Pathology

Marrow Edition 8

MARROW

Instructions

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General Pathology

Hematology

Cardiovascular System

Genitourinary System

Gastrointestinal System

Respiratory System

Endocrine System and Breast

Skin and Musculoskeletal System

Nervous System

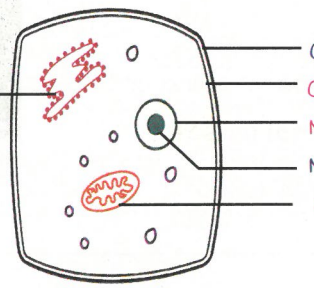
Miscellaneous

CELL ADAPTATIONS

----- Active space -----

Cell Injury

00:02:20



Normal structure of cell

Causes :

Hypoxia :

- m/c cause of cell injury.
- ↓ O_2 to tissues.
- m/c cause : Ischemia (↓ blood supply to tissue).
- Severity of cell injury : Ischemia (↓ O_2 & nutrients) > hypoxia (↓ O_2).
- Sensitivity to hypoxia
  - Most : Neurons
  - Least : Skeletal muscle/fibroblasts

Other agents :

- Physical : Radiation.
- Chemical : Drugs.
- Infectious : Bacteria, virus, fungi.
- Immunologic : Autoimmune disorder.
- Nutritional : Vitamin deficiencies.
- Genetic factors.

Factors affecting cell injury :

- Type of cell.
- metabolic state of cell.
- Duration of injury.
- Type of injury.

Cellular response :

Based on causes and factors

- Small stimulus → Cellular adaptation : Hypertrophy. Hyperplasia. metaplasia. Atrophy.
- Persisting stimulus → Reversible cell injury (Reversed to normal state on removing stimulus)
  - Persisting stimulus → Irreversible cell injury → Cell death → Necrosis, Apoptosis, Pyroptosis, Necroptosis, Ferroptosis
- Intracellular accumulations
- Pathological calcification

----- Active space -----

Cell Adaptation

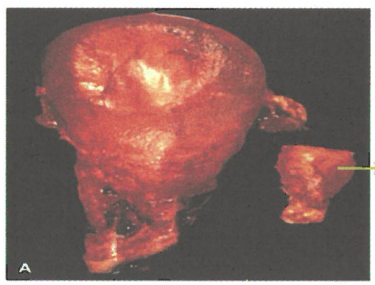
00:14:00

HYPERTROPHY

↑ cell size (No ↑ in cell number).

Mechanism :

- ↑ Synthesis of proteins.
- Occurs in permanent/non-dividing cells (Neurons, cardiac/skeletal muscles).



Hypertrophy + hyperplasia of gravid uterus

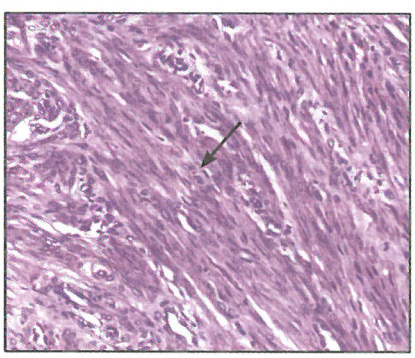
Examples :

Physiological :

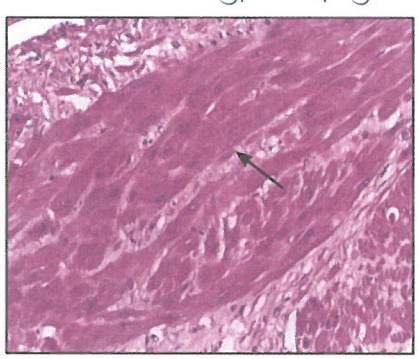
- Uterine myometrium during pregnancy.
- Breast during lactation.
- Skeletal muscle in body builders (↑ work load).

Pathological :

- Left ventricular hypertrophy (Hypertension → ↑ work load).
- Bladder obstruction by stone → Proximal area hypertrophy.



Normal myometrial cells



↑ size of smooth muscle cells

HYPERPLASIA

↑ number of cells → ↑ size of organ.

On persisting can lead to carcinoma.

Mechanism :

- Growth factor induced proliferation of cells.
- Occurs in dividing cells.

Note :

Examples of hypertrophy + hyperplasia :

- Breast during puberty
- Uterus during pregnancy.

