heart but it may occur in other organs also

Liver: Fatty liver changes may not affect the gross appearance of the cell due to accumulation of small fat vacuoles in the cytoplasm and around the nucleus. With the proceeding accumulation progresses these vacuoles create clear space that display the nucleus to the periphery of the cell consuming cell rupture and enclosed fat globules produced fatty acid cysts.

Heart: lipids are sometimes found in heart muscles in the form of small droplets. Prolonged moderate hypoxia due to anemia causes intercellular deposits of fat, which creates bands of yellow myocardium with alternating darker red brown bands.

Process of intracellular accumulation: There are four steps involved in the process of intracellular

(1) Abnormal metabolism as in a fatty change in the liver,

(2) Mutations causing alterations in protein folding and transport so that defective proteins accumulate,

(3) Deficiency of critical enzyme responsible for lysosomal degradation,

(4) An inability to degrade phagocytosed particles such as coal dust.
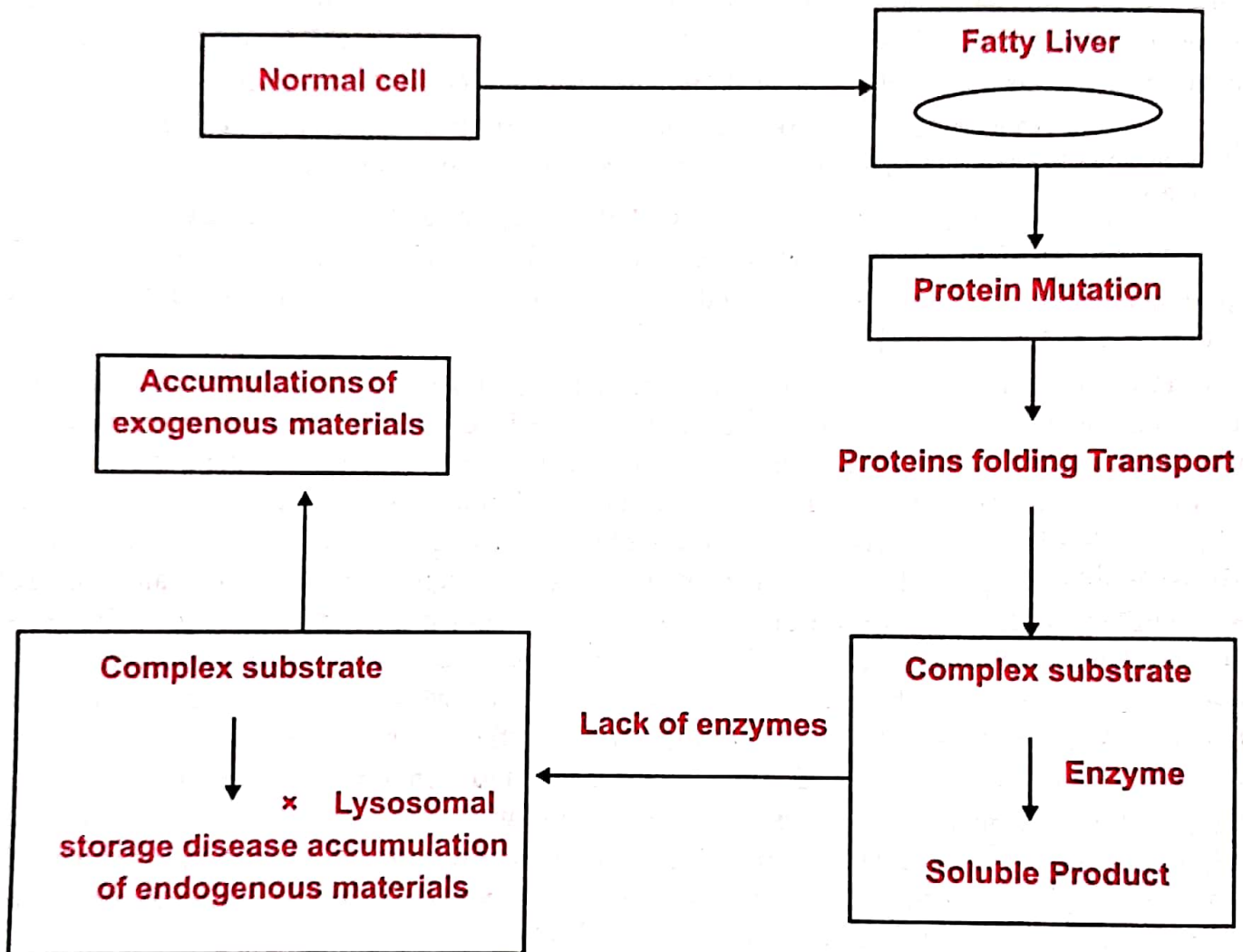
Fig. 1.15 Mechanisms of intracellular accumulation

