Date: _____

Pathology:-

Study of structural, biochemical, and functional changes in cells., tissue and organs. That underline disease.

* invastigation of cause of diseases.- also involve the study of sign and symptoms

Two Part

(1) General Pathology
(2) Systemetic Pathology

General Pathology:-

Concered with common reactions of cells and tissues to injuries stimuli

Acute inflamation

Systemic Pathology:-

examines the alteration and underling mechanism in organ specific diseare. Such as heart attack, ischemia.

Four aspect:-

1) Etiology
2) Pathogenesis
3) Morphological changes
4) Functional deragment and clinical are

Date:

Etiology:- "origin of diseases including caures and modified factors."

It mean caures factor which caure direare

① Genetic factor:-
Inherited mutation
Dèseare associated e-
Gene variation.

② Acquired factor:-
infectous, nutritional, chemical, physical

Pathogenesis:- (How disease develops.)
mean biochemical and molecular mechanism of direare development

Morphological changes:-
Structure alteration in cell

Functional Derangments:-
Functional changes
What symptom and sign.

Reversible	**Irreversible:-**
Reversible sublethal and short acting treated with drugs. Results in cell swelling and fat accumulation	✓ Lethal and long lasting Permanent cell loss. ↓ Result in necrosis and apoptosis.

(2) variety of stress that change (morphological, metabolic changes) internal enviorment of cell

Date: _____

small clear vacule within cytoplasm

Types of Injury:-

Reversible Injury:-

Incomplete injury of cell. cell can recover.

mild transition

(1)- Decreas ATP synthesis:- by oxidative phos-pho-rylation.

(2)- cell swelling

Dec function of Na^+, K^+ pump:- cellular swelling

(4) and swelling of ER.

↑ anaerobic glycolysis:- ↓ glycogen, ↑ lactic Acid production., ↓ PH

dec Protein synthesis:-

(5)- detachment of ribosome

Plasma membrane bolbs and myelin figures.

(5)- fatty change

Appearence of TAGs, contain lipid vacoule in cytoplasm on liver.

failure of energy dependent ion pump → inability to maintain ionic + fluid homostasis

Ir Reversible Injury:-

Complete cell injury severe and progressive cann't recovere

Apoptosis | Necrosis

(1)- Severe membrane damage:- ↑ influx of Ca^+ in cell. exflux of enzyme and protein in blood / swelling

(2)- Ca^{+2} influx

(3)- mitocondrial dysfunction:- mitocondrial swelling ↓ ATP

(5)- Rupture of lysosomes:- autolysis start releare lysosomal digestive enzyme in to cytosole

(4)- Nuclear Change:- clumping of chromatin ✓ degenration of nuclear

(1) chromatin (pyknosis) ✓ Nuclear fragmentation.

(2)- (Karyorrhexis) dissolution of nucleus

(3)- (Karyolysis)

Date:

Causes of cell injury:-

1. Hypoxia
2. Ischemia → ↓ Blood flow.
3. Physical Agent.
   - Truma
   - Temperature
   - Pressure
   - Radiation
   - electric Shock
4. Chemical Agent
   - Air pollutant, Insectside, CO, Asbestas, ethanal → cell injury
   - Arsenic
   - Cyanide

   Glucose↑ → salt↑ → H2O↑ cell injury.
   Poisiongas → alter peneability
   " osmotic homeostatics
   " enzyme cofactor
   lead to death
5. Drug :-
   - Alchole
   - Monooxide
   - Theraputic drug
6. Infectious Agents:-
   - Bacteria
   - fungi
   - Parasites.
7. Immunologic Reaction:-
   - Antigen / Antibody Rx.
8. Genetic factor:-
   - sex chromosome defect
   - down Syndrome
   - DNA damage

Aging :- Alteration in replicative and repairing abalities of individuals cell
↓
diminshed those abalities
↓
Leads to cell death.

④

⑨ Nutritional Imbalance :-

deficency of protein
deficency of calorie
" " Vitamins.

Adaptation of Cellular Growth :-

→ Reversible change in the size no. phenotype and function of cells due to response of enviormental changes is called Adaptation.

① Hypertrophy
② Hyperplasia
③ Atrophy
④ Metaplasia

Hypertrophy :-

→ Increare in size of cells due to this increare in sige of organ.