Examples :

- **Physiological**
  - Compensatory : Liver post partial hepatectomy
  - Hormonal : Breast during → Puberty, Pregnancy
- **Pathological**
  - Estrogen excess : Endometrial hyperplasia
  - Androgen excess : Benign prostatic hyperplasia

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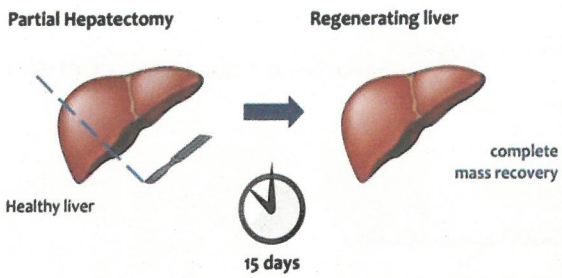
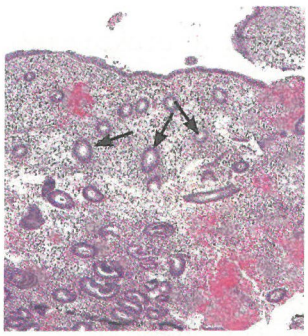
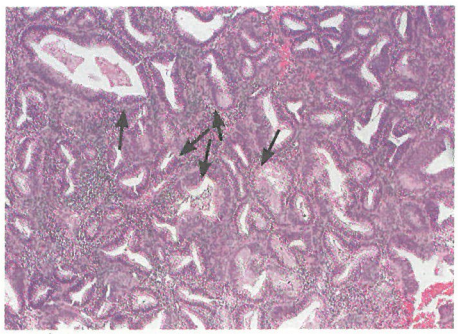


Hyperplasia of liver



Normal endometrium



↑ number of endometrial glands

ATROPHY

↓ cell size, ↓ cell number.

Mechanism :

- ↓ protein synthesis.
- ↑ protein degradation.
- Autophagy.

Examples :

Physiological :

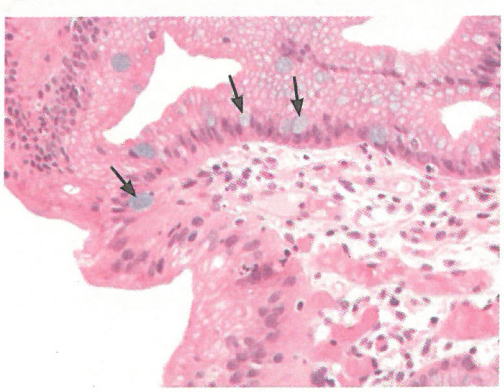
- Disappearance of notochord/thyroglossal duct.
- Involution of uterus during parturition.

Pathological :

- Senile : Ageing of organs.
- Disuse : Muscular atrophy after fracture.
- Denervation atrophy : ↓ nerve supply.
- ↓ blood supply.
- Nutritional atrophy : Kwashiorkar/marasmus.
- Pressure atrophy : Area surrounding tumors.

METAPLASIA

- Reversible change.
- One differentiated (mature) cell type converted into another.
- Types → Epithelial (Conversion of epithelium).
  → Mesenchymal (Conversion of connective tissue).



Alcian blue stained goblet cells

Mechanism :

- Reprogramming of stem cells.
- Risk factor : Vitamin A deficiency.

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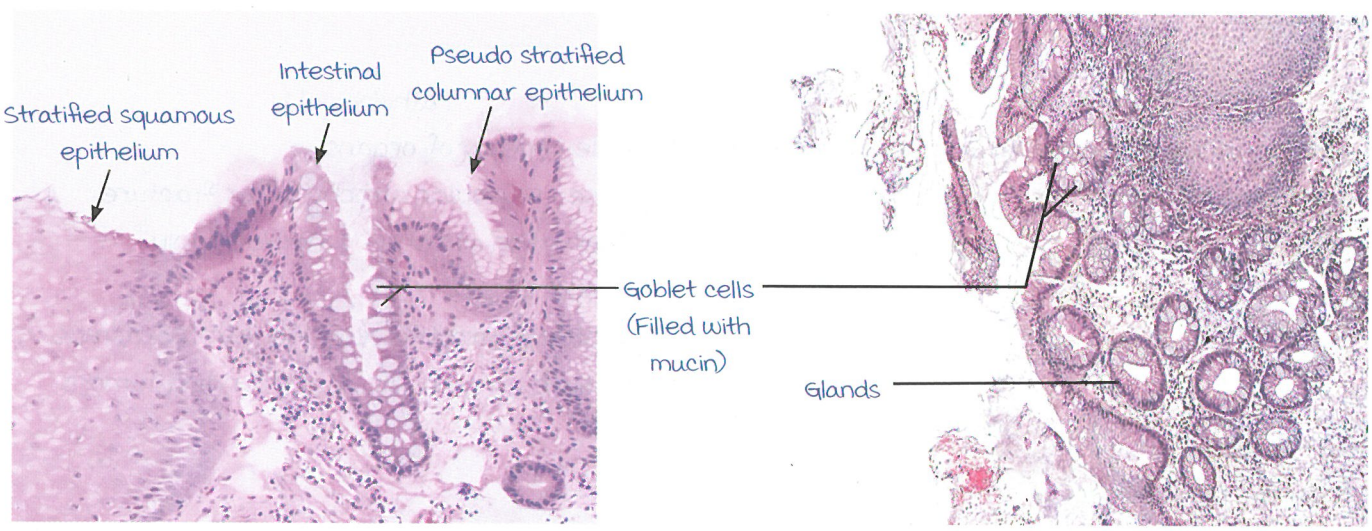
Examples :