(b) Cholesterol and cholesterol ester: The fatty change is due to overloading of parenchymal cell with triglyceride by different mechanism. The phagocyte cell becomes overloaded with lipids (triglyceride, cholesterol and cholesterol ester) macrophages gets loaded with lipids due to there phagocytosis activity and when they come in contact with lipid debris of necrotic cells or abnormal plasma lipids they get filled with minute's vacuoles of lipid forming foaminess to the cytoplasm (Foam cell), which may cause atherosclerosis

Proteins: Accumulation of proteins is due to either excess availability to the cell or excess synthesizes in the cell. Tracer of albumin are filtered through the glomerulus, are reabsorbed in the proximal convoluted tubules. Any disorder which produces heavy protein urea leads to the pinocytotic reabsorption of proteins. When these pinocytotic vesicle in the epithelial cell fuse with lysosomes, hyaline cytoplasmic droplets are formed. If the proteins urea is repaired the proteins droplet are metabolized and disappear.

Glycogen: excessive intracellular deposits of glycogen are seen in patients with abnormalities in either glucose or glycogen metabolism or these glycogen masses appear as vacuoles in the cells. Diabetic mellitus is the disorder of glucose metabolism. In diabetes mellitus glycogen is found in renal tubules epithelial as well as in liver cells of beta cell of langerhans and heart cells. Due to genetic disorder produced by the accumulation of glycogen referred as glycogen storage disease or glycogenesis.

In such cases normal or abnormal glycogen cannot be metabolized which lead to secondary injury and cell death.

4. Complex Lipids and Carbohydrates: In some form of storage diseases which is due to the error in metabolism in newborn, causes abnormal accumulation of complex carbohydrates and lipids which are not metabolized. These substances will get collected within the cells through out the body particularly in reticuloendothelial system causes hepatomegaly, charidoses, gaucher's disease, try-sachs and neimann-pick disease in which abnormal products are complex lipids complex which causes death to the cell and to the patients.

5. Pigments: pigments can either be exogenous coming from outside the body or endogenous synthesized within body. The most common exogenous pigments are carbon or coal dust when inhaled it is picked up by alveolar macrophages and transported through lymphatic channels to the regional tracheobronchial lymph nodes. Aggregation of coal dusts leads to fibroblastic reaction or even emphysema causes serious lungs diseases known as coal worker pneumoconiosis.

Endogenous pigments: include lipofucin, melanin and certain derivative of hemoglobin. Lipofucin is seen in cells undergoing slow regressive changes and is prominent in the liver and heart. The melanin brown black pigment formed when the enzyme tyrosine catalyzes the oxidation of tyrosine to dihydroxyphenylalanine in melanocytes. The hemosiderin is hemoglobin-derived golden yellow to brown granular or crystalline pigment in which iron is stored in the cell. Iron is normally stored in association with protein, apoferritin micelles. Under normal conditions small amount of hemosiderin can be seen in the mononuclear phagocytes of the bone marrow, spleen and liver which are actively engaged in the breakdown of red blood cells. Excess of iron causes of hemosiderin accumulate within the cell either a localized process or as systemic derangement. When there are causes for systemic accumulation of iron deposition in many organs and tissues, a condition called hemosiderosis occurs. It is seen with (1) Increased absorption of dietary iron (2) Impaired utilization of iron (3) hemolytic anemia and (4) Transfusions, as the transfused red cells constitute as exogenous load of iron. In most instances of hemosiderosis the pigment does not damage the parenchymal cells or impaired organ function. When there is excess

accumulation of iron in hemochromatosis diseases due to liver and pancreas damage will result in liver fibrosis and diabetic mellitus.

