Cell Injury & adaptations.

Cell Adaptations: Reversible changes (neither normal/injured)
↓ on removal of stress
Normal - without loss of physiology

Types -
1) Hypertrophy
2) Hyperplasia
3) Atrophy
4) Metaplasia.

1) **Atrophy** → Both size & number of cells ↓
→ associated with autophagy (performed by Lysosomes)
→ ↑ Risk of TB infection - macrophage associated gene deletion ATG1S-5.

Q. endometrial adenoCa associated with - atrophy & Hyperplasia
Hyperplasia - Type I endometrial adenoCa.
Atrophy - Type II (Type II poor prognosis)

2) **Hyperplasia** - Number of cells ↑; Size same.

3) **Hypertrophy** - Size of cell ↑; number same.

4) **metaplasia**: Adult cell replaced → another type of adult cell
Q → Stem cell reprogramming - mechanism

Q Hypopharynx columnar → Squamous

Respiratory tract columnar → Squamous.

associated with which vitamin def Vitamin-A Def; ex

Barett's esophagus: Squamous → columnar.

Intestinal metaplasia Q - Hallmark of Barett's esopha

- Risk for oesophageal & Gastric Adenoca Q

mucin in barett's: acidic - pH 2.5

Stain used - Alcian blue.

Both Hyperplasia + Hypertrophy:

Pregnant uterus - major - Hypertrophy

minor - Hyperplasia

Pregnant/pubertal Breast: Both hypertrophy + Hyperplasia

Q Lactating Breast - only Hypertrophy

CELL INJURY:

Q m/c Cause of cell injury - ischemia/Hypoxia.

Neurons → 3-4 mins.

Cardiac Tissue → 20-40 mins.

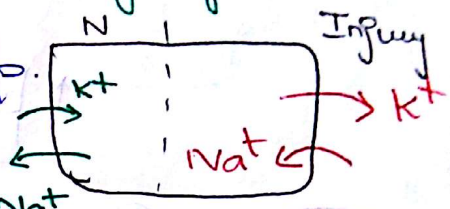
most Resistant - Fibroblasts Q

Reversible Irreversible

↓ Oxidative Phosphorylation.

↓ ATP (5-10% ↓ – cell injury)

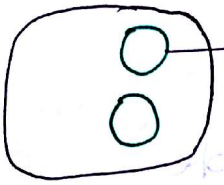
↓ Failure of Na^+ – K^+ pump.



I. **Cell Swelling** – 1st Sign of cell injury.

eg – Ballooning degeneration of Hepatocytes

Q Except – Apoptosis. shrinkage 1st Sign

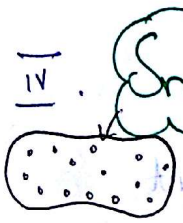
II.  → water / Na^+ appear as vacuole due to insolubility

– Hydropic degeneration / cytoplasmic vacuoles /

cloudy Swelling (ATN)

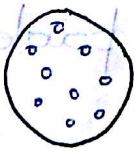
III. **Ribosomal Degeneration** – detachment due to swelling up of endoplasmic Reticulam.

* To d/f. Reversible & Irreversible injury Cell membrane damage

IV.  Small amorphous densities in mitochondria – Reversible

Flocculent large densities → Irreversible.

→ ultrastructural findings.

V. **Nuclear change** –  granular nuclear chromatin.

↓ change to

Disaggregation of granular nuclear chromatin

Most important Event in cell injury - Ca^{2+} cytosolic Rise

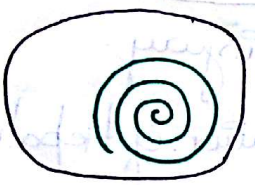
mild ↑ Severe ↑

Reversible injury ↓ Irreversible injury

↓

↑ phospholipase

↓



Damage to cell membrane of organelle

Concentric lamellated figure (phospholipase + Ca)[Q]

myelenoid bodies / myelin figures

→ Present in both Reversible, Irreversible

Irreversible > Reversible.

Irreversible Injury

Ca level ↑↑↑ - activates 3 enzymes

1) Phospholipase - myelin figures ↑↑ - maximum.

Mitochondria - large amorphous flocculent densities

2) Protease - damage cytoskeletal protein damage.