1. Squamous metaplasia in respiratory tract :
   - Pseudostratified ciliated columnar $\underset{\text{Smoking cessation}}{\overset{\text{Chronic smokers}}{\rightleftharpoons}}$ Stratified squamous epithelium.
   - ↑ risk of infections.

2. Barrett's esophagus/Columnar lined esophagus (CLO) :
   - Stratified squamous epithelium $\underset{\text{On treatment}}{\overset{\text{GERD/Risk factors}}{\rightleftharpoons}}$ Columnar epithelium.
   - Histopathological remark (H&E) :
     - Intestinal metaplasia.
     - Goblet cells present.
   - Risk factor for adenocarcinoma of esophagus.
   - Special staining : Alcian blue/Mucicarmine (Stains mucin inside goblet cells).

3. Myositis ossificans : Muscle → Bone.



Esophageal biopsy : Barrett's esophagus

CELL INJURY

----- Active space -----

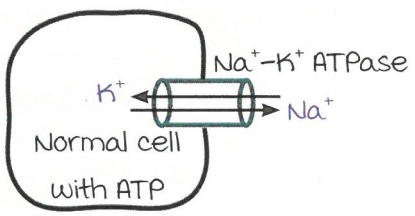
Injurious stimulus (m/c : Hypoxia) → Cell adaptation —Persisting stimulus→ Reversible cell injury —Persisting stimulus→ Irreversible cell injury

Reversible Cell Injury

00:01:10

mechanism :

