1. CELL INJURY AND CELLULAR ADAPTATION

1. CELL INJURY AND CELLULAR ADAPTATION

INTRODUCTION:

- Pathophysiology is described as the study of the biological and physical manifestations of disease as they correlate with the underlying abnormalities and physiological disturbances.
- Pathophysiology does not deal directly with the treatment of diseases but it explain the processes within the body that result in the sign and symptoms of the disease.
- In short pathophysiology means study of the nature and cause of disease or the result of disease in the body.
- Pathophysiology is a required area for nearly all healthcare professional school and college programs in India and other countries.
- In short pathophysiology is an advanced field of study beyond anatomy and physiology and it's concerned with the study of diseases, infections, illness and dysfunctions in the human body.

DISEASE:

- The term disease broadly refers to any condition that impairs normal function i.e functional abnormality. It may be cause by external factors such as infectious disease or it may be caused by internal dysfunctions like autoimmune diseases.
- There are four main types of diseases are pathogenic disease, deficiency disease, hereditary disease and physiological disease.

DISORDER:

- Anatomical abnormalities or disturbances known as disorder like fracture, alzheimer etc.
- Disorders are mainly categories into mental disorder, physical disorder, genetically disorder, emotional and behavior disorder and functional disorder.

INFLAMMATION:

- Inflammation is a protective mechanism of the body to remove the injurious stimuli or complex biological response of vascular tissue against the harmful stimuli like pathogen, damaged cells or irritants.
- Inflammation is not the synonyms of infection. But sometimes inflammation is caused by the infections.

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INFECTION:

- Infection means the growth of a parasitic organism within the body except the normal growth of the usual bacterial flora in the intestinal tract.

IMMUNITY:

It is the defense mechanism to avoid the infection, disease or other unwanted biological invasion.

HOMEOSTASIS:

- Ability to maintain relatively stable internal conditions despite a changing external environment. Dynamic state of equilibrium, or balance.
- The body is said to be in homeostasis when its cellular needs are adequately met and functional activities are occurring smoothly.
- Virtually every organ system plays a role in maintaining the internal environment.

A homeostatic regulatory mechanism consists of 5 parts:

1. **Receptors:** It respond to a stimulus. It monitors change in control condition and send the input information to control center/integrated center via sensory receptor.
2. **Sensory Neurons:** It receives information from receptor and sends input messages to integrated center.
3. **Integrated center:** It analyze the incoming messages and send the reply via motor receptor. (Brain and spinal cord)
4. **Motor receptor:** It send the reply coming from integrated center to effector.
5. **Effectors are the cell or organ** that responds according to output command of the control center via motor receptor.

TYPES OF FEEDBACK SYSTEM

Receptor, sensory neurons, integrated system, motor receptor and effector form mainly two kinds of feedback mechanisms.

1. **Negative feedback:**

- When the response of effectors opposes the original stimulus, it is called negative feedback because it negates the stimulus.
- An example of negative feedback is the temperature thermostat in your home.

- Temperature sensors turn the air conditioner off and on to maintain air temperature within a specific, limited range.
- In the same way, the brain controls normal body-temperature homeostasis by negative feedback.
  - Some stimulus (Stress) disrupts homeostasis (control condition) by an increase in body temperature.
  - Due to this condition thermoreceptors (temperature sensitive receptors) in the skin and brain activate and send input message via nerve impulse to control center.
  - Control center analyze the input message and send output message to effectors (skin).
  - Effectors according to output message of control center increases sweating from sweat glands causes increased heat loss by evaporation.
  - Finally, decreases the temperature in the form of response and normalize the body temperature (control condition).

2. Positive feedback:

- The effector adds to the initial stimulus instead of negating it, speeding up the process.
  - Labor contraction is the example of positive feedback system.
  - Labor contractions force baby's head or body into birth canal.
  - It produces effect on control condition and increases distention of cervix of uterus.
  - It activates the stretch receptors of cervix and send input message to control center via sensory nerve impulse.
  - Control center activates the hypothalamus and pituitary gland and send the output message to increase oxytocin secretion in blood.
  - Oxytocin produces their effect on to the effector (cervix of uterus) and cause distention of cervix of uterus than the normal value to push the baby further into birth canal.
  - Birth of the baby decreases distention of cervix of uterus and interrupts positive feedback cycle.

CELL INJURY

Cell injury occurs as a result of Physical, Chemical or biological insults or as a result of vital substrate deficiency.

The term **cell injury** is used to indicate a state in which the capacity for physiological adaptation is exceeded. This may occur when the stimulus is excessive or when the cell is no longer capable to adapt without suffering some form of damage.

The capacity for adaptation and the sensitivity to different types of injury varies according to cell type (i.e. myocardial cells and neurons are highly sensitive to ischemic injury; hepatocytes are more sensitive to chemical than ischemic injury).

Cell injury may be reversible (non-lethal damage which generally can be corrected by removal of the stimulus) or irreversible (lethal damage).Genetical defect, abnormalities of several dietary factors, immune reaction, physical or chemical agent may cause the cell injury.

Generally, Ischemia and hypoxia are the most common form of the cell injury.

1. Reversible cell injury:

If the hypoxic or ischemic effect is for short duration then it produce reversible cell injury because this kind of effect is restore by the vascular circulation. Eg.: Coronary arteries occlusion, myocardial contractility etc.

Some of the sequential biochemical and ultra-structural changes in reversible cell injury are as under:

i. Depletion of ATP:

ATP is the primary requirement for the synthesis of lipid, protein, cell membrane etc. In human body ATP is produce by aerobic and anaerobic process. Aerobic process is carried out by mitochondria and anaerobic ATP is produce by the glucose/glycogen.

In the ischemic condition, the supply of oxygen and Glucose both are affected. So decrease the production of ATP. Due to this effect protein synthesis, cell membrane formation, lipid synthesis process get affected and it leads to cell injury.

Due to insufficiencies of oxygen supply RBC disorder, Heart disease, Lungs Disease will form. Generally anaerobic cell injury are less severe than the aerobic cell injury.

ii. Intracellular lactic acidosis & nuclear clumping:

Due to low oxygen supply aerobic ATP formation process get affected and mitochondria fails to work. So anaerobic glycolytic pathway start to produce ATP. This results in rapid depletion of glycogen and accumulate lactic acid. It lower the intracellular pH due to intracellular acidosis and produce clumping of nuclear chromatin. This effect release the lysosomes and it produce cellular digestion.

iii. Effect on plasma membrane:

Plasma membrane required phospholipid for continuous repair but due to lack of ATP fatty acid not form the phospholipids. Due to this effects plasma membrane pumps get affected and the regulation of calcium, sodium and potassium get affected.

a) Failure of Na^+-K^+ ATPase pump:

- Na^+-K^+ ATPase pump is useful for the exchange of Na^+ inside to outside and K^+ outside to inside from the cell.
- Lower ATP level affect the activity of this pump and Na^+ get accumulate inside the cell and potassium out of the cell.
- Accumulation of Na^+ inside the cell retain the water and increase intracellular water level and hydropic swelling occur due to disruption in osmatic pressure.

b) Failure of Ca^{++} pump:

- Accumulation of Na^+ inside the cell produce affect in the intracellular level of Ca^{++}.
- Excess Ca^{++} accumulate inside the cell as well as into the mitochondria leads to reversible cell damage.

iv. Decrease protein synthesis:

Lack of oxygen effect disturb the intracellular osmatic balance of the cell so endoplasmic reticulum and golgi apparatus swell up. So the ribosome detach from the granular endoplasmic reticulum and it get inactive. This effect decrease the synthesis of protein.

