PATHOPHYSIOLOGY

Physiology:- is the branch of Biological sciences, which deals with the normal functioning of living organism, & their parts or Human organs & system.

Physio → Fysis – Nature
logy → Logos → Science

~~Pathophy~~

Pathology – "Study of a Disease" – is the branch medical sciences, that deals with the study of nature, causes, mechanism & development of disease & also mechanism of disease infestat^{n} & transfer

↳ Patho – Disease, illness, injury, pain etc.

Pathophysiology:- "Physiology of Disease"
- is the study of disordered physiological processes that associated with disease or injury.

↳ Etiology – Causes of the disease – pathogenesis Factors
↳ Nature – Inflammat^{n}, Degeneration, infection, Neoplastic –
↳ Pathogenesis – Mechanis of Disease Formatn
↳ Prognosis – expected dis. outcome

→ It becomes a bridge b/w Biological Sc. & medical Sciences

Major objectives & task of Pathophysiology:-

1. To understand the Diseases
2. Describe the etiology & pathogenesis of selected disease state.
3. To help to understand the Health
4. To understand the complications of Disease
5. To understand the logic of life under pathological cond^{n}.
6. To understand the relationship b/w Biological & medical Sci.

BASIC PRINCIPLES OF CELL INJURY & ADAPTATION

Cellular Basics :-

↳ Cellular dysfunctn → Organ Dysfunctn → clinical expression
↳ This concept was given by "Rudolph Virchow", the father of ~~medicine~~ modern pathology at 19th century.
↳ "All forms of organ injury start with molecular or structural alteration in cells.
↳ Key Concepts :-

Normal cells have a fairly narrow range of function or steady state :- "Homeostasis"

Homeostasis :- is the ~~steady~~ state of steady internal physical & chemical conditions maintained by living systems.

" Balancing of Internal Enviroments"

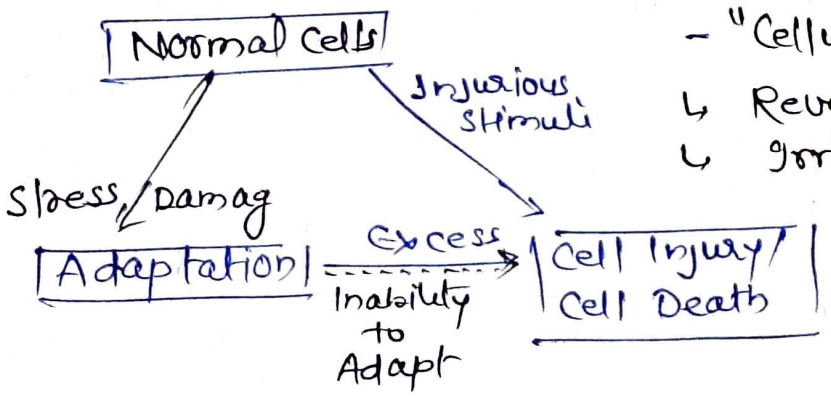
Excess physiological or pathological stress may force the cell to a new steady state → "Adaptation"

Adaptation :- changes in cellular morphology & function in response to a stimulus. " Riversible"

↳ Hypertrophy → ↑ size
↳ Atrophy - ↓ size
↳ Hyperplasia → ↑ no. of cell (similar)
↳ Metaplasia - ~~↑ no of~~ change in cell type

To much stress exceeds the cell's adaptive capacity - "Cellular injury"

↳ Reversible
↳ Irriversible



Homeostasis :- "Balancing of Internal steady Environment"

- is any self-regulating physiological process by which an organism including Human tends to maintain stability while adjusting to conditn that are best for its survival.

→ "Homeostasis is necessary to survived in life"

→ "Disturbance in Homeostasis lead to Disaster or Death of the organism."

Components :-

① Receptor (Sensors) :- They monitor conditions inside & out side the body.

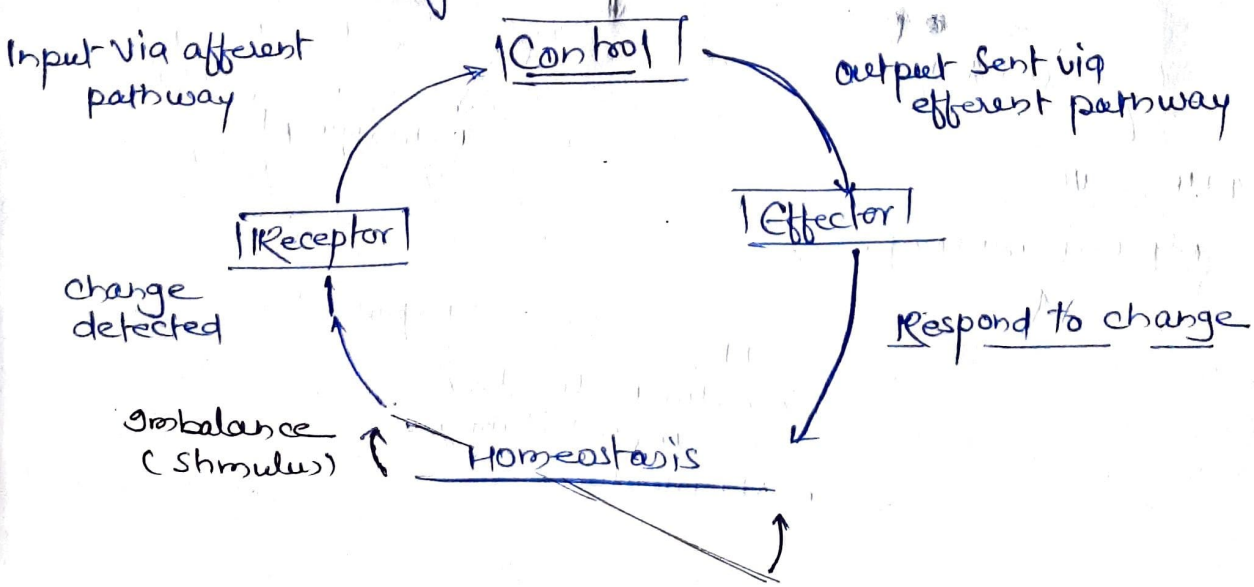
- → Baroreceptor
- → Chemoreceptor
- Thermoreceptor
- mechanoreceptor

② Control :- Control system/centre that responds to signals from receptors / sensors & compare the changes from normal.

