

PATHOPHYSIOLOGY

Pathology

Pathos - Suffering of disease

logos - Study of.

Pathology - Study of disease / study of suffering of disease.

Pathophysiology - Study of normal function.

Physiology - function of organs.

Defination: Pathophysiology is the scientific study changes in structure and function of body in disease condition.

cell - Structure and function of life.

tissue - Group of cell.

organs - Group of tissue.

System - Group of organ.

Health - Any individual who is comfortable with the surroundings and environment.

According to 'WHO', health is defined as the state of complete physical, mental and social well being and not merely the absence of disease or infirmity.

Disease: Loss of comfort to the body is known as disease.

Physical - strong, Mental - Strong, Social well being - Good.

So this person is called healthy person. If three portion any one is not strong or not good then the person is not healthy in according to WHO.

Any person is physical strong but Mentality and Social well being not good so the person is not healthy.

Physical - This person have some disease.

Mental - This person is not prepare in your mental.

Social well being - (A) and (B)

A is well being society or family, but B is not support in the society or family.

Terminology:

i) patient: Any individual person suffering or affected of disease, called as patient.

ii) Lesions: ~~change~~ characteristics changes in cells and tissues produced by disease condition.

iii) Morphology OR, Pathologic change: Examination of this tissue which has been change during disease condition.

Etiology: cause of disease.

i) Genetic cause - Disorder in gene.

ii) Acquired cause - outside the body (physical, chemical, Microbial agent)

pathogenesis: Mechanism of disease.

[How the micro organism damage the body part]

Clinical features:

Signs: Discovered by the physician or medical practitioner. [Before diagnosis the doctor write the median after the again come doctor]

Symptoms: Lesions felt by the patient.

[Any lesions which ask the patient by changes]

Diagnosis: Lab investigation to find out disease.

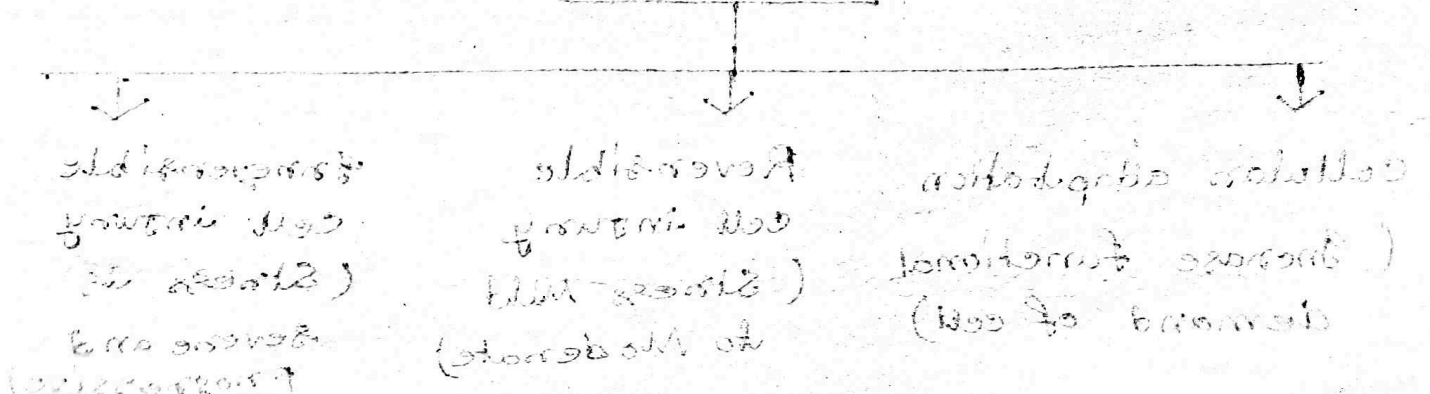
Prognosis: what is going to happen.

Treatment: what can be done to it (give medicine)

Prevention: Steps which is taken to avoid the spread and complication of disease.

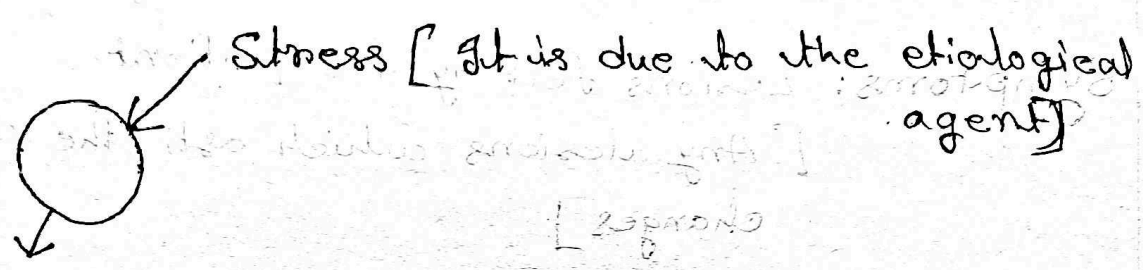
- The cell injury classified into 3 types -
- (i) Reversible cell injury
 - (ii) Irreversible cell injury
 - (iii) Apoptosis

Normal cell



Cell Injury

Rudolf Virchow given the theory is known as "cellular theory of Disease", means that the disease occurs due to ~~an~~ abnormality or disorders at the level of cells [on the beginning of the disease is due to loose of cellular function].



changes internal and external environment.

Defination:

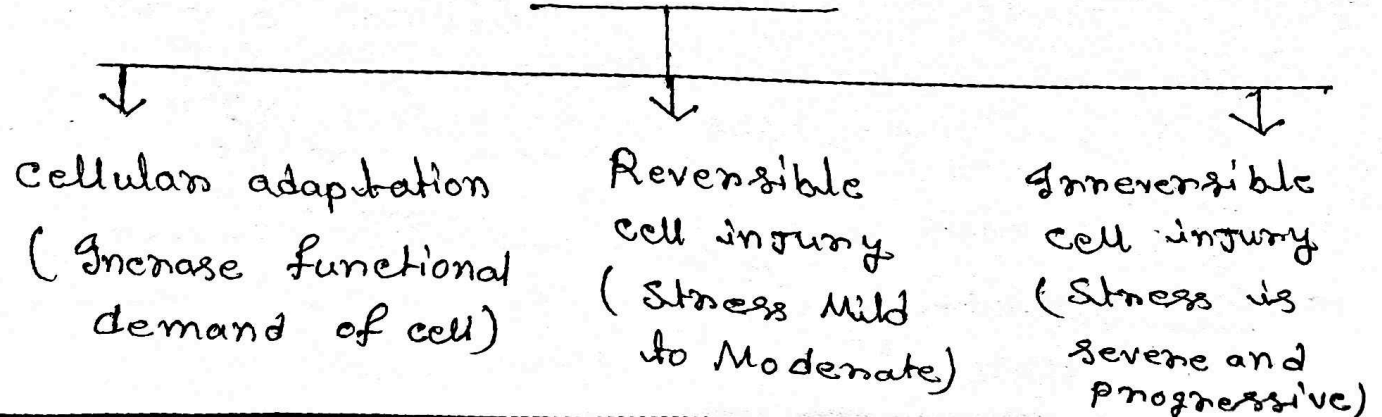
The change in the internal and external environment of the cell due to the stress encountered by the cell is known as cell injury.

classification of cell injury:

The cell injury classified into 3 types.-

- These are -
- (i) cellular adaptation.
 - (ii) Reversible cell injury.
 - (iii) Irreversible cell injury.

Normal cell



cellular Adaptation:

When there is increase functional demand of the cell, the cellular undergo some changes. or they will adopt some changes that is known as cellular adaptation.

It is two part -

- i) physiological and ii) pathological
- i) physiological (according physiological need ^{change} of our body)

Ex - During pregnancy. (Enlargement muscle of the uterus space is increase ^{for} baby)

- ii) pathological (During disease condition)

Ex - cardiovascular disease (Hypertension)

Reversible cell injury:

If the stress is mild to moderate, the injured cell can recover it self, remove the stress of the cell and go to normal level. this process is known as reversible cell injury.

Stress is mild to moderate. Injured cell can recover it self.

↓ process
Reversible cell injury.

Irreversible cell injury:

If the stress is severe and ^{persistent} ~~progressive~~ then that will lead to the cell injury which not come in normal level of cell and any power cell ~~set~~ death. This type of cell injury called as Irreversible cell injury.

Etiology of cell injury

① Etiology of cell injury meaning causes of cell injury. [Etiology means cause]

① Etiology of cell injury are 2 types. These are:

— (i) Genetic Cause

(ii) Acquired Cause.

Genetic Cause:

① The meaning of ~~gen~~ genetic cause is due to the abnormalities or dysfunction in the gene.

① There are different defects which can come under Genetic causes which will lead to the cell injury.

These are:

(a) Development defects:

The defects which occur to the embryo.

① It occurs due to the morphogenesis.

① Morphogenesis meaning formation and differentiation of cells in the tissue, or cells in the organs.

① Due to the error in the morphogenesis and the agent such as physical agent, chemical agents or drugs can cause the defects in the morphogenesis, such agent is known as "teratogens".

① This teratogens will lead to developmental defects which come under the genetic cause which will be lead to the cell injury.