Hypoxia (↓O_2) → mitochondria → ↓Oxidative phosphorylation → ↓ATP synthesis

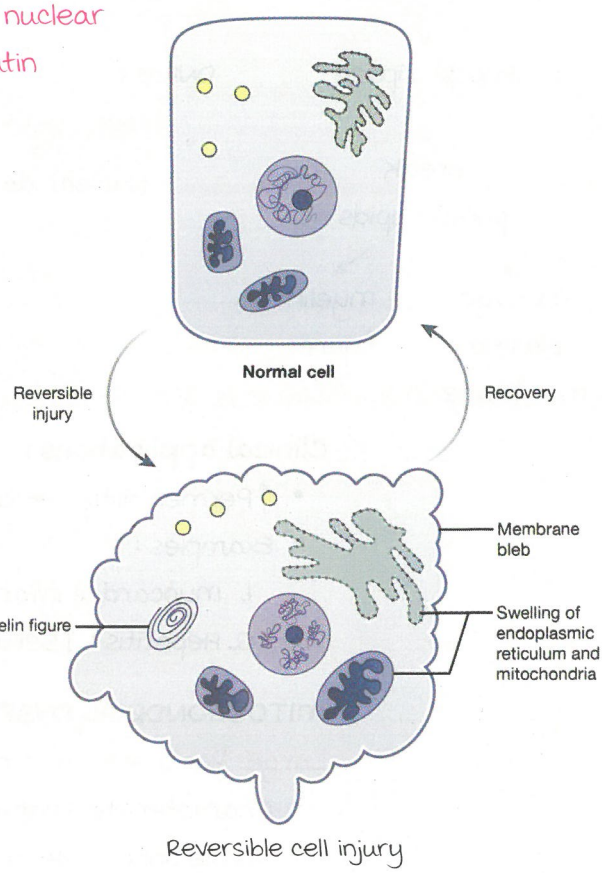


- ↓Activity of Na^+-K^+ ATPase pump → Influx of Na^+ and H_2O + Efflux of K^+ → Cellular swelling : Hydropic change
  (most important morphological feature) :
  - Organelle swelling :
    - Mitochondria (m/c affected).
    - Endoplasmic reticulum.
  - Membrane blebs.
  - Myelin figures :
    - Seen in reversible < irreversible cell injury.
    - Produced d/t plasma membrane damage.
    - Composition : Phospholipids + Ca^{2+}.
- ↑Anaerobic glycolysis → Lactic acidosis → ↓pH → Clumping of nuclear chromatin
- Detachment of ribosomes from rough endoplasmic reticulum → ↓Protein synthesis + ↑Lipid synthesis

Note :

Mitochondria :

- Most important organelle affected in :
  Reversible cell injury, apoptosis.
- Calcification (Earliest appearance).



Reversible cell injury

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Irreversible Cell Injury

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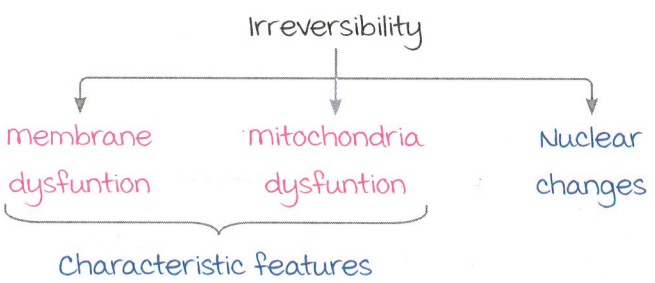

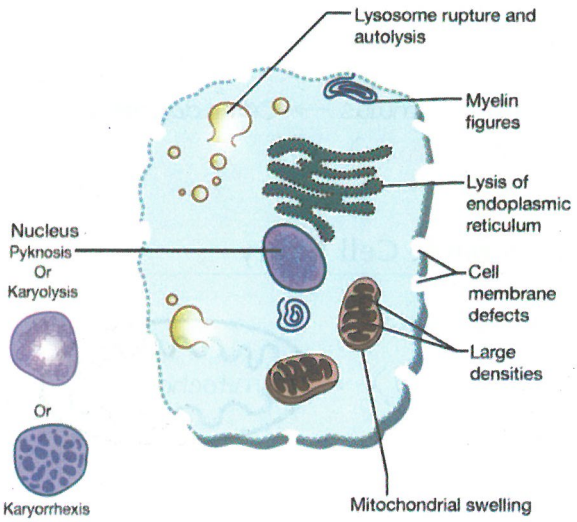

Irreversible cell injury

MEMBRANE DYSFUNCTION

Mechanism :

Cell membrane : Loss of selective permeability → Completely permeable.

Organelles membrane :

Loss of permeability → ↑Cytosolic Ca^{2+}

Activate

- Phospholipase → Break phospholipids → Damage plasma membrane; myelin figures
- DNAase, Endonuclease → Nuclear damage
- Protease → Protein breakdown
- ATPase → Activation/ degradation of ATP

Clinical applications :

- ↑Permeability → Release intracellular enzymes in circulation.
- Examples :
  1. Myocardial infarction : ↑Serum levels : CK-MB, LDH, Troponin I/T.
  2. Hepatitis : ↑Serum enzymes : SGOT, SGPT.

MITOCHONDRIAL DYSFUNCTION

Large, flocculent, amorphous densities in mitochondria :

- Characteristic feature of irreversibility.
- Visible only on electron microscopy.

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NUCLEAR CHANGES

Most important light microscopic feature of irreversibility.

1. Pyknosis : Shrinkage of nuclear chromatin.
2. Karyorrhexis : Fragmentation of nuclear chromatin.
3. Karyolysis : Dissolution of nucleus.

Free Radicals

00:23:45

Molecules with ≥1 unpaired electrons in their outermost orbit.

Unstable configuration → Release high energy → Damage cells.