- ↳ Brain
- ↳ spinal cord
- ↳ ~~ANS~~ ANS

③ Effectors :- Effectors responds to changes & try to maintain the equilibrium

- ↳ Endocrine Hormons
- ↳ Neurotransmitters
- ↳ Paracrine Glands
- ↳ Organ



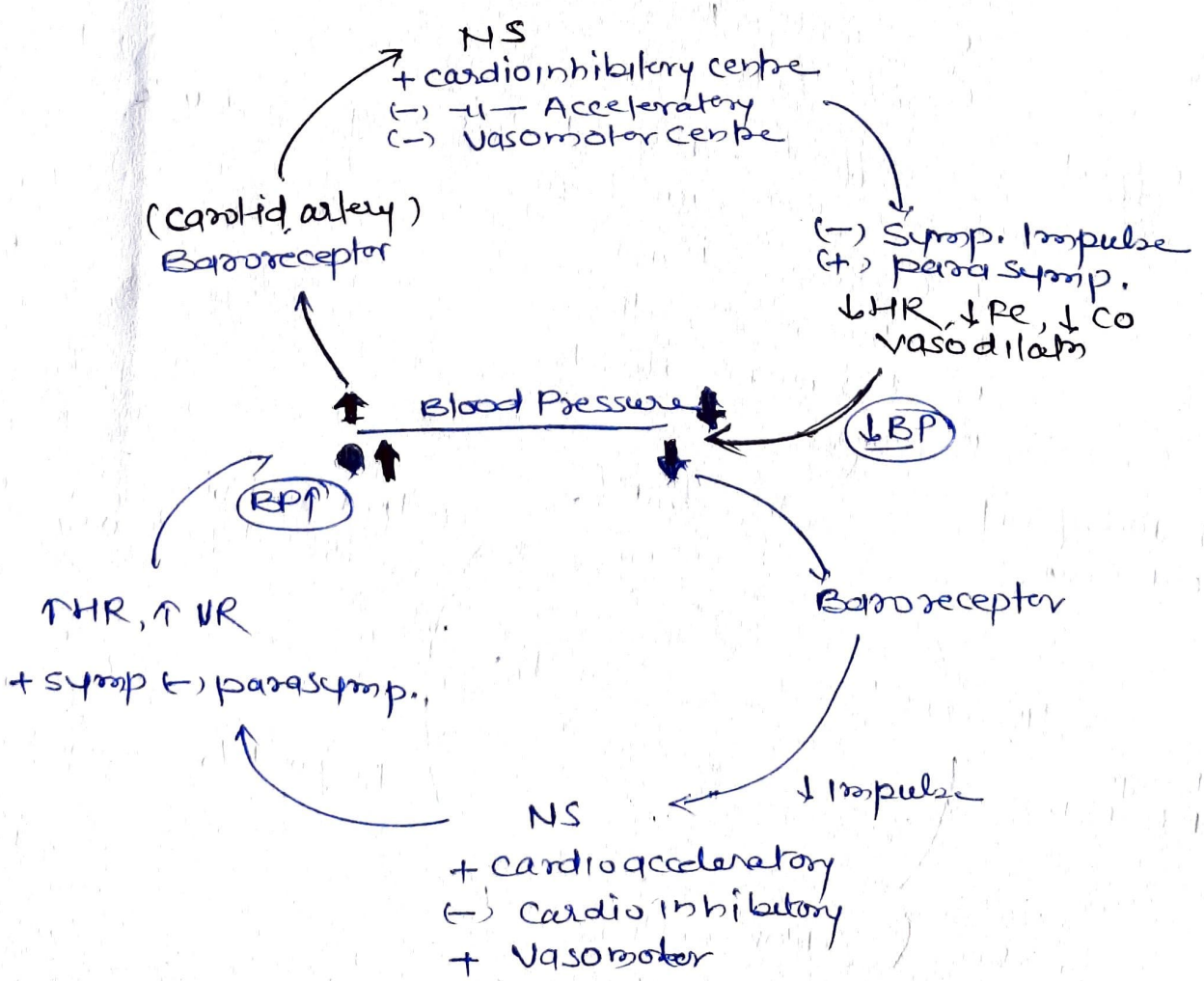
Feed-Back System:- Compensatory Pathway / Loop

① Negative feed back System :- This kind of feedback loop acts to resist or reverse the ~~the~~ process when conditions go outside the rage range

> Normal level → Activate ↓ Negative FBS

ex.- > Body temp → Sweating
> Blood pressure → ↓HR by Ach release
> Blood glucose → Insulin release
> blood calcium → calcitonin

ex- < Blood glucose - Glucagon release
< BP - Adrenaline release
< CO - Renin Release
< blood Ca^{+} - Parathormone release



Cell INJURY

↳ Cells are the fundamental unit of structural & functional unit of the body that forms Organs & System.

↳ Traditionally, body cells are divided into two main type ① Epithelial & ② Mesenchymal cells.

↳ In Health, the cells remain in accord with each other.

↳ In 1859, R. Virchow (Father of Pathology) first published Cellular theory of Disease

↳ Diseases occurs due to abnormalities at the level of cells.

↳ Since then, Study of abnormilities in structure & funct of cells in disease has remained the focus of attention in understanding of disease.

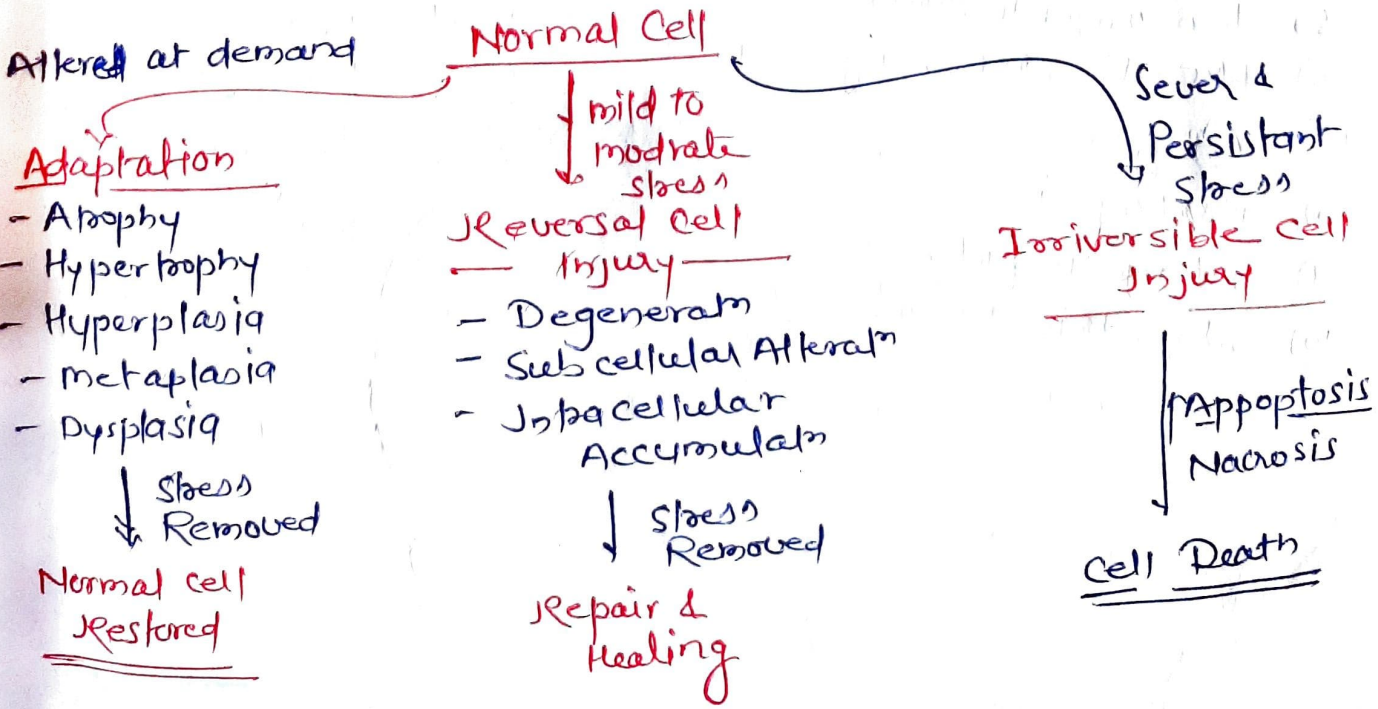
↳ Thus, most forms of diseases being with cell injury followed by consequent loss of cellular function.