(b) cytogenetic (karyotypic) Defects:

chromosomal Abnormalities.

Ex → Turner Syndrome *

(7)

* [It is a syndrome in which a female is born with the deficiency of one sex chromosome]

23 pairs of chromosomes

22 pair = Autosomes

1 pair = Sex chromosomes.

[$45X = \text{Autosome}$
 $X = \text{Sex chromosome}$]

In the Turner Syndrome ($45X, X$)

→ That may lead to the deficiency of fertilization, that will inhibit the fertilization, so such types of chromosomal defect is known as cytogenetic (Karyotypic) Defects.

③ Single gene defects: (Mendelian Disorders)

It occurs due to the sudden mutation of a single gene.

④ Multifactorial Defects:

① Multifactorial means two or more than one are involve.

② In this it consist of both genetic causes and acquired causes.

Ex - Diabetes, hypertension.

Down Syndrome:

Down Syndrome is a genetic cause in which chromosome no 21 and there are extra copy present it is known as down syndrome.

Trisomy 21 - Tri - three no.

Chromosome 21 and three extra copy present.

Acquired cause:-

The agents or the foreign agents which are causing damage to our cell, resulting in cell injury is called as acquired cause.

① Hypoxia:-

Hypo - Decrease, oxia - oxygen (O_2)

Decrease of oxygen level in blood.

Ischaemia: Decrease / Inadequate blood supply.

It occurs due to reduced blood supply. In medical term it is called as Ischaemia.

① O_2 carrying capacity of blood (Anaemia, CO-poisoning)

RBC $\rightarrow$ It is a fluid connective tissue, Hemoglobin carry O_2 to tissue of the cell.

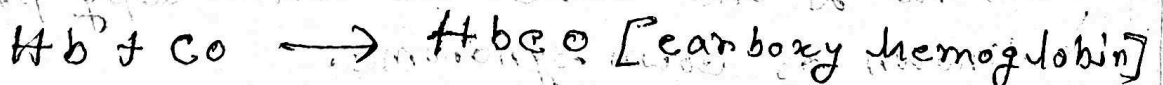
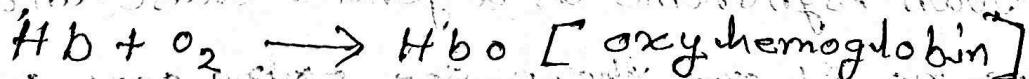
Consist $Hb + O_2 \rightarrow HbO$ (oxygen bind Hemoglobin)

CO-poisoning: [^{carboxy} ~~carboxy~~ ^{mono} poisoning]

CO - body - higher affinity to bind with Hemoglobin

Travel to cell $\leftarrow HbCO \leftarrow$
(Carboxy Hemoglobin)

which is not good for our health.



② Microbial agent:

Such as Bacteria, Virus, Protozoa, Fungi, Rickettsiae etc., that will cause the damage to the cell, resulting in cell injury.

③ Chemical agent:

- ① Strong acids and alkali. $\rightarrow$ HCl , H_2SO_4 , HNO_3
- ① conc. H_2SO_4 Arsenic, cyanide, mercury etc.
- ① Insecticides and pesticides — phannhouse and cultivation
- ① Air pollutants.
- ① Alcohol and narcotic drugs.

④ Psychogenic Agents:

Any agents which damage to the CNS (central nervous system)

Ex - Schizophrenia, Depression etc.

(receptor) Dopamine $\rightarrow$ 5-HT (Hydroxy tryptamine)
Schizophrenia $\rightarrow$ Increase in dopamine and 5-HT.

⑤ Physical agent: (TERM)

① 'TERM' means -

T = Thermal trauma.

E = Electricity.

R = Radiation

M = Mechanical trauma.

Thermal trauma $\rightarrow$ Thermal means temperature.

like Excessive temperature change
like heat and cold.

Electricity $\rightarrow$ Electric shock.

Radiation $\rightarrow$ There are so many rays like α -ray, γ -ray, X-ray, β -ray etc; These are not good for our health.

(10)

Rapid change in atmosphere temperature. Ozone (O_3) gas is present these are protect layers between Sun and earth.

There are two type of ray come to the sun harmful and not harmful.

What about harmful ray good to come to earth. And not harmful ray do not entry the ozone layer to reflect back to sun.

UV ray do absorb the body skin convert cholesterol or fatty acid to produce vitamin D.

Mechanical trauma: In any kind of Road accident.

⑥ Ageing:

① On growing age on an old age or ageing can also be the cause for cell injury.

② Inability of cells to undergo replications and repair.

⑦ Immunological:

① The study of immunity is known as immunology.

② Autoimmune disorders.

[In this the production of Auto antibody that will damage our body cells.]

Ex - Rheumatoid arthritis.

③ Hypersensitivity reaction.

[Due to inappropriate antigen antibody reaction]

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⑧ Iatrogenic: (Error in Judgement)

- ① Relating to illness caused by medical examination or treatment.
- ① Drugs may cause side effects which can lead to Iatrogenic disease.
- ① Ex - radiation therapy and chemotherapy - necessarily aggressive for therapeutic effect: frequently produced such iatrogenic effects as hair loss, hemolytic anemia, diabetes insipidus, vomiting, nausea etc.

⑨ Idiopathic: (unknown cause)

- ① Relating to or denoting any disease or condition which arises spontaneously or for which the cause is unknown.

Ex - Primary hypertension.

⑩ Nutritional Imbalance:

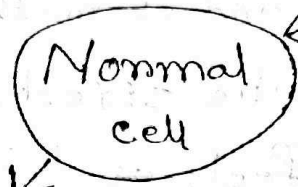
- ① Nutritional imbalance is caused by inability of the body to absorb certain nutrients or result from a

Ex - Marasmus, Kwashiorkor etc.

Cellular Adaptations

Cellular Adaptation:

When there is increase functional demand of the cell, the cell undergo some changes or they will adopt some changes that is known as cellular Adaptation.



① Cellular Adaptation may be physiological or it can be pathological.

② physiological:

It means the cell will adjust itself according to the physiological need of the body.

③ pathological: (pathology means suffering disease)

④ But in this the cell will adapt non-lethal pathologic injury.

⑤ They provides the cells with the ability to survive in their environment and perhaps escape injury.

⑥ cellular adaptation may be reversible.

⑦ But sometimes if there is a irritant stimulus in body than it may lead to dysplasia which may progress to carcinoma during the death of the cell.

Mechanism of cellular Adaptation:

- ① Alterations in cell surface receptor binding.
- ① Alterations in signal for protein synthesis.
- ① Synthesis of new proteins to from target cells.
- ① Cell can adapt themselves by undergoing 5 different conditions.

1. Atrophy.

2. Hypertrophy.

3. Hyperplasia.

4. Metaplasia.

5. Dysplasia.

1. Atrophy:

- ① Decreased in both size and number of parenchyma cells of an organ or tissue.
- ① Acquired loss of size due to reduction of cell size and number of parenchyma cells in an organ.

Causes of atrophy:

i) physiologic

ii) pathologic

i) physiologic:

① Atrophy of brain with ageing.

① Atrophy of gonads after menopause.

① Atrophy of lymphoid tissue in lymph nodes, appendix and thymus.

① A normal process of aging of in some tissue which could be due to loss of endocrine stimulation or anorexia.

Menopause:

It is also known as the climacteric, is the time in most women's lives when menstrual periods stop permanently.

It typically occurs between 40 to 52 years of age.

ii) Pathologic:

- ① Starvation (deficiency of the nutrition) atrophy.
Eg - Marasmus, Kwashiorkor etc.
- ① Ischaemia Atrophy (Decrease / Inadequate blood supply)
Eg - Arteriosclerosis.
- ① Disuse Atrophy (It is a muscle atrophy)
- ① Neurophatic Atrophy
- ① Endocrine Atrophy.
- ① Idiopathic Atrophy.
- ① Pressure Atrophy.

3. Hyperplasia:

① 'Hyper' means 'increase' and 'plasia' means 'the growth of the new cells'

- ① Increase in the number of parenchymal cells resulting in enlargement of the an organ.
- ① An increase in the number of cells in an organ or tissue, which may then have increased volume.

Cause:

(i) Physiologic:

- ① Hyperplasia of the female breast epithelium at

Puberty on in pregnancy.

① Normal endometrium after a normal menstrual cycle.

① Regeneration of epidermis after skin abrasion.

ii) pathologic :

① Formation of granulation tissue during the wound healing.

① Pseudo-carcinomatous hyperplasia of the skin.

① Endometrial hyperplasia.

4) Metaplasia :

① 'Meta' means 'transformation' and 'plasia' means the growth of the new cells.

① It is defined as the reversible change of one type of epithelial or mesenchymal adult cells into another type in response to abnormal stimulus and revert back to normal on removal of stimulus.

causes :

① Changes in environment.

① Irritation or Inflammation.

① Nutritional

5) Dysplasia :

① It means disordered cellular development.

① It is accompanied by metaplasia and hyperplasia.

① It also known as atypical hyperplasia.

① Dysplasia occurs in epithelial cells.

