Homeostasis

Word derived from Greek word

homeo : same

stasis : stable.

i.e "remaining stable by remaining same"

Process in which body's temp, biochemical variables. O_2, Na, Ca, Glucose & pH was maintained with in a narrow set point range.

Examples

1. Temperature regulation
2. Regulation of blood CO_2 level
3. " " glucose level.

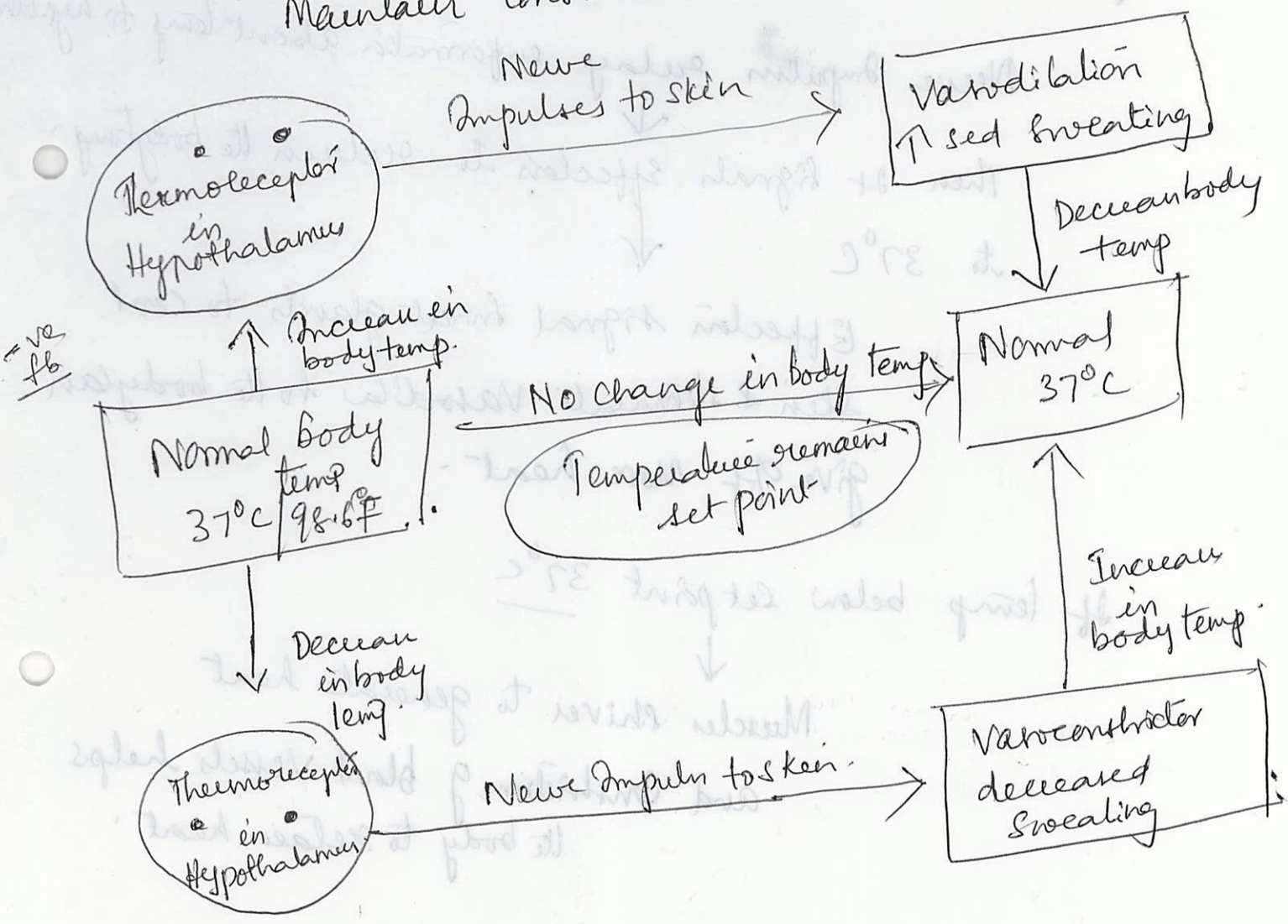
Homeostasis involves -ve feed back loops that counteract changes of various properties from their target values

+ve feed loops amplify their initial stimuli

-ve feedback control system

They oppose a change by creating response that is opposite in direction to initial disturbance

-ve feedback sys are responsible to Maintain constant internal environment.



Positive feedback control sys.

As it is stimulating: It does not operate to help the body to Maintain a stable Condition.

It is often harmful .. instead of opposing

Feed back system

-ve feed back systems are inhibitory

+ve " " " are stimulatory

Feedback system consists of 3 basic components -

1. Sensory Mechanism
2. Control center
3. Effector mechanism -

} 3 components in every feed back loop.

- If any deviations from Normal occurs the sensor generates a signal from nerve impulse or hormone to transmit that information to second component

- When control center receives input from sensor the information is analyzed & specific action is initiated to maintain homeostasis. If significant deviation exists then control center sends its own specialized signal to 3rd component of that loop.

- Effectors are organs like Muscles or glands that influence Physiological Variables.

a change in internal Environment & causing
reletn to normal
It amplify ~~~~ the change.

Temp control is -ve feedback Mechanism

Nerve Impulses relay information about temp to hypothal
↓
Then it signals effectors to retain the body temp:
to 37°C ↓

Effectors signal sweat glands to cool
Skin & stimulate Vasodila to the body can
give off more heat.

If temp below set point 37°C
↓
Muscles shiver to generate heat
and Constriction of blood vessels helps
the body to retain heat.

Introduction of Pathology

"Pathophysiology" → Disordered Physiological processes associated with disease

Pathology : Logos : Study
Pathos : Disease.

It is study of structural biochemical & functional changes in cells / tissues / organs that underlie disease.

Study of Pathology. → divided into (1) general pathology
(2) Systemic "

Gen patho : Concerned w reaction of cells, tissues to abnormal stimuli } Main causes of disease.
& Inherited defect }

Systemic " : Any alteration in specialized organ and tissues that are responsible for disorders that involve the organs.

4 Aspects of Disease process that form the core of pathology are

1) Etiology : Cause.
2) Pathogenesis : Mechanism of its development
3) Molecular & Morphological changes : Biochem

Biochemical & structural alteration induced in cells & organs of body.

4) Clinical Manifestation : That are functional consequences of these changes.

Normal cell confined to

Narrow range of function

- by its state of Metabolism, differentiation and specialization
- by its constraints (restriction or limit) of Neighbouring cells
- by availability of Metabolic Substrates

despite of that able to handle physiologic demands maintaining steady state called Homeostasis.