Cell Injury:- is the defined as the effect of a veriety of stresses due to etiologic agents a cell encounters resulting in changes in its internal & External environment

The cellular response to stress may vary & depends upon following two variables :-

① **Host factors:-** type of cell & tissue involved

② Factors related to injurious agent - extend & type of cell injury



To Understand the fundamentals of Diseases, we should know understand "Cause/Etiology" & mechanism /pathogenesis of cell injury & cellular adaptaln

ETIOLOGY of CELL INJURY :-

(A) Genetic Causes

(B) Aquired Causes

(A) Genetic Causes :-

- Developmental Defect - Teratogenic
- Cytogenetic Defect - karyotypic
- Single-gene Defect - mendelian disorder
- mutifactorial inheritance disorder
- Inborn errors of metabolism

Developmental Defect -

→ Thalidomide malfermaln - Limb-Reductn
→ Foetal Hydantoin Syndrome - Congenital Heart Dis
- Foetal Alcohol Syndrome - Growth & mental Retardat

Aquired Causes :-

1. Hypoxia / Ischemia
2. Physical Agent
3. Chemical Agent & Drug
4. microbial Agent
5. Immunogenti Agent
6. Nutritional Derangement
7. Aging
8. Psychogenic
9. Jatrogenic factor
10. Idopathic Disease

1. Hypoxia & Ischaemia :-

↳ Cells & Tissues essentially require O_2 to generate energy & perform metabolic functions. Deficiency of O_2 causes failure th to carry out the normal metabolic function.

↳ Hypoxia is the most common cause of cell injury. Hypoxia may result from the following 2 way -

↳ (1) Ischaemia :- Reduced or lake of Blood Supply

↳ (2) Impaired Blood supply due to Blood related Disorders -
- ↳ Anaemia, CO poisoning,
- & Other Disorders - Heart Disease, Lung Disease, ↑ tissue demand.

2. Physical Agents :-

- ↳ mechanical trauma - Accidents
- ↳ Thermal Trauma - Heat / Cold
- ↳ Electricity
- ↳ Radiation (UV, Ionising)
- ↳ Rapid changes in atm. pressure

3. Chemicals & Drugs :-

- ↳ Chemical poisoning - Cyanide, As, Hg
- ↳ Strong Acid / Alkali
- ↳ Environmental pollutants
- ↳ Pesticides / Insecticides
- ↳ O_2 at high conc
- ↳ Hypertonic glucose & salt
- ↳ Alcohol & Narcotic drugs
- ↳ Drugs - Barbiturates, Digitalis etc

4) Microbial Agents :- pathogenic microbes

↳ Bacteria, fungi, virus, protozoa, parasites

5. Immunological Agents :- ↳ Immunity is a "Double-Edge Sword"

It protects the host against injurious agents but sometime it may turn to lethal & cause cell injury

- ↳ Hypersensevity Allergic Reactn - Steven Johnson Syndrome
- ↳ Anaphylactic Reaction
- ↳ Auto immune Disease

6. Nutritional Derangements :⇒ Deficiency or excess of nutritional nutrients may result in nutritional Imbalance.

↳ Nutritional Deficiency disease may be due to overall deficiency of nutrients - "Starvation", of protein calorie - (Marasmus, kwashiorkor), of minerals (Anaemia) or of trace elements.

↳ Excess Nutritial may cause - obesity, HTN, Heart Dis.

7. Psychogenic :- There are no specific biochemical changes / morphological changes in common acquired mental dis. due to "mental stress", Anxiety, depression, schizophrenia,

Addictn of Drug - Alcohol, Smoking, morphine, may cause serious disease - Liver Damage, bronchitis, Lung cancer, Ulcer, HTN, Renal failure etc.

8. Iatrogenic Cause - due to diagnostic & therapeutic procedure undertaken on a patients. - multiple drug prescriptn, Drug interactn, mechanical/surgical procedure Radiatn, ADR of Drug,

9. Idiopathic Disease : "Unknown Cause or origine"

ex - Essential HTN (90%) - Idiopathic
Idiopathic polyneuritis
idiopathic pulmonary fibrosis

PATHOGENESIS OF CELL INJURY

↳ Cell membrane Damage
↳ Mitochondrial Damage
↳ Ribosome Damage
↳ Nuclear Damage

Common scheme applies to most forms →

(1) Factors related to etiologic agent & Host) –

(a) type, duration, & severity of injurious agent
- small dose of toxic agent & short durat° cause reversible cell injury
- large dose or long durat° may cause irriversible damage

(b) Type, status & adaptibility of target cell –
e.g.- skeletal muscle can withstand hypoxic injury for long-time while Cardiac muscle

(2) Common Underlying mechanism –
→ Cell mem. damage - disturbing the metabolic functn & transmem. exchange.

→ Free Radicals release

(3) Usual morphological Changes: – Biochemical & molecular changes underlying cell injury from various agents become apparent first, and are associated with appearance of ultra-structure changes in the cell injured cell.
The morphological changes of riversible cell injury (hydropic swellings) appear earlier while later morphologic altaratn of cell death are seen. (M, infarctn)

(4) Functional Implication & Disease Outcome –
Cell injury affects cellular function adversely. Consequently, Clinical features in the form of Symptoms & Sign would appear.

PATHOGENESIS OF ISCHAEMIC AND HYPOXIC INJURY

Ischemia & Hypoxia are the most common forms of cell injury.

Hypoxia leads to Riversible & Irriversible cell injury

Reversible Cell Injury :- Short durat^n of hypoxia or Ischemia may cause riversible cell injury. the harmfull effect may reversible on rapid restorat^n of circulation.

e.g. - In Coronary artery occlusion ⇒ Myocardial Contractility, metabolism & ultrastructure changes are reversed if the circulat^n is quickly ~~reve~~ restored.

Hypoxia causes →

① Decreased generation of cellular ATP

→ O_2 require to ATP product^n & ATP is essential for cellular function →

- ↳ Membrane Transport
- ↳ Protein Synthesis
- ↳ Lipid Synthesis
- ↳ Phospholipid metabolism.

ATP produced by –

① Aerobic Respirat^n – Oxidative Phosphorylat^n in the mitochondria.

② Anaerobic glycolytic oxidat^n to maintain constant supply of ATP (from glucose/glycogen in –nce of O_2)

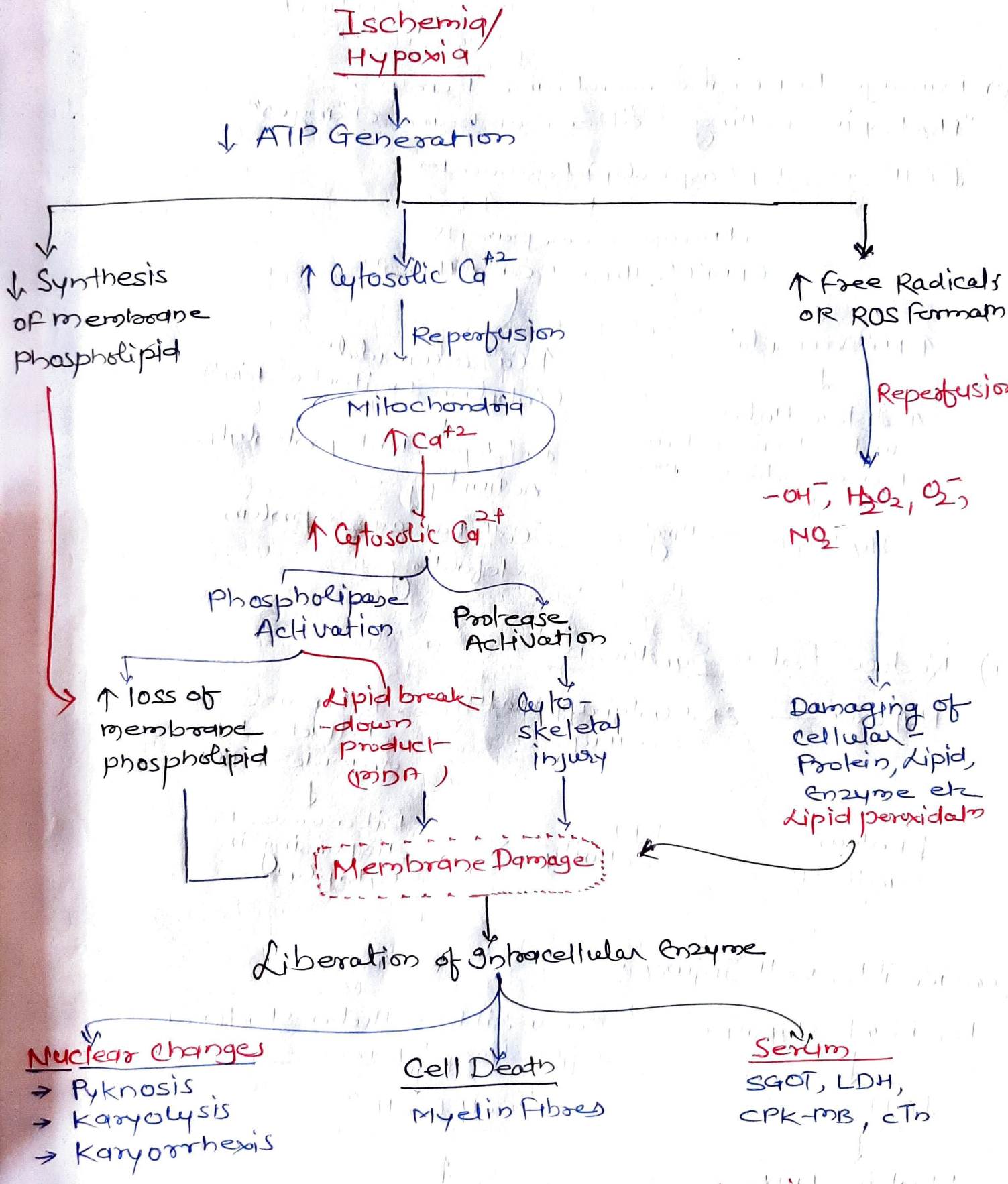
Lack of O_2 ATP product^n is compromised