① Epithelial dysplasia characterized by cellular proliferation and cytological change.

① Dysplasia may progress to carcinoma in situ.

Cancer on surface layer or invasive cancer)

2. Hypertrophy:

- ① Hyper means 'increase' and trophy means nourishment or growth.
- ① Increase in the size of parenchymal cells resulting in enlargement of an organ or tissue.
- ① An increase in the size of the cells and with such change, an increase in the size of the organ.

Cause:

i) physiologic - physiologic growth of the uterus during pregnancy involves both hypertrophy and hyperplasia. (Enlargement of size of uterus during pregnancy)

ii) pathologic:

Enlargement of cardiac muscle.

Ex - Systemic hypertension.

- ① Increased workload, hormonal stimulation and growth factors stimulation.
- ① Hypertrophy of heart the most common stimulus is chronic hemodynamic overload.

Pathogenesis of Reversible Cell Injury

Due to Hypoxia and Ischaemia



Decrease in ATP



Decrease in Intracellular pH (cytosol)

Damage to Na⁺ Pump (membranes)

Decrease in protein synthesis (RER) [Rough endoplasmic Reticulum]



Ultrastructural / Functional changes

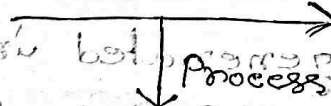


Reversible cell injury

If the stress is mild to moderate, the injured cell can recover itself, this process is known as Reversible cell injury.

Stress is

mild to moderate



Injured cell can Recover itself.

Reversible cell injury

Pathogenesis of means 'mechanism', how the reversible cell injury is caused and how the injured cell can recover itself and that is due to the hypoxia and Ischaemia.

Hypoxia:

Decrease in O_2 supply or O_2 level to our cells and the tissues.

① This condition can occur in our body when there is a RBC disorders or any disorders of RBC and lung disease. In that case there will be the decrease in the supply of the O_2 to our respective cells and the tissues.

Ex - Anaemia.

Ischaemia:

① Decrease in blood supply to the cells and tissues is term as Ischaemia.

① Due to Hypoxia and Ischaemia, there will be a decrease in ATP. ATP is a energy molecules, [For the metabolism, protein synthesis, lipid synthesis and all the other biochemical process etc.]

ATP $\rightarrow$ Adenosine Triphosphate.

For an example - Coronary Artery Occlusion Myocardial contractibility.

Decrease in Intracellular pH:

① The ATP can be generated in our body by two ways — ① Aerobic Respiration.

(Oxidative phosphorylation)

② Anaerobic Respiration.

① Aerobic Respiration:

① It means the respiration where taking place with the presence of oxygen.

① The ATP can be generated in the presence of oxygen which is known as Aerobic respiration.

② Anaerobic Respiration:

① It means the respiration where taking place without the presence of oxygen.

② the ATP can be generated to without the presence of oxygen which is known as Anaerobic respiration.

Due to hypoxia ($\downarrow O_2$ Supply):

- i) In this condition No Aerobic respiration takes place
- ii) In this condition Anaerobic respiration takes place

③ In this case the glucose or glycogen converted into lactic acid or lactate.

So more the anaerobic respiration more the formation of lactic acid which takes place which will lead to the Accumulation of lactic acid which causes Lactic Acidosis.

on, Accumulation of lactic acid is known as Lactic acidosis.

Anaerobic respiration:

Glucose $\rightarrow$ Lactic Acid $\rightarrow$ Accumulation of lactic acid causes Lactic acidosis.

↓
leads to clumping

of a nuclear chromatin.

↓
Decrease intracellular pH

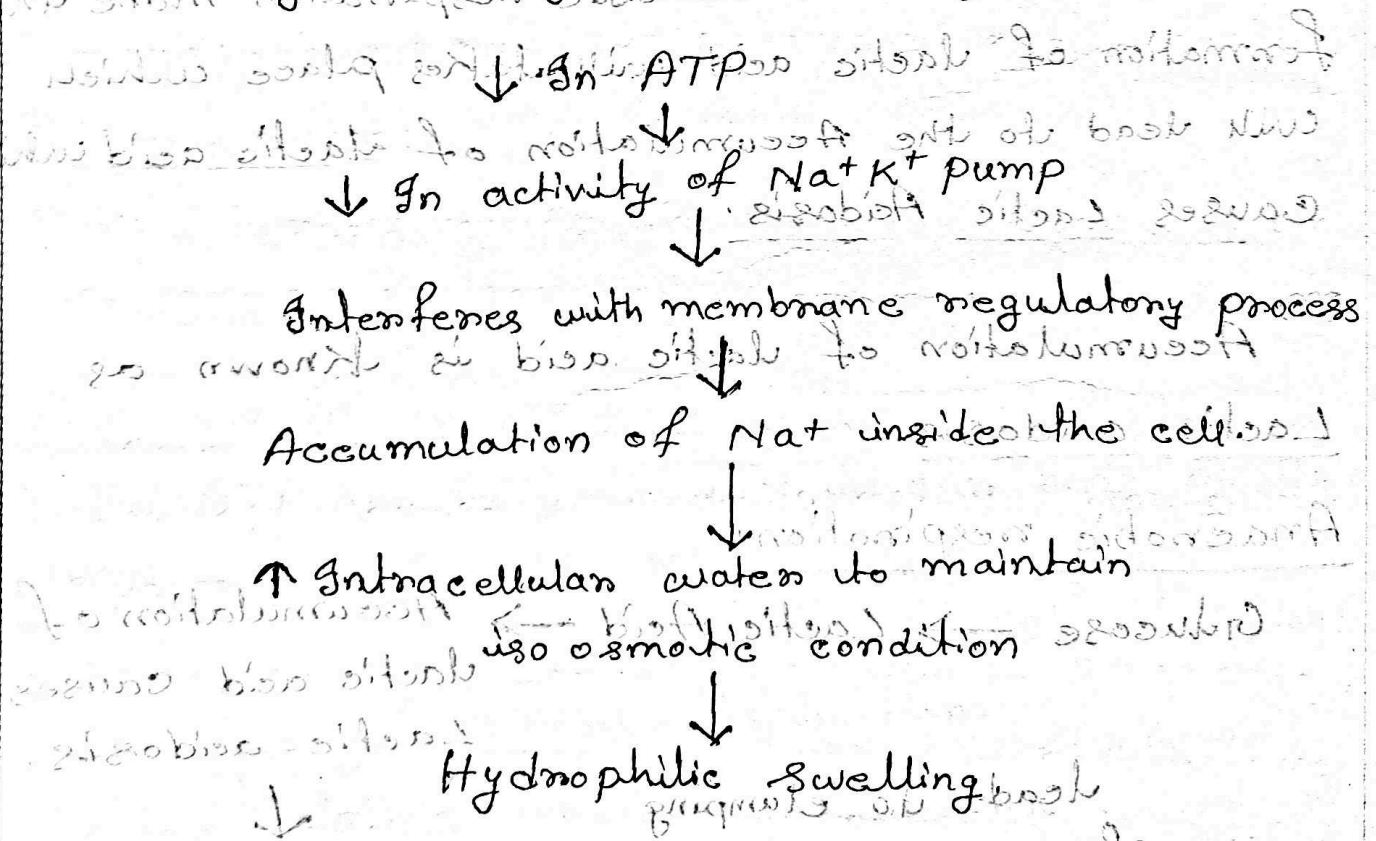
* clumping $\rightarrow$ gathering.

① Damage to Na^+ pump (membrane):

plasma membrane act as a semi-permeable membrane which helps to exchange the intracellular and extracellular in by diffusion.

$\text{Na}^+ + \text{K}^+ + \text{ATPase} \Rightarrow$ In normal condition Na^+ (extracellular ion) will go inside to the cell and K^+ (intracellular ion) will come out of the cell through the diffusion.

But the condition in decrease in ATP will lead to the decreases in activity of $\text{Na}^+ \text{K}^+$ pump and this interferes with membrane regulatory process. More number of Na^+ will go inside the cell that will lead to the accumulation of Na^+ inside the cell and lead to increase intracellular water to maintain iso-osmotic condition and finally caused hydrophilic swelling.



Failure Ca^{2+} pump

↓ Influx

Swelling and phospholipids amorphous density
(especially in mitochondria)

① Decrease in protein Synthesis (RER):

Due to hypoxia, endoplasmic reticulum and golgi apparatus are swells up.

The normal function of ribosomes is protein synthesis which are present in rough endoplasmic reticulum.

Due to hypoxia and ischaemia the ribosomes are detached from RER and polysomes are converted into monosomes and dispressed in cytoplasm inactivating their function.

If the stress or etiological agent is removed, there are some ultrastructural and functional changes and biochemical changes takes place and injured cell recover and comes to the normal label, it is called as reversible cell injury.

Morphology of reversible cell injury:

What are the changes takes place during curement of injured cell, termed as morphology of reversible, cell injury.

1. Hydropic change:

- ① Accumulation of water within the cytoplasm of cell.
- ② Also known as cloudy swelling or vacuolation, degeneration.
- ③ It occurs when there is membrane damage and loss of ability to maintain ionic and fluid homeostasis.