2. Irreversible cell injury:

Long lasting/persistence ischemic or hypoxic effect produce cell death or irreversible damage. If cell fails to reverse mitochondrial function as well as disturbance in cell membrane/plasma membrane function cause irreversible cell injury.

i. Ca_+ influx produce excitotoxicity into the cell:

Large amount of intracellular Ca_{++} produce damage in mitochondrial cell wall as well as excitotoxicity (activation of number of enzymes like phospholipase, endonuclease, protease etc.). This effect damage the cell structure such as component of cytoskeleton, plasma membrane, DNA etc.

a) **Effect of activated phospholipase:**

Activated phospholipase degrade the membrane phospholipids which is the main constituents of plasma membrane. As well as due to lack of ATP generation new phospholipid will not form and it exaggerate the effects.

b) **Effect of activated protease:**

Activated protease damage the cytoskeleton of the cell membrane leads to irreversible cell injury.

c) **Effect of activated endonuclease:**

Activated endonuclease damage the nucleoprotein as per below process:

- Condense or clumps the nucleus
- Produce fragments of nucleus
- Dissolve the nucleus

ii. Low pH of cell activate and release the lysosomal hydrolytic enzyme:

Lack of oxygen decrease the intracellular pH and it activate or release the lysosomal hydrolytic enzyme like lactic dehydrogenase (LDH), Creatine kinase (CK), hydrolase, RNAse, DNAse, glycosidase, phosphatase, lipase, amylase, cathepsin etc. Activation of this enzyme digest the cellular components through the phagocytic effects and cause the irreversible cell injury.

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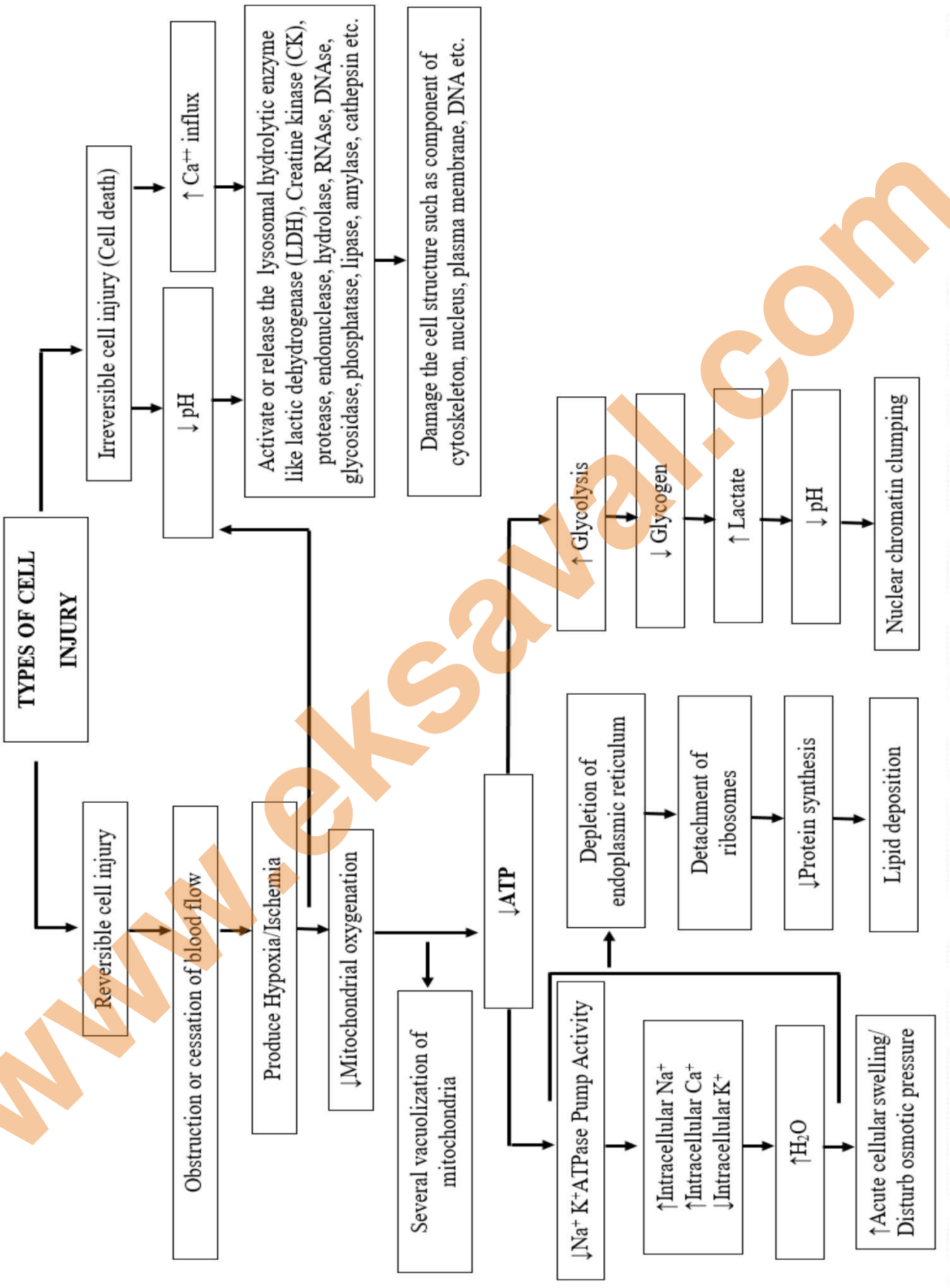