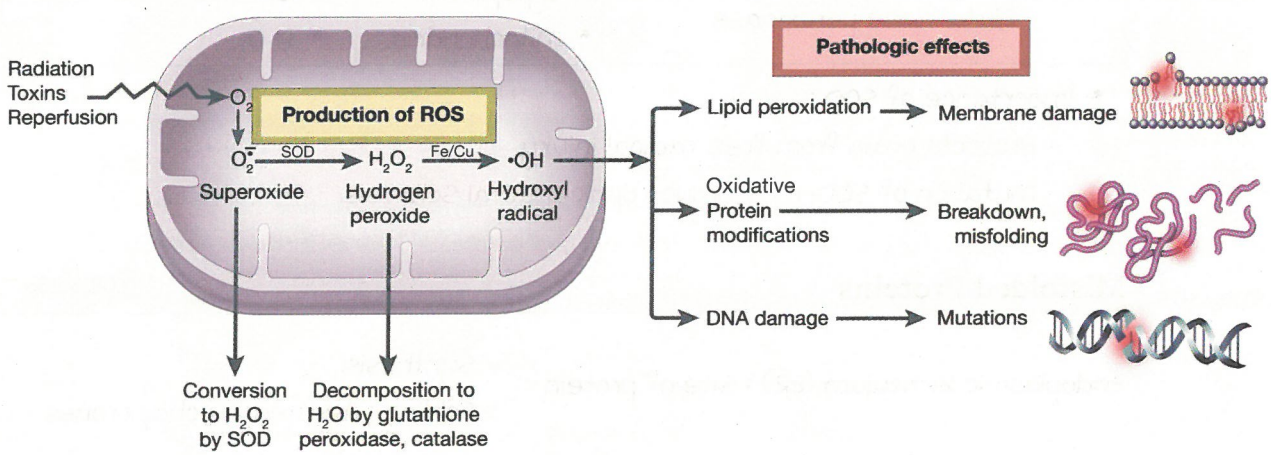
Examples :

- OH^- (Hydroxyl) : most potent.
- O_a^- (Superoxide).
- H_aO_a (Hydrogen peroxide).
- $ONOO^-$ (Peroxynitrite) : Phagocytosis in O_a-dependent killing pathway.

Role of free radical injury :

- Ageing (Mx : ↑use of antioxidants).
- Neurodegenerative disease : Alzheimer's disease.
- Cancer.
- Reperfusion injury.

Production and effects :



SOD : Superoxide Dismutase

Trace elements producing free radicals : Fe, Cu.

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Fenton's Reaction : Fe^{2+} involved in production of free radicals (FR).

- ↓Fe^{2+} in body d/t :
  - Fe^{3+} >> Fe^{2+} in vivo.
  - Presence of binding proteins : Transferrin (For Fe)/Ceruloplasmin (For Cu)
    ↓
    ↑Bound form (Limit availability for FR production).

Protective mechanisms against free radicals :

Exogenous/endogenous.

Antioxidants

Enzymatic :
- Catalase.
- Superoxide dismutase.
- Glutathione peroxidase.

Non-Enzymatic :
- Vitamins E, A, C.
- Selenium.
- Zinc.

Antioxidants & Targets :

		Location	Free radical inactivated
Superoxide Dismutase (SOD)	Cu-Zn SOD (SOD 1)	Cytoplasm	O_2^-
	Mn-SOD (SOD 2)	Mitochondria	
Catalase		Peroxisomes	H_2O_2
Glutathione peroxidase		• Cytoplasm • mitochondria	• OH^- • H_2O_2

- Importance of SOD :
  - Protects brain from free radical injury.
  - Mutation of SOD-1 → Amyotrophic Lateral Sclerosis.

Misfolded Proteins

00:35:35

Endoplasmic Reticulum (ER) : Site of protein → Synthesis.
→ Folding : Assisted by chaperones.

Mechanism :

Chaperone in ER → Normal folding of protein

ER stress | Defective chaperones

↓

Misfolded protein

↓

Degradation by Ubiquitin proteasome pathway

↓ If defective

↑Accumulation of misfolded proteins

Clinical application :

Disease	Affected protein
Cystic fibrosis	CFTR
Familial hypercholesterolemia	LDL-receptor
Tay Sachs disease	Hexosaminidase α-subunit
Creutzfeldt Jakob disease	Prion
α-1 Antitrypsin deficiency	α-1 Antitrypsin
Alzheimer's disease	Aβ

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CELL DEATH

Mechanisms of cell death :

- Necrosis.
- Necroptosis.
- Pyroptosis.
- Ferroptosis.
- Apoptosis.
- Autophagy.

Necrosis

00:01:45

- Accidental death of multiple cells : Always pathological.