Two way
① Physiological (weight lifer, pregnancy)
② Pathalogical (cardiac enlargment bcz of HTN)

Pathalogical :-

* hypertension of cardiac effect
* Aortic value stenosis

heart, skeletold muscle → division
↑ metabolic demand
↑ protein
↑ no. myofilaments

Date:

Physiological:-

* Uterine hypertrophy
* increare estrogen.

Cell enlarge by estrogen hormones

→ Stimulation by hormones and growth factor.
→ increare smooth muscle proteins. and increare in cell size.

✓ **Mechanism of hypertrophy:-**

→ Increared production of cellular Protein.
→ Ocure by stress Through stretch Receptor
→ Increared RNA synthesis
→ Increared expression of gene
→ alpha adrengeric Receptor activate on the surface of myocytes.

Organ:-

• Hypertrophy of
Cardiac muscle
heart valve
Uterine smooth muscle

Date:

Hyperplasia:-

→ increared no. of cells in an organ. which lead to increare size of organ.

Ocure at dividing cells.

Two way:-

① Physiological
② Phalbalogical

Physiological:-

Action of hormone
Growth factor
Proliferation of glandular epithelium of female breast

Pathalogical:-

(i) Cancer
(ii) Benign prostatic hyperplasia
endometrial hyperplasia

Mechanism:-

→ dividing cell undergoes influence of growth factor and hormone

↓

→ Profiration of growth cells / mature cells

↓

→ Increare the number of cells. cause hyperplasia

Date:

Organ:-

→ Breast, endometrium of utrus
Prostate, liver
↓

Atrophy:-

↓ → "Reduction of size of the cell and no. of cell decreare the size of the organ."

n-auto phogy

Two way
Physiological
Pathalogical

Pathalogical:-

↓ Protein synthesis
↑ Protein degradation

① Loss of innervation
damage of nerve leads to atrophy

↓ Protein (Nutrients)
Aging (Senile)

② Diminshed blood supply:-
Ischemia

③ Loss of endocrin system:-
loss of estrogen stimulation.

④ Deacreare Work load:-

Physiological:-

① decrease size of utreus.
② Notochord and thyroglossal duct undergoes Atrophy.

Date:

Mechanism:-

→ Decreased protein synthesis.
→ Reduced metabolic Activity.
→ Degenration of cellular protein occures
→ mainly by the ubiquitin proteosome pathway.

Metaplasia:-

→ "Revesible change in which one differentiated cell type is replaced by another cell type. Change in phenotype" (due to reprogming of stem cells)

→ Columner to saquamous.

Example:-

Gastric Reflux - stratified sqv. → Columner → oesophagus

* Smokers:- ciliated columner epithelial cells of trachea and bronchi reptaced by stratified squamous epithelial.

* Stone in Pancreare, bile duct. convert in to squamous epithelial

Mechanism:-

→ Reversible changes in which one type of cell convert in to other.

↓

Date:

Differentiation of cells and replace.

Organ :-

- oesophagus
- Cervix
- Urinary bladder

① growth
② for protection

Cellular death :-

Necrosis :- (due to inflamatory Response)

→ cell death in living tissue
→ denaturation of intracellular protein and enzymatic digestion.

Types :-

1. Coagulation Necrosis. heart attack
2. Liquefection Necrosis CNS
3. Caseous Necrosis. Limbs
4. Gangrenous Necrosis Tb infection
5. Fat Necrosis Acute Pancreatitis
6. Fibrinoid Necrosis Blood vessels

Apoptosis :- (without inflamatory Response)

→ programmed cell death
→ degrade the cells nuclear DNA and nuclear and cytoplasmic protein.

Date:

Necrosis:-

"Cell death in living tissue due to inflamantory Response denaturation of intracellular Protein enzymatic digestion"

* Premature cell death.

→ Necrotic cell unable to mainlain membrane integrity
→ loss of plasma Mem integrity
→ Nuclear changes occure

* Karyolysis
  dissolution of cell nucleus
* PyKnosis
  Nuclear shrinking
* Karyorrhexia
  Nucleus undergoe fragmentation

Type:-	Imp feature
① Coagulation Necrosis	cell enlarge
② Liquefactive Necrosis	Swelling
③ Gangrenaus Necrosis	P.M disrupted
④ Caseous Necrosis	enzyme digestion
⑤ Fat Necrosis	Irreversible cell injury
⑥ Fibrinoid Necrosis	

Date:

Coagulation Necrosis:-

- Cell death
- texture remain same
- Denature of Protein & enzyme
- Phagocytosis of cell by lysosomes
- this ocure due to ischemia and hypoxia

Organ:- ① This necrosis ocure all except brain

② Ischemia heart diseale

Infarct:-

A localize area of necrosis is called infarct.