* Adaptations are reversible, functional & structural responses to more severe physiologic stresses and some pathologic stimuli

Physiologic stress & Pathologic stimuli

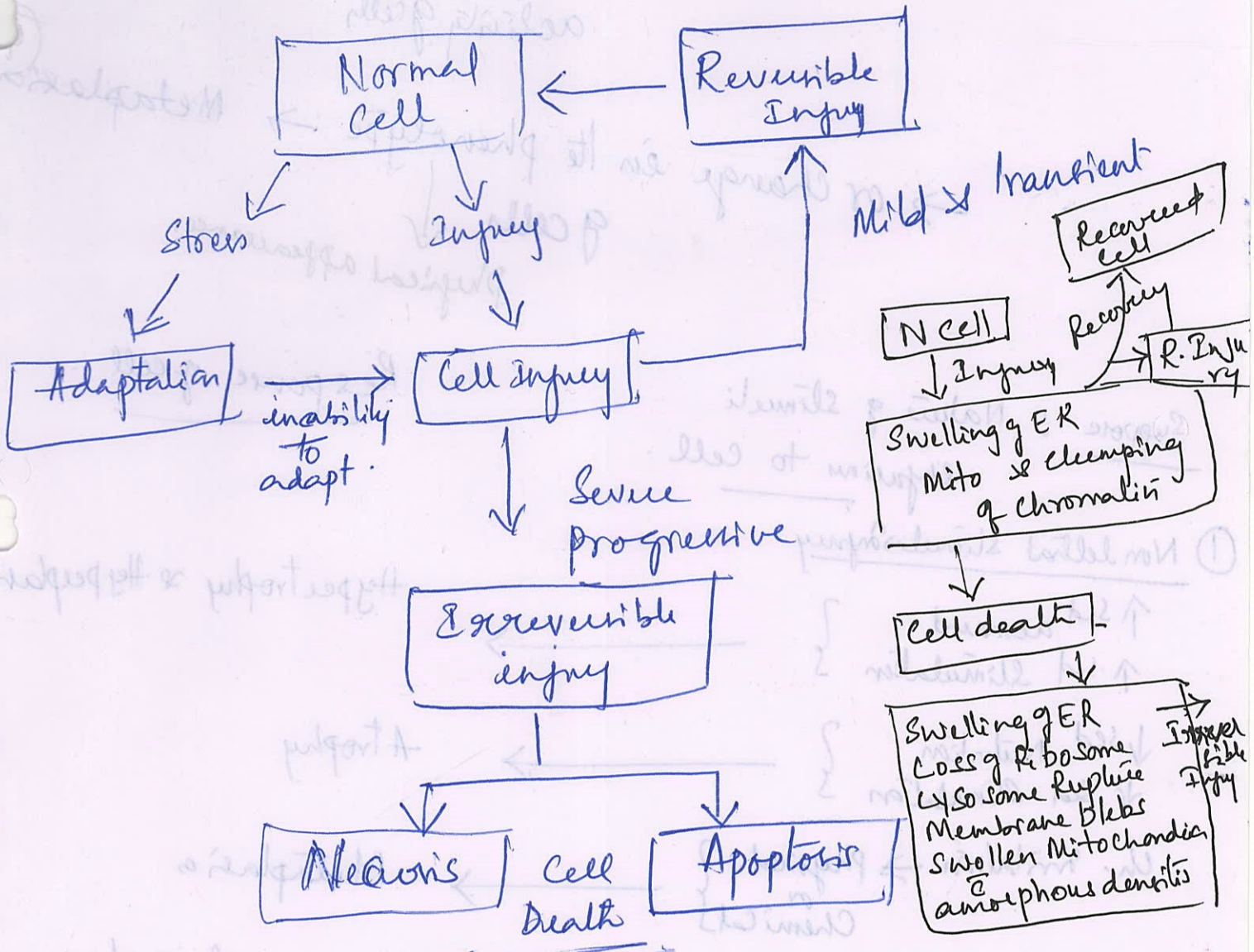
↓

due to which new but altered steady states are achieved, allowing

Progressive & Severe including DNA damage. → Irreversible injury → Cell death (Necrosis, Apoptosis)

(3) Metabolic Alterations, genetic or Acquired Ch. Injury → Intracellular
- accumulations
- Calcifications

(4) Cumulative Sublethal injury over long life Span → Cellular Aging.



Cell Injury is reversible upto certain point but if stimulus persists → cell suffers irreversible injury and death occurs ultimately

For Example → Response to Increased Haemodynamic loads, like

the cell to survive and continue its function.

Adaptive response consists of

(1) — ↑se in the size of cells → Hypertrophy
— ↑se in their number " → Hyperplasia (2)
→ ↓se in size & Metabolic activity of cells → Atrophy (3)
→ or change in the phenotype of cells → Metaplasia (4)
↓
Physical appearance

Response of cell.

Suppose : Nature of stimuli injurious to cell.

① Non lethal stimuli → Injury

↑ sed demand
↑ sed stimulation } → Hypertrophy & Hyperplasia

↓ sed Nutrition
↓ sed stimulation } → Atrophy

Ch. Irritation → physical or Chemical } → Metaplasia

② Reduced O2 Supply, Chemical Injury, Microbial Infection
cell Injury

Acute & transient → Ac. reversible injury
Cellular Swelling, fatty chan

to the Heart

↓

Heart Muscle becomes Enlarged (A form of Adaptation

↓ If continues

Heart Muscle undergo injury

Another Ex

If blood Supply to Myocardium

Compromised

or

inadequate

↓

Muscle suffers reversible injury by Certain small cytoplasmic changes

↓

Eventually cells suffer irreversible injury & die.

"Cell death is End result of cell injury"

Causes → Includes → ① Ischemia
② Infection
③ Toxins.

There are 2 pathways of cell death

✓ ① Necrosis

✓ ② Apoptosis

Nutrient Deprivation triggers an adaptive Cellular response which called autophagy

Ultimately leads to cell death

ROS :-
Reactive oxygen species are formed in reperfusion of ischemic tissues also cause membrane damage

Arteries

Ischemia

Reversible Injury

Mitochondria oxidative Phosphorylation

"Nuclear" damage

"Cell Membrane"

"Ribosome" damage

↓ ATP

↓ Na^+ K^+ ATPase pump

Glycolysis

Detachment of Ribosomes

Fatty acid oxidation

Influx of Ca, H_2O & Na Accumulation Efflux of K

↑ Glycogen ↓ pH

↓ protein synthesis

Fatty acid accumulation

Cellular Swelling & blebbing ER Swelling

Clumping of Chromatin

Lipid deposition

Lipotoxicity

Nuclear Protein digestion

Intracellular release & activation of lysosomal Enzymes

Membrane damage

↑ CK, LDH Exit of cellular Enzymes.

Ca influx

Irreversible Injury

↑ Ca in Mitochondria Mitochondrial damage

Reactive oxygen species

Necrosis

Apoptosis

Causes of cell Injury → Acquired
→ Genetic

Acquired
1. Hypoxia & Ischemia → O_2 is required to perform Metabolic functi
2. Chemicals & drugs
3. Physical agents
4. Microbial "
5. Immunological reaction
6. Nutritional Imbalance
7. Aging.

"HEPMINA" / "HCP – MENA"

when Blood supply is used, venous drainage is restricted by Vascular disease or thrombi

Anemia → Due to used O_2 carrying capacity Co poisoning

Genetic:
1. Developmental defect
2. Cytogenic defect
3. Single gene defect
4. Disorders & Multifactorial inheritation

"DCSD"

② Chemical poisons strong acids, alkali Environmental pollutants insecticides, Pesticides O_2 at High concentration Narcotic drugs
↓
Cause cell injury by acting on Vital function of Cell Membrane permeability, ② Osmotic Homeostasis ③ functional capacity of Enzyme

① * ③

3. Physical agents: Road accidents, Thermal trauma, Electricity, Radiation } Have effection the cell.

4. Micro Such as Bacteria, Viruses, fungi & other parasites } affect the cells

5. Immunologic reactions: Hypersensitivity, Anaphylactic, Auto immune diseases } cause cell injury as they act defense

Anaphylactic Reaction
↓
To foreign protein thought to be responsible for auto immune diseases

6. Nutritional Imbalance } Either Nutritional deficiency or Excess
↓
Result in Imbalances

Deficient diseases are Malasmus & Kwashiorkor
Protein deficient ↗ ↘

Mineral → Anaemia
Iron

High fat diet → Atherosclerosis
Obesity.