Accumulat^n of metabolic waste product in the cell

↳ **Severe Cell injury due to Ischemia**

Hypoxia due to other Disorder (RBC, Heart, Lungs dis.) anaerobic glycolytic ATP generat^n continues & thus cell injury is less sever.

However – Myocardium, PCT, kidney & Neurons are dependent solely on Aerobic Respirat^n thus these tissues suffer rapidly.



② Intracellular Lactic Acidosis :- Nuclear clumping

- Anaerobic respiration leads to rapid depletion of glycogen & accumulation of Lactic acid & ↓ the intracellular pH

↓

Lactic Acidosis

↓

"Nuclear clumping"

③ Damage to Plasma membrane Pump →
"Hydropic swelling & other membrane changes"

↓ ATP → ↓ phospholipid generatn
↓
damage mem. pumps
(Na⁺K⁺ ATPase & Ca²⁺ ATPase)

↑ Na⁺ Accumulatn
↓
↑ Intracellular water to maintain iso-osmotic condn
↓
Hydropic Swelling

↑ Ca⁺² accumulatn
(Cytoplasm & mitochondria)
↓
Ca²⁺ dependent proteolytic Activity
↓
Cell Damage & protein defolding

④ Reduce Protein Synthesis :-

Hypoxia → ER & Golgi apparatus swell up → Ribosomes are detached from granules (RER)
↓
Ribosome is disperbing in cytoplasm
← ↓ Rb. Activity
← ↓ protein synthesis

Irreversible Cell Injury :=

Persistant Hypoxia → Irreversible Cellular structural & functional Damage
↓
"Cell Death"
↓
↓ ATP
↓
↓ protein, ↓ PH & leakage of lysosomal enzyme → Ultrastructural changes

① Ca^{2+} Influx → Mitochondrial Damage

② Activated Phospholipase :- membrane Damage
↓ ATP → (+) phospholipase → ↓ phospholipid
↑ Ca^{2+} (+)
↓
membrane Damage

③ Intracellular Protease: → Cytoskeletal Damage

- Protease → Proteolysis – Cytoskeleton (microfilament, microtubules, & Intermediate Filament)

④ Activated Endonuclease → Nuclear Damage

Lysosomal Enz
Protease & Endonuclease → Nuclear Damage

Nuclear Damage in three forms -

① Pyknosis – Condensation & Clumping of Nucleus which becomes dark basophillic

② Karyorrhexis – Nuclear fragmentation into small bits dispersed in the cytoplasm.

③ Karyolysis – Dissolution of the nucleus

⑤ Lysosomal Hydrolytic enzyme - Lysosomal Damage, cell Death & phagocytosis

↳ Hydrolytic Enzymes
(Hydrolase, RNAase, DNAase, Protease, Glycosidase, Phosphatase, Lipase, amylase)

↓

Damaged macromolecules

↓

Cell Death

↓

dead cell replaced by masses of phospholipid that called "Myelin Figure"

they are either phagocytosed by macrophages or there may be formation of Ca^{2+} Soaps

↓

Enz leaks to Serum ROS

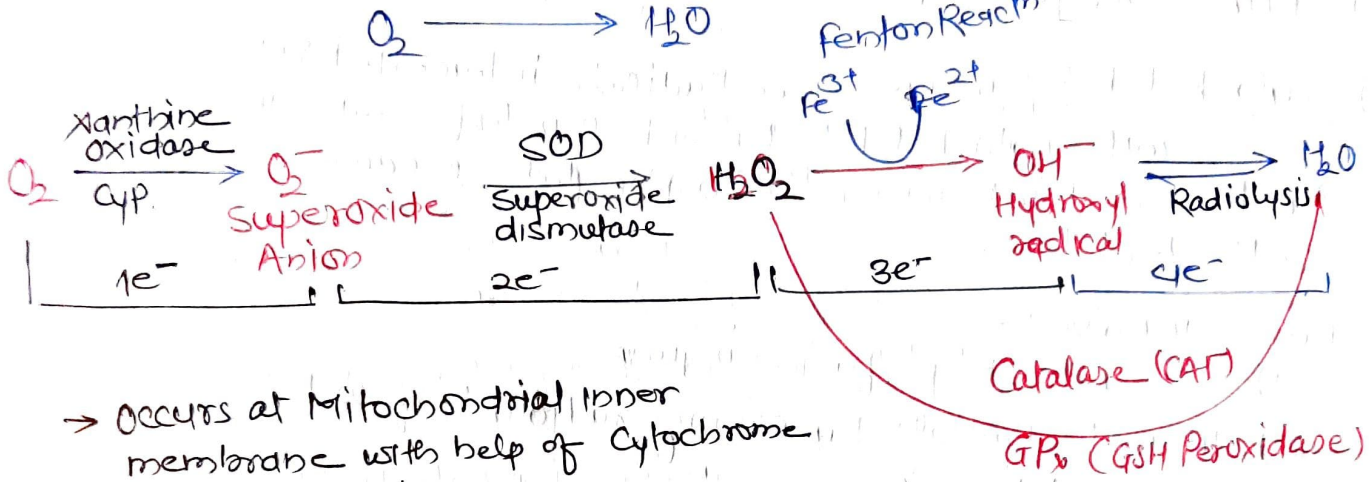
Enz	Disease
Aspartate Amino-transferase (AST/SGOT)	Liver disease
Alanine Amino-transferase (AST, SGPT)	Viral Hepatitis
Creatine kinase-MB (CK-MB)	Myocardial Infarction
Lactate DH (LDH)	Acute MI
Cardiac Troponin (CTn)	Acute MI

Free Radical Mediated Cell Injury

ROS :- "Reactive Oxygen Species"

↳ Redox reactn in the metabolism of cell involves generatn of ATP by oxidative stress process in which biradical Oxygen (O_2) combines with hydrogen atom (H), & formed H_2O molecules

$$O_2 \longrightarrow H_2O$$



→ Occurs at Mitochondrial inner membrane with help of Cytochrome oxidase catalysis

RNS - Reactive Nitrogen Species → Nitric Oxide (NO)
Peroxynitrite - ONOO

$$NO + O_2^- \rightarrow ONOO$$

Others - $Cl + O_2^- \rightarrow HOCl$ Hypochlorus acid

Other Sources of Free Radical → Environmental Pollutant
Smoking, Alcohol etc.

