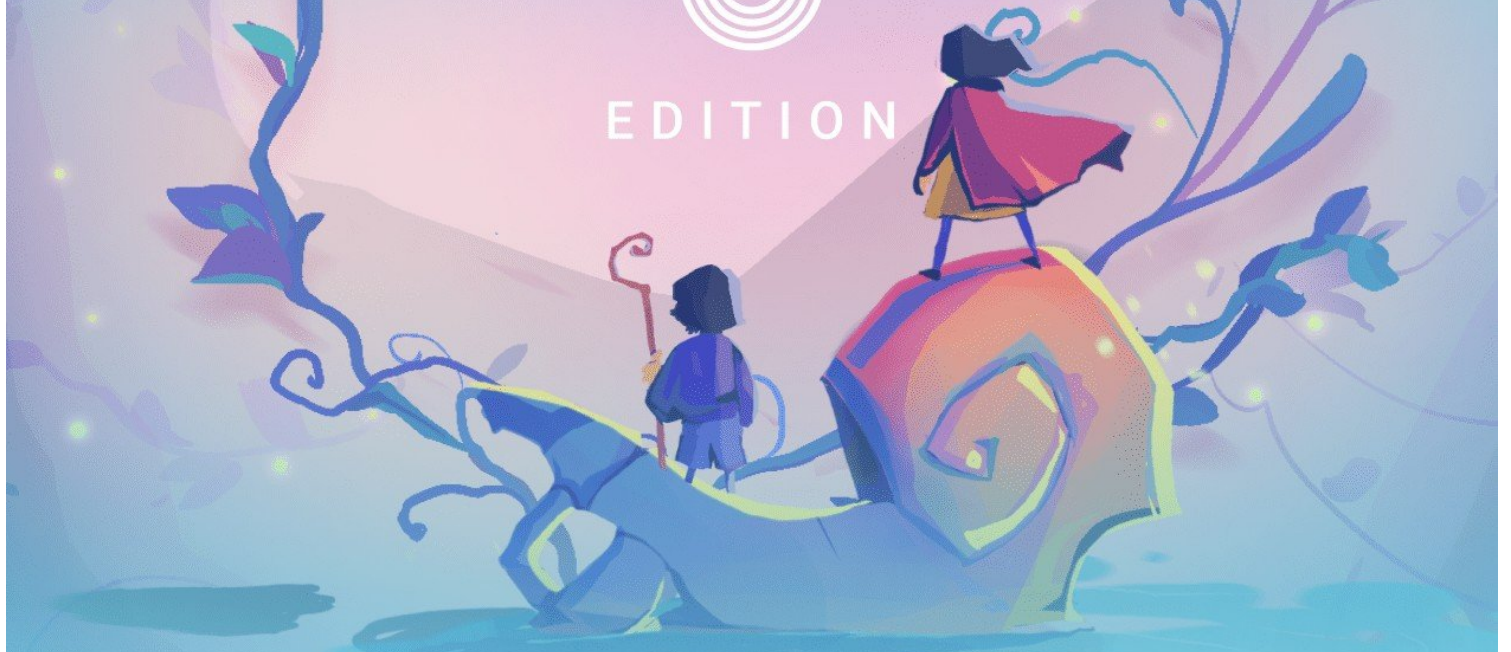




EDITION



PATHOLOGY

ED.08

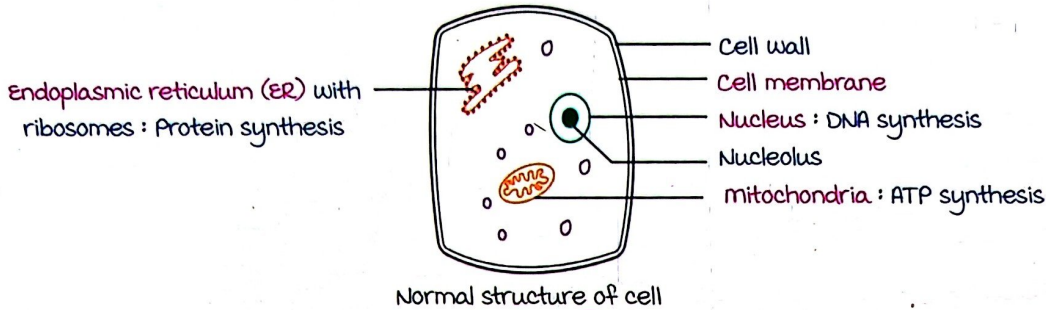


CELL ADAPTATIONS

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

Cell Injury

00:02:20



Causes :

Hypoxia :