Figure 1.1: Types of cell injury

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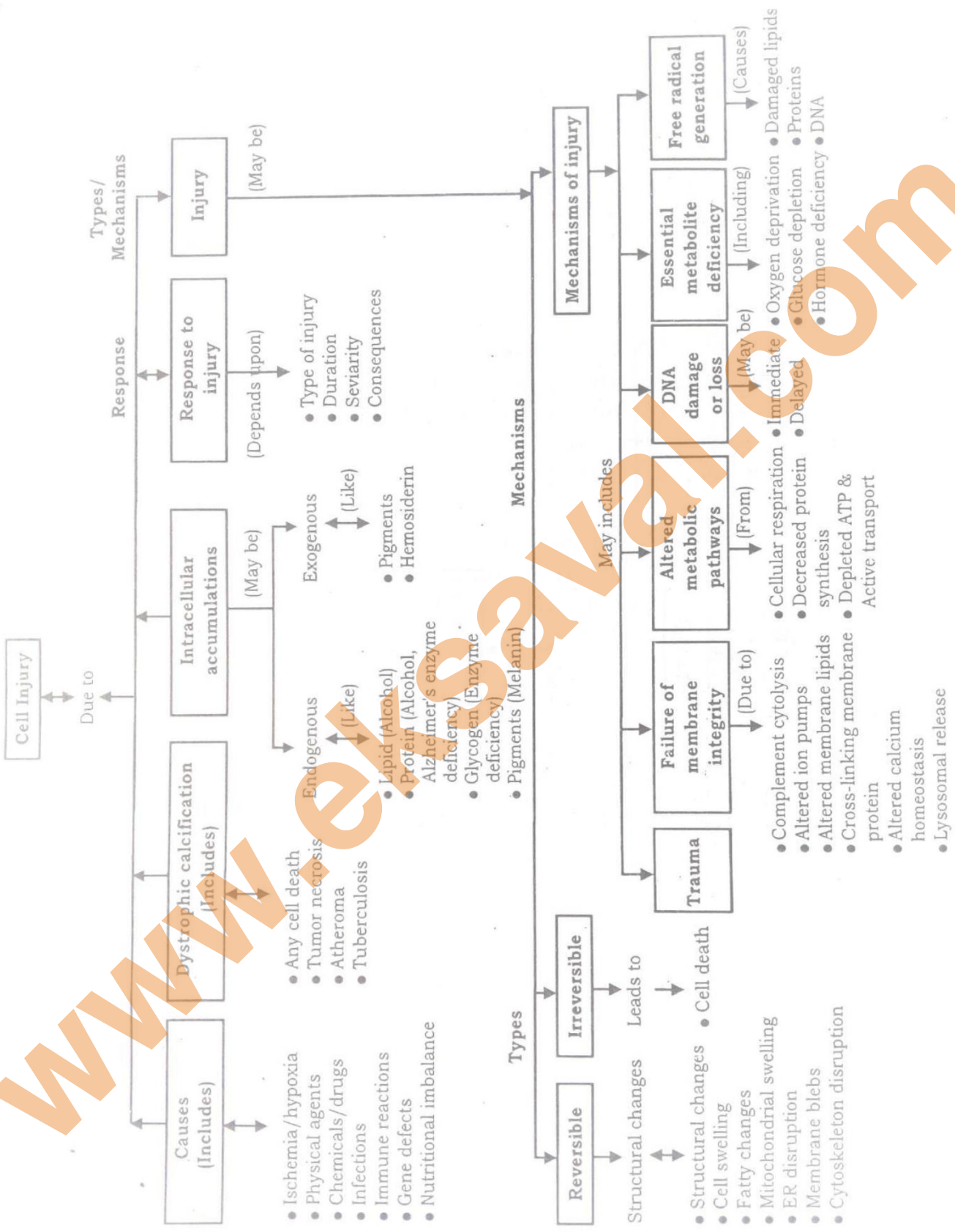

Figure 1.2: Introduction of cell injury

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CAUSES OF CELL INJURY:

Type	Examples
Genetic	Gene defects, chromosomal anomalies
Nutritional	Deficiency or excess of dietary substances, e.g. iron, vitamins
Immune	Immune system works in a defense against biologic agents but some times immune reactions may cause cell injury -Eg.: 1) anaphylactic reaction - to a foreign protein or drug 2) autoimmune diseases endogenous self-antigens are responsible for to damage cell
Endocrine	Deficient or excessive hormone activity
Physical agents	Mechanical trauma, thermal damage, irradiation (UV and ionizing)
Chemical agents	The list of chemicals that may cause cell and tissue injury includes -poisons-arsenic, cyanide, mercuric salts,etc -air pollutants -insecticides and herbicides -alcohol, narcotic drugs Chemicals induce cell injury by one of two major mechanisms: 1. Some chemicals act directly by chemical bindings with some critical molecules or cellular organelles for example: mercuric chloride poisoning (mercury binds directly to sulphydryl groups of cell membranes) in GIT and kidney or anticancer drugs and some antibiotic drugs also induce cell damage by direct cytotoxic effects 2. Other chemicals are not biologically active but convert into reactive toxic metabolits (for example role of free radicals and Reactive oxigen Species)
Infective	Infection by viruses, bacteria, parasites, fungi and other organisms
Ischemia (hypoxia)	Deficit of blood supply or direct oxygen deficit

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PATHOGENESIS AND MECHANISMS OF CELL INJURY:

1. ATP depletion or Hypoxia
2. Loss of calcium homeostasis
3. Oxidative stress (excess Reactive Oxygen Species)
4. Damage to mitochondria, and increased permeability of membranes

1. ATP depletion or Hypoxia:

- Hypoxia first causes loss of phosphorylation in mitochondria and decrease the production of ATP which is a source for energy.
- Loss of ATP (which is a energy source) has widespread effects on many systems in the cell.
- for example: Neurons and cardiac myocytes are rapidly injured by ATP decreases that occur as a consequence of ischemic injury. A major component of the injury is the alteration of membrane permeability caused by decreased activity of ATP-dependent ionic pumps.
- Decreased ATP results in increased anaerobic glycolysis, accumulation of lactic acid, and therefore decreased intracellular pH.
- Decreased ATP causes decreased action of Na+ / K+ pumps in the cell membranes, leading to increased Na+ and water within the cell (cell swelling).

2. Injury produced by loss of calcium homeostasis:

- Cytosolic free calcium is kept at concentrations that are at least 10-fold lower than the extracellular levels.
- Mitochondria and endoplasmic reticulum keep intracelluar calcium under control.
- If the intracellular calcium level may rise it produces:
  - ✓ Increase Glutamate Release.
  - ✓ Activation of protease and lipases, causing membrane damage.
  - ✓ It Activate Nitric oxide and Reactive oxgen species which increase the oxidative stress and damage the cell.

3. **Oxidative stress (excess Reactive Oxygen Species)**
   - Cells generate reactive oxygen forms as byproducts of metabolic reactions that reduce molecular oxygen to water. These reactive forms, called **reactive oxygen species**, can damage lipids, proteins and DNA.Figure 1.3: Oxidative stress
4. **Damage to mitochondria, and increased permeability of membranes:**
   - Mitochondria are important primary or secondary targets for most agents that cause cell injury. Alterations in mitochondrial membrane permeability generally lead to apoptosis Loss of the capacity of the plasma membrane to maintain a proper ionic balance between the intra-and extracellular compartments.
   - Distribution in mitochondrial function produces:
     - ✓ Reduce ATP Synthesis so it decreases the formation of energy for the cellular activity.
     - ✓ Increase the accumulation of intracellular calcium in endoplasmic reticulum.
     - ✓ Formation of Reactive oxygen species also enhanced.
     - ✓ These all mechanism may lead to damage the cell and produce cellular injury.