Free Radicals are potent Oxidant & they are neutralise by Endogenous antioxidants like SOD, CAT, GSH, GPx, & minimise their Cytotoxic action.

In pathological stress condition, formation of ROS are increased that can not be neutralize by endogenous antioxidant & these increased ROS can lead to Oxidative Stress with in the cell.

ROS → Cellular Oxidative Damages

① Lipid Peroxidation :-

Polyunsaturated fatty acid (mem. Lipid) (PUFA) —ROS→ Lipid hydroperoxy radical / Lipid hypoperoxide → Lipid Peroxidation

Lipid Peroxidant (MDA)

↓

membrane Damage

② Oxidation of Proteins -

Protein Macromolecules $\xrightarrow[\text{Damage}]{\text{Oxidative}}$ Protein & misfolding
Degradation
↓
Cell Distruction

③ DNA Damage :- Mutation

④ Cytoskeletal Damage - free Radicals ~~interact~~ interact with Cytoskeletal element & interfere with mitochondrial aerobic phosphorylation & cause ATP depletion

* ROS → involve in
1. Ischemic Reperfusion injury
2. Ionisation Radiation by causing radiolysis of water
3. Chemical toxicity
4. Chemical carcinogenesis
5. Hyperoxia / Hypoxia
6. Cellular Aging
7. Killing of microbial Agents
8. Inflammatory Damage
9. Destruction of tumor cell
10. Atherosclerosis

Antioxidants -
1. Enzymatic - SOD, CAT, GPx
2. Vitamin E, A, & C
3. Sulfahydryl - containing Compound - Cysteine & glutathione
4. Serum proteins - ~~Cell~~ Ceruloplasmin & transferrin

Stress proteins - Protective Protein
1. Heat shock protein (HSPs) - act as molecular chaperones (housekeeping)
2. Ubiquintin - direct intracellular molecules either digradation or Synthesis.
produced mostly in - Alzheimer, Parkinson etc

Pathogenesis of Chemical Injury :-

Chemicals → ROS formation
→ Direct cytotoxic action

Direct Cytotoxic Action ;-

$HgCl_2$ — direct cytotoxic action, — Alimentary tract & kidney

Cyanide → ↓ Mitochondrial cytochrome oxidase
↓ Oxidative phosphorylation
↓ Cell injury / Cell Death

Toxic Heavy Metals — Hg, Pb, iron

Anticancer Drugs

CCl_4, Acetaminophen, bromobenzene → Toxic Metabolite

Pathogenesis of Radition injury -

H_2O
↓ Radiolysis
OH^-

Proliferating cell → (Epithelial cell) → DNA Damage
- Genetic Damage → Mutation
- Inhibition of DNA Replication → Apoptosis

Non-proliferation cells (neuron) → Lipid Peroxidation → Cell membrane Damage → Necrosis

Morphological / Morphology of Reversible Cell Injury :-

→ Retrogressive changes of cell injury are applied to non-lethal cell injury

- ↳ Hydropic changes
- ↳ Hyaline changes
- ↳ Mucoid change
- ↳ Fatty change

↳ **Hydropic Change** :- Accumulation of water within the cell (Hydropic swelling)

* etiology – Mostly all, mainly - bacterial toxins, chemicals, poison, burn, high fever, IV - Saline/glucose

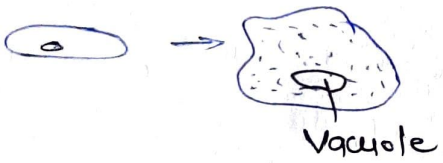
* Pathogenesis – → Damage Na^+K^+ ATPase pump

↓

↑ Na^+ & ↓ K^+ intracellularly

↓

↑ water entry to maintain iso-osmotic



↳ **Hyaline Change** :- Hyaline or Hyalin - means glassy (hyalos - glass)

- Homogeneous, eosinophilic appearance of proteinaceous material in haematoxylin & eosin - stained Sect.
- Though Fibrin & Amyloid have ~~bak~~ hyaline appearance

↳ **Mucoid Changes** : Mucoid means mucus-like

- ↳ Epithelial mucin ~~co~~ accumulation
- ↳ Connective Tissue Mucin

INTRACELLULAR ACCUMULATIONS

↳ Intracellular accumulation of substances in abnormal amounts can occur within the cytoplasm (especially lysosomes) or nucleus of cell. This phenomenon was previously referred to as ~~infiltration~~ "infiltration".

Infiltration – Entry or infiltration of unusual thing from outside

⇒ Groups of intracellular accumulation –

① Normal cell metabolic constituents produced in excess –
- → Water
- → Lipids (fatty change, cholesterol deposits)
- → Proteins
- – carbohydrates

② Abnormal metabolic constituents produced by abnormal Metabolism.
- → Inborn error of metabolism

Ex	Deficiency of Enz	Metabolite	Organ	Disease
	Glucose-6-phosphatase	Glycogen	Liver, Kidney	Von Gierke's disease
	Acid-α-glucosidase	Glycogen	Heart muscle	Pompe's dis.
	α-galactosidase	Ceramide	Fabry's disease	Skin, kidney, Heart, Spleen
	~~Sphig~~ Sphingomyelinase	Sphingomyelin	Niemann-Pick Disease	Spleen, Liver bone marrow

③ Accumulation of pigments → endogenous pigment
exogenous pigments

Site of Accumulation :-
- (a) Cytoplasm (phagolysosomes)
- (b) Nucleus

Source of Accumulation
- (a) Produced by affected cell
- (b) Produced elsewhere in the body, but stored in the cell

Important Accumulatn

- Fatty change
- Protein
- Carbohydrate
- Pigments

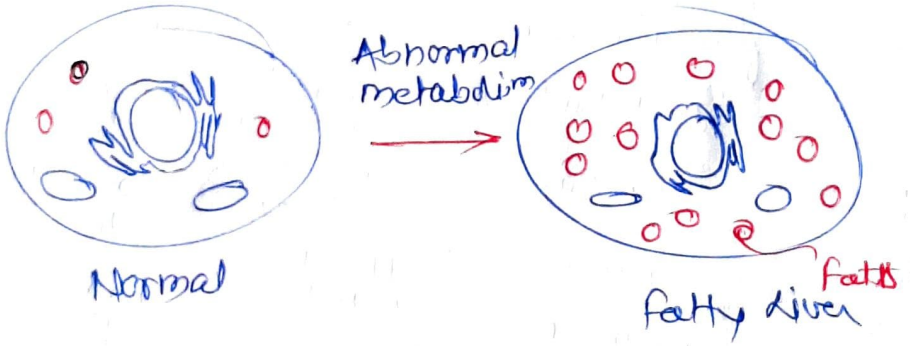
Process of Accumulatn / Mechanism

(1) Productn of a normal endogenous substance at normal or increased rate, but rate of metabolism is ~~not~~ inadequate to remove it