Liquefactive Necrosis:-

- digestion of dead cell and tissue convert into the liquid Viscous mass
- due to bacteria / fungal infection creamy yellow dead leukocytes form pus.

Organ:- ① CNS

Gangrenous Necrosis:-

- Loss of blood supply (hypoxia) in limbs
- Bacteria superimpose on liquefactie necrosis Then action of degenrative enzyme ocure
- Wet gangrene formation
- swelling and blistering of tissue

Date:

and pus discharge:

Organ:- ① Limbs (lower leg) (Diabetes)

Caseous Necrosis:-

- Collection of white fragmented or lysed cells and amorphous granular debris endore within inflamatory boader. This appeare also called **granoloma** multinuclear giant cell
- White appearence

Organ:- ① Tb infection.

Fat Necrosis:-

- Inflamation caure releare of activated pancreatic lipase from acinar cell
- ↓
- enter in peritonium
- ↓
- split or break down of TAGs caure liquification
- ↓
- bind with Ca^{+2} and form white chocky apperence called sponification
- ↓

Condition:- ① Acute pancreatitis.

Date:

Fibrinoid Necrosis:-

- Complex antigen and antibody deposite in wall of vessele
- Complex bind ← fibrin
- Then attach with fibrin and bright pink stain form on H-E stain

Organ: ① Blood Vessels Vescolitis

Reversible	Irre
↓ ATP synthesis	Mitocondrial dmage
Cellular swelling	Ca^{+2} influx
Fatty change	Plasma Mem damage
↓ glycogen	Lysosomal Ruptre
Nuclear chromatin clumping	↓ protein Synthesis
Dispersion of ribosome	Nuclear pyknosis

Fatty change:-

Failre of energy depend ion pump
↓
Inability to maintain ionic and fluid homostasis
hydropic change
vacule degnrate

Microscopy:-
- small, clear vacule within cytoplasm

Date:

APOPTOSIS :- No cancer Risk

→ "Programmed cell death to eliminate harmful substance
cell activate intrinsic enzyme maintain no. of cells
and degrade nuclear DNA and
cytoplasmic protein."

→ Apoptotic cell break into
fragment called Apoptotic bodies.
* also have pro cytoplasm and
nucleus.

① Does not cause inflamation
② Plasma mem intact
alter in such a way
make it good for phagocytosis

Causes of Apoptotis:-

Physiological
Pathalogical

Physiological:-

① Apoptosis is normal phenomenon
to eliminate there cells no longer
needed
② to maintain no. of cells population
in tissue.

(1) Destruction of cell during embryogenesis:-
during fatal development
implatation, organogenesis
metamorphosis.

Date:

Hormone dependent involution:-

endometrial cell breakdown during menstural Cycle.

Ovarian follicular atresia in menopause.

Regression of lactating breast after weaning.

Prostatic atrophy after castration

Cell loss in prolifrating cell population:-

Immature lymphocytes in bone marrow.

epithelial cell in GIT tract.

Elimination of harmful self-reactive lymphocytes:-

Other caures:-

Death of host cells for usefull purpore.

Neutrophills → actue inflammation responre

Lymphocytes → end of immune responre

Physiologically

Cell destruction due to embryogenesis

Eliminate → self-reactive lymphocyte

Cell death due to cytotoxic T lymphocytes

Pathology:-

DNA damage

accumulation of misfold Protein

atrophy in parenchymal cell

Date:

Pathalogically condition :-

cells which eliminate that are injured beyond repair without eliciting a host Rx. Thus collateral tissue damage.

DNA damage :-

DNA damaged due to Radiation and chemotherapy. And Anticancer drugs. also hypoxia by free radicals

If repair mechanism not ocure Then intrinsic Pathway ocure cause apoptosis.

of mutation in damage DNA which cause malignant Transformation

Accumulation of proteins :-

Any extrinsic factor (free radicals)
↓
cause mutation in gene of folded protein
↓
excess of there protein in ER lead to ER stress
↓
cause apoptosis.