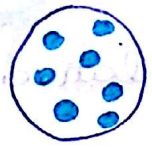
↓

Loss of cell architecture.

5) Endonuclease

eosinophilic - cytoplasm
nucleus - basophilic.

Damage of DNA / nucleus -

Pyknosis  clumping of chromatin.

↓

Karyorrhexis - fragmentation.

 - pieces.

↓

Karyolysis - chromatin lysis → chromatin removed

↓ Basophilia of cell (chromatin dissolution)

Cell Death.

- Events after cell death → Necrosis
- Apoptosis
- Necroptosis
- Pyroptosis

Necrosis:

Denaturation of protein

↓

Tissue architecture Normal / intact

↓

Coagulative N

→ m/c type

→ m/c cause - Hypoxia.

m/c affecting - Heart (solid organs), Liver, kidney, spleen etc

enzymatic actions.

↓

Hydrolytic action

↓

Tissue architecture - lost

↓

Liquefactive N.

Bacterial / Brain infections

→ Solid organs Hard - collagen

Brain donot have - Fibrous stroma - collagen

Hypoxia - all organs Coagulative necrosis

Brain - liquefactive

i) No collagen

ii) Rich in liquefactive enzymes.

m/c. Cause in Brain → Infections.

→ Thermal Burns - Coagulative.

Coagulative Necrosis -

TB

1st Coagulative necrosis

↓

Liquefactive necrosis.

Cheesy material - Caseous N

due to mycotic acid.

→ variant of coagulative N.

*Gangrene.

m/c site - lower limb.

Dry - default.

Tissue N. → coagulative N

Architecture preserved.

Wet Liquefactive.

Necrosis.

Coag. Necrosis } TB < dry gangrene; TB > Wet gagrene

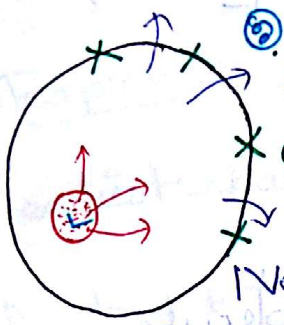
Zenker's degeneration Necrosis - Prototype of Coagulative

Zenker's > Gangrene > TB > Wet gangrene

Necrosis

↑ Lysosomal Permeability
↓
↑ enzymes.
↓
* cell membrane damage
↓
Leakage of content
↓
* Inflammation

Only pathological.



No cell membrane Damage.

No Inflammation

Physiological > pathological

Q. Programmed Cell Death.

- without Caspase activation
  - Necroapoptosis.
    - Hybrid - Necrosis + Apoptosis
    - cell membrane damage
    - inflammation.
    - → Variant of necrosis.
    - → Both physiological & pathological.
    - Physiological - eg - mammalian growth plate formation.
    - Pathological -
- Caspase
  - C-I, II
  - Pyroptosis
    - Neither apoptosis, nor necrosis.
    - Pyrogen Induced Apoptosis
    - IL-1
    - Inflammation ⊕
    - cell membrane damage.

Apoptosis - Literal - falling off > Programmed cell Death

Active Process - due to usage of ATP from mitochondria.

Active process > Programmed cell Death

→ Apoptosis induced by loss of adhesion molecule

↓

ANOIKIS Q.

Physiological

→ Organogenesis.

- Cell deletion
- Cell deletion of auto reactive cells.

protective against autoimmunity.

Pathological

Misfolding of proteins.

↓

stress.

↓

Apoptosis

eg- Familial Hypercholestaeolemia

Parkinson's, Alzheimers

Huntingtons GVHD

Cystic fibrosis. → Salivary gland.

Tumor cell death. duct

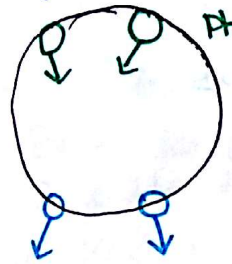
→ Chemotherapy + Radiotherapy - Necrosis / Apoptosis.

(eg- (Severe stimuli) → mild stimuli - only apoptosis to cell) ∅

Q Glucocorticoid - induce apoptosis.

Councilman Bodies - Pathological Apoptotic Body.
- Viral Hepatitis.