productn → ≥ Normal

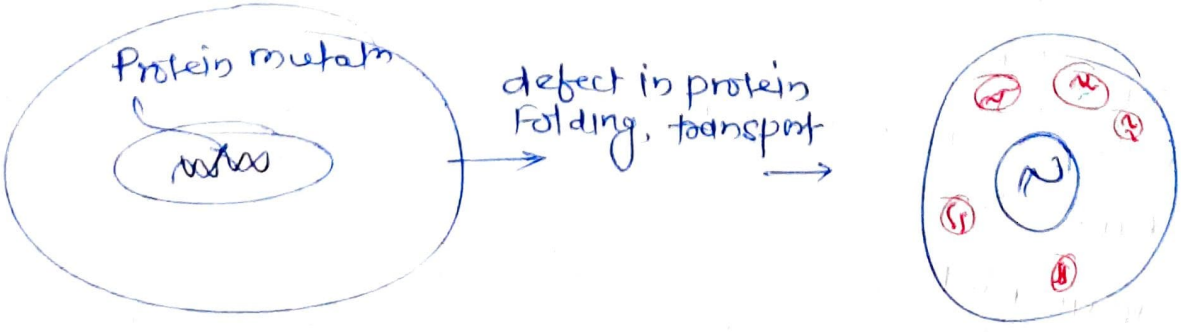
remove → ↓ normal

eg. - Fatty liver, reabsorptn protein droplets in Renal tubules



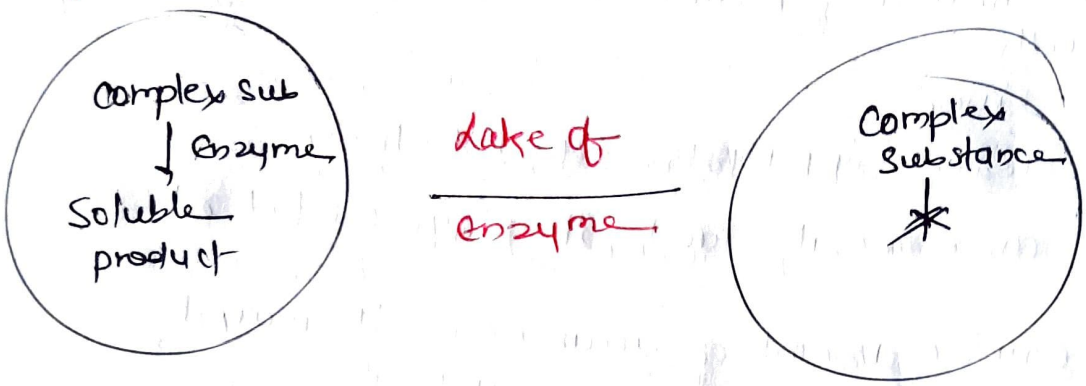
(2) Accumulatn of an abnormal endogenous substance (product of mutated gene) due to defect of protein folding, transport & inability to degraded abnormal protein effectively

eg. Accumulatn of mutated proteins in liver cell



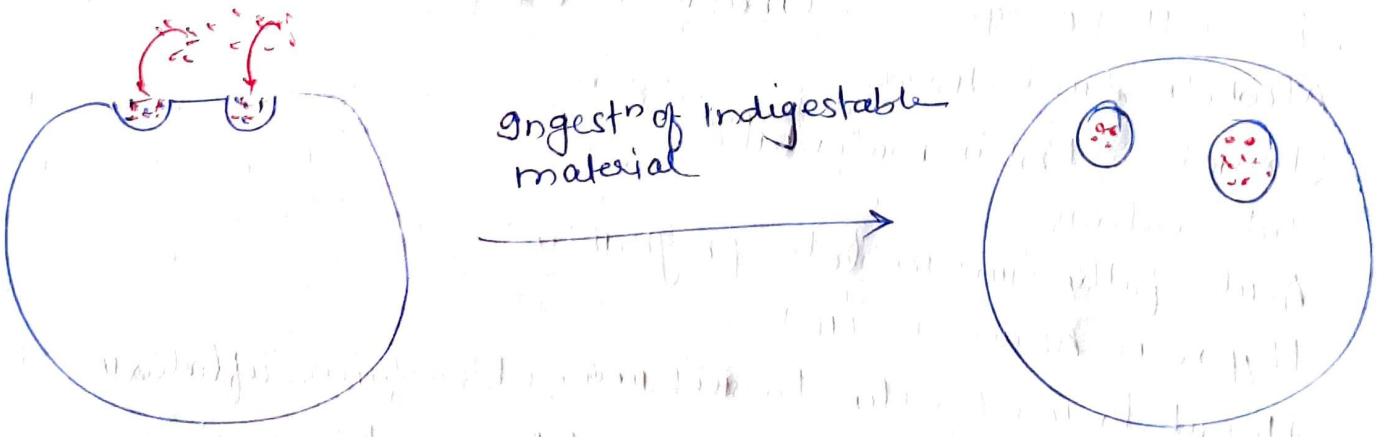
(3) Accumulation of ~~Abnormal~~ normal endogenous substance due to inherited defect in enzymes required for metabolism of substance

e.g. - Lipids & Glycogen Storage disease



(4) Accumulation of abnormal exogenous substance due to unavailability of enzyme & transport mechanism to degrade & transport it to other site

e.g. - Silicosis, & Anthracosis



Fatty Change / Accumulation of Lipids

→ Triglyceride, Cholesterol, phospholipids

* **Steatosis / Fatty liver**

→ Intracellular accumulation of natural fat (TG) within the parenchymal cells

→ Common site — liver

→ other site - Heart, Skeletal muscle & kidney

Liver is the common site due to it plays central role in fat metabolism

→ Depending upon cause & amount of accumulation it may be reversible or irreversible cell injury & cell death