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

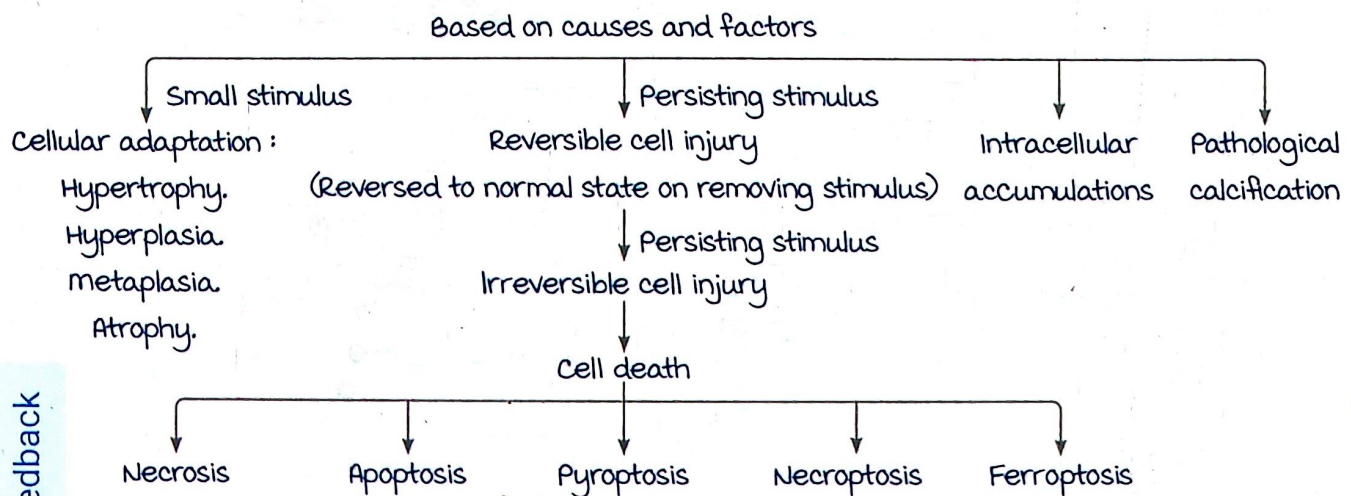
Other agents :

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

Factors affecting cell injury :

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

Cellular response :



Pathology • v1.0 • Marrow 8.0 • 2024

Feedback



HYPERTROPHY

↑ cell size (No ↑ in cell number).

Mechanism :

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

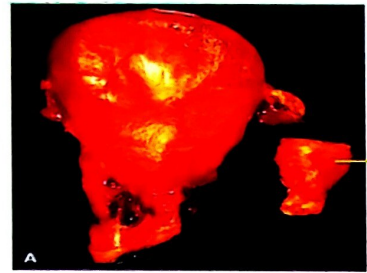
Examples :

Physiological :

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

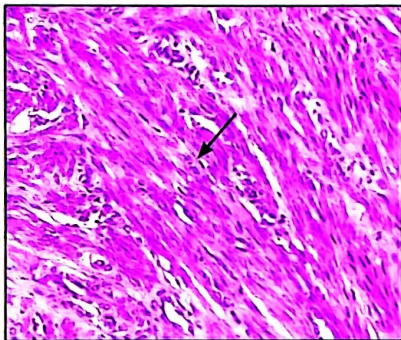
Pathological :

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

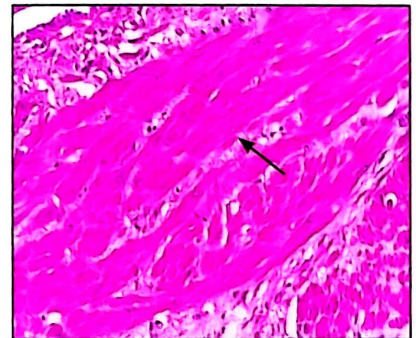


Normal uterus

Hypertrophy + hyperplasia of gravid uterus



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.

Examples :

Physiological

Compensatory :
Liver post partial hepatectomy

Hormonal :

Breast during Puberty
Pregnancy

Pathological

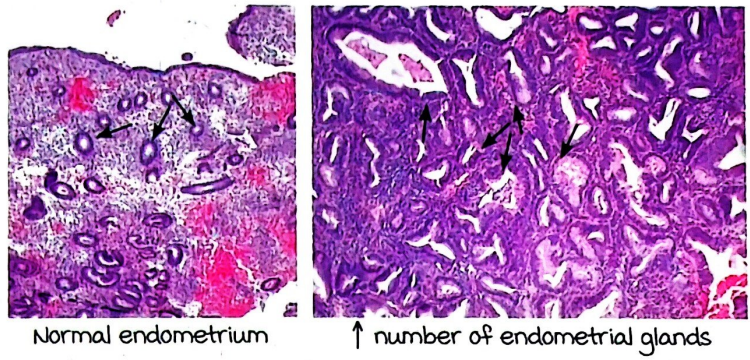
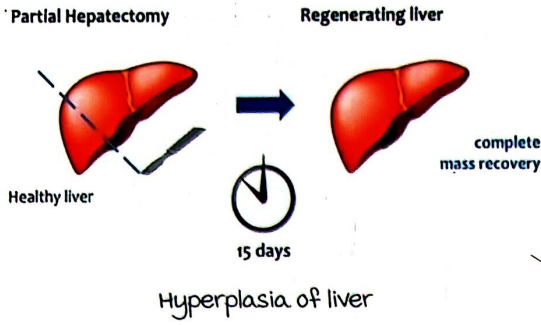
Estrogen excess :
Endometrial hyperplasia

Androgen excess :
Benign prostatic hyperplasia

Note :

Examples of hypertrophy + hyperplasia :

- Breast during puberty
- Uterus during pregnancy.



ATROPHY

↓ cell size, ↓ cell number.