MECHANISM

Denaturation of proteins — Enzymatic digestion of cells

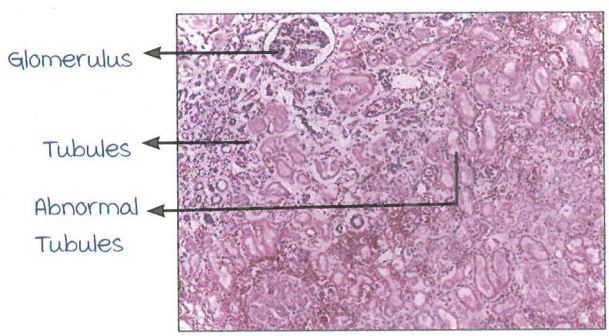
Irreversible cell injury : Damage to plasma membrane

↓

Leakage of cellular contents

↓

↑ Inflammatory infiltrate to clean debris



Kidney biopsy : Necrosis on HPE

MORPHOLOGY

On HPE :

1. Densely eosinophilic cells : D/t loss of cytoplasmic RNA.
2. more glassy/shiny appearance : D/t loss of glycogen.
3. moth-eaten appearance : D/t digestion of organelles by lysosomes.

TYPES

Coagulative — Liquefactive — Caseous — Fat — Fibrinoid — Gangrenous

Coagulative vs liquefactive necrosis :

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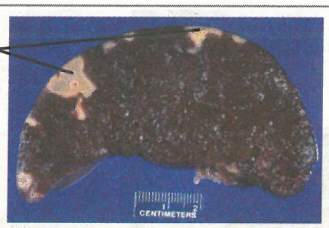
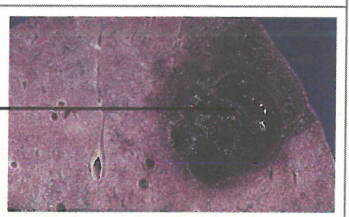
	Coagulative necrosis	Liquefactive necrosis
Occurrence	m/c type of necrosis.	AKA colliquative necrosis
morphology	Cell outlines are preserved	Cell outlines not preserved
mechanism	Denaturation of protein	Enzymatic digestion of cells
Examples	• Infarct of all solid organs except brain : – Heart (m/c affected) – Kidney – Liver – Spleen • Burns • Dry gangrene • Zenker's degeneration (In typhoid fever) : – Affects skeletal muscle (Rectus abdominis).	• Brain • Fungal infection • Wet gangrene • Abscess
Appearance	Infarct 	Liquid appearance 

Caseous Necrosis :

Intermediate form of coagulative and liquefactive necrosis.

morphology : Cheese-like appearance.

Gross specimen of lung

Examples :

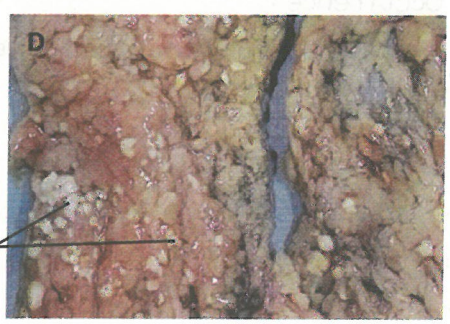
- Tuberculosis : Caseating granuloma.
- Fungal infections : Histoplasmosis, blastomycosis.

Fat necrosis :

Types	Examples
Traumatic	Breast
Enzymatic	• Omentum • Pancreas • Mesentery

D/D : Breast cancer.

morphology : Chalky white deposits.



Gross specimen of intestine

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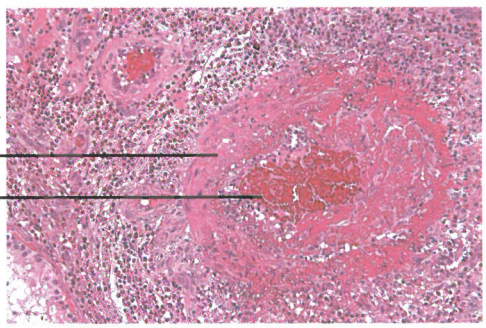
Fibrinoid necrosis :

Morphology : Fibrin like (Pink coloured).

Pathology : Type II, III hypersensitivity reactions (HSN).

D/t immune complex deposition.

- Examples :
  - Aschoff nodules : Pathognomic of rheumatic heart disease.
  - Polyarteritis Nodosa (PAN) : Type II HSN.
  - Malignant Hypertension (HTN leading to organ damage) : Onion skin appearance.