7. Aging: Lipofuscin → Brownish yellow granular
Intracellular pigment accumulated in a
variety of tissues of Heart
liver
Brain

This pigment represents complexes of lipids & proteins
derived from Oxidation of polyunsaturated
lipids of Subcellular Membrane.

Genetic causes 1: Developmental defects: abnormalities during of
fetal life during
Embryogenesis.

2. Cytogenetic → Numerical → Chromosomal abnormalities
↘ Structural Occur due to Rise
or Use in Number
↓ of total Chromosomes
Changes in appearances
of Chromosomes

3. Single gene defect: Due to Mutation of single gene.
Mendellian Syndrome

4. Disorders Multifactorial: Concern Multiple genes in
Combination with life style & Environmental factors
Eg: Heart disease, Diabetes & Obesity

(2) Nuclear damage: ↓ in ATP ∝

~~Gastric~~ ↑ se in cyclic AMP

Stimulates Enzyme phosphofructokenase

↓ causes

Glycolysis to Maintain Energy sources from glycogen.

↓

Glycolysis results in accumulation of lactic acid

and reduces Intracellular pH & Glycogen which results in clumping of Chromatin → Reversible

↓

If persists → cell reaches Irreversible injury

↓

fall of pH leads leakage of Enzymes from lysosomes into cytoplasm

results in Enzymatic digestion of Cytoplasmic & Nuclear components.

(3) Ribosome damage: ↓ se ATP

↓ causes

Detachment of Ribosomes from ER

and ↓ sed protein synthesis; lipid deposition lipid toxicity

↓

Reversible injury

↓ If Hypoxia continues

Leads to ↑ sed Membrane permeability & diminished Mitochondrial function and leads to Apoptosis

by Necrosis Apoptosis autophagy mechanisms

(4) Mitochondrial Damage

leads to ↑ sed Intracellular & Mitochondrial Ca levels

Cell Swells & Ruptures — Death

As a result of ↓ se ATP & lactate accumulation

↓

ATPase dependent ion transport mechanism becomes dysfunctional (Reversible)

↓ Hypoxia continues

Free Radical Mediation of cell Injury

Free radicals like Hydroxyl ($^{\cdot}OH$), Hydrogen (H), Superoxide ($O_2^{\cdot-}$) } in cells

they attack & degrade nucleic acids, Proteins, lipids & Carbohydrates

and initiates autocatalytic reaction "where the Molecules will react & start the chain of damage"

Due to absorption of (1) Radiant Energy : i.e UV Rays, X rays

or in (2) reduction reaction during Normal physiology

(3) also due to Metabolism of Exogenous chemicals.

Free radicals in cells

Accumulation of free radicals in aging results in oxidative damage to DNA, Proteins & lipids.

Pathogenesis

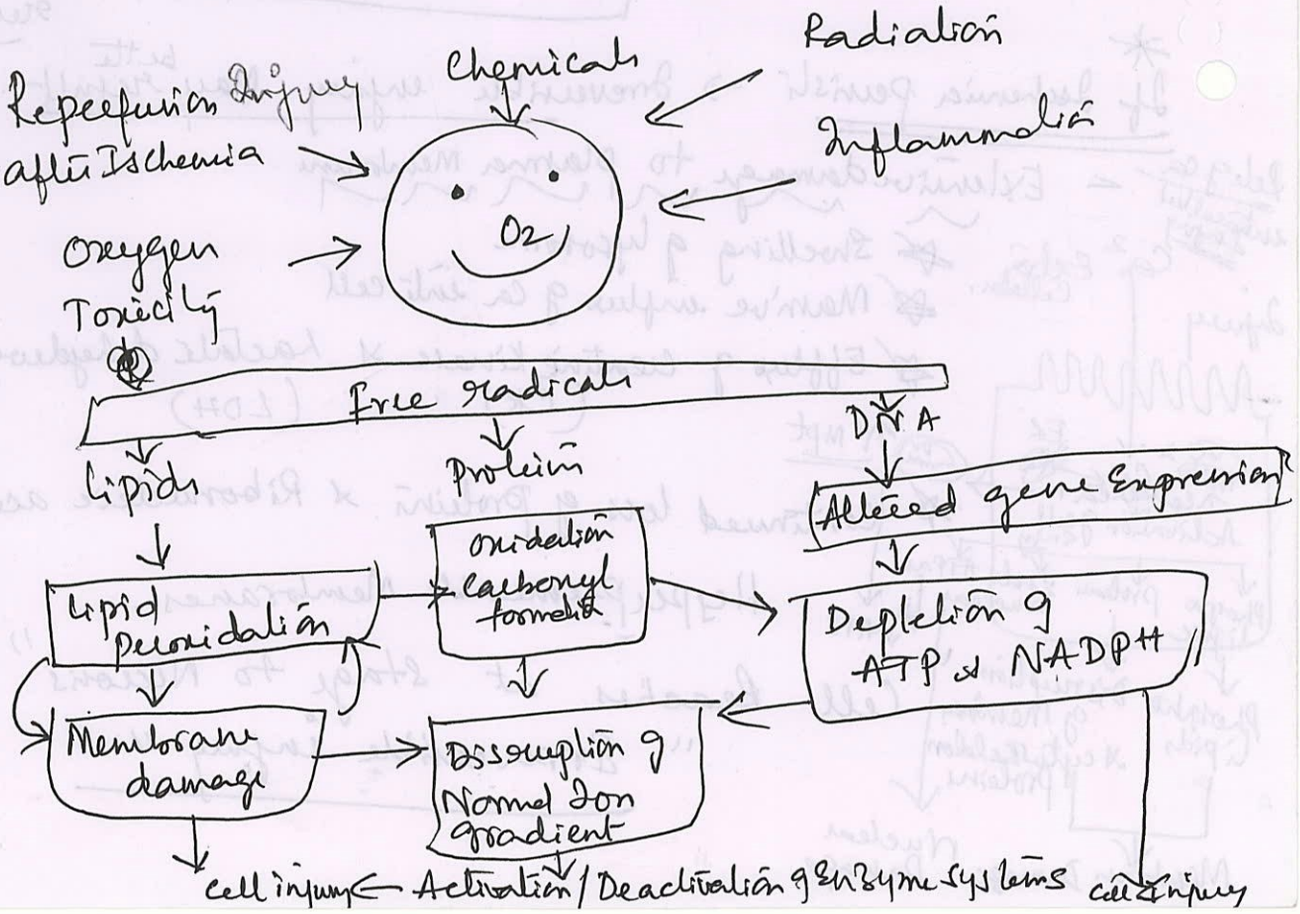
Mechanism of cell Injury

→ As you know there are many causes for injury oxygen plays a central role in the cell injury as the cellular components, Enzymes with in cell are interdependent.