② Hyaline change:

- ① Hyaline is a proteinaceous material.
- ① This change occurs during heterogenous pathological condition.
- ① The change is seen maybe intracellular and extracellular.
- ① Intracellular hyaline change is seen in epithelial cells.

Ex - Hyaline droplets.

- ① Due to excessive reabsorption of plasma proteins in proteinuria in proximal tubule epithelial cell the intracellular hyaline change is seen.
- ① Extracellular hyaline is seen in connective tissue.
- ① Ex - Hyaline arteriosclerosis in renal vessels during hypertension.
- ① Hyalinised glomeruli in chronic glomerulonephritis.

③ Mucoid change:

- ① Mucoid means mucous like, such that secondary product of mucous gland combined with proteins and mucopolysaccharides.
- ① Mucin which is released by epithelial cells, mucous gland and connective tissue, which is mainly contains glycoproteins.
- ① Epithelial mucin, Ex - cystic fibrosis of pancreas.
- ① Such that accumulation of mucous in pancreas tube which helps to transfer hormones like glucagon (α cell), insulin (β cell) and somatostatin (δ cell).
- ① Other examples of epithelial mucin are ovarian tumor.

Stomach cancer.

① Connective mucin, Ex - myxomas such that benign, to tumor of heart.

① other ex is neurofibromas.

4. Fatty change:

① Also called as steatosis.

① Accumulation of neutral fat in the parenchymal cells.

① Maximum accumulation occurs in liver due to presence of fat tissue.

① Fat can also accumulated in non-fatty tissues in heart skeletal muscle, kidney etc.

Mechanism:

1) Increase peripheral mobilization of free fatty acids and uptake into cells.

Ex - Diabetes mellitus.

2) Increase conversion of fatty acids into triglycerides during disease condition.

3) Reduce oxidation of triglycerides into acetyl-CoA.

Eg - Hypoxia.

4) Deficiency of lipid acceptor proteins (apoproteins) during genetic disease and protein malnutrition, the apoproteins can't carry the triglycerides to the respective cells and tissues may lead to the accumulation of fat.

↑
[accumulation of fat]
↓

Pathogenesis of Irreversible cell injury

Irreversible cell injury:

If the stress is severe and persistent than that will lead to the cell injury which not come in normal level of cell and any power cell death. This type of cell injury called as Irreversible cell injury.

Due to Hypoxia / Ischaemia ($\downarrow$ level of blood supply)



Decrease ATP Generation.



($\downarrow$) Synthesis of membrane phospholipid

$\uparrow$ In cytosolic Ca^{++} : Toxic O_2 radicals

Reperfusion

Reperfusion

Mitochondria $\uparrow Ca^{++}$ O_2 , H_2O_2 , OH^-

$\downarrow$ Ex-Diaphorase

$\uparrow$ Cytosolic Ca^{++}

Lipid peroxidation

DNA damage.



phospholipase activation

Protease activation.



$\uparrow$ Loss of membrane phospholipid

Lipid breakdown products.

Cytoskeletal injury (microfilaments, microtubules)

Membrane Damage

Membrane damage

↓
Liberation of Intracellular Enzymes



↓	↓	↓
Nuclear changes pyknosis. karyolysis karyorrhexis	cell death myelin figures	Serum enzyme estimation SCOT, LDH, CPK-MB, CTn.

Pathogenesis of Irreversible cell injury:

- ① Due to hypoxia and ischaemia the generation of ATP become decrease by the anaerobic respiration AND it lead to
- ① Due to decrease in ATP generation the synthesis of membrane phospholipid and it lead to the injury of plasma membrane.
- ① So the extracellular Ca^{2+} ions are influx rapidly and the concentration of Ca^{2+} become increased in cytoplasm, called cytosolic Ca^{2+} .
- ① After influx of Ca^{2+} ions it will enter into the mitochondria and leads some morphological changes like, it make vesicles or cavity inside that will lead to the mitochondrial injury.
- ① When the concentration of Ca^{2+} become increase inside the cell phospholipids and protease enzyme become activate.
- ① Once the phospholipase enzyme become active, it will break down the lipid formation and phospholipid which are present in the membrane, and lead to the damage of plasma membrane.

① After activation of protease enzyme, it will lead to the injury of cytoskeletal which are small strands of protein fibres like microfilament and microtubules.

① Microfilament are smallest protein fibres, it helps to the cell and maintain its size.

① Microtubules are largest protein fibres, it helps to movement of organelles inside the cell.

① Due to the injury of cytoskeletal protein fibres the cell membrane become damaged.

① Due to the decrease of ATP generation the toxic O_2 radicals like O_2 , H_2O_2 and OH^- are produced and lead to DNA damage by lipid peroxidation, it also lead to the membrane damage.

① other lytic enzymes such as ATPase is activated due to the increase in cytosolic Ca^{2+} which cause further depletion of ATP.

① Due to the membrane damage the liberation of intracellular enzyme takes place, DNA or nucleoproteins are damaged by activated lysosomal enzymes.

Ex - endonucleases, proteases, that will lead to the irreversible damage of nucleus or some nuclear changes takes place like pyknosis, karyorrhexis and karyolysis.

Pyknosis → condensation and clumping of nucleus.

Karyorrhexis → Nuclear fragmentation or divided into smaller bits.

Karyolysis → Dissolution of nucleus.

- ① Due to DNA damage it will activate the proapoptotic proteins which are going to injure the cell and leading to cell death.
- ② By the decrease in ATP the membrane of lysosomal membrane become damage the hydrolytic enzymes. once the lysosomal membrane become damage the hydrolytic enzymes are escape or release. These enzymes are ATPase, DNAase, RNAase, protease etc.
- ③ After activation of this enzymes by the deficiency of O_2 and acidic pH, enzymatic digestion of cellular compartment takes place and leading to the cell death.
- ④ The death cells are replaced by mass of phospholipides, which is known as myelin figures. The dead cells are phagocytized by macrophages.
- ⑤ Some of these hydrolytic enzymes enters into the serum, which are used as a clinical parameters of cell death.
- ⑥ There will be some imbalance of SGOT (serum glutamic oxaloacetic transferase and ~~SGPT~~ SGPT (serum glutamic pyruvate Transaminase) and these these will guide liver necrosis or biohepatic, etc.
- ⑦ When the creatin kinase (CK) - MB and Troponins which are present in heart muscle, become imbalance, the myocardial infarction (MI) is indicated.



myocardial infarction

Morphology of Irreversible cell Injury

1. Autolysis: Self digestion.

Autolysis is the disintegration of cell by its own hydrolytic enzymes liberated from lysosomes.

- ① It occurs in living body when surrounded by inflammatory reaction.
- ① It is rapid in tissue rich in hydrolytic enzymes. Such as ~~pan~~ pancreas and gastric mucosa.
- ① Slow in fibrous tissue.
- ① Intermediated in heart, liver, kidney.

2. Apoptosis:

In greek - falling off or dropping off. Apoptosis means co-ordination and programmed cell death.

- ① It is a form of cell death and is controlled or regulated by the rate of cell division.
- ① If the cell is not needed in our body it will undergo cell death which is known as apoptosis.

Mechanism of Apoptosis:

Normal cells

↓
Cell shrinkage; chromatin condensation

↓
Blebs (bubbles or vesicle like structure) on membrane.

↓
Nuclear collapse; continued blebbing.

↓
Apoptotic bodies formation.

↓
Lysis of apoptic bodies.

3. Necrosis:

Localised area of death tissue by hydrolytic enzymes liberated from dead cells.

①. The difference between autolysis and necrosis is - if the hydrolytic agents causing cell death which are released lysosome, is known as autolysis. But after causing damage to the cell, these hydrolytic enzymes which are present in the damage cell, they will cause damage to the other normal cell, this is known as necrosis.

Difference between Apoptosis and Necrosis:-

Apoptosis	Necrosis
i) Causative agents. ii) physiologic: Developing embryo, Intramatrial celling. iii) pathogenic: cell death in tumen by chemotherapeutic agents, during biohepatitis.	i) Hypoxia, Ischaemia, Chemicals, Toxins, Immunological agents etc.
2) Formation of apoptic bodies.	2) Damaged organelles.
3) No inflammatory reaction takes place.	3) Inflammatory reaction takes place.
4) Death of single cell takes place.	4) Death of multiple cell
5) phagocytosis of apoptic bodies by macrophage	5) Formation of cell debris (storage of dead cell)

6) cell shrinkage takes place.

6) cellular swelling takes place.

7) chromatin condensation takes place.

7) Nuclear disruption / dislocation.

8) cytoplasmic blebs on membrane.

8) Membrane disruption takes place.

Type of Necrosis:

There are five types of Necrosis —

- i) coagulative Necrosis
- ii) Liquefaction Necrosis
- iii) Caseous Necrosis
- iv) Fat Necrosis
- v) Fibrinoid Necrosis.

i) coagulative Necrosis:

This is the most common type of necrosis caused by irreversible focal injury, mostly from sudden cessation of blood flow and less often from bacterial and chemical agents. The organs commonly affected are the heart, kidney and spleen.