1.9 CALCIFICATION

The calcification occurs in two main pathological situations as well as physiologically in developing or healing bone. Pathological Calcification is a common process in which is a wide range of disorders. It occurs in normal tissues in the presence of high circulating levels of calcium ions (metastatic calcification) and in pathological tissue in the presence of normal serum levels of calcium (dystrophic calcification). Most calcium deposits are calcium phosphate in the form of hydroxyapatite and contain small amounts of iron and magnesium and other mineral salts.

Dystrophic Calcification: It occurs in two stages: initiation and propagation, leading ultimately to the formation of crystalline calcium phasphate. Intracellular calcification begins in mitochondria, it is earliest indicator of cell death, the influx of calcium into mitochondria. Extracellular initiation of calcification begins in small, membrane-bound matrix vesicles by its affinity for acidic phosphate lipids, which seem to be derived from damaged or ageing cell membranes. They accumulate calcium and also appear to have phosphatases in them, which release phosphate, which binds the free calcium. Propagation is by subsequent crystal deposition which may be affected by a lowering of calcification inhibitors and the presence of free collagen. Collegen enhances the rate of crystal growth, and other proteins such as osteopontin appear to be involved involved.

Metastatic Calcification: Metastatic calcification or calcinosis is caused by the deposition of calcium salts in the lung tissue due to a systemic increase in serum calcium levels. The cause of hypercalsimeia include primary endocrine disorder, it has been seen in association with hyperparathyroidism and paraneoplastic syndromes. The effect of tumors, such as in increased bone catabolism associated with multiple myloma, metastatic cancer, and leukemia; ingested exogenous substances, resulting vitamin D intoxication. It may also be seen in sarcoidosis, systemic sclerosis, hypervitaminosis D, and cancers with extensive bone disease. Metastatic calcification is distinguished from the much more commonly occurring dystrophic calcification. Dystrophic calcifications are typically found in scarred or necrotic tissue caused by previous infections or injuries.

1.10 ENZYME LEAKAGE AND CELL DEATH

Intracellular degradation and subsequent recycling of cellular constituents, the lysosomes receive both hetero- and autophagic cargo, which in the degradative lumen of this organelle find their final destination. The degradation is carried out by a number of acid hydrolases (phosphatases, nucleases, glycosidases, proteases, peptidases, sulfatases and lipases, etc) capable of digesting all major cellular macromolecules. Lysosomal hydrolases are the cathepsin proteases which can be divided into three sub-groups according to their active site amino acid, i.e. cysteine (B, C, H, F, K, L, O, S, V, W and X/Z), aspartate (D and E) and serine (G) cathepsins. The function of

lysosomes and their cathepsins was thought to be limited to intralysosomal protein-turnover, and the degradation of the extracellular matrix once secreted. Cathepsins plays a vital role in bone remodeling, antigen presentation, epidermal homeostasis, prohormone processing, which maintenance the central nervous system, angiogenesis, cell death and cancer cell invasion. Regulation of overall cell number as well as the amount of cells constituting the different tissues along with the need for a mechanism of eliminating unwanted cells is of fundamental importance in multicellular organisms. Apoptosis is the primary means to this end, endowing the multicellular organism with the potential to rid itself of unwanted cells without the leakage of cellular constituents, thus avoiding the inflammation associated with necrosis, the conceptual counterpart to programmed cell death. For example Biphosphinic Palladacycle Complex BPC-induced
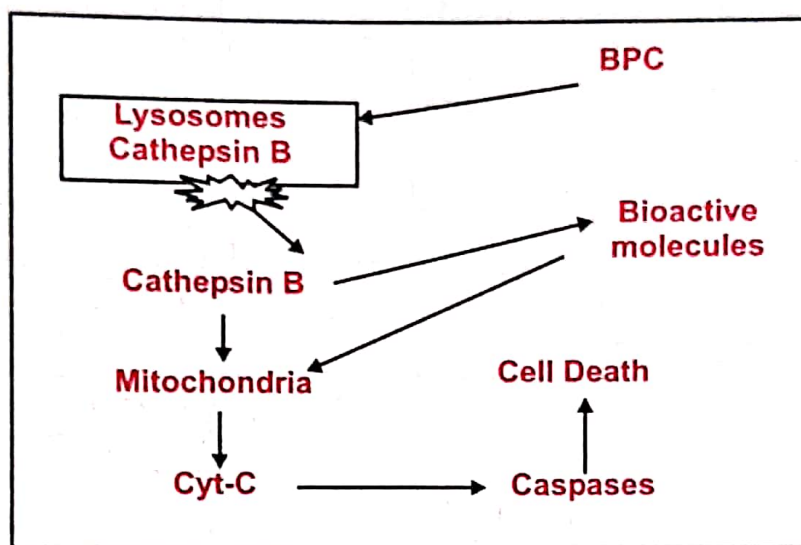
Fig.1.16 Enzyme leakage and cell death