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MORPHOLOGY OF CELL INJURY:

1. Ultrastructural changes include:

- **Cellular swelling**: Decreased ATP causes decreased action of Na+ / K+ pumps in the cell membranes, leading to increased Na+ and water within the cell (cell swelling).
- **Mitochondrial changes:** occur very rapidly in ischemic injury, but are delayed in some types of chemical injury. Early after ischemia it produces swelling of mitochondrias due to changes in ions small to large size amorphous densities in mitochondrias. It produces abnormality n proteins and lipid and alters the calcium level.
- **Endoplasmic reticulum:** Changes of ER occur early after injury due to changes in ion and water regulation produce detachment of ribosomes and disaggregation of polysomes result in decrease of proteosynthesis
- **Alterations of lysosomes in cell injury:** Generally appear later because lysosomes become swollen, and after the onset of lethal injury lysosomes rupture and this event causes leakage of the lysosomal enzymes at this stage irreversible cell injury arise.
- **Heterophagy:** It is the uptake of materials from the external environment by phagocytosis. Eg. Phagocytosis and degradation of bacteria by leukocytes, removal of necrotic debris by macrophages, reabsorption of protein
- **Autophagy:** It is the phagocytosis by lysosomes of deteriorating intracellular orgtanelles, including mitochondria and endoplasmic reticulum. Autophagy is particularly pronounced in cells undergoing atrophy. Lysosomes with undigested debris- are called autophagic vacuoles and may persist within the cells as residual bodies or may be extruded from the cell

2. Light microscopic changes:

a) Reversible changes:

- In Pathology the nonharmful or nonlethel injury to cells were termed degenerations, dystrophies, but now a day it is common known as reversible injuries or regressive changes

- Two patterns can be recognized by light microscopy:

1. Cellular swelling:

- Appears whenever the cell is not capable of maintaining ionic and water homeostasis

2. Fatty change:

- It is more often encountered in the cells involved in fat metabolism, such as hepatocytes.
- Fatty change is most commonly seen in the liver, heart, muscle,etc.

b) Irreversible changes (Cell Death):

- Cell death is an irreversible change in the cell associated with its end.
- According to morphological and pathological changes aspects, we can distinguish cell death in two different types
- These are 1) Apoptosis and 2) Necrosis

APOPTOSIS:

Definition: "Apoptosis in Physiologic Situations programmed destruction of cell during embryogenesis."

- Apoptosis can be physiological or pathological and often results in the elimination of abnormal or "unwanted" cells.
- In normal human, cell proliferation and cell destruction process is controlled by positive and negative regulation. In positive control, two families of proteins; cyclin and cyclin dependent kinases (cdks) have a major role. Each cdk is inactive until it binds to a cyclin, the binding enabling the cdk to phosphorylate the protein(s) necessary for a particular step in the cell cycle. After the phosphorylation take place cyclin is degraded by ubiquitin/protease system.
- There are eight groups of cyclins. Those important in the control of the cell cycle are cyclins A, B, D and E. each cyclin is associated with and activates the particular cdk(s). Cyclin A activates cdks 1 and 2; cyclin B activates cdk 1; cyclin D activates cdks 4 and 6; cyclin E activates cdk 2.
- In negative regulation, the mediators either stop the cell cycle or produce cell death means apoptosis. Different mediators are Rb protein that holds the cycle in Go phase while it is hypophosporylated. Another two families inhibitors are, one

is CIP family (cdk inhibitor proteins, also termed KIP or kinase inhibitory proteins) – p21, p27, and p57. Other is Ink family (inhibitor of kinase) – p16, p19 and p15. p 21 is the under control of the gene p51. Here the below figure shows the normal cell cycle include S (synthesis) phase, M (mitosis) phase, G1 (Check point 1 between M and S phase where cell is preparing for S phase by synthesis messenger RNAs and proteins need for DNA replication), G2 (check point 2 between S and M phase where double the number of chromosomes), Go is the quiescent phase where the cell is not constantly divide, here the Rb protein is hypophosporylated. If the DNA or cell is damaged the repairing of cell is take place either in check point 1 or check point 2. if the repair is fails then cell goes in to the apoptosis.

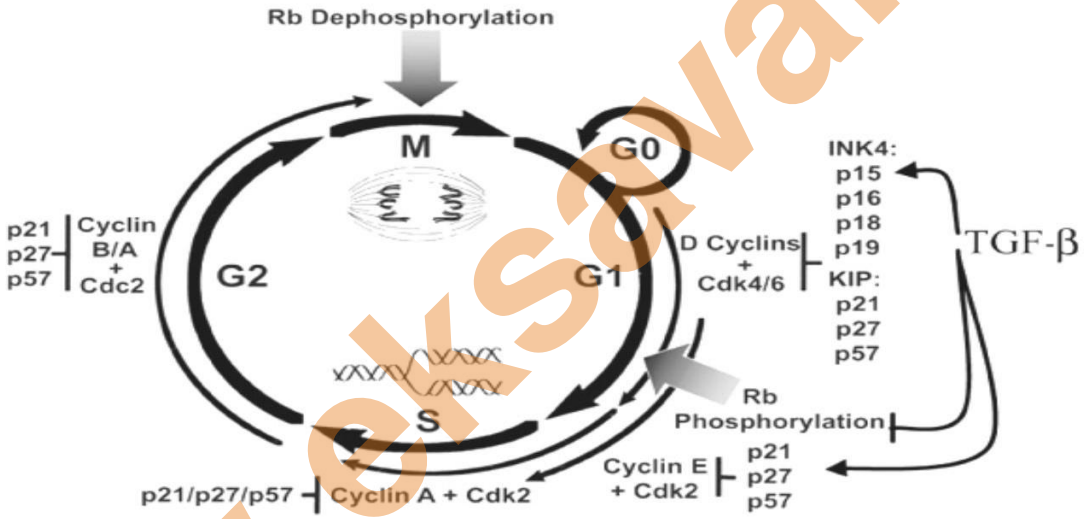

Figure 1.4: Cell cycle

Mechanisms or pathway of apoptosis:

Apoptosis is very well expain by mainly two pathways

1. The death receptor Pathway
2. Mitochondrial Pathway.

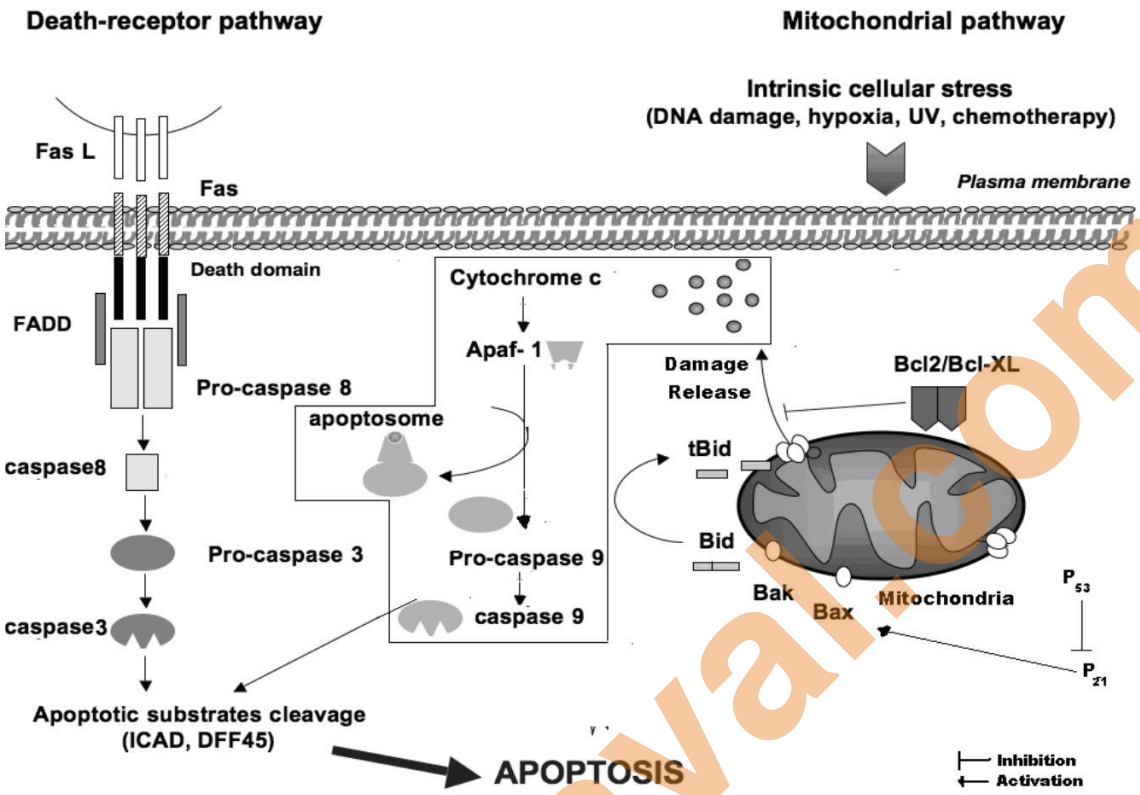

Figure 1.5: Pathway of apoptosis

1. The death receptor pathway:

- Our plasma membrane consist tumornecrotic factor receptor family which is known as a death receptor.
- Each death receptor consist death domain which is faced n to the cytoplasma.
- The death receptor pathway is activated when agonist or ligand like TNF or Fas Ligand bind to tumornecrotic factor receptor.
- After the activation or stimulation of tumornecrotic factor receptor it activates the death domain in to the cytosol.
- Activation of death domain produce positive effect means stimulate the procaspase 8 to caspase 8 which is known as initior caspase.
- Caspase 8 activate the procaspase 3 to caspase 3 known as effecor caspase and finally activated caspase 3 produce inactivation of cellular enzyme, fragmentation of DNA and leads to cell death or apoptosis.

2. Mitochondrial Pathway:

- It is activated in the condition,
  - ✓ DNA damage and not to repair.
  - ✓ Withdrawal of survival factor take place.
- These condition activates the the p53 gene which has a control on p21 protein so p21 get activates.
- p21 activate the pro-apoptotic Bh3 family (Bad, Bax, Bak) and produce the damage of mitochondrial cell wall damage which release cytochrom-C.
- Cytochrom-C activate the APAf-1 (apoptotic protease activating factor-1) which activate the procaspase 9.
- The combination Cytochrom-C, APAf-1 (apoptotic protease activating factor-1) and procaspase 9 known as apoptosome produce activation of caspase 9 and finally activate the effectors caspase 3 and follow the common pathway like death receptor pathway and leads to cell death or apoptosis.

NECROSIS:

- Necrosis, derived from the Greek word *neckros* for 'corpse', is a type of irreversible and pathological cell death.
- It is mainly caused by early plasma membrane rupture , mitochondrial dysfunction, cell injury, infarction, inflammation and lysosomal rupture . There are several patterns of necrosis classified based on morphological criteria,

Morphological types of Necrosis:

1. Coagulative
2. Liquefactive
3. Caseous
4. Fat Necrosis
5. Fibrinoid Necrosis

1. Coagulative necross:

- Most common pattern of necrosis is characteristic of hypoxic cell death.
- This pattern of necrosis-most commonly results from sudden severe ischemia (is encountered mostly in solid organs, such as kidney, heart, spleen, adrenal gland)

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- Ischemia results in decreased ATP, increased cytosolic Ca++, and free radical formation, which each eventually cause membrane damage and shows appearance like firm consistency, yellowish colour, dry appearance of the cut section
- Decreased ATP results in increased anaerobic glycolysis, accumulation of lactic acid, and therefore decreased intracellular pH.
- Decreased ATP causes decreased action of Na+ / K+ pumps in the cell membranes, leading to increased Na+ and water within the cell (cell swelling).
- Other changes are ribosomal detachment from endoplasmic reticulum, blebs on cell membranes, swelling of endoplasmic reticulum and mitochondria.
- Up to here, the changes are reversible if oxygenation is restored by reversing the ischemia but if the ischemia continues, necrosis results, causing the cytoplasm to become eosinophilic, the nuclei to lyse or fragment or become pyknotic (hyperchromatic and shrunken).
- The best example of coagulative necrosis is myocardial infarction