The necrosed cells are swollen and appear more eosinophilic than the normal, along with nuclear changes.

ii) Liquefaction Necrosis:

Liquefaction Necrosis occurs commonly due to ischemic injury and bacterial or fungal infections. It occurs due to degradation of tissue by the action of powerful hydrolytic enzyme.

Ex - Infarct brain and abscess cavity.

The cyst wall is formed by proliferating capillaries, inflammatory cells and gliosis in the case of brain and proliferating fibroblasts in the case of abscess cavity.

iii) Caseous Necrosis:

caseous Necrosis is found in the centre of foci of tuberculous infections. It combines features of both coagulative and liquefactive necrosis.

The Surrounding tissue shows characteristic granulomatous inflammatory reaction consisting of epithelioid cells with interspersed giant cells of Langhans or foreign body type and peripheral mantle of lymphocytes.

iv) Fat necrosis:

Fat necrosis is a special form of cell death occurring at two anatomically different locations but morphologically similar lesions. These are, following acute pancreatic necrosis and traumatic fat necrosis commonly in breasts.

In the case of pancreas, there is liberation of pancreatic lipases from injured or inflamed tissue that results in necrosis of the pancreas as well as of the fat depots throughout the peritoneal cavity, and sometimes, even affecting the extra abdominal adipose tissue.

Fat necrosis hydrolyses neutral fat present in adipose cells into glycerol and free fatty acids. The damaged adipose cells assume cloudy appearance.

v) Fibrinoid necrosis:

Fibrinoid necrosis is characterised by deposition of fibrin-like material which has the staining properties of fibrin. It is encountered in various exam of immunologic tissue injury, arterioles in hypertension, peptic ulcer etc.

Fibrinoid necrosis is identified by brightly eosinophilic, hyaline-like deposition in the vessel-wall. Necrotic focus is surrounded by nuclear debris of neutrophils. Local haemorrhage may occur due to rupture of the blood vessel.

Pathogenesis of cell injury due to free radicals.

Although oxygen is the lifeline of all cells and tissue, its molecular forms as reactive oxygen molecules or reactive oxygen species can be most devastating for the cells.

$$\begin{aligned} \text{Atomic No. of } O_2 &\rightarrow 8 \\ 8 - 2 \\ &= 6 \end{aligned}$$

valency,

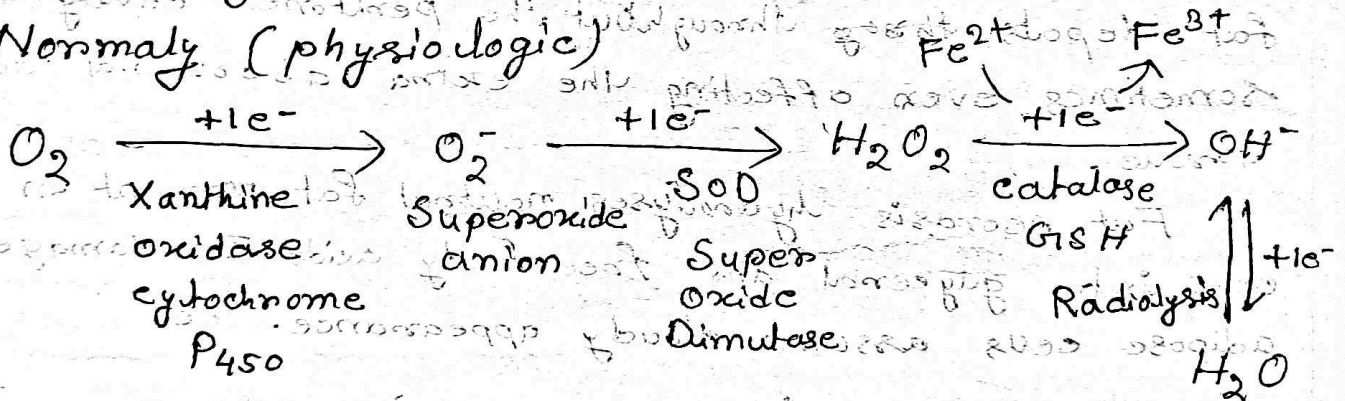
$$\begin{aligned} v &= \text{Atomic No. of atom} - n (\text{outer part of atom electron}) \\ &= 8 - 6 \\ &= 2. \end{aligned}$$

In cell injury there are two type of condition:-

① Normal (physiologic)

② Abnormal (pathologic condition)

① Normal (physiologic)



② Abnormal (pathologic condition)

- i) Ionizing radiation
- ii) Inflammation
- iii) Heavy metals
- iv) Drugs and chemicals
- v) Management.

In abnormal pathology condition.

i) **Ionising radiation:**

when the water (H_2O) falls on the skin then breakdown water molecule produce OH^- and cause cell injury. (Ion will be breakdown water molecule produce formation result cell injury.)

ii) **Inflammation:**

There are some neutrophils formation of free radicals and damage to cell cause cell injury. In inflammation cell is not oxidase and not produce water because this condition cell already injury by neutrophils.

iii) **Metals:**

There are some metals cause cell injury like Fe^{2+} , Cu^{2+} .

Transferrin - which is regulant iron, increase iron label in the blood and cause cell damage.

Accumulation of Fe^{2+} hemochromatosis.

Accumulation of Cu^{2+} Wilson's disease.

iv) **Drugs and chemicals:**

Most of the drugs are metabolised in liver formation free radical and finally liver cell will damage.

Acetaminophen, paracetamol.

v) **Management:**

Anti-oxidant - vit A, vit C, vit E.

Serum protein - Transferrin.

Pathogenesis of cell injury due to chemicals:

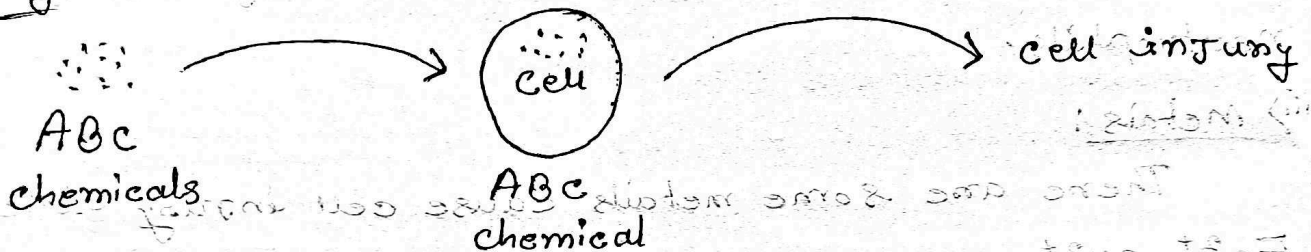
In chemically there are two process for causes cell injury. These are -

- 1) By direct cytotoxicity.
- 2) conversion of chemicals into reactive metabolites.

1) By direct cytotoxicity:

Some chemicals combine with components of the cell and produce direct cytotoxicity without requiring metabolic activation.

Eg -



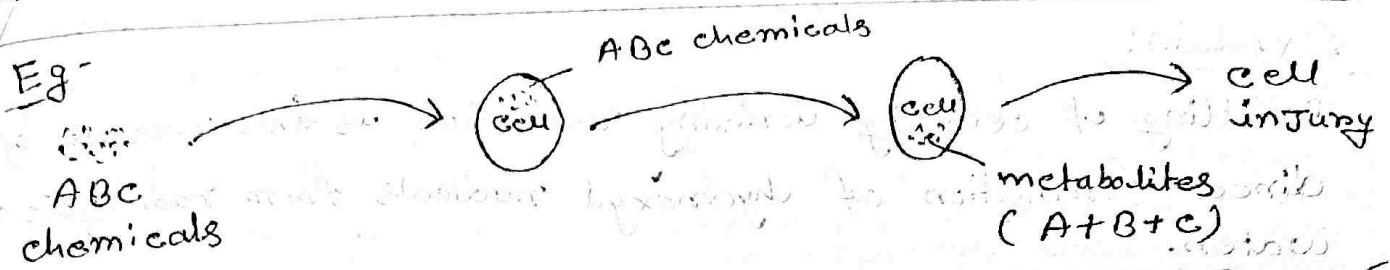
The cytotoxic damage is usually greatest to cells which are involved in the metabolism of such chemicals like Eg -

$MgCl_2$ (Mercuric chloride) poisoning, the greatest damage occurs to cells of the alimentary tract where it is absorbed and kidney where it is excreted.

Chemotherapeutic agents used in treatment of cancer toxic & heavy metals such as mercury, lead and iron.

2) Conversion of chemicals into reactive metabolites: (metabolism / Break down)

The mechanism involves metabolic activation to yield ultimate toxin that interacts with the target cells, the target cells in the group of chemicals may not be the same cell that metabolizes the toxin.