→ in CNS.

Date: _____

Cell death in infections:-

* Viral infection
↓
loss of infected cell by apoptosis

→ Such as HIV viruses
→ host immune Response (Hepatitis)

* Cytotoxic T Lymphocytes
↓
specific for viral protein.

Atrophy of organ after obstruction :-

obstruction of duct
↓
Cause Atrophy of organ

Example:-

Parotid Gland
Pancreare
Kidney

Morphologically changes:-

Cell Shrinkage
Chromatin condensation
Formation of cytoplasmic bells
Apoptic bodies formation

Oval mass - e - eosinophilic cytoplasm
Chromatin condense
Cells rapidly shrink
form blebs → apoptotic body
No inflamation

(18)

Date:

PM intact
No loss of lysosomal enzyme
DNA fragmentation
Non inflammatory
Response

Cell Shrinkage :-

Cell size is small.
cytoplasm dense.
organelle more tightly packed.

Chromatin Condensation :-

chromatin aggrigates peripherally
Nucleus break up and produced
fragments.

Formation of cytoplasmic blebs and apoptotic bodies :-

extensive surface blebbing of cytoplasm
↓
under goes fragments
form apoptotic bodies

Phagocytosis of apoptotic bodies by macrophages :-

Apoptotic body ingested by phagocytosis.
by lysosomal enzyme.
Plasma membrane intact with in
apoptotisis.

Date:

Mechanism of Apoptosis:-

Results from activation of enzyme
↓
called caspase
↓ depend upon
Production of Pro and anti-apoptotic protein

Contains two pathways.

① Mitocondrial Pathway
② Death receptor Pathway

Mitocondrial Pathway:-

also called intrinsic Pathway
contain protein → capable to induced apoptotic.
↓
includes-
cytochrome C, other protein. → Naterilize endogenous inhibitor of apoptosis

Choice - cell death, cell survival → depend upon a family of 20 or mitocondrial protein
↓
Bcl-2

When no growth factor:
Misfold protein
Damage DNA.

Mechanism:-

↓
Activate No of Sensor (Members of Bcl-2 family)
↓
called BH3 protein.
↓
Activate O2 pro-apoptotic membrane
↳ ① Bax Dimerize inert in MM (Mitochondrial Membrane) form chanal
② Bak
Perform O2 function.

↓ ①
① Inhibits the anticapoptotic molecule Bcl-2, Bcl-X1

↓ ②
② Through channals release following into cytosol

↓
Cytochrom C
↓
with some cofactor
↓
activate caspase-9

↓
other mitocondrial protein
↓
blocks caspase antagonists.

(Net Result)
- Activation of caspase cascade
- Nuclear fragmentation
- Apoptosis.

When - Growth factor
other survival signals present
↓
Activate anti-apoptotic members.
↓ Bcl-2
Bcl-xl
↓ antagonize - Bax
Bak

Date:

limits the escape of mitocondrial content
↓
cell survival

Common Pathway of apoptosis.

During this pathway

↑ Bax
↑ Bak
— Ultimately ↓ Bcl
↓ Bcl-xl

leads to cell death.

Death Receptor Pathway :-

extrinsic Pathway

contain Receptor (More belong to TNF)
↓
Region of cytoplasm
↓
called death domains

2 Type of Receptor:

Type 1 TNF
FAS (CD95)

Mechanism:-

FasL- (Membrane protein- expressed on T-lymphocytes.)
↓
Due to which binds to receptors.
↓
FAS (CD95) cross through FasL
↓
Activate caspase-8
↓
caspase 8 may cleave
↓
activate Pro-apoptic mem. of family Bid-2

FasL ↓ bind on FAS ↓ bind on FAD

Date:

↓

thus feeding into mitocondrial-P

↓

These 02 Pathway · Combines.

↓

Apoptosis

Function:-

- Elimination of self-reactive lymphocytes
- Involve in killing of target cell by some cytotoxic lymphocytes.