Mechanism :

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

Examples :

Physiological :

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

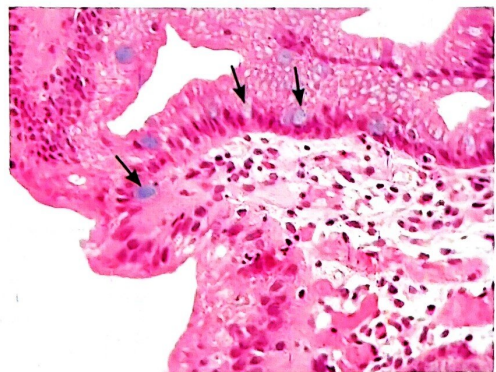
Pathological :

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

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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.**

Feedback

4

General Pathology

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

Examples :

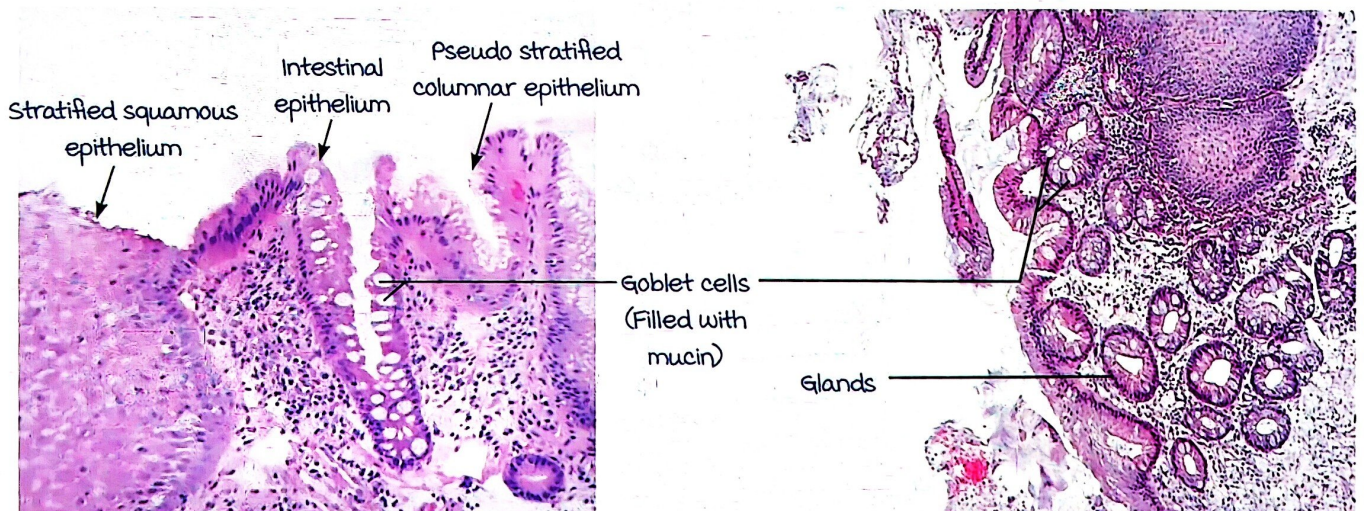
1. Squamous metaplasia in respiratory tract :

- Pseudostratified ciliated columnar $\xrightleftharpoons[\text{Smoking cessation}]{\text{Chronic smokers}}$ Stratified squamous epithelium.
- ↑ risk of infections.

2. Barrett's esophagus/Columnar lined esophagus (CLE) :

- Stratified squamous epithelium $\xrightleftharpoons[\text{On treatment}]{\text{GERD/Risk factors}}$ 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).

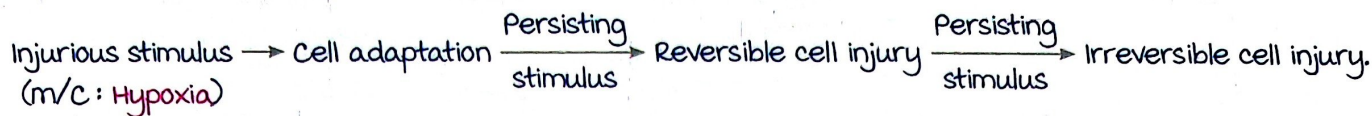
3. Myositis ossificans : muscle → Bone.