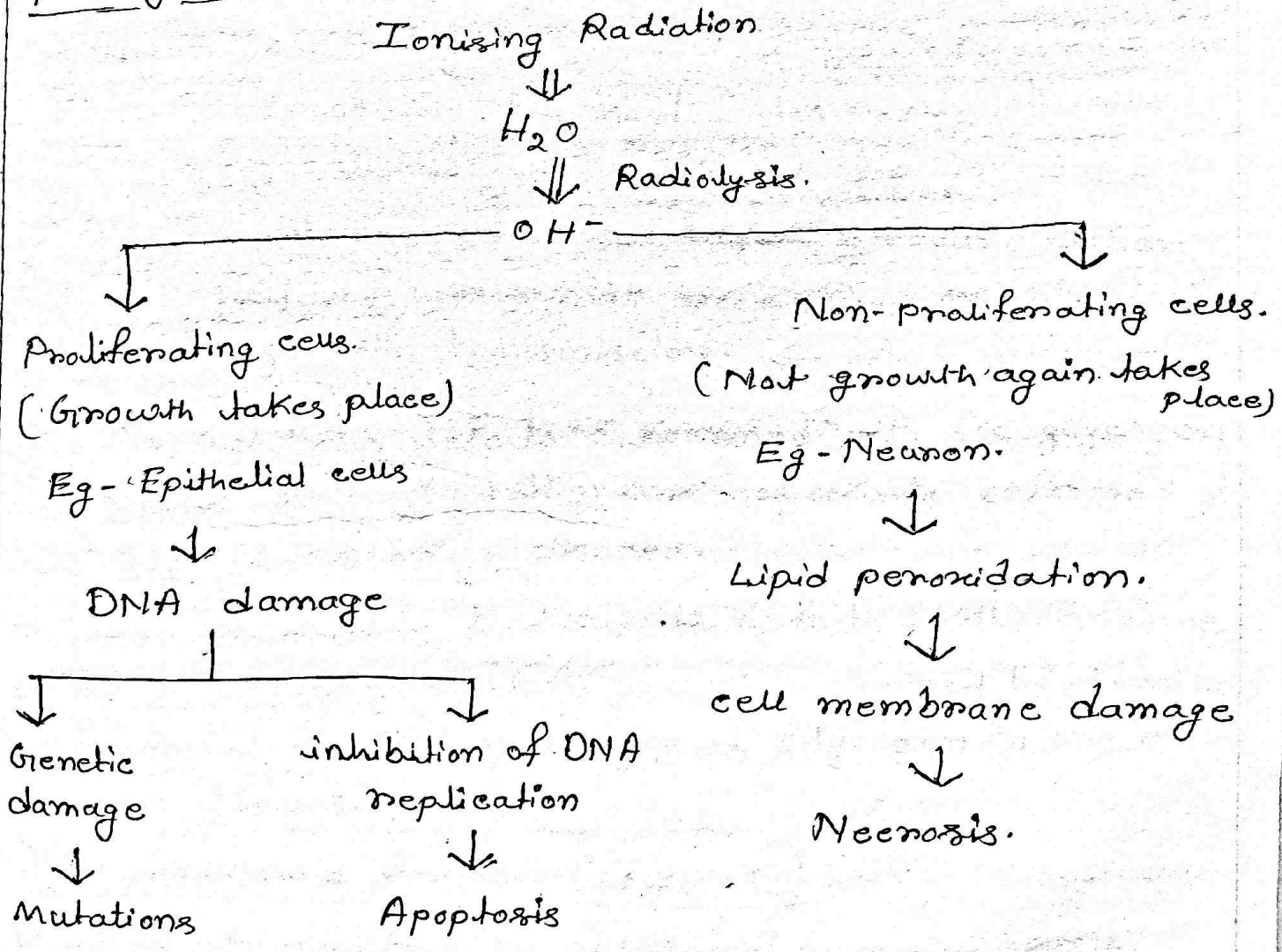


chemicals → produce toxin (harmful for cell) ↓

Eg - Toxic liver necrosis caused by (cell) acetaminophen and Bromobenzene. interact to target cell. ↓ cell injury

It produces profound liver cell injury by free radical generation. Other mechanism of cell injury includes direct toxic effect on cell membrane and nucleus.

Pathogenesis of cell injury due to physical agent:

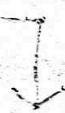


Explain:

- ① Killing of cells by ionising radiation is the result of direct formation of hydroxyl radicals from radiolysis of water.
- ② These hydroxyl radicals damage the cell membrane as well as may interact with DNA of the target cell.
- ③ In proliferating cells, there is inhibition of DNA replication and eventual cell death by apoptosis.
- ④ In non proliferating cells there is no effect of inhibition of DNA synthesis and in these cells there is cell membrane damage followed by cell death by necrosis.

Pathogenesis of cell injury due to physical agents

Ionising radiation



Proliferating cells

Non-proliferating cells

(Not forming new cells)

Storage Disease:

- i) Storage disease or inborn error of metabolism is for chemically distinct group of disorder occurring due to genetic defect in the metabolism of carbohydrate lipid and protein resulting in intracellular lipid and protein resulting in intracellular accumulation metabolites.
- ii) These substances may collect within the cell through out the body.
- iii) Since lysosomes undergo intracellular digestion the material is naturally stored in lysosome and hence generic name lysosomal storage disease.
- iv) Organ containing numerous phagocytic cells like the liver and spleen are most commonly involved in storage disease.
- v) All the storage diseases occurring occurs either as a result of autosomal recessive or sex linked recessive genetic transmission.

- ① The metabolic defects concerned with the glycogen synthesis and degradation are collectively referred to as glycogen storage disease.
- ② These disorders are due to defects in the enzymes.
- ③ The inherited disorders are characterized by deposition of normal or abnormal type of glycogen in one or more tissues.

Von Gierke's disease (Type - I)

- ① It is transmitted by autosomal recessive trait.
- ② Enzyme deficiency: glucose 6-phosphatase.
- ③ The enzyme is absent in liver cells and intestinal mucosa.

- ① Liver cells, intestinal mucosa and renal tubular epithelial cells are loaded with glycogen. which is normal in structure but metabolism not available.

Clinical and Biochemical Features:

① Fasting hypoglycemia:

→ Hypoglycemia, decreases insulin secretion which in turn inhibits protein synthesis causes stunted growth.

Lactic acidemia:

→ Glucose is not synthesized from lactate produced in muscle and liver.

Lactate level in blood increases and the pH is lowered.

Hyperlipidemia:

① Fat is utilized as energy source, which leads to lipaemia, acidaemia and ketosis.

① Excess of acetyl CoA resulting in increased cholesterol levels. produce xanthomas.

① There is a blockade in gluconeogenesis.

Hyperuricemia →

① Glucose 6-phosphate that accumulates is diverted to ATP shunt, leading to increased synthesis of ribose phosphates which increases the cellular levels of phosphoribosyl pyrophosphate and enhance the metabolism of purine nucleotides to uric acid.
(gouty arthritis)

Pompe's disease (Type - II)

① Enzyme deficiency: lysosomal, α -1,4-glucosidase (acid maltase)

① Glycogen accumulates in lysosomes in all most all the tissues.

- ① Enlargement of heart (cardiomegaly)
- ① Nervous system is also affected.
- ① No hypoglycemia.
- ① Death occurs due to heart failure.

Cori's disease (Type - III) Limit dextrinosis (Fombe's Disease).

- ① Enzyme deficiency $\rightarrow$ Amylo α -1,6-glucosidase.
- ① Organs affected $\rightarrow$ Liver (Hepatomegaly), muscle, Heart, leucocytes.
- ① Branched chain glycogen accumulates.
- ① Clinical manifestations are similar to von von Gierke's disease but glycogen is abnormal.
- ① Moderate hypoglycemia.

Anderson's disease (amylopectinosis) (Type IV)

- ① Enzyme deficiency $\rightarrow$
 - ① Glucosyl 4,6-transferase (branching enzyme)
 - ① Glycogen deposited is abnormal.
 - ① Glycogen with only few branches accumulate.
 - ① Organs mainly affected - liver, heart, muscle and kidney.
- ① Moderate hypoglycemia, ascites, cirrhosis of liver and hepatic failure and usually fatal.

Mc Ardle's

Mc Ardle's disease (Type V)

Enzyme deficiency $\rightarrow$

- ① Muscle glycogen phosphorylase.
- ① Glycogen deposited is normal in structure.
- ① Organs involved - skeletal muscle.
- ① Muscle cramps on exercise, pain, weakness and stiffness of muscles.

- ① No lactate is formed.
- ① Muscle may get damaged.

Her's disease (Type - VI)

Enzyme deficiency →

- ① Liver glycogen phosphorylase.
- ① Glycogen deposited is normal in structure.
- ① organs mainly affected liver.
- ① Hepatomegaly, moderate hypoglycemia, mild acidosis
liver glycogen ~~cannot~~ cannot form glucose
L pyruvate and lactate can be precursors for glucose

Tanul's disease (Type VII)

- ① Enzyme deficiency → phosphofructokinase.
- ① organs affected → skeletal muscles.
- ① Accumulation of glycogen in skeletal muscles.
- ① Glucose 6-phosphate and fructose 6-phosphate is also ~~also~~ accumulated.
- ① Muscle cramps.

(Type - VIII)

Enzyme deficiency →

- ① Hepatic phosphorylase kinase.
- ① Failure of hepatic glycogen phosphorylase activity
leading to decrease in glycogenolysis.
- ① Hepatomegaly mild to moderate - hypoglycemia.