Clearence:-

Apoptotic cell. - phagocytes by producing Eat me signals
~~Phag~~ Phosphatidylserine flips to outside making it recognizable for phages (Macro)
Dying cells secrete soluble factors that recuit phagocytes ↓

Facilitates early removal to save it from causing inflamation

Some apoptotic bodies

↓ express - adhesive Glycoprotein

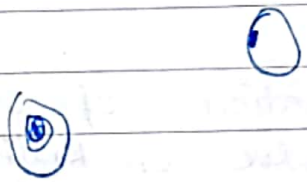
macrophages attach.

All above factors caure clearence

Date: _____

beginning — small fat vacuole

late stage — size of vacuole ↑
push nucleus periphery
signet ring Appearance
hepatocyte smell
Neutrophil infiltration



(10) (2-3) Date:

Difference b/w

Apoptosis	Necrosis
Programmed cell death	Premature cell death
Caspade dependent Pathway	Caspade independent Pathway.
No inflammatory Respons	inflammatory Response
Cell shrinkage	cell swelling
Membrane integrity maintain	loss of membrane integrity
No leak of lysosomal enzyme	Leak of lysosomal enzyme
DNA cleavage Non Random DNA fragmentation	No DNA cleavage Random DNA degradation
Single cell involve	Numerous cell involve
Causactive Agents:-	
Physiological Pathalogical factor	hypoxia toxins
Require ATP	No ATP

niceday

Date:

What are The consequence of misfold protein?. enlist and explain diseaseses related to it?

Normally in Protein synthesis, Chaperones in ER control proper ~~mis~~folding of protein.

↓

If any mulation due to enviormental factor

↓

Lead to acumulation of misfold protein

↓

Adaptation process responre active

↓

↑ amount of cheprons

↓

↓ misfolded protein

If responre fails. → cause disease cell injury

↓

ER stress

↓

Activate caspases

↓

Apoptosis

Cell death due to protein misfold caure Alzehmir, Hunitigon, parkinso. type 2 diabetes.

Date:

Disease	Affect protein	Pathogenesis
Cystic fibrosis	Cystic fibrosis trans-membrane conductance regulator (CFTR)	Loss of (CFTR) leads to defects in cloride transport.
Hypercholesterde-mia	LDL Receptor	Loss of LDL receptor leading to hyper-chlosterbemia
Tay Sachs disease.	Hexosaminidase β subunit	Lack of lysosomal enzyme, storage of GM2, ganglioside in neurons
Alpha-1-antitryp-sin deficency	α-1-antitrypsin	Storage of nonfunctional Protein in hepacytosis distruction of tissue
Creutzfeld-Jacob disease	Prions	Abnormal folding of PrP caure neuronal cell death.
Alzheimer disease	Aβ peptide	Abnormal folding of Aβ peptides caure aggregation e- neurons

Date: _____

What is phenomenon of autophage?

Define :-

- "Self eating
- Lysosomal digestion of cell's own component"
- It is survival machanism in case of nutrient deprivation.
- eating own content and recycle These content
- for provide nutrition and energy
- In this process
  1. organelles and portion of cytosole are sequestered within autophagic vacoule.
  2. vacule fuse with lysosomes and form autophagolysosome
  3. lysosomal enzyme digest cellular component

Function :-

1. clearence of misfold protein
2. Neurodegenrative disease
3. Aging
4. Starvation
5. Bacterial infection
6. Reduce liver fibrosis

Date:

7. Cell death
8. cancer
9. IBD
10. embryogenesis
11. Defective autophagy may be cause of neuron death.

Pathological Classification:-

Dystrophic calcification clasification	Metastatis calcification clasification:-
1. Deposit of Calcium salt in dead and degenrative tissue	Deposit of calcium salt in normal tissue
2. Normal calcium metabolism	Derangedcalcium metabolism
3. Normal serum Ca^{+2} level	hypercalcemia
4. Disordered cellular development	Malure cellular development
5. **Pathogenesis:-** binding of phosphate with degenrative tissue which bind to ca+ and form Calciumphosphate ppt	Gnc Pericipilate of calcium phosphate due to hypercalcemia at lung, stomach and vesseles

Date:

Example:-

- Fat necrosis
- Haemolomas
- Sclerosis in arterial walls
- atherosclerosis plaques
- Tumor cysts
- Papillary carcinoma of Thyroid and ovary
- Hyperparathyroidism destruction of bone (Paget disease)
- Hypervitaminous D
- Hypercalciumia in infancy
- Multiple Myeloma