Lack of oxygen
↓ leads
~~Causes~~.
Ischemia which is Main cause of Pathogenesis of cell injury

1) Flowchart of pathogenesis (8)

2) Schematic Representation of formation of free radicals ✱ action on lipids, Protein ✱ DNA



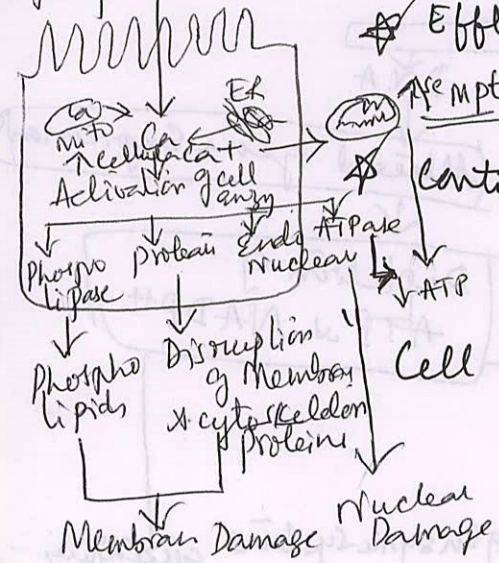
Ischemic and hypoxic Injury (Pathogenesis) ⑧

Cellular injury : Ischemia
↓ denote
Deficient blood supply
↓ due to obstruction
Most frequent cause of cell injury

① Cell damage : Hypoxia in aerobic respiration cells involve Oxidative phosphorylation in mitochondria
↓ which slows or stops ATP generation
↓
Causes failure of Active Na pump in Membrane
↓
which leads accumulation of sodium intracellular and ~~H2O~~ H2O
Efflux of K out of the cell
↓
Produces cellular Swelling which is reversible if O2 restore

* If Ischemia persist → Irreversible injury May better result.

Reduced extracellular Ca → Extensive damage to plasma membrane
- Swelling of lysosome
- Massive influx of Ca into cell
- Efflux of creatine kinase & Lactate dehydrogenase (CK) (LDH)



Affect MPT
- Continued loss of proteins & Ribonucleic acid from Hyperpermeable Membranes.

Cell Reaches at stage to Necrosis "Irreversible injury"

Morphology of cell Injury

In order to carry out the functions
the cell requires Energy needs, some
transport Mechanisms
to facilitate the import of Metabolites
and the Export of waste products.

Injurious agents like
① Radiation
② Chemicals
③ viruses
④ Bacterial & fungal
⑤ Toxins.

} bring Cellular changes in Cellular Morphology

Cellular Morphology

Divided into 3 patterns

1. Pattern of acute cell injury i.e – Reversible → Irreversible ↓ leads Necrosis Apoptosis
2. Subcellular alteration in response to More Chronic persistant injury
3. Intracellular Accumulation – i.e lipids carbs Proteins

Results in degradation in Cell Membrane

Pattern of Acute cell injury

The Morphological changes resulting from Non Ethical injury to cells called Reversible injury

It is of 2 types : Cellular Swelling & fatty changes.

Cellular Swelling occurs when cells are incapable to Maintain Ionic & fluid homeostasis.

Necrosis : Here the cells are recognised as dead when it undergoes sequence of Morphological changes.

There are 2 processes which bring about Necrosis

1. Enzymatic digestion of cell
2. Denaturation of proteins.

Enzymes are derived from dying cells — i.e from lysosomes

↓

Denaturation of proteins / Enzymatic digestion

↓ ↓

Where coagulative Necrosis results (1) | Liquifactive Necrosis (2).

1. Ischemia → Damage to Mitochondrial components

↓ Leads

Hydrolysis of ATP ↓ ↑ Ses free phosphate

↓

Reduce Energy for Ion pump activity

2. ↑ Sed Intracellular Ca^{2+} } In Normal physiological state there is 10,000 fold Excess in Ca^{2+} Conc Extracellularly

Failure of Pl Membrane Ca^{2+} Atpase Results

↑ Sed ~~Motor~~ Ca^{2+} ions intracellular cytoplasmic

Ca activator ↓

Number of Effectors of Necrosis

↓

~~Caplains~~ Calpains

x

Phospholipases

Promotes Mitochondrial damage

Calpain activation :

Calpains are Neutral proteases required for disruption of lysosomal membranes

↓ leading

To release of cathepsins (Which is a degenerative proteases which cleave cytoskeleton proteins and Na/Ca Exchange pumps.

↓ causing

Ca^{2+} influx

Ca^{+} Increase disrupt krebs cycle leading

↓

↑sed ROS ↓ Mitochondrial permeability transition (mpt)

↓ resulting

↓sed ATP production

ROS permeabilize lysosomes

↓

Failure depolarize Mitochondria through activity of Cyclophilin-D (cyPD)