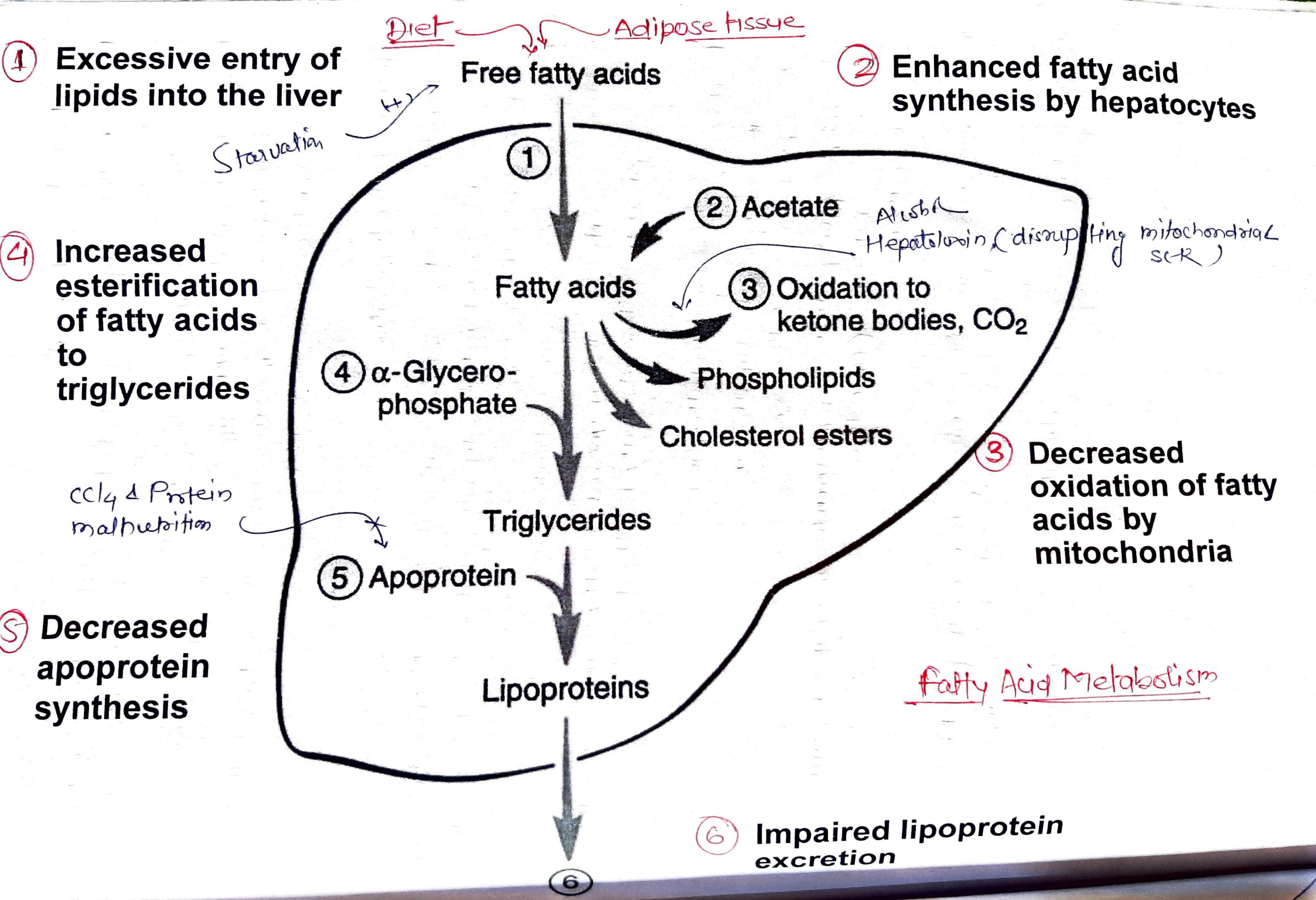
Etiology / Cause –

(a) Cond^n with excess fat — beyond the liver metabolic capacity
- ↳ Obesity
- ↳ Diabetes
- ↳ Congenital hyperlipidemia

(b) Liver cell damage → Unable to adequate metabolism of fats
- ↳ Alcoholic liver disease
- ↳ Starvation / Protein malnutrition
- ↳ Tuberculosis
- ↳ Acute fatty liver in late pregnancy
- ↳ Hypoxia (Anaemia, HF)
- ↳ Hepatotoxins (CCl4, Paracetamol, chloroform, aflatoxin etc)
- ↳ Drug induced - CCl4, PCM, MTX, halothane, tetracycline)
- ↳ Reye's Syndrome – Aspirin induced

* In fatty liver — Accumulation of TG occurs due to defect at one & more of the following 6 step in normal fat metabolism process

1. ↑ entry of free fatty acid into liver
2. ↑ Synthesis of fatty acid by the liver
3. ↓ Conversion of fatty a into ketone bodies
4. ↑ α-glycerophosphate causing increased esterification of fatty acid to triglycerides
5. ↓ lipid accepter protein (Apoprotein)
6. ↓ excretion of lipoprotein from the liver


Diet
Adipose tissue
Free fatty acids
1 Excessive entry of lipids into the liver
Starvation
2 Enhanced fatty acid synthesis by hepatocytes
1
2 Acetate
Alcohol
Hepatotoxin (disrupting mitochondrial SER)
Fatty acids
3 Oxidation to ketone bodies, CO_2
4 Increased esterification of fatty acids to triglycerides
4 α-Glycero-phosphate
Phospholipids
Cholesterol esters
3 Decreased oxidation of fatty acids by mitochondria
CCl_4 & Protein malnutrition
Triglycerides
5 Apoprotein
5 Decreased apoprotein synthesis
Lipoproteins
Fatty Acid Metabolism
6 Impaired lipoprotein excretion
6

⇒ Cholesterol Deposits

↳ Intracellular diposits of cholesterol & its esters in macrophages may occurs when there is hypercholesterolaemia.

↳ This turns macrophages into foam cell

↳ e.g. - ① Fibrofatty plaques of Atherosclerosis

② Clusters of foam cell in tumor like masses called Xanthomas & Xanthelasma

Stromal Fatty Infiltration

↳ Deposits of mature adipose cells in the stromal connective tissue in contrast to intracellular diposits of fat in the parenchymal cell in fatty changes/liver

↳ In Obesity → organs = Heart & Pancreas

* Heart - site for intramyocardial fatty changes as well as epicardial (Stromal) fatty infiltration

Morphological Changes in Fatty liver ; —

↳ Liver enlargement (Hypertrophy)

↳ Dark brown to yellow color, soft & greasy

↳ Microscopical feature - Small vacuoles in cytoplasm around the nucleus. (Early stage)

↳ cell ruptures

Xanthomas - Formed by clusters of foamy cells found in the subepithelial connective tissue of skin & in tendons

Xanthelasma - yellowish diposit of cholesterol underneath the skin

Protein Accumulation

occurs in following cond^{n} –

① In "Proteinuria" – excessive renal tubular reabsorption of protein by proximal tubular epithelial cells which show pink hyaline droplets in their cytoplasm.

– Renal Disease (Proteinuria)
↳ This change is reversible process

② Proteins Accumulation may be normal-secreted proteins that are produce in excessive amount as occurs in certain plasma cells engaged in active synthesis of "Immunoglobulins". ER becomes hugely distended producing large, homogenous eosinophilic inclusions called "Russel Bodies"

③ Defective intracellular transport & secretion of critical proteins
e.g. – α_1-antitrypsin deficiency :– they cytoplasm of Hepatocytes shows eosinophilic globular deposits of a mutant protein

④ Accumulation of Cytoskeleton proteins :–
e.g. – microtubules, Actin filament, myosin filament, Intermediate filament (Keratin filaments, neurofilaments, vitamin filament & glial filament)
→ Mallory's body or alcoholic haline in hepatocyte is intracellular accumulation of intermidiate filaments of cytokeratin & appears as amorphous pink masses

Hyaline change :–

– Refers to alteration within cells or in the extracellular space that gives a homogenous, glassy, pink appearance in routin histologic section stain with H&E
→ Reabsorption droplet
→ Russell bodies
– Alcoholic hyaline
– Hyalinization of wall of renal arteriotes in long standing HTN & DM

Cellular Adaptation

Adaptation are reversible changes in the size, number, phenotype, metabolic activity, or funct^n of cells in response to changes in their enviroment.

Adaption may occurs either in Physiological or in Pathological condition

1. **HYPERPLASIA** :→ Increase in the no. of cells in tissue that may lead to ↑ size of organ. Occurs only in dividing cell that capeble of DNA synthesis

Mechanism – ↑ expression of Growth Factors & Receptors

e.g.,→ # Hormonal – Breast & Uterus during lactation & pregnancy →(Physiological)

Regenerat^n of liver cell after partial hepatectomy

Benign nodular Prostatic Hyperplasia → excess of Androgen

2. **HYPERTROPHY** : – Increase in the size of cells due to increased synthesis of cellular component. Occurs in both non-dividing cell (Myocardial fibres) & diviniging cell

Mech. – ↑ Gene transcript^n, protein syn., GF&R, etc

e.g., – # Uterine & breast enlargement during pregnancy & lactat^n

enlargement of kidney after uni-nephractomy

Myocardial infarction — Myocardial Hypertrophy

3. **ATROPHY** : – ↓ in the size of cell, tissue, & organ due to disease, injury, or lack of use

Mech – ↓ Gene transcript^n & protein synthesis

e.g., – ↓ uterus size after parturition
– Brain shrinkage during Aging
– Ischemia, Nutritional deficiency

4. **METAPLASIA** : – changing in the cell type, one to another.

Mech. – Altered differentiat^n of stem cells due to reprogramming

e.g., – # Columnar to squamous metaplasia in respiratory tract in response to chronic Smoking & Vit A deficiency.

5. **DYSPLASIA** : – indicates disordered Cellular development

loss of orientat^n of cell
Lack of uniformity of individual cell

Charecteristic Features –

↑ Cell proliferat^n
Nuclear abnormility (Hyperchromasia)
↑ Nuclear-Cytoplasmic ratio

CALCIFICATION :-

It is the abnormal tissue diposition of calcium salt, together with smaller amount of Fe, Mg & others.

Types - 1. Dystrophic 2. Metastatic Calcification

1. Dystrophic Calcification :- Local diposits of calcium may occurs in -

Ⓐ **Necrotic tissue** - old caseous lesions of TB, old infarction, collectn of pus, & fat necrosis.