** Pathalogical Accumulation:-

Lipid:-

Abnormal accumulation of TAGs within parenchymal cells.
Often seen in liver and also in kidney heart sketetal muscle

Cholestrol:-

cholestrole can accumulate intracellularly.
Phagocytic cell may be overloaded by lipids
This ocure in atherosclerosis

Protein:-

Protein acumulate less common than lipid

→ Normally:-

Trace amount of albumin filtered by glomerulus and reabsorbed in Proximal C.T. by pinocytosis

Date:

But in disorder
large amount of protein filter by glomerulus and accumulate in PCT (Proteinuria) and form Russel bodies. (accumulation of imunoglobins)

Other example:-
Alcholic hyaline.

Glycogen:-
excessive Intracellular deposition of glycogen caure abnormalities.

Example:-
In poorly controlled diabetes melitus
i- abnormal glucose metabolism
ii- Glycogen accumulate in renal tubular epithelium, cardiac myocyles and B cells of islets of langerhans
Reffered to glycogen storage disease

Pigments:-
Coloured substances.
Two type
exogenous → coming from outside of body
endogenous → synthesized in body

Date:

Exogenous:- Anthracosis

anthracotic pigments of lungs
(inhalation of carbon dust / coal)
tattoos
lead (Renal tubular lead deposits.

Endogenous:-

Lipofuscin:- Wear-tear pigment
Seen as yellow brown pigment
It is due to indigestable material in lysosome
present in liver and heart

Melanin:-
black brown pigment
derived by tyrosine
found in melanocytes

Function:- Act as screen against UV radiation

Hemosiderin:-
Golden yellow brown pigment
found in areas of hemorrhage or bruises.
Accumulate in tissue when iron is excess
Prussian blue stain identify iron.

Billirubin:-
accumulate in newborn.
in basal ganglia

Date:

Mechanism of cell injury:-

Cell injury result from functional and biochemical abnormality of one or more essential cellular component.

Principal Target:-

Mitocondria :-

↓ ability to generate ability ATP.

ROS :-

Reactive Oxygen Species. are also effected in cell injury

Disturbance in Ca^{+2} haemostasis :-

Damage to plasma membrane.

Damage to lysosomal membrane.

Damage to DNA

misfolding of protein

DNA depletion:-

Depletion of ATP:-

ATP mainly produced → phosphorylation of ADP in mitocondria.

In addition produced → Glycolytic pathway in absence of O_2

Date:

Tissue with greater glycolytic Pathway can survive better. and vise versa (brain)

High energy phosphate in the form of ATP for synthetic and degradative process like.

1. Protein Synthesis.
2. Lipolysis
3. De-acylation and re-acylation for phospholipid turnover.

* A healthy human burns 50 to 75 Kg of ATP every Day

Major causes of ATP depletion.

- ↓ supply of oxygen
- ↓ nutrients
- Mitocondrial damage
- Due to toxins.

Date:

Effect of ATP depletion:-

Ischemia
↓
less oxygen in mitocondria
↓
↓ oxidative phosphorylation
↓
↓ ATP

↓ Na^+/K^+ pump
↓
accumulation of Na^+ in cell
↓
↑ efflux of K^+
↓
- cellular swelling
- Mitocondrial swelling
- Loss of Microvili blebs

↑ Anarobic glycolysis
↓
↑ Lactic acid
↓
↓ glycogen
↓
↓ PH
↓
Clumping of nuclear chromatin

Failure of ATP dependent Ca^+ pump
↓
influx of Ca^{+2}
↓
damaging effect on Cellular component

Deatchment of Ribosome
↓
↓ protein synthesis
↓
irrevesible damage
↓
necrosis

Date: _____

MITOCONDRIAL PATHWAY

↓ O2 supply
Toxin
Radiation
↓
Mitochondria
↓
M-damage/
Dysfunction
↓ ATP Generation
↑ ROS
↓
Cellular Abnormalities
↓
Necrosis

Protein
↓ damage DNA
↓
↑ pro apoptotic protein
↓
↓ anti apoptic protein
↓
Mitochondria
↓
Leakage of M Protein
↓
Apoptosis

Ca^{+2} Role

Ca^{+2}
↓
influx into cell
Mitochondria → Ca^{+2} ← ESR
↓
↑ Systolic Ca^{+2} level