↓

Damage DNA

↓ Activate

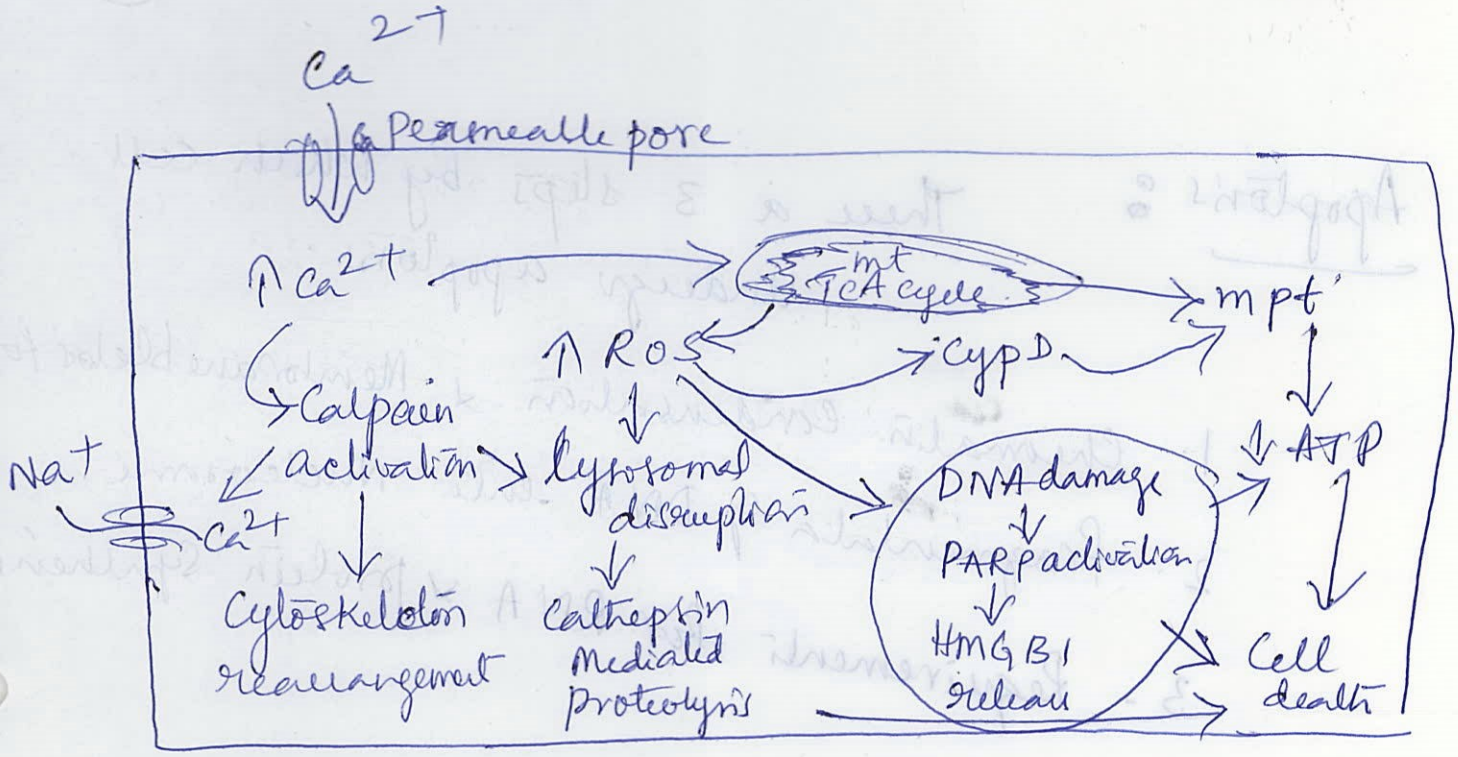
PARP Poly ADP Ribose polymerase

↓

Deplet ATP ↓ Nuclear Cytosolic translocation of HMGB1

HMGB1

High Mobility group protein



Phospholipase activation : Ca^{2} activates phospholipases

↓

Hydrolyse phospholipids

↓

Affecting stability of cell

↓

Organelle Membranes

Mitochondrial damage : ↑se Intracellular Ca^{2+}

↓ Result in

↑ing Mitochondrial Calcium

↓ Lead

Mito Injury by mpt

During mpt inner membrane forms pores leading to depolarization uncoupling of Electron transport failure of ATP Production →

→ Mitochondrial Swelling & Lysis.

Apoptosis: There a 3 steps by which cell undergo apoptosis.

1. Chromatin condensation & Membrane blebs formation
2. fragmentation of DNA into Nucleosome
3. Requirements for RNA & protein Synthesis

Apoptosis Means: falling off

Apoptotic cell death starts by

1. Cellular shrinkage
2. Chromatin Condensation
3. formation of Membrane blebs
4. organelles & Nucleus fragments & blebs begin forming of Apoptotic bodies
5. Eventually Engulfed by Macrophages or Neighbouring cells by Endocytosis or phagocytosis

No inflammation: Actg release cellular components extracellular.



Subcellular changes to injury : (16)

(A) Lysosomes : Membrane bound cytoplasmic bodies.

Contain Hydrolytic Enzymes

↓

Involved in breakdown of Phagocytosed Materials

2 ways

1. Heterophagy
2. Autophagy

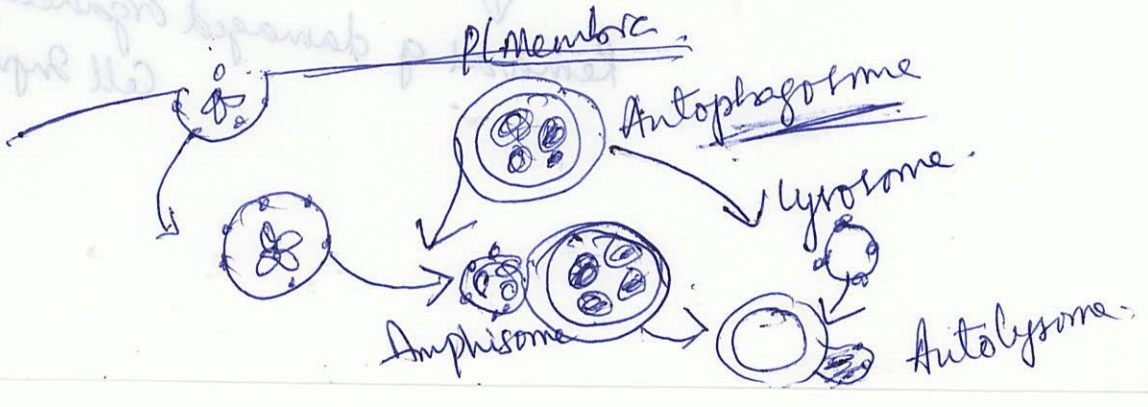
Heterophagy :

Material taken from External through

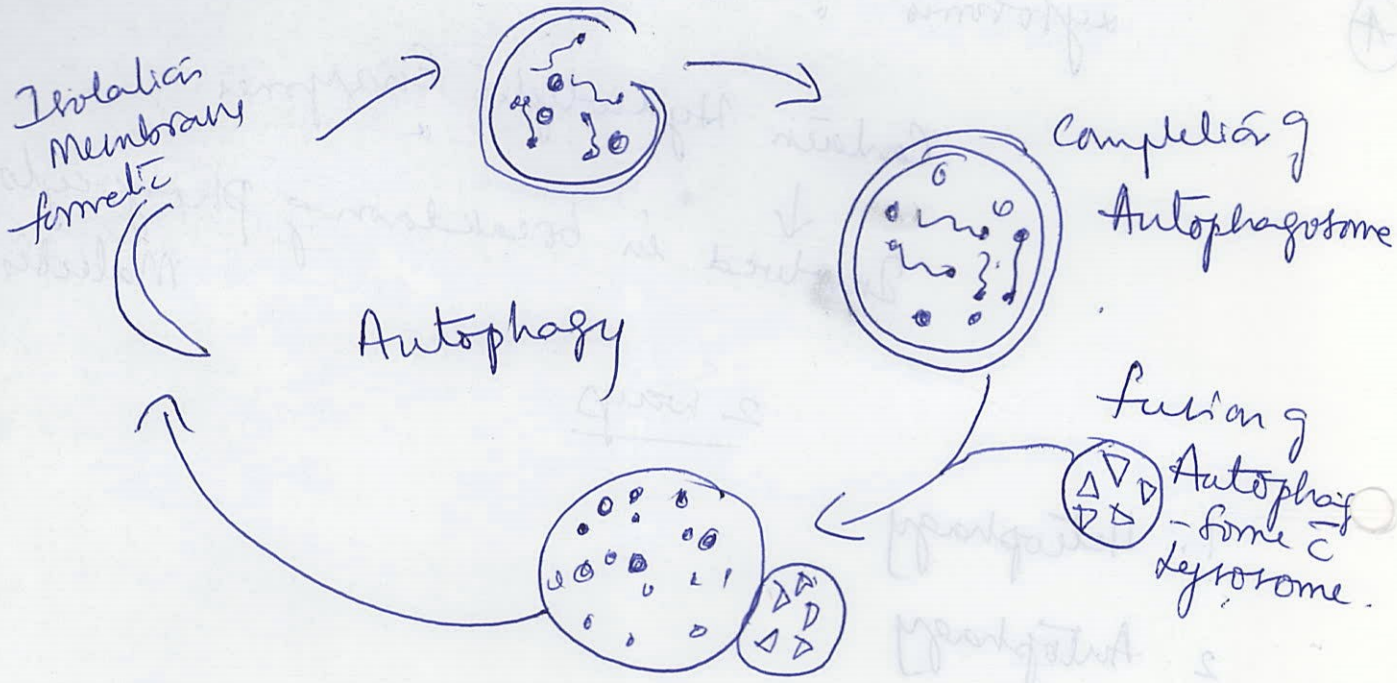
(1) Endocytosis — Engulfing called phagocytosis.

Seen in Neutrophils & Macrophages.

(2) Fusion of Phagocytes Vacuoles & lysosomes will occur & Eventual digestion of Engulfed Materials



Autophagy :



Intracellular organelles and portion of cytosol get seperated from cytoplasm in an autophagic vacuoles formed from ribosome free region of RER which fuses with

Pre existing primary lysomes

↓ to form

Autophagolysosome

↓

Removal of damaged organelles during Cell Injury.