Esophageal biopsy : Barrett's esophagus

CELL INJURY

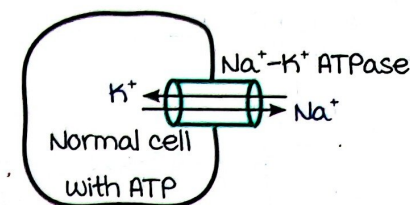
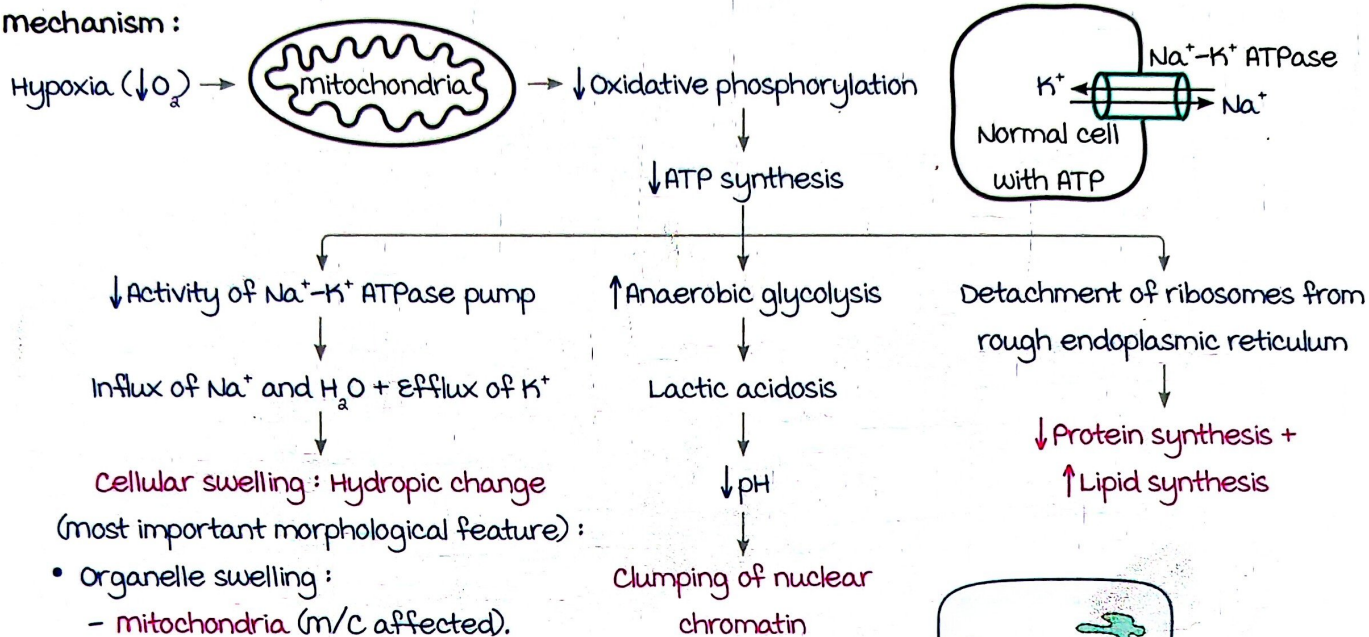
----- Active space -----



Reversible Cell Injury

00:01:10

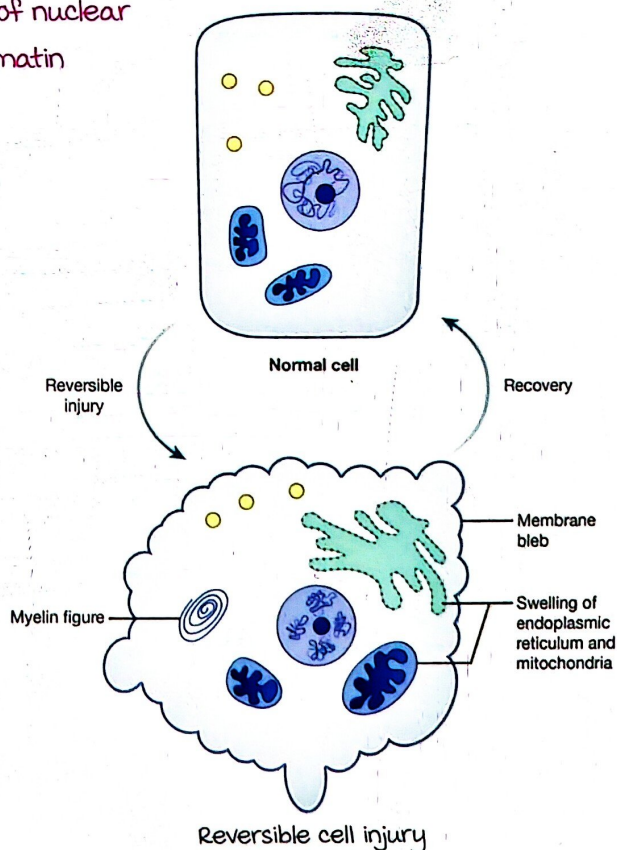
Mechanism:



Note:

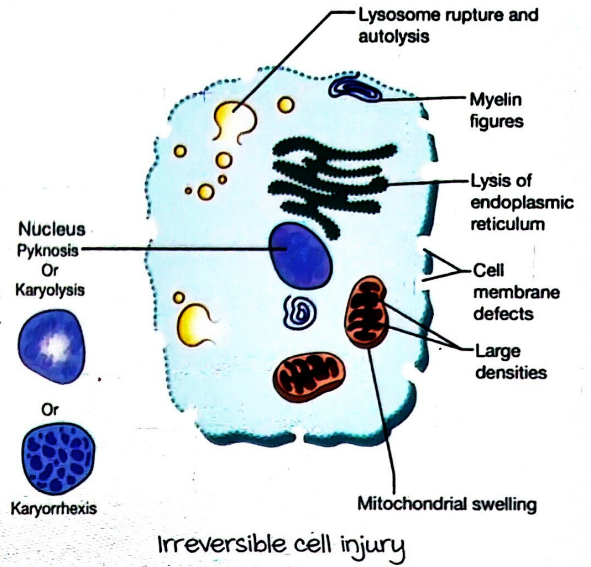
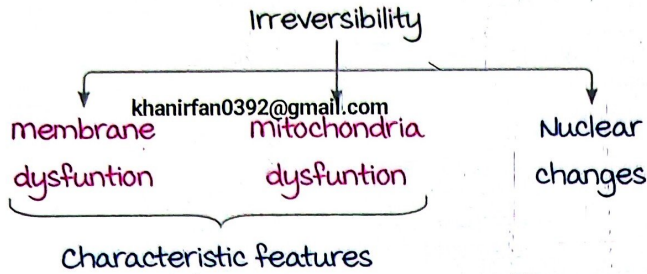
mitochondria:

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



Feedback

Irreversible Cell Injury



MEMBRANE DYSFUNCTION

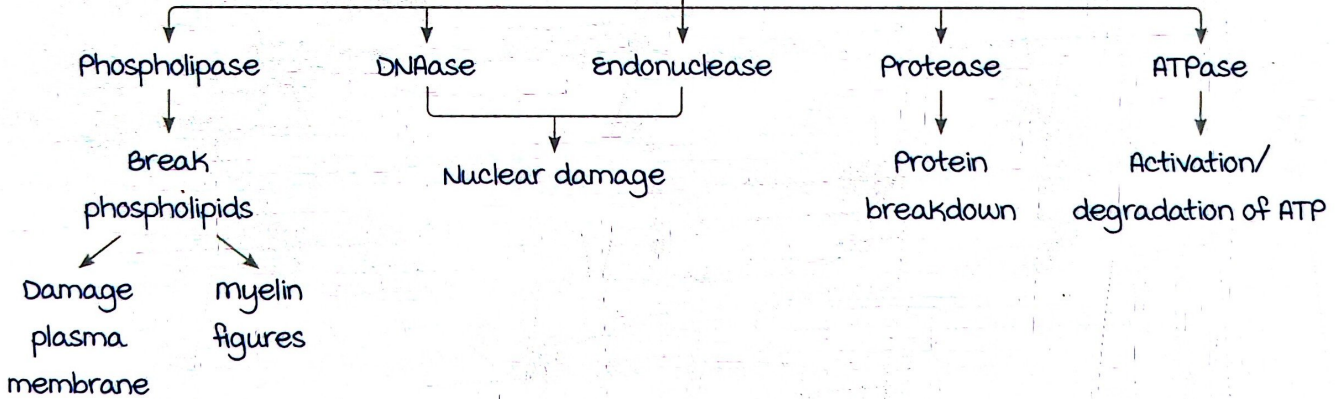
Mechanism:

Cell membrane: Loss of selective permeability → Completely permeable.

Organelles membrane:

Loss of permeability → ↑ Cytosolic Ca²⁺

Activate



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.

Feedback

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.

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

Free Radicals

00:23:45

molecules with ≥ 1 unpaired electrons in their outermost orbit.

unstable configuration \rightarrow Release high energy \rightarrow Damage cells.

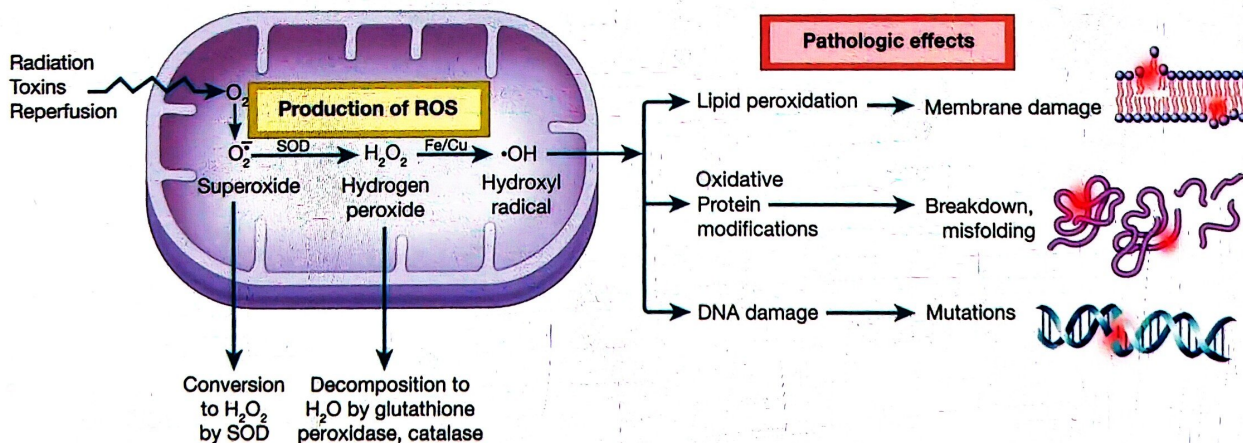
Examples :

- OH^\cdot (Hydroxy) : most potent.
- O_2^\cdot (Superoxide).
- H_2O_2 (Hydrogen peroxide).
- ONOO^\cdot (Peroxynitrite) : Phagocytosis in O_2^\cdot -dependent killing pathway.

Role of free radical injury :

- Ageing (mx : \uparrow use of antioxidants).
- Neurodegenerative disease : Alzheimer's disease.
- Cancer.
- Reperfusion injury.

Production and effects :



SOD : Superoxide Dismutase

Trace elements producing free radicals : Fe, Cu.