- phospholipase → ↓ Phospho lipid
- Protease → disruption of Memb
- endonuclease → Nuclear damage
- ATPase → ↑ Mitochondral Permeability Transition → ATP↓

Phospho lipid + disruption of Memb → Membrane damage

Date:

Free Radical Mediated Cell Injury

Reduction, Toxins: Reperfusion

↓

Mitocondria

↓

Production of ROS

Superoxide $O_2^{\cdot}$

$H_2O_2^-$

OH^-

↓

- Lipid peroxidation
  - ↓ Memb-Damage
  - ↓ Free Radical + lipid
  - ↓ Formation of Peroxidases
  - ↓ Unstable
  - ↑ Reactive
  - ↓ Membrane damage
- protein modification
  - ↓ break down Misfolding
    - Free Radicals
      - ↓ Polypeptide Fragmentation
    - Promote sulfhydryl Mprotein C-L
      - ↓ ↑ degrade
      - Loss of enzyme activity
- DNA damage
  - ↓ Mutation
  - ↓ Free radical + Thymine
  - ↓ Single strand break
  - ↓ Aging
    Death
    Malignancy

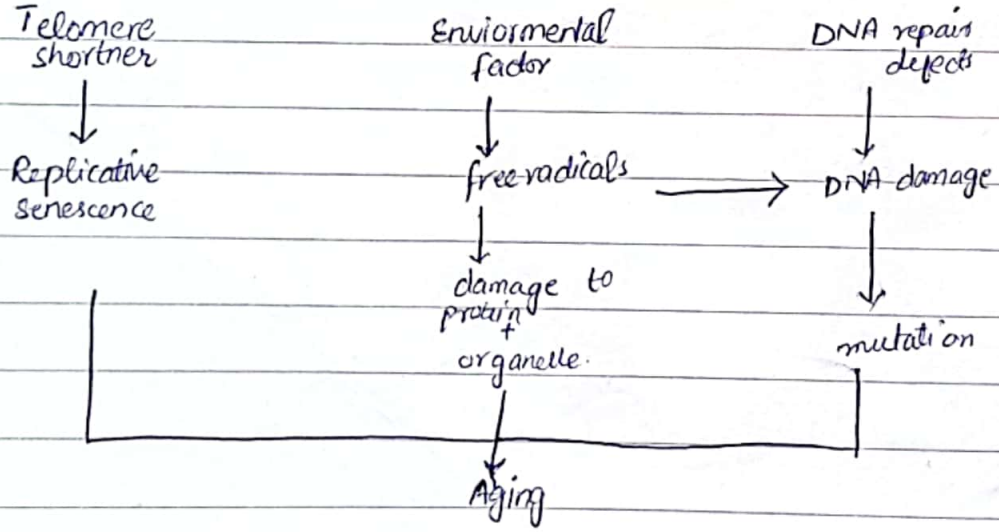
Date:

Cellular Aging:.

- Combination of cellular damage,
- reduced capacity to divide,
- reduced abality to repair;
- damage DNA
- defective protein homeoslasis
- Progressive decline in cellular function