(B) Induction of Hypertrophy of SER:

↓ Bringing about

This is due to Induction of ↑sed Volume of SER of Hepatocytes

Barbiturates are detoxified in liver by oxidation demethylation

↓ Involves

Cytochrome P-450 Centered Mixed function in SER.

↓

Cells able to detoxify drugs & Adapt-altered Environment

Cytochrome / Cyto P450

Absorbs light of 450 nm wavelength when exposed to CO — Carbon Monoxide

This Mixed function oxidase system of SER → Involves in Metabolism of

- Carcinogenic hydrocarbons
- Steroids
- Carbon tetrachloride
- Alcohol
- Insecticides

(C) Mitochondrial alteration: In acute cell injury

Alteration in Number, Size & Shape, occurs in pathologic conditions

For Ex. Hypertrophy & Atrophy ↑se & ↓se in No of Mitochondria in cells.

Mega Mitochondria → Abnormal large shape seen in Alcoholic Cirrhosis & certain Nutritional diseases

In Mitochondria Myopathy : Due to inherited (19)

Metabolic diseases of skeletal Muscle

↓

Mitochondria Metabolism is affected ∵

↑se in Mitochondria which become large &
having abnormal Cristae &
Certain crystalline.

(a) Cytoskeleton lesion:

Cytoskeleton consisting → Microtubules → thin filaments → Actin
Thick " → Myosin
Intermediate filamen

If any abnormalities are present with these filaments the following results.

(1.) Defect in cell function such as locomotion ✓ & Intracellular Movement. ✓

(2.) Leukocyte Migration & phagocytosis — due to functional deficiency of cyto skeleton

(3.) Inhibit Sperm motility causes Male infertility

(4.) Intracellular accumulation.

Adaptations of cellular growth

Adaptations are reversible changes

- in Size
- Number
- phenotypic
- Metabolic activity
- function of cell

} in Response to changes in their Environment.

Such Adaptations are

1. Hypertrophy
2. Hyperplasia
3. Atrophy
4. Metaplasia.

1. Hypertrophy: Refers to ↑se in Size of cells.
↓ as
Resulting in pancreas in the Size of organ

Hypertrophied organ has No new cells
just larger cells

↑se Size is due to Synthesis of More structural Components

Hypertrophy can be

→ Physiologica

→ Pathologic

Caused by ↑sed demand ①
or
② by stimulation by hormones or Growth factors.

Most common stimulus for Hypertrophy of Muscle is ↑sed workload.

For Eg : In Heart → stimulus is ch hemodynamic overload as a result of Hypertension or faulty valves.

Heart muscle have limited capacity for division and hence it responds to ↑sed demands by undergoing hypertrophy.

Another Eg : Physiologic growth of uterus during Pregnancy

Stimulus : Hormone (Estrogenic Hormones) acting on ↑se in Size of organ resulting Hypertrophy of Muscle fibers and ↑sed synthesis of smooth muscle proteins. ↑se in Size of cell

Estrogenic receptors are present in smooth muscle of uterus.

(22)

Hypeeplasia : ↑ in NO g cells in an organ or tissue.

↓

Resulting in ↑sed Mass g organ.

Hyperplasia ⊻ Hypeetrophy frequently occur together

Hypeeplasia triggered by External stimuli

Takes place if cell population is capable g dividing

Can Physiologic or pathologic

Physiologic : 1. Hormonal Hypy → ↑ses functional Capacity g tissue

2. Compensatory Hypy

↓

↑ses tissue Mass after damage or partial resection.

Ex g Hormonal Hyperplasia : Glandular epithelium g female breast at puberty & during pregnancy accompanied by Enlargement (Hypertrophy)

Ex g Compensatory : Partial Hepatectomy has been is an example that stimulate regeneration g liver.

Pathologic Hypes : Caused by Excess g hormones or Growth factors acting on target-cells.

(23) Ex: Endometrial Hyperplasia :

Balance b/w Estrogen & Progesteron is disturbed resulting in ↑se in Estrogen with consequent g Hyperplasia g Endometrial glands ∴

↓ leads to

Abnormal Menstrual bleeding

Normally: After Menstration a rapid proliferative activity in epithelium is stimulated by ovarian hormone estrogen. It is brought to halt by raising levels of Progesteron about 10-14 days before next Menstrual period.

Pathologic Hyperplasia is distinct from cancer but constitutes as fertile soil in which cancerous proliferation may arise.

Growth factors produced by viral genes or infected cells stimulate cellular proliferation

Thus it with may be due to certain viral infections as papilloma viruses. → cause skin warts
→ several mucosal lesions.

(24)

Atrophy : Reduced size of organ or tissue resulting from decrease in cell size & Number

Physiological & pathological

↓

Common during Normal development

Ex - Some Embryonic structures like Notochord, Thyroglossal duct undergoe - Atrophy during fetal life.

Ex Uterus ↓ses in size after parturition →

Pathological : (1). ↓sed workload : Skeletal muscle atrophy when restricted to complete Bed rest

↓se in size is reversible when activity is resumed.

If Prolonged disuse → skeletal fibers ↓ in number

(2) Loss of Innervation : Damage to Nerves leads to atrophy of Muscle fibers

(3) Diminished blood supply : In late adult life Reduced blood supply as a result of atherosclerosis → called Senile atrophy of brain

Inadequate nutrition : Protein calorie Malnutrition and disease

Malnutrition is associated with the use of skeletal Muscle as a source of Energy after other reserves such as adipose stores have been depleted.

Along Endocrine stimuli :

Hormone responsive tissue like reproductive organs & breast are dependent on Endocrine stimulation for Normal Metabolism & function.

Physiological atrophy Endometrium breast -

Pressure → Tissue compression eg. for length of time Cause atrophy.

Ex : Enlarging benign tumor Cause Atrophy in the surrounding tissue.

Changes are seen in Cervical epithelium & Resp tract

↓

There are thought to be Neoplastic growth Seen adjacent to Cancer cells Mild, moderate severe

Metaplasia : One differential cell type is replaced by another cell type

Most common Epithelial Metaplasia is Columnar to Squamous → in Resp tract in response to ch-Irritation

In cigarette Smokers → Normal ciliated columnar cells of trachea & bronchi are replaced by squamous epithelial cells.

Vit A deficiency induces squamous Metaplasia in resp Epithelium.

The Influences that predispose to Metaplasia if Persistant may initiate Malignant transformation

Dysplasia : often called as Atypical hyperplasia Not considered as true adaptive process.

Intracellular Accumulations

Normal cells accumulate abnormal amounts of

Various substances

1) Normal cellular constituent- as H_2O, lipids, proteins, carbohydrates

2) abnormal substances either Exogenous such as Minerals, infectious agents

Endogenous such as product of abnormal synthesis or Metabolism

Then substances accumulate either transiently or permanently

They may be harmless to cells

or

Sometimes (toxic) severely toxic.

Substance located in cytoplasm Nucleus

or

abnormal substances sometimes store elsewhere in the body.

Normal Endogenous substance at Normal or Used Rate

but- rate of Metabolism is inadequate to remove it.

Ex: Fatty change in liver, Heart & Kidney

2. Abnormal Endogenous sub: the product of Mutated gene
↓
accumulates because of defect in Protein folding & Transport & inability to degrade the abnormal protein efficiently.
Ex: Accumulation of Mutated α_1 Trypsin in Liver cells.