Enzyme deficiency →

- ① Muscle glycogen phosphorylase.
- ① Glycogen deposited is normal in structure.
- ① Cramps involved. skeletal muscles.
- ① Muscle cramps on exercise, pain, weakness and stiffness of muscles.

Cancer

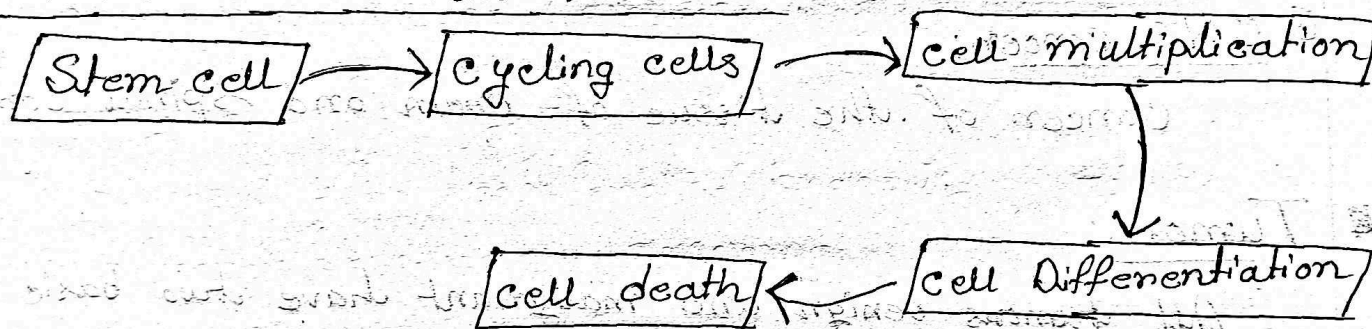
Cancer is a class of diseases in which a group of cells display uncontrolled growth, invasion and sometimes metastasis. Most cancer is called for the organ or type of cell in which they start. e.g.

Eg → Lung cancer. Cancer is caused due to malignant tumour.

There are three principle modalities of treatment -

- 1) Surgery.
- 2) Radiation.
- 3) chemotherapy.

General mechanism of cancer:



Neoplasm:

The term of neoplasm means new growth, the new growth produce called neoplasm or tumor. However all the new dose are not neoplasm, since ex of new growth of tissue and cells also exist in the process of embryogenesis, regeneration and repair, hyperplasia called stimulation the proliferation and Maturation of the cell normal adult is control as a result of which some of the corporates through out life, some have limited proliferation why other do not replicate.

Cancer Type:

① Carcinoma:

Cancer of skin or in tissue that line / cover internal organs.

② Sarcoma:

Cancer of bone cartilage fat muscle, blood vessels or connective tissue.

③ Leukemia:

Cancer of blood forming tissue such as bone marrow and cause large number of abnormal blood cell.

④ Lymphoma and myeloma:

Cancer of cell of immune system.

⑤ CNS Cancer:

Cancer of the tissue of brain and spinal cord.

Tumors:

All tumors benign and malignant have two basic components -

- ① The parenchyma made up of transformed or neoplastic cells.
- ② The supporting stroma made up of connective tissue, blood vessels, and possible lymphatics.

a) Benign Tumors:

A benign epithelial tumor arising in fibrous tissue is a Fibroma, a benign cartilaginous tumor is a chondroma. They are not spread since their site of origin, but it can crowd out adjacent cells.

It is classified three type -

- ① Adenoma ② Papilloma ③ Cystadenomas.

b) Malignant Tumors:

Malignant neoplasm arising in mesenchymal and tissue in or its derivative is called ~~sarcomas~~ sarcomas. They can spread from the unique site and cause secondary tumours. They obstruct with adhesion & with adjuvant.

Malignant neoplasm disseminated by one of the three pathways
 i) seeding with body cavities ii) Lymphatic spread iii) Haematogenous spread.

~~Epidemiology~~

Epidemiology:

- ① Estimated number of people living with the disease around 2.5 million.
- ① Every year new cancer patients registered: Over 7 lacs.
- ① Cancer related deaths 5,56,400.
- ① Age b/w 30-69 years.
- ① Total death 3,95,400.
- ① Men: 2,00,100
- ① Female: 1,95,300.
- ① 1 woman dies of cervical every 8 min. In India.
- ① 2500 dies per day due to tobacco related disease.

Factors:

- ① 1. Familial and hereditary factors.
 - a) Retinoblastoma.
 - b) Breast Cancer.
- 2. Racial and geographical factors.
- 3. Environmental factor / cultural.
 - a) Smoking.
 - b) Excess - alcohol.
 - c) cervical cancer.
 - d) cancer due to bad nut.
 - e) cancer of penis.
- 4) Age
- 5) Sex.

Sign and Symptoms:

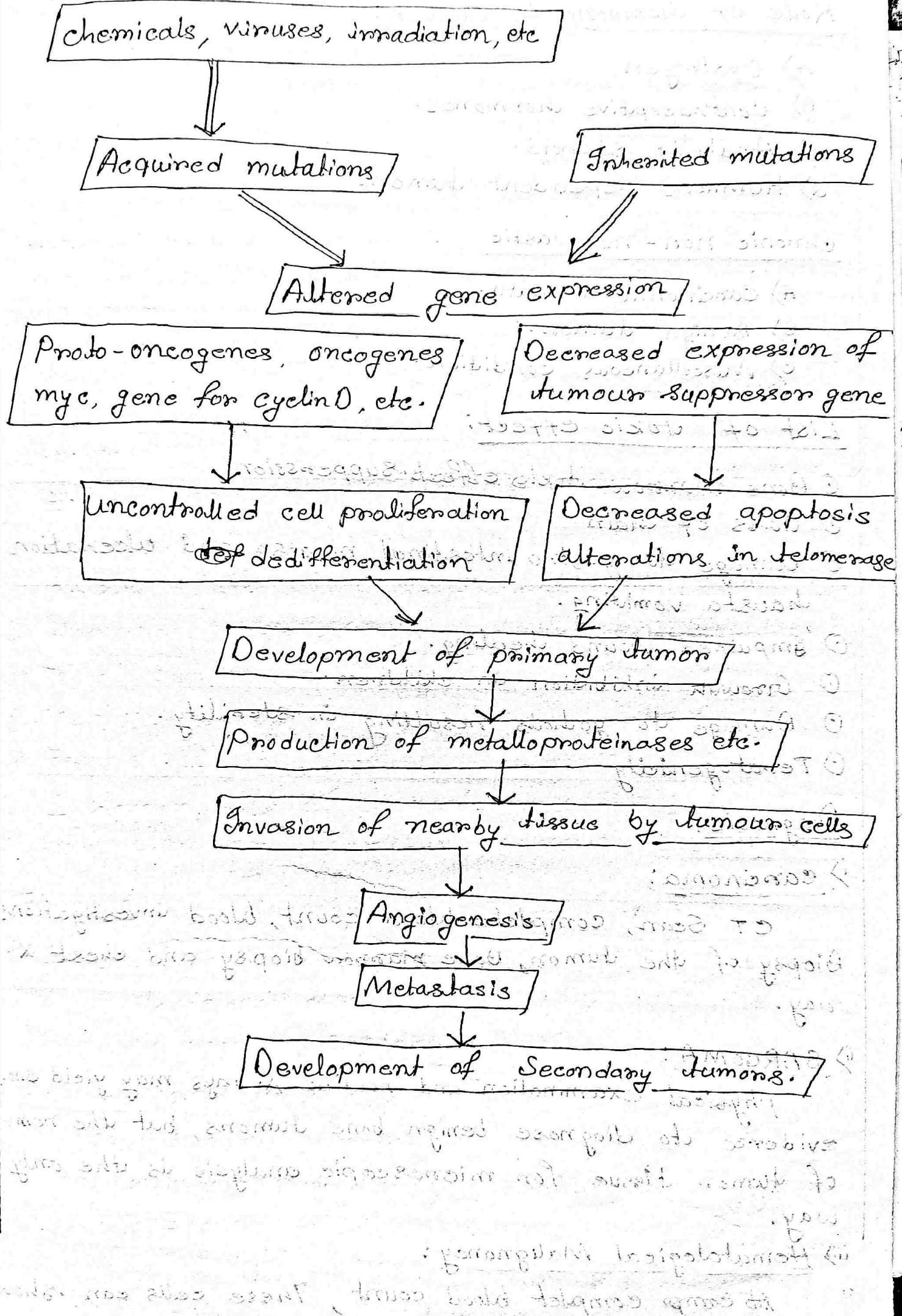
- ① Lumps.
- ① Coughing breathlessness.
- ① changes in bowel habit.
- ① Bleeding
- ① Unexplained weight loss.
- ① Fatigue.

Etiology:

- ① Viruses.
- ① Radiation exposure.
- ① Environmental / Industrial carcinogens.
 - ① Asbestos.
 - ① Aromatic amines
 - ① Bischloromethyl ethers.
 - ① Beta naphthalene and benzedene.
 - ① Nickel.
 - ① Vinyl chloride.
 - ① Diet and nutrition.
 - ① Isopropyl alcohol.
- ① Tobacco and alcohol consumption.
- ① Genetic ~~sex~~ susceptibility Syndromes.