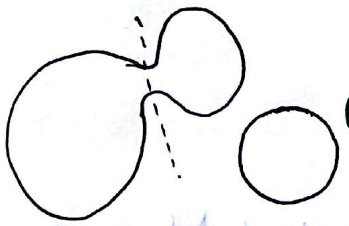
Morphology:-

1) earliest change → cell shrinkage.
2) MT/characteristic : Chromatin condensation > cell membrane intact
3) → No inflammation.
4) Cytoplasm — ↑eosinophilic.
5)  Phosphatidyl Serine Receptors. (lipid Receptors) - facing inwards.
↓ Apoptosis.
Flip outside

Annexin V Dye - detects the flip :. marker of Apoptosis.
- stain used for Lipid

Lipid Stain - Oil Red stain.
Sudan IV / Black.
Osmium Tetraoxide

Glycogen → PAS.

6) 
- Cell membrane bleb
↓
Detach
Apoptotic Bodies
→ cell membrane bound structure with organelle,
may / may not have nuclear remnants.

End

Phagocytosis — Final Product of apoptosis.

Receptor mediated - (∴ no Inflammation)

Biochemistry of Apoptosis:

ProCaspase.

Hallmark of Apoptosis

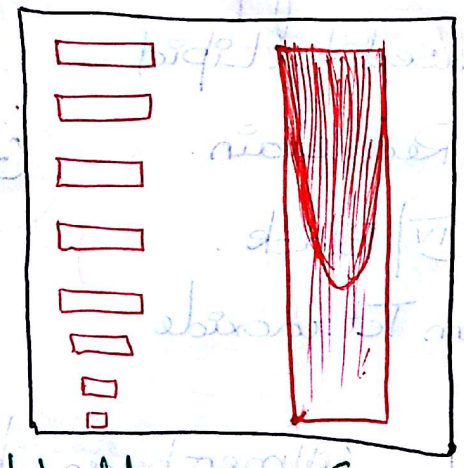
Caspase → endonuclease → DNA damage → Chromatin Condensation

⇒ DNA damage → Restricted fragment.

multiples of ×200 Base Pairs

Internucleosomal DNA damage

Agarose Gel Patten -



Step Ladder Patten due to endonuclease.

Smeared Patten

→ Seen in apoptosis & necrosis, But characteristic of Necrosis. Apoptosis

→ Smearing Patten - Necrosis.

1) Initiation Caspases.
- a) Intrinsic - major pathway - Caspase-9
- b) Extrinsic - Caspase-8 (animals), Caspase-10

↓ execution caspases.

↓ Caspase-3,6,7 — Cas-3 m/I.

↓ endonuclease

Protooncogenes

Apoptotic:
- Bcl-X_S (stimulate)
- BAX, BAK.
- BH3 Proteins.

Anti-apoptotic
- Bcl-2
- Bcl-X_L (lowering)
- MTCL-1 Q. (m/c mutated in drug resistance)

Drug Resitance -

P53 > MCL-1

P53 - Tumor suppressor.

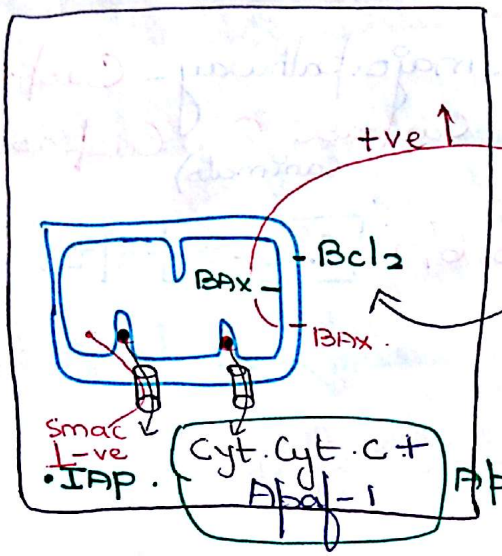
MCL-1 Drug Resistance · protooncogene.

BH3 Proteins. Stress Sensors.
- Bim
- Bad
- Bid.

→ PUMA Q.

→ NOXA Q.

a) Intrinsic Pathway (Mitochondrial Pathway)



Stress → BH3 → Inhibited Bax expressed on outer membrane.