3. Normal Endogenous substances accumulate because of defect which of inherited in Enzymes required for Metabolism like: Lipid Metabolism
Carbohydrates
↓
resulting intracellular deposition largely in lysosomes.

4. An abnormal Exogenous sub accumulates or deposited because the cells has neither Enzymatic Machinery to degrade nor ability to transport it to other sites. Ex: Carbon particles & Non Metabolized products like Silica

Accumulation is reversible if the overload can be Controlled or stopped.

In Inherited storage diseases accumulation is Progressive & overload. Cause cellular death & Part death

(28) Fatty liver: Steatosis or fatty change.

↓

Describe abnormal accumulating Triglycerides in parenchymal cells.

Liver is Major organ involves in fat Metabolism

Also occur in Heart
Muscle
Kidney.

Most common causes of fatty change
1. are alcohol abuse
2. Non alcoholic fatty change
Diabetes ✗ Obesity

In the liver: fatty acids are esterified to triglycerides
↓
converted into cholesterol
phospholipids
oxidized to ketone bodies.

Excessive accumulation of triglycerides in liver
↓
Result from Excessive Entry of
or defective Metabolism ✗ Export of lipids

Such defects are induced by alcohol
(Hepatotoxin)

↓

Alters Mitochondria & Microsomal functions leading to ↑ Fatty synthesis & reduced breakdown of lipids

Cholesterol accumulation

Atherosclerosis.

↘ Seen in pathological conditions like

1. Atherosclerosis
2. Xanthomas

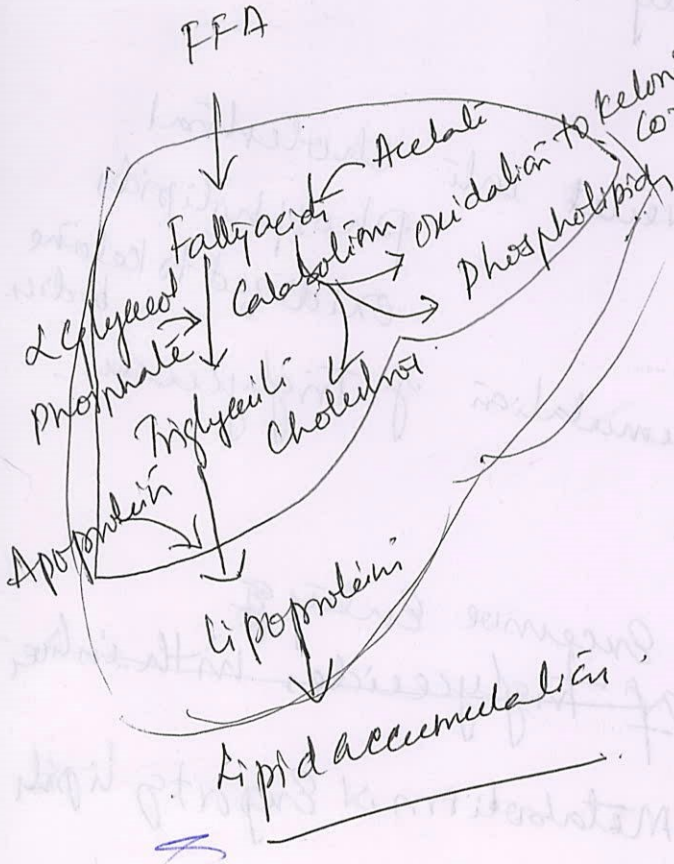
Plaques made up of cholesterol & fibers aggregated in intima layers of aorta

↓

Intracellular accumulation of Cholesterol within Macrophages.

Heidelberg ✱ Acquired

found in subepithelial connective tissue of skin & tendons.



Lipid accumulation.



(30)

PV books
Madan
Kaushik

Proteins: Accumulation of Proteins

↓ due to

Availability to the cell or Excess synthesizes in the plasma cell
Engaged in synthesis of Immunoglobulins.

In Renal Diseases associated with protein loss in Urine
small amounts of protein filtered through glomerus
are reabsorbed by pinocytosis
in proximal tubule

In conditions of heavy protein leakage there is used
reabsorption of the protein into vesicles appears as
Pink hyaline droplets with in cytoplasm of tubular cells.

This process is reversible
some of proteinuria diminishes
Protein droplets are metabolized & disappeared

Defective intia Cellular transport & secreting protein

eg, anti trypsin deficiency

↓

Mutations in protein

↓

slows folding

↓

Resulting Partially folded intermediate which
aggregate in ER of liver → are not secreted

(31)

Accumulation of Cytoskeletal proteins - Intermediate filaments

Provide flexible intracellular scaffold that organizes the cytoplasm & resists forces applied to cell

Among 5 types of filaments

Keratin filaments → Epithelia
Neurofilament → Neurons
} Accumulate are associated with certain types of Cell Injury.

Alcoholic liver disease
↓
Cytoplasm in liver cells
Composed predominantly
of Keratin filaments.

Glycogen: Excessive intracellular deposition of Glycogen seen in part of abnormality in either glucose or glycogen Metabolism.

In DM: glycogen found in renal tubular epithelial cell & in liver cells, β cells of Langerhans & Heart Muscle cells.

Glycogen storage diseases are group of genetic disorders where glycogen accumulates in the cells due to Enzymatic defect in Synthesis or breakdown of glycogen → Resulting in Massive Accumulation causing Cell Injury & Cell death.

Pigments → Exogenous → from outside of body
Endogenous → synthesized within body.

Carbon or coal when inhaled picked up by Macrophages
↓
transported through lymphatics to
↓
Regional tracheobronchial lymphnodes.
Aggregation of coal dust leads to fibroblastic reaction or Emphysema → lung disease known as coal worker pneumoconiosis.

Tattooing: form localised pigmentation of skin
↓
pigment phagocytosed by skin / dermal macrophages in which they reside for life.

Endogenous:
Lipofuscin → Insoluble pigment composed of polymers of lipids & phospholipids with protein
↓
derived by lipid peroxidation of poly unsaturated lipids of subcellular membranes.

4) Renal failure: Causes retention of phosphate leading to secondary Hyperparathyroidism

Metastatic calcification occurs throughout the body but principally affects

1. ~~Intestinal tis~~ Interstitial tissues of gastric mucosa
2. Kidneys
3. Lungs
4. systemic arteries
5. pulmonary veins.

On Native involvement of lungs → Respiratory deficits

" " kidney → Nephrocalcinosis may cause renal damage.

Dystrophic calcification: Seen in areas of Necrosis ↓ where they are of coagulative or liquefactive type

Calcification almost present in atheromas of Advanced atherosclerosis.

Commonly develops in aging or damaged heart Valves leading hampering their function

Ca Salts appear as fine white granules or clumps

It appears as yellow brown granular cytoplasmic Perinuclear pigment

Seen in cells undergoing flow & regressive changes in liver & heart of aging pts & severe Malnutrition & Cancer cachexia.

Ex: Haemosiderin: golden yellow pigment to brown

↓

Haemoglobin derived. serves as storage form of Iron

Excess of Iron Causes

Haemosiderin accumulate in the cell

Either localized or systemic

↓

accumulation of Iron in organs & tissues called as Hemosiderosis.

Seen in ① ↑ed Absorption of dietary Iron

② Impaired Iron utilization

③ Haemolytic anemia

④ Transfusions.

Systemic Haemosiderosis → pigment does not damage the Parenchymal cells or impair function

Haemochromatosis: An inherited disease associated with liver, heart & pancreas → Resulting in liver fibrosis Heart failure & Diabetes Mellitus.