apoptosis in leukemia cells. BPC may directly target lysosomes and induce lysosomes leakage or partial rupture leading to the release of cathepsin B from lysosomes to the cytosol. Cathepsin B may convert certain unknown substances to bioactive molecules, which may attack other cellular organelles (e.g. mitochondria, nucleus). Moreover, cathepsin B may directly attack the organelles. As a result of the attack of cathepsin B and/or other bioactive molecules, mitochondria may undergo apoptotic alteration. Thus, apoptotic factors, such as cytochrome-C and caspases, are released or activated and execute apoptosis.

1.11 ACIDOSIS AND ALKALOSIS

The normal pH value for the body fluids is between pH 7.35 and 7.45. When the pH value of body fluids is below 7.35, the condition is called acidosis, and when the pH is above 7.45, it is called alkalosis

Respiratory acidosis: Inadequate ventilation of the lungs causes respiratory acidosis. The rate of carbon dioxide is eliminated less from the body fluids due to abnormality of the lungs. This increases the concentration of carbon dioxide in the body fluids. If carbon dioxide levels increase, the excess carbon dioxide reacts with water to form carbonic acid. The carbonic acid dissociates to form hydrogen ions and bicarbonate ions. The increase in hydrogen ion

concentration causes the pH of the body fluids to decrease. If the pH of the body fluids falls below 7.35, symptoms of respiratory acidosis become apparent. Buffers help resist a decrease in pH, and the kidneys help compensate for failure of the lungs to prevent respiratory acidosis by increasing the rate at which they secrete hydrogen ions into the filtrate and reabsorb bicarbonate ions.

Respiratory alkalosis results from hyperventilation of the lungs. This increases the rate at which carbon dioxide is eliminated from the body fluids and results in a decrease in the concentration of carbon dioxide in the body fluids. As carbon dioxide levels decrease, hydrogen ions react with bicarbonate ions to form carbonic acid. The carbonic acid dissociates to form water and carbon dioxide. The resulting decrease in the concentration of hydrogen ions causes the pH of the body fluids to increase. If the pH of body fluids increases above 7.35, symptoms of respiratory alkalosis become apparent. The kidneys help to compensate for respiratory alkalosis by decreasing the rate of hydrogen ions secretion into the urine and the rate of bicarbonate ion reabsorption. If an increase in pH occurs, a time period of 1 or 2 days is required for the kidneys to be maximally effective. Thus the kidneys are not effective if respiratory alkalosis develops quickly. However, they are very effective if respiratory alkalosis develops slowly.

Metabolic acidosis: It is a condition that decrease the pH of the body fluids below 7.35, with the exception of conditions resulting from the altered function of the respiratory system. As hydrogen ions accumulate in the body fluids, buffers first resist a decline in pH. If the buffers cannot compensate for the increase in hydrogen ions, the respiratory center helps regulate the body fluid pH. The reduced pH stimulates the respiratory center, which causes hyperventilation. During hyperventilation, carbon dioxide is eliminated at a greater rate. The elimination of carbon dioxide also eliminates excess hydrogen ions and helps maintain the pH of the body fluids within a normal range. If metabolic acidosis persists for many hours and if the kidneys are functional, the kidneys can also help compensate for metabolic acidosis. They begin to secrete hydrogen ions at a greater rate and increase the rate of bicarbonate ion reabsorption. Symptoms of metabolic acidosis appear if the respiratory and renal systems are not able to maintain the pH of the body fluids within its normal range.