8



General Pathology

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

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

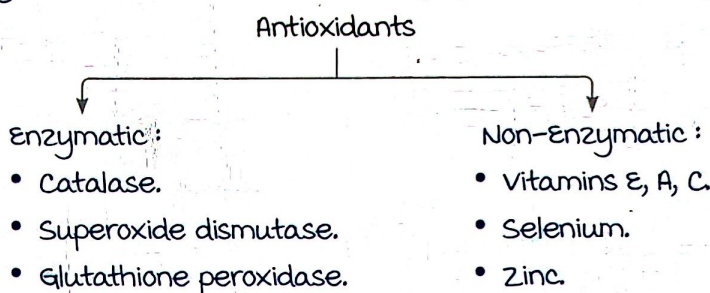
- $\downarrow Fe^{2+}$ in body d/t :
 - $Fe^{3+} \gg Fe^{2+}$ in vivo.
 - Presence of binding proteins : Transferrin (For Fe)/Ceruloplasmin (For Cu)



\uparrow Bound form (Limit availability for FR production).

Protective mechanisms against free radicals :

Exogenous/endogenous.



Antioxidants & Targets :

		Location	Free radical inactivated
Superoxide Dismutase (SOD)	Cu-Zn SOD (SOD 1)	Cytoplasm	O_a^-
	Mn-SOD (SOD 2)	Mitochondria	
Catalase		Peroxisomes	H_aO_a
Glutathione peroxidase		<ul style="list-style-type: none"> • Cytoplasm • Mitochondria 	<ul style="list-style-type: none"> • OH^- • H_aO_a

- Importance of SOD :
 - Protects brain from free radical injury.
 - mutation of SOD-1 \rightarrow Amyotrophic Lateral Sclerosis.

Misfolded Proteins

00:35:35

Endoplasmic Reticulum (ER) : Site of protein

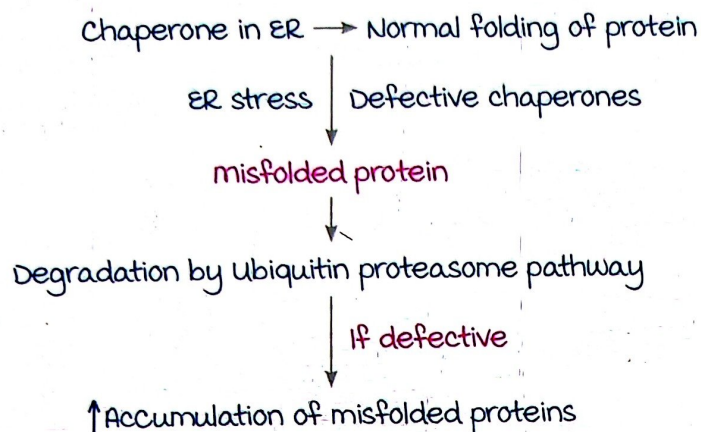
- \rightarrow Synthesis.
- \rightarrow Folding : Assisted by chaperones.

Feedback



Mechanism :

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



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	A β

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

CELL DEATH

mechanisms of cell death :

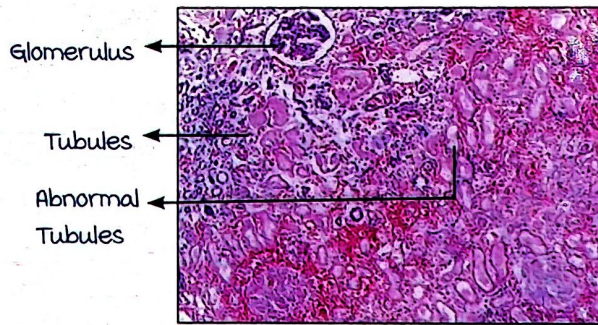
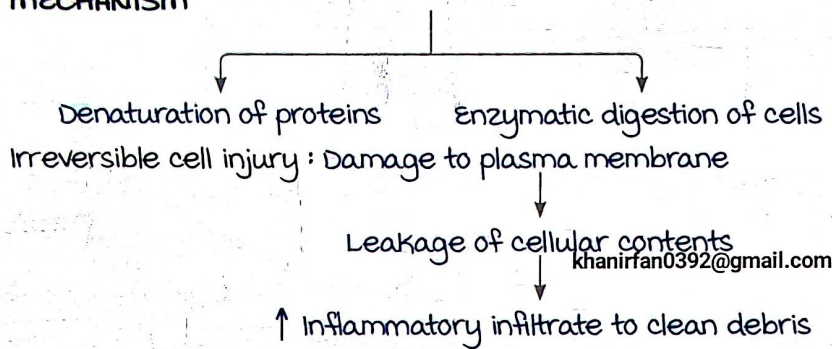
- Necrosis.
- Necroptosis.
- Pyroptosis.
- Ferroptosis.
- Apoptosis.
- Autophagy.

Necrosis

00:01:45

- Accidental death of multiple cells : Always pathological.

MECHANISM



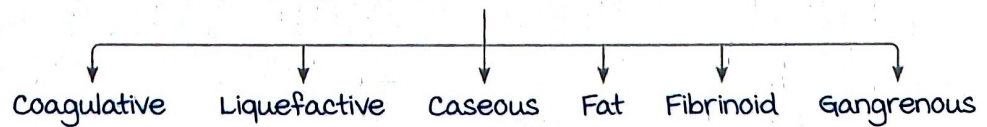
Kidney biopsy : Necrosis on HPE

MORPHOLOGY

On HPE :

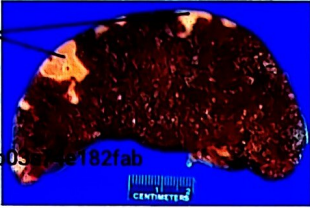
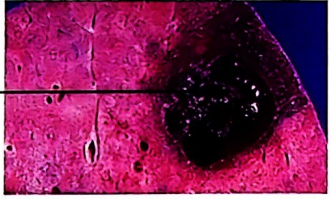
1. Densely eosinophilic cells : D/t loss of cytoplasmic RNA.
2. more glassy/shiny appearance : D/t loss of glycogen.
3. moth-eaten appearance : D/t digestion of organelles by lysosomes.