Calcification:

2 types — Physiological
×
Pathological

Physiological: during bone healing or developing

Pathological: In presence of high circulating levels of Ca ions and depositing in Normal tissue

1) — "Metastatic calcification"

2) Deposition of Normal levels of calcium in Pathological tissues is "dystrophic calcification"

Metastatic Calcification: Caused by deposition of Ca salts in lung tissue due to systemic ↑se in serum calcium levels

Hypercalcimia Causes → Primary Endocrine disorder has been corroborated ✓

↓ cause of Hypercalcemia

1. Hyperparathyroidism: ↑sed secretion of Para thyroid hormone. ~~Paraneoplastic syndromes~~ due to Parathyroid tumors.

2. Destruction of bone tissue
↳ secondary to tumors of bone Marrow
Multiple Myeloma, Leukemia

3. Vit D related disorders, including Vit D intoxication in which Macrophages activate Vit D precursor

felt as gritty deposits.

(36) Sometimes a tuberculous lymph node is virtually connected to bone.

Ca is concentrated in Membrane bound vesicles in cells by a process initiated by Membrane damage

1. Ca ions binds to phospholipids present in Vesicle Membrane
2. phosphatases associated with Membrane generate phosphate groups bind to Ca
3. Cycle of Ca + phosphate binding is repeated raising local concentration & producing a deposit near the membrane
4. Structural change occurs in the arrangement of Ca + phosphate groups generating Micro Crystal lead to more calcium deposition.

Acidosis & Alkalosis

Normal pH value for body fluids is b/w 7.35 & 7.45

When below 7.35 in body fluids } condition called acidosis.

When above 7.45 — Condition called Alkalosis

Metabolism → is a process which produces acidic products → lowers the pH of body fluids.

CO_2 is by product of Metabolism

CO_2 + & combines with water to form carbonic acid

Anaerobic Metabolism → lactic acid is a product

Protein Metabolism → phosphoric & sulfuric acids

lipid " → fatty acids.

All these acidic substances continously eliminated from body to maintain pH homeostasis.

If elimination rate is higher of acidic products → Results Alkalosis.

If failure to eliminate acidic products. results in acidosis

(38) Respiratory alkalosis : Due to Hyperventilation of lungs

↓

↑sed rate of CO_2 elimination from the body fluids resulting ↓se conc of CO_2

↓

As CO_2 levels ↓se → H+ react c bicarbonates ions to form carbonic acid.

↓

Dissociate to H_2O & CO_2

↓se in H+ causes ↑sed pH in body fluids above 7.35

↓

Respiratory alkalosis occurs

Here kidneys compensate for a resp alkalosis by ↓sing the rate of Hydrogen ions secretion into urine & rate of bicarbonate ion reabsorption

(39) Resp system & kidneys regulate the PH of body fluids.

Altered function of Resp or kidney can result in acidosis & Alkalosis.

Resp acidosis : Inadequate ventilating lungs.

↓

Resp acidosis

as Rate of CO_2 Elimination is less from body fluids due to abnormality of lungs

↓

Excess of CO_2 in body reacts with water to form carbonic acid.

carbonic acid → H^+ Hydrogen ions & HCO_3 bicarbonate ions

↑se in H^+ concentration causes PH of body to ↓ i.e. If it falls below 7.35

Symptom of Resp acidosis occurs.

Buffers resist, & the kidney compensate for failure of the lungs. to prevent resp acidosis by using the rate of H^+ secretion into filtrate and reabsorb bicarbonate ions.

(40) Metabolic acidosis : condition that ↓se pH of body fluids below 7.35 resulting from altered function of Resp sys

When Hydrogen Ions accumulate in body fluids buffers first resist decline in pH.

If buffers cannot compensate for ↑ses H+

The Resp center helps regulate pH of body fluids

↓se pH stimulate Resp center causing Hyperventilation.

↓ Where

CO_2 is eliminated at greater rate.

↓ along

also eliminate Excess H+ Ions & helps to Maintain pH of body fluids within normal range

If M.A persists for Many hrs & Kidneys are normal functional compensate for M. Acidosis.

They excrete H+ at Greater rate & ↑ rate of bicarbonate reabsorption.

Symp of Metabolic acidosis appear if resp & Renal Systems are not able to Maintain the pH of the body fluids within Normal range.

(a) Metabolic alkalosis :- Results from all condition that ↑se pH of body fluids above 7.45 Except the condition resulting from altered function of Resp system :

As H^+ ↓se → buffers will resist first an increase in pH.

If buffers cannot compensate for ↓se H^+ Resp center helps to regulate pH

↑sed pH inhibits respiration.

↓

Reduced respiration allows CO_2 to accumulate in the body fluids

↓

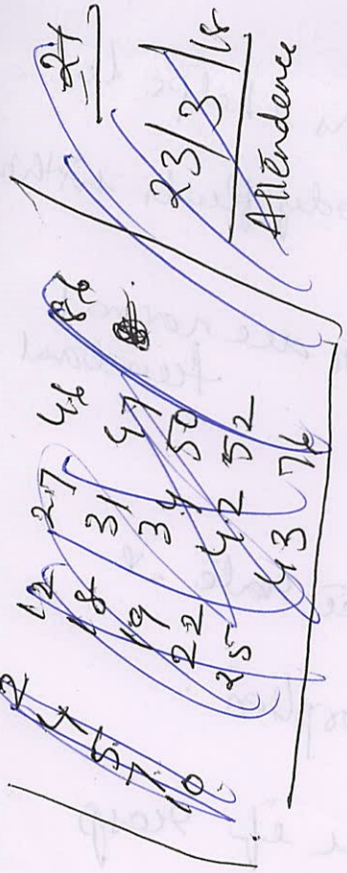
CO_2 reacts with H_2O to produce carbonic acid

↓

If persists for several hrs & kidneys all functional

↓

kidney reduce rate of H^+ secretion to help reverse alkalosis



(42)

Electrolyte imbalance

Electrolytes are Essential for life to survive,

Sodium
Chloride
Potassium
Magnesium
Calcium

} Most prominent Electrolytes

- they Maintain osmotic pressure
- conduct electricity which is Essential for Muscle & Nerve function
- Maintain Acid base balance.

Causes of Electrolyte imbalance

1. Kidney disease
2. Vomiting for prolonged period
3. Severe dehydration
4. ~~Acide/base pH~~ Congestive Heart failure
5. Cancer treatment
6. Diuretics

Symptoms of Electrolyte Imbalance :

Convulsions
fatigue
Muscle spasms

Irregular heartbeat
Twitching
Weakness
Blood pressure Changes
Bone disorders
Confusion Seizures
Numbness

43

	Pl	CSF	Urine	Imbalance ↑	Imbalance ↓
Na^+	136-146 mM	138-150	40-220 mm	Hypernatremia	Hypo
K^+	3.5-5 mM	0.35-3.5 mM	25-125 mM	Hyperkalemia	Hypoka
Cl^-	98-107	118-132	110-250mm	Hyperchloremia	Hypo
HCO_3^-	22-29	—	—	Alkalosis	Acid-is
Ca^+	2.15-2.5 mmol	—	upto 7.49 mmol/day	Hypercalcemic	Hypo

More sweating cause ~~do~~ significant loss of Na^+ & Cl^-

Severe vomiting or diarrhea causes → Cl^- & ~~bicar~~ HCO_3^-