Ⓑ **Tissue undergoing slow degeneration** - Hyaline areas in benign tumours (Fibroids) in arteries due to atheromatous degeneration in old age, in old thrombi, disease of Heart valve

Necrotic/degenerative tissues → Release of Enzymes → breakdown of Org. Phosphate
Release of Enzymes → Alteratn of pH
Alteratn of pH → Deposition of Calcium

2. Metastatic Calcification -

In this case there is increase in the calcium phosphate product in blood (Hypercalcaemia)

Hypercalcemia is due to

↑ PTH (Parathormone)
Parathyroid overactivity
(Tumour, Hyperplasia)
→ Metabolism of Ca^{2+} from bone

Vit D overdose
→ ↑ Absorptn of Calcium

↑ blood Ca^{2+}
↓
deposition of Ca^{2} on diving tissues

CELL DEATH / IRREVERSIBLE CELL INJURY

Stress → Adaptation → Revercible cell injury
1. Mitochondrial damage
2. Ca^{2+} Accumulation
↓
Irreversible Cell injury
Cell Death

1. **Autolysis** – "Self digestion" by its own hydrolytic enzymes released by lysosomes. It can occurs in the living body when its surrounded by inflammatory reactn → Term used for postmortem change.

2. **Necrosis** - It is defined as localised area of death of tissue followed by degradation of tissues by hydrolytic enzyme liberated from death cell.

Features - 1. Cell Swelling → mem. disappear → Brusting
2. Autolysis, Cytoplasming & Mitoch. Swollen, mem. rupture, Calcification, Meylin figures
3. Nuclear Damage – Pyknosis, Karyorrhexis, karyolysis

Types - (A) Coagulative :– cell basic outline is tnt but details are lost. Protein denaturatn predominates Enz. digestion
e.g → Necrosis in Myocardial & kidney infarction
etiology → "Hypoxia" – Ifarction

(B) Liquefactive / Colliquative : → Transformation of tissue into liquid viscous mass
Hydrolytic Enz in tissue degradation have dominant role in causing semifluid material
Etiology – Hyporia, Bac & fungal Infection
e.g.) – Infarct brain & abscess cavity

(C) Caseous Necrosis → "cheese like" found in centre of foci of the tuberculosis infection.
Combine feature of Coagulative & Lequefactive Necrosis

(D) Fat Necrosis : – Necrosis of the Fat cell.
Release of TG —lipase→ FFA & Glycerol
Fatty a + Ca^{2+} (from blood) → Ca - Soap
May be Traumatic or Enzymatic

(E) Fibrinoide Necrosis - Deposition of fibrin like material mainly on vascular wall.

3. **APOPTOSIS** :– "Programmed Cell Death" → Single Cell
Physiological → Embryogenesis, Menstruatn, Homeostasis etc
Pathological → Organ Atrophy, Acute inflammatn, Graft-rejection

Feature :– 1. Cell Shrinkage, loss of microvilli & cell junction
2. Nucleus → Regular DNA fregmentation
3. Cell mem → mem. bleeping & formatn of Apoptotic bodies
4. Surrounding inflammatn – Absent
5. Rapid phagocytosis of Apoptic bodies

ACIDOSIS & ALKALOSIS

← Acidosis — 7.35 - 7.45 — Alkalosis →

↳ Normal function

Regulation

Respiratory – Lungs flush acid out of the body by CO_2 exhaling

Acidosis → ↑CO_2 expiration → ↓blood CO_2 → ↑ pH

Alkalosis → ↓O_2 inspiration → ↓blood O_2 → ↓ pH

* Resp. depresion may cause — Acidosis
# Hyperventilation — Alkalosis

Excretory :— Kidney regulates the pH by excreting HCO_3^- (bicarbonate, base)

Acidosis — ↓Exc. of HCO_3^- → ↑pH

Alkalosis – ↑ Exc. of HCO_3^- → ↓pH

ACIDOSIS

→ ① ↑ metabolic acid product^n – carbonic ā, lactic ā etc

② ↑ consumption & ↓ Exc. of Acid increasing product

③ ↑ Exc. of base

Sign & Symptoms

↳ Breathlessness, Restlesness, lethargy, Tremors, Flusing

Manifestation/Outcome –

→ CNS depression (↓ Synaptic transmission)

– Sever Acidosis – Disorientat^n, coma, Death

ALKALOSIS –

① Electrolyte imbalance — Vomiting & Diarrhoea

② ↑ consumpt^n & ↓Exc. of base (HCO_3^-)

③ Hyperventilation (↑ CO_2 expirat^n)

④ Endocrine disorders

Sign & Symptoms –

↳ Respiratory Slow

↳ Hyperactive reflexes (tetany)

↳ Atrial Tachycardia

↳ Dysrhythmias

Outcomes/ Manisfestation –

↳ Nervousness

↳ Muscle spasm

↳ Convulsion

↳ loss of Consciousness

↳ Death

ELECTROLYTE IMBALANCE

Water-electrolyte imbalance is an abnormality in the concentration of electrolytes in the body

Electrolytes → Na^+, K^+, Ca^{2+}, Cl^-, PO_4^{-3}, Mg^{2+}, etc

They play a imp role to maintain Homeostasis and Regulate the Muscles & Neurological functn, Fluid balance, Fluid balance, Acid-base balance

ETIOLOGY :→ Improper intake, kidney disease, Vomiting & Diarrhoea, Dehydration, Heatwave, Acid-base imbalance, CHF, Drugs (Diuretics) Bulimia, etc

1. Na^+ (Normal - 135-145 mEq/L) Impulse Generatn

Ⓐ Hyponatremia - (low Na^+, < 135 mEq/L)

symptoms - Appetite loss, weakness, low BP, confusion, nausea, vomiting, Agitation

Causes → HF, CKD, Liver disease, Diuretics,

Ⓑ Hypernatremia - (high Na^+, > 145 mEq/L)

Symptoms - Fatigue, restlessness, Thirst, Tachycardia, dehydration, low urine productn

Causes - kidney disease, dehydratn, Diabetes,

2. K^+ → (Normal 3.5 - 5 mEq/L)

Function - Impulse Conduction

Ⓐ Hypokalemia - (low K^+, < 3.5 mEq/L)

Symptoms - at sever (< 2.5 mEq/L) → Muscle Weekness, cramping, cardiac arrythmias

Causes - Endocrine disease, Diuresis, Acidosis, Diabetes ketoacidosis

Ⓑ Hyperkalemia (high K^+, > 5 mEq/L) * Dangerous

Symptoms - Sever (> 7 mEq/L) - muscle cramps, numbness, paralysis, Cardiac arrythmias - death

Causes - Kidney dis., Acidosis, Cell death

3. Ca^{2+} - (normal - 8.5 to 10.5 mg/dL), Contractn & Signalling

Ⓐ Hypocalcemia - (low Ca^{+2}, < 8.5 mg/dL)

Symptoms - Neurological & Cardiac Symptoms, Cramps,

Causes - ↓ PTH, ↓ Vit D, Malnutrition, pancreatitis

Ⓑ Hypercalcemia - (High Ca^{2+}, > 10.5 mg/dL)

symptoms - Abdominal pain, constipation, kidney stone,

Causes - ↑ PTH, ↑ Vit D, Thyroidism, pheochromocytoma

4. Mg^{2+} (normal 0.7 - 1.1 mmol/L) - "Enzyme Reaction"

Ⓐ Hypomagnesemia - arrythmias, seizures, tetany

Cause - GI loss, diuresis, Hypercalcemia, Genetic

Ⓑ Hypermagnesemia - Neurological Symptoms

causes - Abnormal kidney functn, Mg Containing drugs

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PC Pharmacology Concepts By Rajesh Choudhary