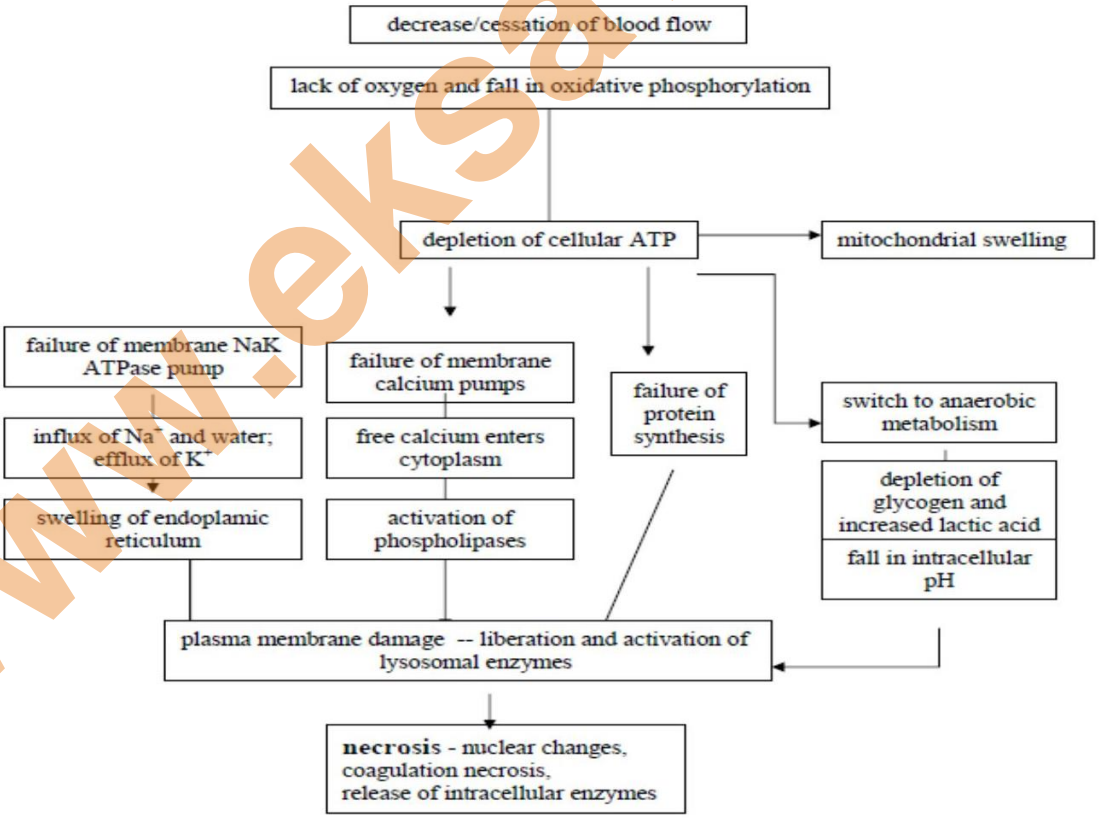

Figure 1.6: Mechanisms of ischemic/hypoxia cell death

2. Liquefactive:

- Usually caused by focal bacterial infections, because they can attract polymorphonuclear leukocytes. The enzymes in the polys are released to fight the bacteria, but also dissolve the tissues nearby, causing an accumulation of pus, effectively liquefying the tissue.
- Good example of liquefactive necrosis is brain infarction.

3. Caseous Necrosis:

- It is a combination of coagulative and liquefactive necrosis.
- Caseous necrosis appears grossly as soft, friable, whitish-gray debris resembling cheesy material so it is term as a caseous necrosis.
- A distinct form of coagulative necrosis seen in mycobacterial infections (e.g., tuberculosis), or in tumor necrosis, in which the coagulated tissue no longer resembles the cells, but is in chunks of unrecognizable debris.
- Usually there is a giant cell and granulomatous reaction, sometimes with polys, making the appearance distinctive.

4. Fat Necrosis:

- It is also refer as refers to necrosis in adipose tissue due to *action of activated lipases*
- A term for necrosis in fat, caused either by release of pancreatic enzymes from pancreas or gut (enzymic fat necrosis) or by trauma to fat, either by a physical blow or by surgery (traumatic fat necrosis).
- The effect of the enzymes (lipases) is to release free fatty acids, which then can combine with calcium to produce opaque and chalky white or yellowish detergents (soapy deposits in the tissues).

5. Fibrinoid Necrosis

- It is a type of connective tissue necrosis seen particularly in autoimmune disease collagen and smooth muscle are affected (for example- in polyarteriitis nodosa- fibrinoid necrosis affects blood vessel walls)
- fibrinoid necrosis is characterized by loss of normal structure of collagen fibres

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	Apoptosis	Necrosis
Histology	Single cell affected	Groups of cells; disruption of tissue structure
Cytology	Shrunken cells Cell fragmentation (apoptotic bodies) Chromatin condensed in the periphery of nuclei Generally morphologically intact mitochondria	Generally swollen, enlarged cells Pyknotic or fragmented nuclei Dilated ER; high amplitude swelling of mitochondria Outline of the cell initially maintained
Effects on Tissue	No inflammation Phagocytosis by adjacent cells	Disrupted membrane permeability; leakage of cellular products into the blood Acute inflammatory response Possible scar formation
Mechanism	Gene activation, endonuclease or mitochondrial pathway	ATP depletion, membrane injury, free radical damage
Inflammatory Response	Absent	Present

CELLULAR ADAPTATION:

- Cellular adaptation refers to changes made by a cell in response to adverse environmental changes.
- Cells die and new cells are formed, and the end result is that the organ remains relatively constant in size but if the balance is disturb then the below conditions will arise:

a) Atrophy:

- Atrophy is means decrease in cell size
- In to the atrophy cell get shrink by losing the cell substance.
- Some causes are decreased workload, loss of innervation, loss of blood supply and aging.
- Eg.: the shrinkage of the ovary at the menopause and the corpus luteum during the menstrual cycle.

- Atrophy can be classified in to:

1. Physiologic atrophy,
2. Pathologic atrophy,
3. Local atrophy and
4. Disuse atrophy.

b) Hypertrophy:

- It is totally opposite to the atrophy means the cell size is increases in to the hypertrophy.
- Cells are not enlarged by simple edema but by increased synthesis of more structural proteins and organelles.
- Eg.: muscles undergo this change in response to increase work.

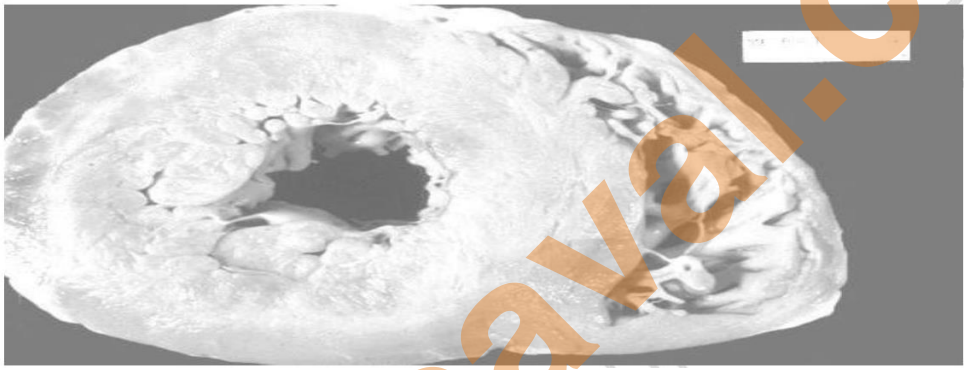

Figure 1.7: Right Ventricle

c) Metaplasia:

- Metaplasia means a differentiated cell of a certain type is replaced by another cell type, which may be less differentiated.
- It is a one kind of disorder in which one mature adult tissue is replaced by another.
- Eg.: The replacement of pseudo-stratified columnar epithelium of the lungs by stratified squamous epithelium. This is caused by chronic irritation, as seen in smokers.

d) Hyperplasia:

- Hyperplasia is an increase production and growth of normal cells in a tissue or organ.
- Here, the numbers of cells are increased instead of the size of cell.
- In these conditions, the affected part become larger but retains its normal form.

- It is because of increased cell mitosis or division.
- Eg.: During pregnancy the breast grow in this manner.