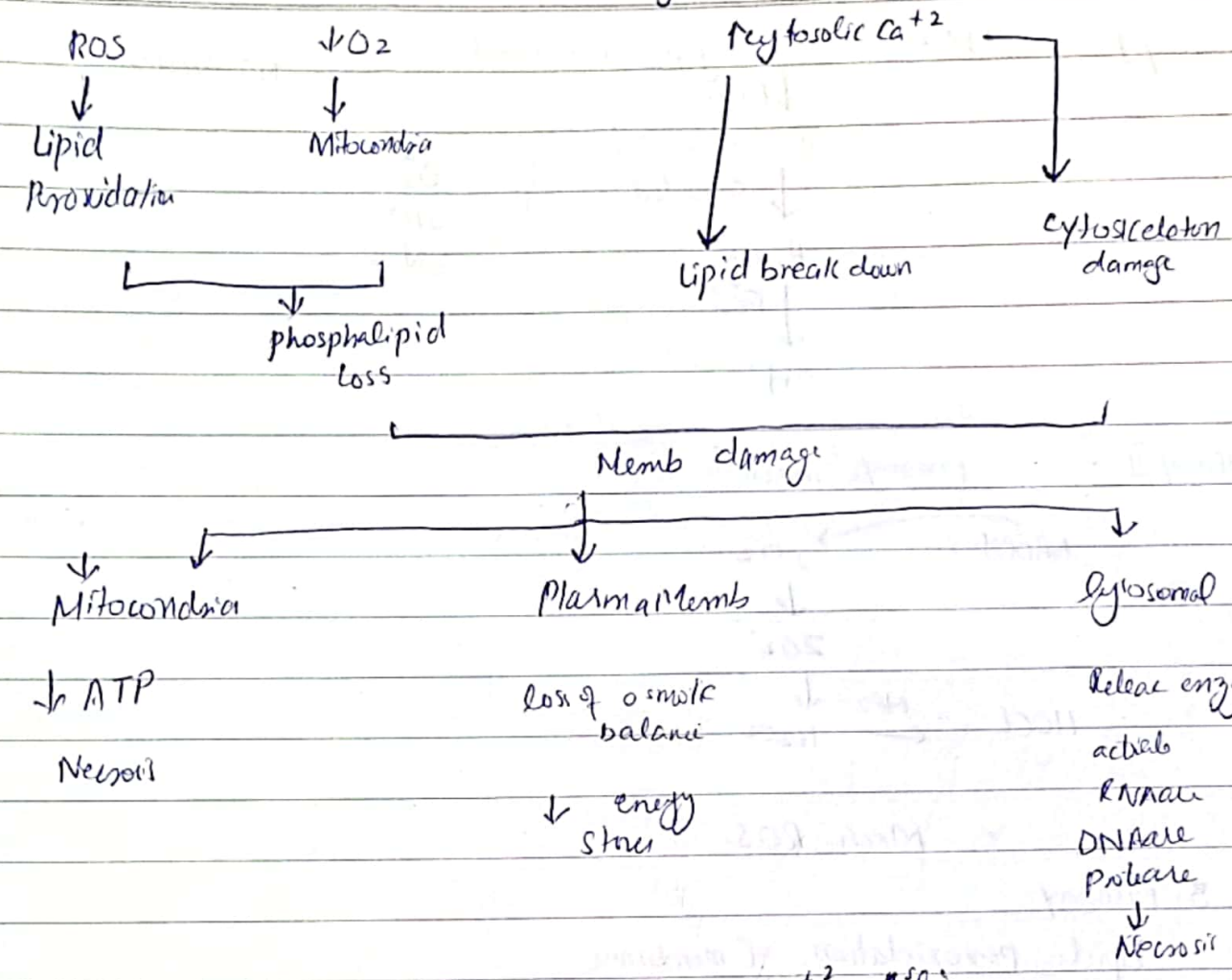
Causes of aging:-

1. Cellular senescence:- → normal cell divide
2. Mitocondrial dysfunction
3. Stem cell exhaustion
4. Telomere attrition → telomere shortning
5. Epigenetic alternation → phenotype change dint effect on DNA sequence
6. Genome instability
7. Alteration of cellular communication
8. Deregulated nutrient sensing



Date:

Membrane Permeability



ROS - ↓ O2 ↑ Ca^{+2} cytolic

Memb - damage

Mito. P. Mem lysosomal

↓ ATP ↓ energy store ↓

Necrosis Release enzyme

Date:

Mech of cell injury by Free Radical

Pathway I:- Mitochondrial oxygen is reduced
↓ Form
superoxide $O_2^{\cdot -}$
↓ converted
H_2O_2
↓ Fe^{2+}
$OH^{\cdot}$

$NO \rightarrow ONOO^-$

$O_2^{\cdot -}$
$OH^{\cdot}$
$ONOO^-$

Pathway II:- Phagocytic oxidase

NADPH → $2O_2$
↓
$2O_2^{\cdot -}$
↓
H_2O_2 ← MPO → HOCL

Mech. ROS.

3. Pathway:

① - Lipid peroxidation of membrane

Free Radical + Lipids are vulnerable attack by ROS
↓
Peroxidases unstable Rx
↓
cause autocatalytic chain

② - DNA Damage:-

Free Radical + Thymine
↳ single strand breaks

Such damage cause Aging
Death

Date:

(3)- Cross linking - other changes in Protein

Free Radical (promote) → Sulf hydryl protein cross linkage

↓

↑ degradation

Loss of enzyme activity