→ mitochondrial permeability channels

→ ↑ permeability / leakage of Proteins.

Cyt-C into cytosol + Apaf 1 → Apotosome → Initiate Caspase-9

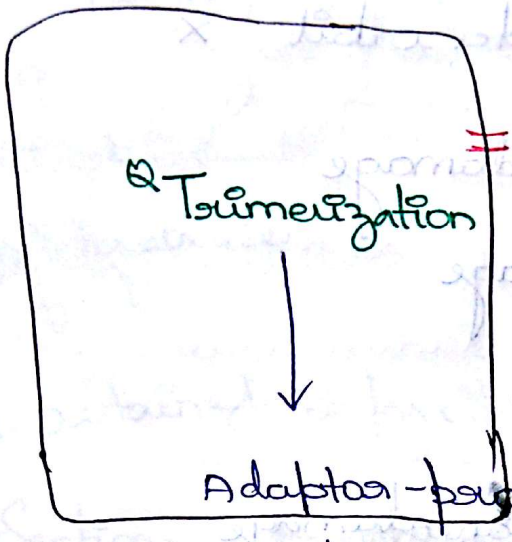
Cyt-C - mitochondria - ETC

cytosolic Cyt-C

Smac - DIABLO protein → Inhibit inhibitor of ~~anti~~ apoptosis

Extrinsic Pathway — Death Receptor mediated.

TNF-R-1 FAS - CD-95



= Death Receptor + Ligaments.

↓ ← -ve Flip.

Procaspases 8, 10.

Flip protein - Inhibitor of extrinsic pathway Increases, the

Final pathway

C-9 C-8, 10.

C, 3, 6, 7

↓

endonuclease → chromatin Condensati

Intrinsic & extrinsic pathway can accu

independly.

→ Hallmark of Neuronal apoptosis — Apoptosis

Inducing factor

(No caspases)

Free - Radicals - Oxidants - ROS

→ Produced normally

- unpaired electon in outer orbit ·x

→ Oxidation - mechanism of damage

cell membrane damage

+

Cytoplasmic protein

+

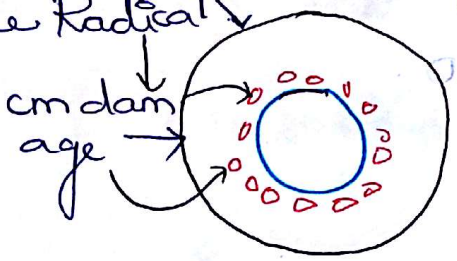
nuclear membrane damage

↓

DNA damage (Somatic damage)

most potent / most Reactive — OH·

Free Radical



Lipofuschin (Braun pigment)

i) Ageing

ii) malnutrition

iii) Cancu cachexia.

→ Tell tale sign of ageing / Free Radical injury

→ Brown atrophy of myocardium.

Carotroid Specimen brown - Lipofuschin.

Lipofuschin (m/c) > Hemosidein

Lipofuschin pigment.

Perl's prussian blue stain

oilRed - O

Sudan Black.

Osmium Tetraoxide.

Annexin - V

Ferrous ferrocyanide Fe^{2+} → Fe^{3+} ferricferrocyanide (insoluble & stained)

Oil Red - O stain - best for oil - Frozen Section.

Frozen Section - Intraoperative Biopsy.

→ Never confirm diagnosis immediately (confirm - 2 days)

Temp: −15 to −30°C

Δ - i) 15 - 20 minutes - ii) D - Benign/malignant.

Tentative Δ iii) can tell metastasis to sentinel lymph node

iv) Resection margin involvement.

i) Theory of Free Radical Damage for Ageing - most accepted theory.

ii) Increased cross linking of collagen Theory for ageing

→ Anti-oxidant vitamins - Vitamin A, C, E.

→ Proteins - Transferrin, Ceruloplasmin Q.

→ Enzymes - Catalase, glutathione per-oxidase, Superoxide Dismutase. } Q Per-oxisomal enzymes

→ Vitreous of eye Vitamin D not present

→ Glutathione - peroxidase - most potent anti-oxidant in body

Peroxisomal enzymes - H_2O_2 production & degradation

Lysosomes - H_2O_2 production only.