TYPES



Coagulative vs liquefactive necrosis :

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

	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	<ul style="list-style-type: none"> • Infarct of all solid organs except brain : <ul style="list-style-type: none"> - Heart (m/c affected) - Liver - Kidney - Spleen • Burns • Dry gangrene • Zenker's degeneration (In typhoid fever) : <ul style="list-style-type: none"> - Affects skeletal muscle (Rectus abdominis). 	<ul style="list-style-type: none"> • Brain • Fungal infection • Wet gangrene • Abscess
Appearance	<p>Infarct</p>  <p>648c85cfce3b05749e182fab</p>	<p>Liquid appearance</p> 

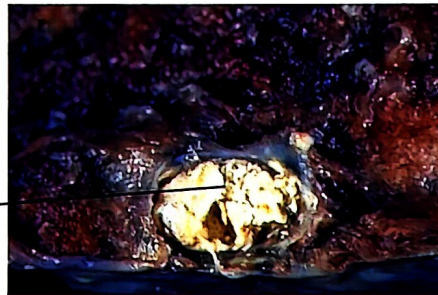
Caseous Necrosis :

Intermediate form of coagulative and liquefactive necrosis.

morphology : Cheese-like appearance.

Examples :

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



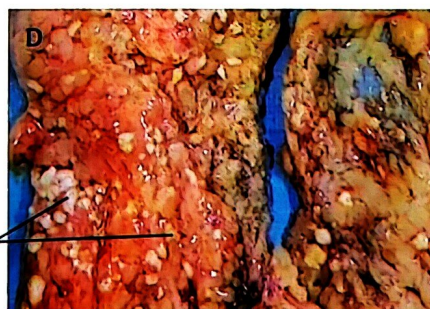
Gross specimen of lung

Fat necrosis :

Types	Examples
Traumatic	Breast
Enzymatic	<ul style="list-style-type: none"> • Omentum • Pancreas • mesentery

D/D : Breast cancer.

morphology : Chalky white deposits.



Chalky white Deposits

Gross specimen of intestine

Feedback

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

Fibrinoid necrosis :

morphology : Fibrin like (Pink coloured).

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

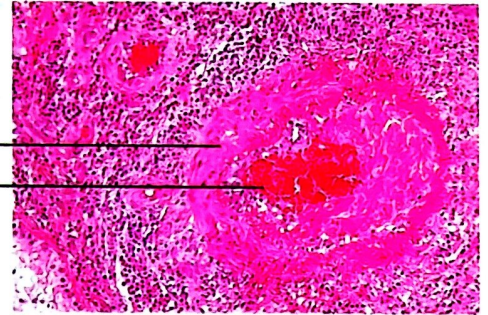
D/t immune complex deposition.

• Examples :

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

Fibrinoid necrosis ←

RBCs in lumen ←



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.

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Occurrence :

a) On completion of function of cell.

b) Damage of cell beyond repair.

EXAMPLES

Physiological :

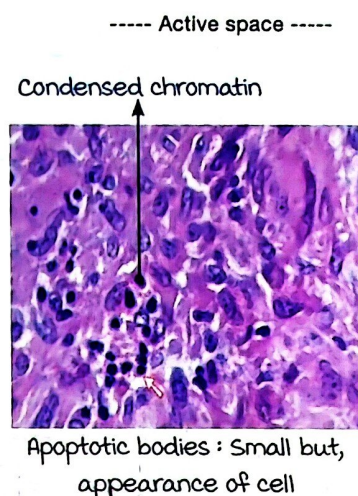
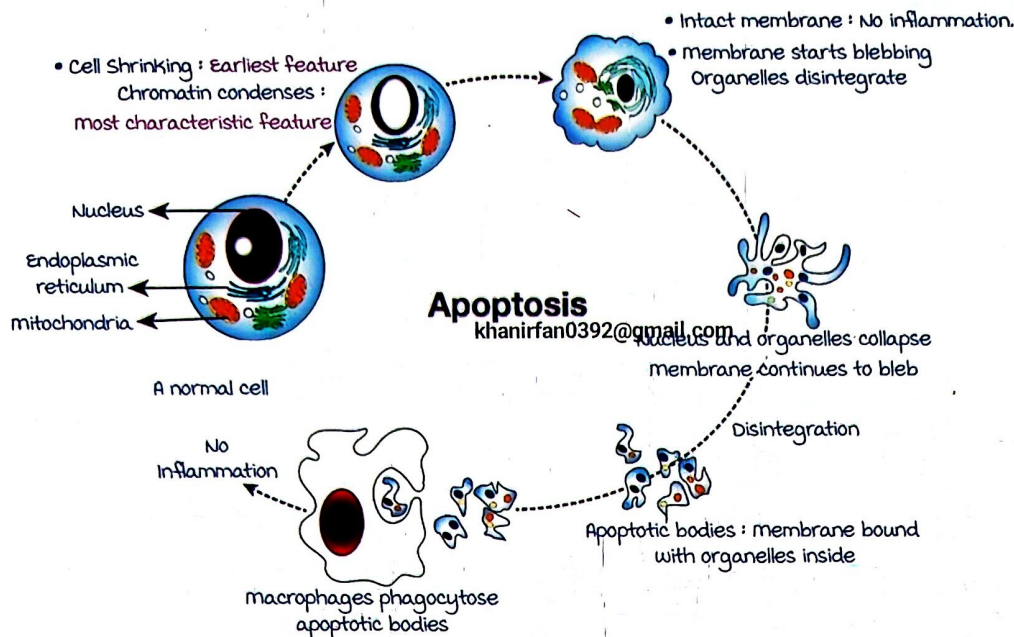
- Organogenesis/embryogenesis : Formation of fingers in limbs.
- Parturition.
- Endometrial shedding during menstrual cycle.
- Death of harmful self-reactive lymphocytes.
- Involution of hormone-dependent tissue upon withdrawal of hormones.