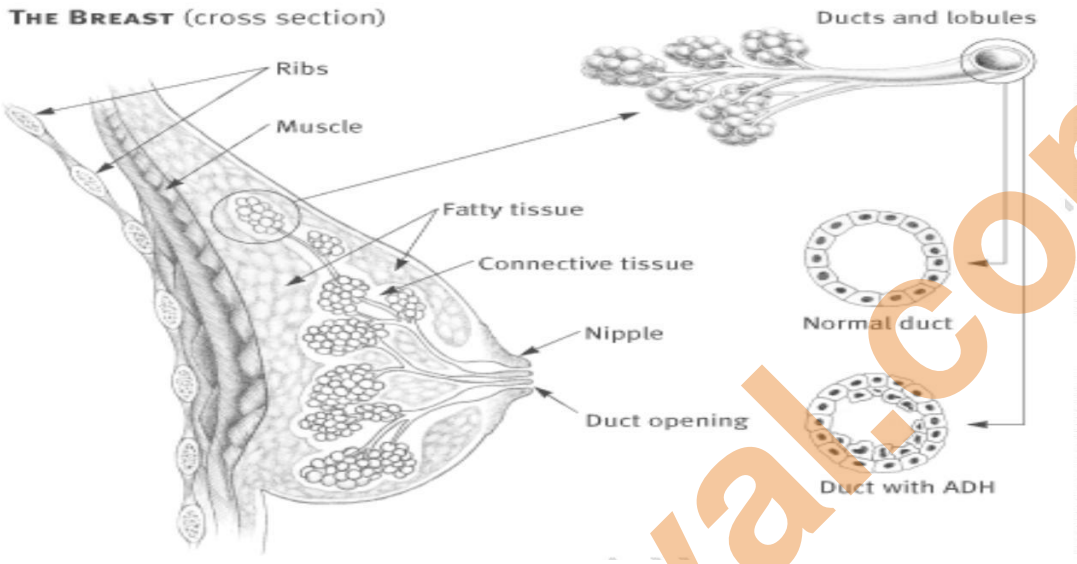

Figure 1.8: Cross section of breast

INTRACELLULAR ACCUMULATIONS:

- Accumulate of abnormal amounts of various substances may be endogenous or exogenous.
- A normal or abnormal endogenous substance accumulates because it cannot be metabolized.
- An abnormal exogenous substance is deposited and accumulates because the cell has neither the enzymatic machinery to degrade the substance not the ability to transport it to other sites.

1. Intracellular alteration or accumulations in lipids:

- Intracellular alteration or accumulations of lipids means abnormal accumulation of fat within parenchymal cells.
- Fatty change occurs mostly in hepatocytes (liver cell). The liver plays a main role in the metabolism of fat because it is largely responsible for the conversion of free fatty acids into a lipoprotein which is more readily utilizable by other cells.
- The lipid metabolism is also occur in heart, skeletal muscle, kidney, and other organs.

- Normally, lipids are transported to the liver from either adipose tissue or from dietary sources.
- In the liver, they are used for several processes including:
  - ✓ The formation of triglycerides,
  - ✓ The production of cholesterol,
  - ✓ Incorporation into phospholipids or utilization as a fuel by mitochondria.
- But in the abnormal condition the accumulation of fat occurs due to:
- Excessive entry of lipids into the liver. This occurs in situations where the dietary intake of fat or the mobilization of lipids from fat stores is excessive.
- Enhanced fatty acid synthesis by hepatocytes.
- Increased esterification of fatty acids to triglycerides.
- Decreased apoprotein synthesis. This protein is necessary for the formation of lipoproteins, the form in which triglycerides are secreted from the liver. Without it, triglycerides accumulate and fatty change develops.
- Impaired lipoprotein excretion.

➢ **Hyperlipoproteinemia:**

- Hyperlipoproteinemia is the condition of abnormally elevated levels of lipids and/or lipoproteins in the blood.
- Lipids are fat soluble molecules and transported by the help of protein molecules.
- Hyper lipoproteinemia is devided in to two, primary hyperlipoproteinemia and secondary hyperlipoproteinemia.
- primary hyperlipoproteinemia is due to the genetical cause and secondary hyperlipoproteinemia is due to the some aquire condition like diabetes.

A) Primary Hyperlipoproteinemia:

- It is inheridetry disorder in which increase the plasma concentration of on or more lipoproteins.
- This disorder affects lipid transport in serum.
- It is devided in to five distinct types:

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Types	Cause and Incidence	Diagnosis finding
I - Frederickson's hyperlipoproteinemia, fat induce hyperlipemia, idiopathic familial	- Deficient or abnormal lipoprotein lipase, resulting in decreased or absent post heparin lipolytic activity - Relatively rare	- Chylomicrons, Very Low Density Lipoprotein (VLDL), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) in plasma 14 Hrs or after last meal. - Highly elevated serum chylomicron and triglyceride levels, slightly elevated serum cholesterol level. - Low serum lipoprotein level. - Leucocytosis.
II – Familial hyperbeta lipoproteinemia, essential familial hyper cholesterolemia	- Deficient cell surface that regulates LDL degradation and cholesterol synthesis, Result in increased level of plasma LDL over joints and pressure points. - Onset between ages 10 to 30 Yrs.	- Increased plasma concentrations of LDL. - Increased serum LDL and cholesterol levels. - Increased LDL levels in Amniotic fluid.
III – Familial broad-beta disease, xanthoma tuberosum	- Unknown underlying defect results in deficient conversion of triglyceride rich VLDL to LDL. - Usually occurs after age of 20Yrs but occur early in some male.	- Abnormal serum beta lipoprotein level. - Elevated cholesterol and triglyceride level. - Slightly elevated glucose tolerance. - Hiperuricemia.
IV – Endogenous hper triglyceridemia, Hyperbeta lipoprotenemia	- Usually occur secondary to obesity, alcoholism, diabetes or emotional disorders. - Relatively common, especially in middle aged men.	- Elevated VLDL level. - Abnormal levels of triglyceride in plasma, variable increase in serum. - Normal or slightly elevated serum cholesterol level. - Mildly abnormal glucose tolerance. - Family history. - Early coronary artery disease.
V – Mixed hyper triglyceridemia, mixed hyperlipidemia	- Defective triglyceride clearance cause pancreatitis, usually secondary to another disorder such as obesity or nephrosis. - Uncommon onset, usually occur late in adolescence or early in adult hood	- Chylomicrons in plasma. - Elevated VLDL levels. - Elevated serum cholesterol and triglyceride levels.

B) Secondary Hyperlipoproteinemia:

- It is also known as aquire hyper lipoproteinemia.
- The most common causes of acquired hyperlipidemia are:
  - ✓ Diabetes mellitus
  - ✓ Use of drugs such as diuretics, beta blockers, and estrogens.
- Other conditions leading to acquired hyperlipidemia include:
  - ✓ Hypothyroidism
  - ✓ Renal failure
  - ✓ Nephrotic syndrome
  - ✓ Alcohol
  - ✓ Some rare endocrine disorders and metabolic disorders

2. Intracellular alteration or accumulations in protein:

- Accumulations of excessive amounts of a proteinaceous material within cells occur primarily in epithelial cells of the proximal convoluted tubules of the kidney and in plasma cells.
- Excessive accumulation of protein in the kidney, produce leakage of proteins from glomeruli into the glomerular filtrate.
- The main protein involved in the accumulation is albumin, but other proteinaceous substances such as hemoglobin and myoglobin are also encountered.
- In the kidney, trace amounts of albumin filtered through the glomerulus are normally reabsorbed by pinocytosis in the proximal convoluted tubules.
- But when the reabsorption process is excessive than the normal rate due to several disorder like nephrotic syndrome pinocytic vesicles containing protein fuse with lysosomes forming a secondary phagolysosome, resulting in the histologic appearance of pink, hyaline cytoplasmic droplets in to the cytoplasm of the renal tubular epithelial cells.