Metabolic alkalosis: results from all conditions that increase the pH of the body fluids above 7.45, with the exception of conditions resulting from altered function of the respiratory system. As hydrogen ions decrease in the body fluids, buffers first resist an increase in pH. If the buffers cannot compensate for the decrease in hydrogen ions, the respiratory center helps regulate the body fluid pH. The increased pH inhibits respiration. Reduced respiration allows carbon dioxide to accumulate in the body fluids. Carbon dioxide reacts with water to produce carbonic acid. If metabolic alkalosis persists for several hours, and if the kidneys are functional, the kidneys reduce the rate of hydrogen ion secretion to help reverse alkalosis.

1.12. ELECTROLYTES IMABALANCE

Electrolytes are essential for life to survive our bodies, An ionic compound, e.g. sodium chloride, in solution in water is called an *electrolyte*. Electrolytes are ions in the body that carry an electric

charge. the four most prominent in the body such as sodium potassium calcium and magnesium. These electrolytes are essential in making sure that whole body functions properly. Electrolytes are important body constituents because they have an own function such as:

(1) Electrolytes have maintained the balance of osmotic pressure,

(2) Electrolyte are maintained the body fluids in their own compartments conducts electricity which is essential for muscle and nerve function.

(3). Electrolyte are maintained the Acid-base balance, as buffers to resist pH changes in the body fluids.

Causes of electrolyte imbalance: There are many caused electrolytes may be imbalance such as Kidney disease, Vomiting for prolonged periods, Severe dehydration, Acid/base (pH) imbalance (acid and alkaline balance in the body is disproportionate), Congestive heart failure, Cancer treatment, Some drugs, like diuretics or ACE inhibitors.

Symptoms of electrolyte imbalance: An electrolyte imbalance can be classified in several ways. The symptoms will depend on imbalance of electrolyte. If the level is too high or too low. The abnormal level of magnesium, sodium, potassium, or calcium may produce one or more symptoms such as Irregular heartbeat, Twitching, Weakness, Blood pressure changes, Bone disorders, Confusion Seizures, Numbness, Nervous system disorders, Convulsions Fatigue, lethargy, and Muscle spasm.

The normal values of electrolytes are in the body, if imbalance the electrolytes disorder takes place. These electrolytes are given in table-I

Electrolytes Values					
Electrolytes normal values in plasma, CSF and Urine				**Imbalance**	
Name	**Plasma**	**CSF**	**Urine**	↑	↓
Sodium Na⁺	136.00–146.00 (mM)	138.00–150.00 (mM)	40.00–220.00 (mM)	Hypernatremia	Hyponatremia
Potassium P+	3.50–5.00 (mM)	0.35–3.5 (mM)	25.00–125.00 (mM)	Hyperkalemia	Hypokalemia
Chloride Cl-	98.00–107.00 (mM)	118.00–132.00 (mM)	110.00–250.00 (mM)	Hyperchloremic	Hypochloremia
Bicarbonate HCO3⁻	22.00–29.00 (mM)	—	—	Alkalosis	. Acidosis

Electrolytes Values					
Electrolytes normal values in plasma, CSF and Urine				Imbalance	
Name	Plasma	CSF	Urine	↑	↓
Calcium Ca+	2.15–2.55 (mmol/day)	—	Up to 7.49 (mmol/day)	Hypercalcemia	Hypocalcemia
Phosphate HPO4	0.81–1.45 (mmol/day)	—	12.90–42.00 (mmol/day)	Hyperphosphatemia.	Hypophosphatemia
Magnesium Mg	1.4-2.1 (mmol/	--------- -	0.7–1 mmol/L	Hypermagnesemia	Hypomagnesemia

Table. I The normal values of electrolytes and there disorders

The ions excretion occurs mainly through the kidneys, with lesser amounts lost in sweat and in feces. More sweating may cause a significant loss, especially of sodium and chloride. Severe vomiting or diarrhea is losing the chloride and bicarbonate ions. The balance in respiratory and renal functions allows the body to regulate the levels of these ions in the ECF.

Electrolytes play important role in many functions of the body. For example electrolytes have plays role in the electrophysiology of the heart. These ions maintained the action potential of cardiac muscle.