→ Brain protected from free radical injury SOD-1

Cu-Zinc SOD-1.

↓ mutation

AMTL (motor neuron disease)

Calcification

Abnormal Tissue - Death/degenerated

Dystrophic Calcification.

→ TB lymphnode.

→ RHD.

→ psammoma bodies

→ Aneurysm.

→ monckeberg's medial Sclerosis.

Tissue normal / Ca ↑

metastatic Calcification

→ Hyperparathyroidism (m/c cause)

1° HPT

m/c - Parathyroid adenoma

→ Hypercalcemic Crisis.

Ca Breast > Ca lung.

Squamous + Small cell

→ Renal failure

→ Vitamin - A/D ↑

non-obstructive

Vitamin D activate → Osteoclasts → lysis — Hypercalcemia

→ Parathyroid - not affected (calcified) / rarely affected

m/c affected alveoli (lung)

→ Calcification starts in mitochondria except kidney, Basement membrain

Special Stain for Calcium - 1) Von-Kossa [m/c, Best] Q
2) Alizarin-Red (most specific) for calcium.
3) Calcein.
4) Tetracycline Labelling stain (Best for bone mineral

Melanin - Fontana-Masson.

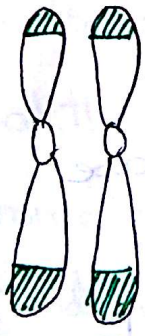
Collagen → Connective Tissue - Masson Trichrome. Collagen - Blue

Fungal Hyphae - Silver methenamine.

Alzheimer's disease - Neurofibrillary tangles - Bielschowsky stain (silver stain)

Ageing -

Telomeres - non coding areas at the end of chromosomes



Progressive size ↓ on further Replication

↓

No Telomeres.

↓

fusions / degradation

↓

Cellular ageing

→ Normal cells are capable of division of 60-70 times

Hayflick limit

Telomeres → Shortening Ageing

Telomere → lengthening - Carcinogenesis

Telomerase → RNA - depended DNA polymerase (Reverse Transcriptase)

(responsible for lengthening)

↓

present in Stem cells > Stem cells.

→ Normal Somatic cell - no telomerase

most effective way of prolonging life span ↓ Calorie

↓

(small amt) Red wine → Resveratrol

↓

↓ Apoptosis ii) Reduce free Radical damage

↑ glucose metabolism ii) ↑ insulin sensitivity

iii)

Werner Syndrome - NTEN I

Werner Syndrome — Premature aging.

defect in DNA Helicase.

(Repair)

Silver methamine Stain - Fungus - Black / Brown

Background green

Septate Branching / acute angle Branching - aspergillus

Immunofluorescence microscopy - Dichroeic mirror (allows only 2 light)

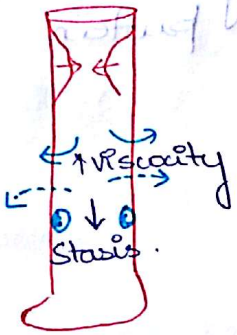
Background - Black

Acanthamoeba - optically greenish white - cell wall
calcofluor white stain.

INFLAMMATION

- Acute Inflammation -

I) Vascular events - Ist Transient vasoconstriction
↓
Vasodilatation
↓
↑ Vascular Permeability - Hallmark of acute inflammat.
↓
Stasis (so that neutrophil can deviate to periphery)



Vascular Permeability

1) Endothelial gap - (m/c - mechanism)
- at the level of venules. except lungs - capillaries.
- Immediate / Transient response.

2) Direct endothelial injury - Immediate + prolonged
mild endothelial injury - Sunburn / radiation,
↓
delayed + prolonged

Telomere → Shortening - Ageing

Telomere → lengthening - Carcinogenesis

Telomerase → RNA-dependent DNA polymerase (Reverse Transcriptase)

(responsible for lengthening)

↓

present in Germ cells > Stem cells.

→ Normal Somatic cell - no telomerase

most effective way of prolonging life span ↓ Calorie

↓

(small amt) Red wine → Sirtuins (↑

↓ Apoptosis ↑) Reduces free Radical damage

↑ glucose metabolism ii) ↑ insulin sensitivity

iii)

Werner Syndrome - NTENT

Werner Syndrome — Premature aging.

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