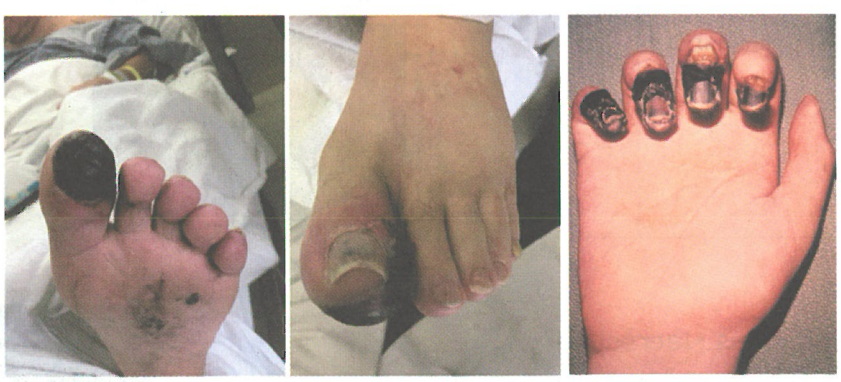


Biopsy of blood vessel

Gangrenous necrosis :

Examples : Limb ischemia.

Types	Example
Dry gangrene	Coagulative necrosis
Wet gangrene	Liquefactive necrosis


Gangrenous necrosis

Apoptosis

00:24:55

- Genetically programmed death of a single cell (suicide of cell).
- Organism used for most of apoptotic studies : Caenorhabditis elegans (Nematode).
- "Apoptosis" : Falling off.

Occurrence :

a) On completion of function of cell.

b) Damage of cell beyond repair.

EXAMPLES

Physiological :

- Organogenesis/embryogenesis : Formation of fingers in limbs.
- Parturition.
- Endometrial shedding during menstrual cycle.
- Death of harmful self-reactive lymphocytes.
- Involution of hormone-dependent tissue upon withdrawal of hormones.

Pathological factors :

- Damage to cell DNA.
- Accumulation of misfolded proteins.
- Infections : Hepatitis B (Councilman bodies).

MORPHOLOGY

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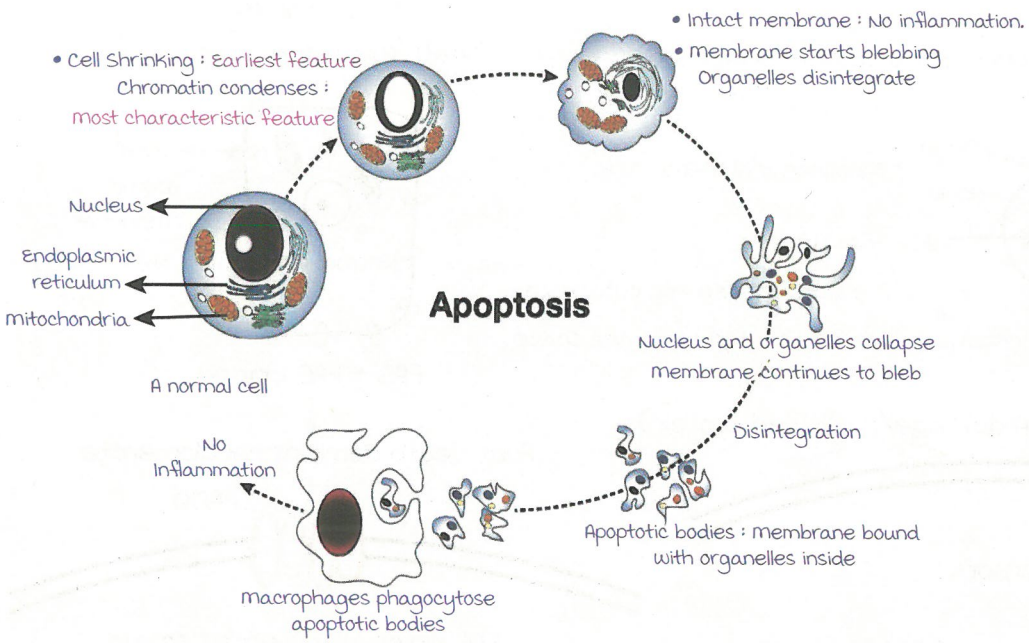
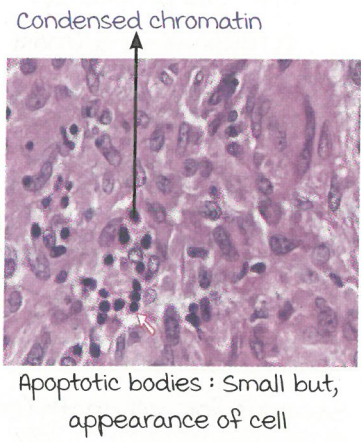




Apoptotic bodies : Small but, appearance of cell

MECHANISM

Phases :

1. Initiation Phase
   - 90% : Intrinsic pathway (Mitochondrial)
   - 10% : Extrinsic pathway (Death receptor mediated)
2. Execution Phase.
3. Removal of dead cells by macrophages.