Pathogenesis of cancer:

1. DNA of a normal cell.
2. Mutation in DNA.
3. Genetically altered cell.
4. Spread and 2nd mutation.
5. 3rd mutation.
6. 4th mutation.
7. Breaking through the membrane.
8. Angiogenesis.
9. Invasion and dispersal.
10. Metastasis.



Role of hormone in Cancer:

- A) Oestrogen
- B) Contraceptive hormones.
- C) Anabolic steroid.
- D) Hormone dependent tumor.

chronic non-neoplastic

- A) Carcinoma in situ.
- B) Benign tumor.
- C) Miscellaneous condition.

List of toxic effect:

- ① Bone marrow ~~toxic effect~~ suppression.
- ① Loss of hair
- ① Damage to gastro intestinal mucosa and ulceration
hauxta vomiting.
- ① Impaired wound healing.
- ① Growth inhibition in children.
- ① Damage to gonads resulting in sterility.
- ① Teratogenicity

Diagnosis:

i) carcinoma:

CT Scan, complete blood count, blood investigations, Biopsy of the tumor, Bone marrow biopsy and chest X-ray.

ii) SARCOMA:

physical examination and routine X-rays may yield enough evidence to diagnose benign bone tumors, but the removal of tumor tissue for microscopic analysis is the only way.

iii) Hematological Malignancy:

Complete blood count, These cells can show

characteristic images on light microscopy.

All specimens are examined microscopically to determine the nature of the malignancy.

Leukaemia:

Acute leukaemia is best treated when diagnosed early. There are no screening tests available.

Management of Cancer:

① ~~Mags~~ Magnetic resonance imaging.

① The earlier the diagnosis the better the prospect for survival.

① Computerized axial tomography scan (CAT scan)

① Regular self exam and checkups.

① Remove less surrounding tissue during surgery.

① Combine surgery with radiation or chemotherapy.

① Immunotherapy

① Gene therapy.

① Stem cell research.

i) Carcinoma:

The options for ~~treat~~ treatment include radiation, chemotherapy, surgery.

ii) Sarcoma:

A treatment is designed for bone cancer after the tumor has been diagnosed and staged.

iii) Hematological Malignancy:

Blood transfusions in MDS, chemotherapy, radiotherapy, and immunotherapy.

④ Leukaemia:

There are two phase - first phase induction therapy. (number of cell is reduce.)

Second phase - Initiated (maintenance therapy):

Benign Tumors.	Malignant tumors
cell characteristics, 1) Similar to cell of origin.	not similar to cell of origin.
2) Rate of growth, Slow growth rate	Rapid growth rate.
3) Degree of necrosis and ulceration, Necrosis and ulceration unusual	Necrosis and ulceration common.
4) Degree of vascularity. Slight vascularity	Moderate is marked vascularity.
5) cause death, often Rarely	Rarely often
6) Differentiation, ^{well} poorly differentiated	Poorly well differentiated.
7) unregulated Irreversible. Yes NO	No yes
8) Growth duration, May stop growing	Rarely stop growing.
9) Metastasis, Absent	May occur.
10) Size of tumor, Usually small	Usually large
11) Pain, Absent or rare	Mostly present.

Inflammation

- ① The inflammation is a protective response to eliminate the initial cause of cell injury as well as necrotic cell and tissue, resulting from triggered stimuli.
- ② It is a local physiological response to tissue injury

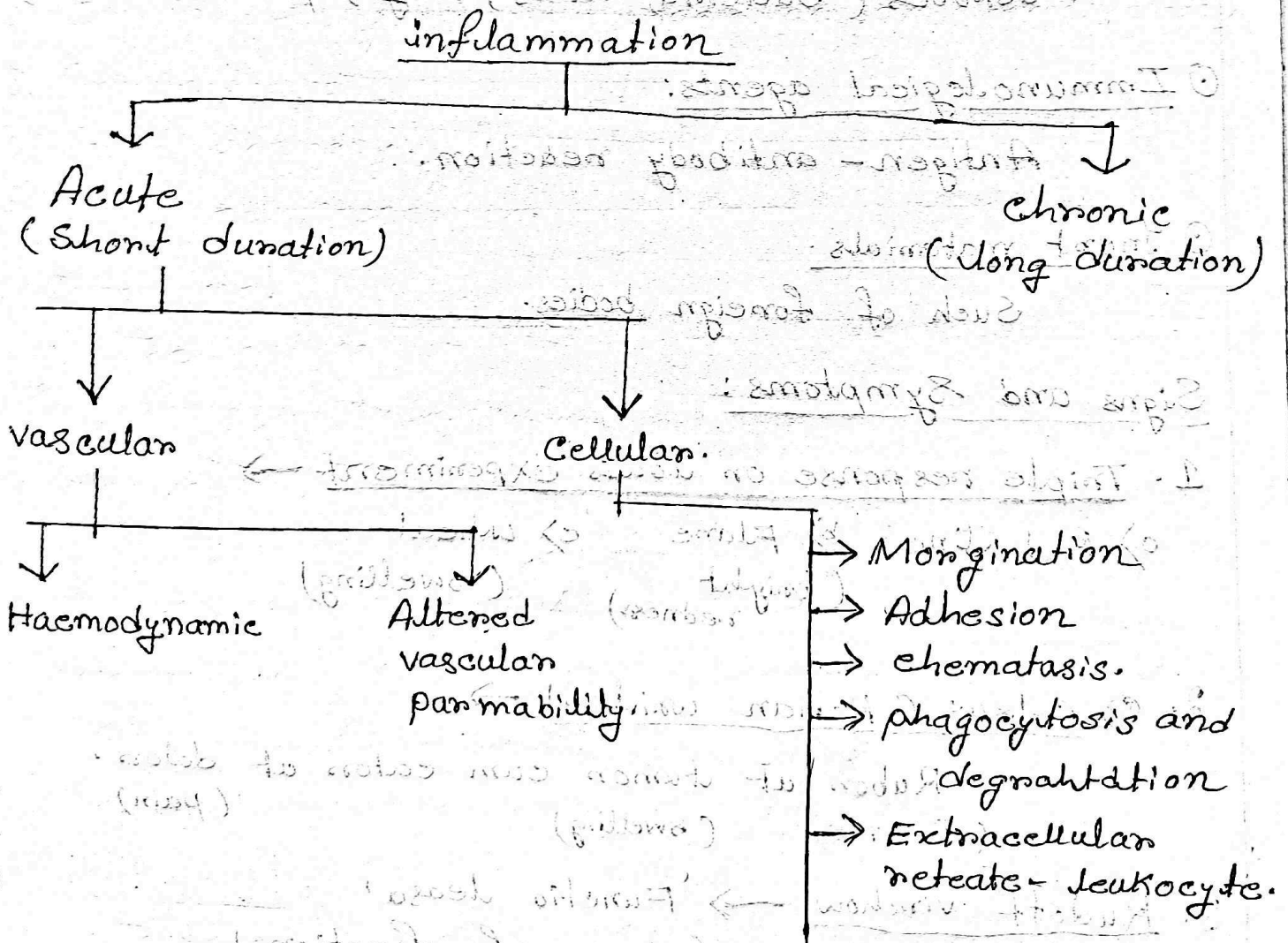
Definition:

It is defined as complex series of events that occurs in vascularized living tissue in response to local injury or tissue damage.

OR,

Inflammation is the reaction of vascularized living tissue to local injury.

Classification:



Etiological agent For inflammation:

- i) Living → Microorganisms.
- ii) non-living → physical, chemical, necrotic, tissue, immune response, endogenous metabolic products.

Agents causing inflammation:

- ① physical agents:
Heat, cold, radiation, mechanical trauma.
- ② Chemical agents:
Strong acids, alkalis, pesticides, Insecticides, Alcohol, Arsenic cyanide etc.
- ③ Infective agents:
Microbes (Bacteria, virus, fungi, protozoa etc)
- ④ Immunological agents:
Antigen-antibody reaction.
- ⑤ Inert materials.
Such of foreign bodies.

Signs and Symptoms:

1. Triple response on Lewis experiment →

a) Red line	b) Flare	c) wheal.
	(bright redness)	(swelling)
2. Celsus (Roman writer) →

Rubor	tumor	cumor	calor	dolor.
(Redness)	(swelling)			(pain)
3. Rudolf Virchow → 'Functio laesa'
(Loss of function)

Acute inflammation

- ① Rapid onset
- ① Short duration
- ① Fluid accumulation
plasma protein (Exudation)
- ① Neutrophils

Chronic inflammation

- ① Onset insidious.
- ① Longer duration
- ① Lymphocytes, macrophages
plasma, cells as inflammatory
cells.
- ① Macrophages plasma cell

Acute inflammation:

It is of short duration and represents.
The early body reaction and followed by repair.

Haemodynamic changes



Transient (short period)
Vasoconstriction of arterioles.



Progressive vasodilation of
arterioles.



Due to vasodilation increase in
hydrostatic pressure.



Due to increase h.p (hydrostatic
pressure)
transudation of fluid into
extravascular surface.



Showing or stasis of microcirculation.