3. Intracellular accumulation of carbohydrate or glycogen:

- Carbohydrate or glycogen accumulaton intracellularly are associated with abnormalities in the metabolism of either glucose or glycogen.

- It can be divided into two basic categories. These categories are **"Glycogen Infiltration"** and **"Glycogen Storage."** They differ mainly in their pathogenetic mechanisms.

1. Glycogen Infiltration:

- Glycogen infiltration means an accumulation of glycogen that occurs due to excessive amounts of glucose in the circulation **(hyperglycemia)**.
- Hyperglycemia is usually encountered in Diabetes mellitus and it is due to insufficient insulin concentrations or tissue insensitivity to insulin. The tissues usually involved in glycogen infiltration include, the epithelial cells of the distal portion of the proximal convoluted tubule and in the loop of Henle in the kidney, leukocytes within inflamed or necrotic tissue, the liver and, on rare occasions cardiac muscle fibers.

2. Glycogen Storage:

- Defects in the processing of glycogen synthesis or breakdown within muscles, liver, and other cell types are known as glycogen storage disease.
- İt is mainly cause genetical defect or acquired deficiency.
- This desease mainly retard the growth of child.
- There are different type of glycogen storage diseases which is caused by deficiency of one or more enzyme shown below:

TYPES	ENZYME DEFİCEİNCY
GSD type I	glucose-6-phosphatase
GSD type II	acid maltase
GSD type III	glycogen debrancher
GSD type IV	glycogen branching enzyme
GSD type V	muscle glycogen phosphorylase
GSD type VI	liver glycogen phosphorylase
GSD type VII	muscle phosphofructokinase
GSD type IX	phosphorylase kinase, PHKA2
GSD type XI	glucose transporter, GLUT2
GSD type XII	Aldolase A
GSD type XIII	β-enolase
GSD type 0	glycogen synthase

4. Extracellular accumulatıons of calcium or calcification:

- Extracellular accumulaton or deposition of calcium is also known as calcification.
- Calcification of soft tissue (arteries, cartilage, etc) can be caused by Vitamin K deficiency or by poor calcium absorption due to a high calcium/vitamin D ratio.
- There are mostly two types of calcification;

1. Dystrophic calcification:

- Dystrophic calcification refers to the deposition of calcium salts in dead or dying tissues.
- Dystrophic calcification occurs in the presence of normal levels of serum calcium (**around 10 mg/100 ml).**
- İt is mostly seen in the necrotic area and produce atheromas.
- İt also affect the heart or artery valve by producing stenosis

2. Metastatic calcification:

- The deposition of calcium salts in normal tissues is known as *metastatic calcification.*
- Metastatic calcification can occur widely throughout the body but principally affects the interstitial tissues of the vasculature, kidneys, lungs, and gastric mucosa.
- The usual causes of the hypercalcemia include:
  a. Hyperparathyroidism, either primary or secondary,
  b. Vitamin-D intoxication,
  c. Deficiency of magnesium and
  d. Hypercalcemia of malignancy.

Some basic symptoms of the calcifications are:

- Tartar on teeth
- Calluses
- Arthritic bone spurs
- Kidney stones
- Gall stones
- Heterotopic bone

ACID BASE IMBALANCE

Metabolic process of cell produce CO_2 and metabolic acid. CO_2 combine with the water molecules (H^2O) to form bicarbonate (H_2CO_3). Metabolic product excreted via kidney

and lungs. Kidney excreted metabolic acid and lungs excreted CO_2. This factor maintain the blood pH between 7.3 to 7.4.

Serum concentration of bicarbonate and partial pressure of CO_2 that determines the concentration of carbonic acid play a main role in maintaining the blood pH.

- Alteration in the blood bicarbonate levels produce either metabolic acidosis or alkalosis.
- Alteration in pCO_2 produce respiratory acidosis or alkalosis.

1. Metabolic acidosis:

In the blood increase the amount of H_+ ions and decrease the bicarbonate HCO_3^- ions level due to metabolic process decrease the pH of blood. This occurs in the following conditions:

- Production of large amount of lactic acid due to vigorous exercise, shock like condition
- Uncontrolled diabetes mellitus
- Starvation
- Chronic renal failure
- Therapeutics administration of ammonium chloride or acetazolamide.

High level of H_+ ions in metabolic acidosis stimulate the respiratory centre and it increase the rate of breathing with deep respiration. Bicarbonate level in the plasma get fall.

2. Metabolic alkalosis:

Increase the level of bicarbonate HCO_3^- ions and decrease the amount of H_+ ions in the blood rise the pH of blood and it is known as metabolic alkalosis.

This occurs in the following conditions:

- Sever and prolonged vomiting
- Administration of alkaline salts like sodium bicarbonate.
- Hypokalemia such as cushing's syndromes, increase secretion of aldosterone

Clinically, metabolic alkalosis is characterized by depression of respiration, depressed function with uraemia and increase bicarbonate excretion in the urine. Bicarbonate level in the blood get increased.

3. Respiratory acidosis:

Rise in the pCO_2 level in the lungs decrease the blood pH and it is known as respiratory acidosis.

This occurs in the following conditions:

- Air obstruction as occur in chronic bronchitis, asthma like condition
- Restricted thoracic movement in pregnancy, ascites like conditions
- Impaired neuromuscular functions like poliomyelitis, polyneuritis

If there is sever retention of CO_2 patent may develop confusion, drowsiness and coma.

The arterial pCO_2 level get rise.

4. Respiratory alkalosis:

Decrease in the pCO_2 level in the lungs (Excess removal of CO_2) rise the blood pH and it is known as respiratory alkalosis.

This occurs in the following conditions:

- Hysterical over breathing
- Working at high temperature
- At high altitude
- Meningitis, encephalitis
- Salicylate intoxication

Peripheral vasoconstriction, consequent pallor, lightheadedness and tetany like characteristics are the identical mark for the respiratory alkalosis. The arterial pCO_2 level get decreased.

ELECTROLYTES:

An electrolyte is a substance that conducts electricity when dissolved in water. They are essential for a number of bodily functions.

The main electrolytes in the human body are sodium, potassium, calcium, bicarbonate, magnesium, chloride, phosphate etc..

Intracellular compartment has higher concentration of potassium, calcium, magnesium, and phosphate ions in the blood. While extracellular fluid has higher concentration of sodium chloride, bicarbonate etc. Balance between these electrolytes inside the body is essential for maintaining the good health.

Calcium

Calcium is a vital mineral that your body uses to stabilize blood pressure and control skeletal muscle contraction. It's also used to build strong bones and teeth.

Chloride

Chloride is necessary for maintaining the proper balance of bodily fluids.

Magnesium

Magnesium is a critical mineral that regulates many important functions, such as:muscle contraction, heart rhythm, nerve function.

Potassium

Potassium is particularly important for regulating heart function. It also helps maintain healthy nerves and muscles.

Sodium

Sodium is needed in the body to maintain fluid balance and is critical for normal body function. It also helps to regulate nerve function and muscle contraction.

Phosphate

The kidneys, bones, and intestines work to balance phosphate levels in the body. Phosphate is necessary for a wide variety of functions and interacts closely with calcium.