Enzymes :

1. Caspases :
   - Contains caspases.
   - Cleaves near aspartic acid residue.
   - Types :
     - Initiator caspases : 8, 9, 10.
     - Executioner caspases : 3, 6, 7.
2. Endonuclease : Breaks down DNA to fragments.

Note :

Mitochondria : Most important organelle affected in :

- Apoptosis.
- Reversible cell injury.
- Calcification (Begins here).

Regulators :

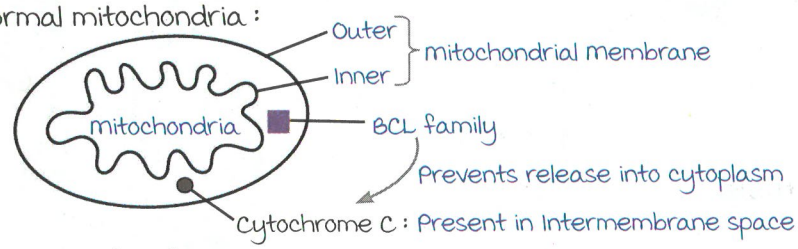
1. Pro apoptotic :
   - BAX.
   - BAC.
2. Anti apoptotic :
   BCL family :
   Prevents release of cytochrome C.
   - BCL-2.
   - BCL-XL.
   - MCL-1.
3. Stress sensors (Regulated initiators) :
   - BIM.
   - BID.
   - BAD.
   - PUMA.
   - NOXA.

----- Active space -----

Intrinsic pathway :

In mitochondria (most important organelle affected).

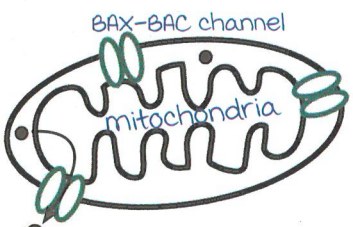
Normal mitochondria :



Upon noxious stimuli :

Stimulus for cell death (DNA damage/misfolded protein)

Activation of stress sensors



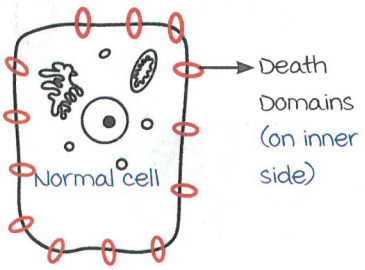
APAF-1 → Apoptosome

Activate

Caspase 9

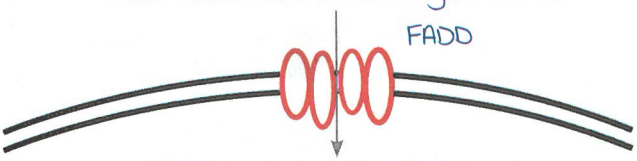
Extrinsic pathway :

Death Receptors : FAS, TNF



FAS + FAS Ligand

Four death domains conglomerate



FAS Associated Death Domain

Pro-caspase 8

Activates

Caspase 8

Execution phase

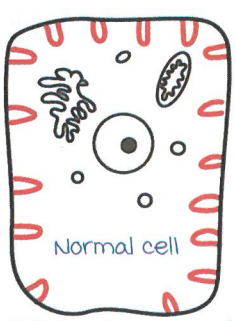
Activates

Activates

Caspase 3, 6, 7

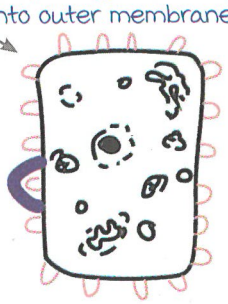
Removal of dead cells by macrophages :

Apoptosis



Phosphatidyl serine present inside inner membrane

Phosphatidyl serine flip (onto outer membrane)



Binding of Annexin V

Recognised by Macrophages