Pathological factors :

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



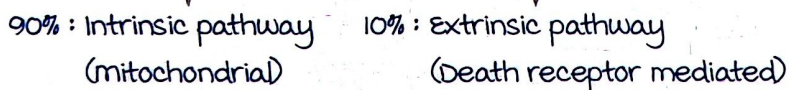
MORPHOLOGY



MECHANISM

Phases :

1. Initiation Phase



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.

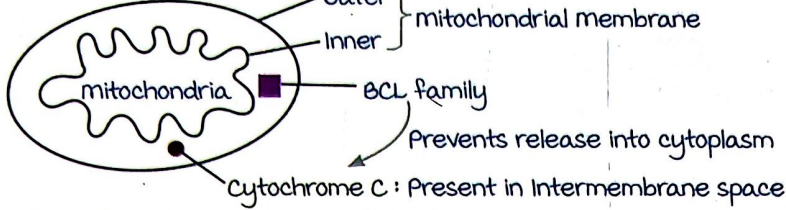


----- Active space -----

Intrinsic pathway :

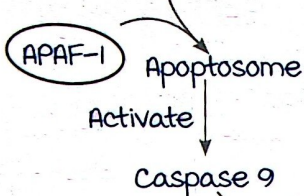
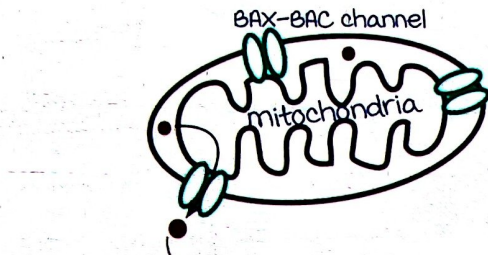
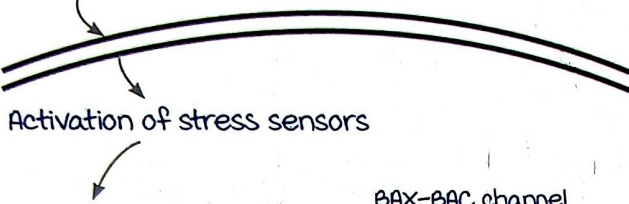
In mitochondria (most important organelle affected).

Normal mitochondria :



Upon noxious stimuli :

Stimulus for cell death (DNA damage/misfolded protein)



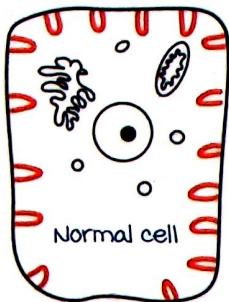
Execution phase

Activates

Caspase 3, 6, 7

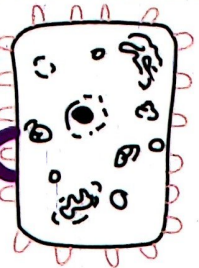
Removal of dead cells by macrophages :

Apoptosis



Phosphatidyl serine present inside inner membrane

Phosphatidyl serine flip (onto outer membrane)



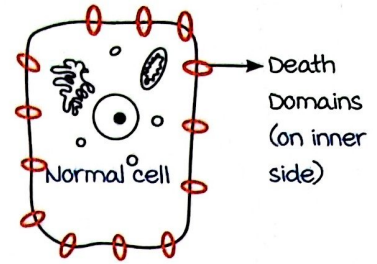
Binding of Annexin V

Recognised by macrophages

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Extrinsic pathway :

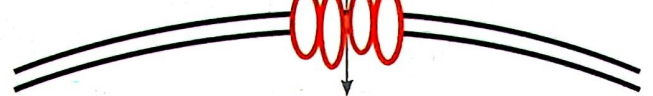
Death Receptors : FAS, TNF



FAS + FAS Ligand

Four death domains conglomerate

FADD



FAS Associated Death Domain

Pro-caspase 8

Activates

Caspase 8

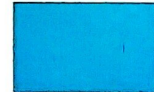
Activates

Feedback



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Cell Death



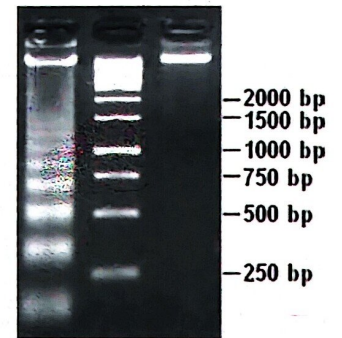
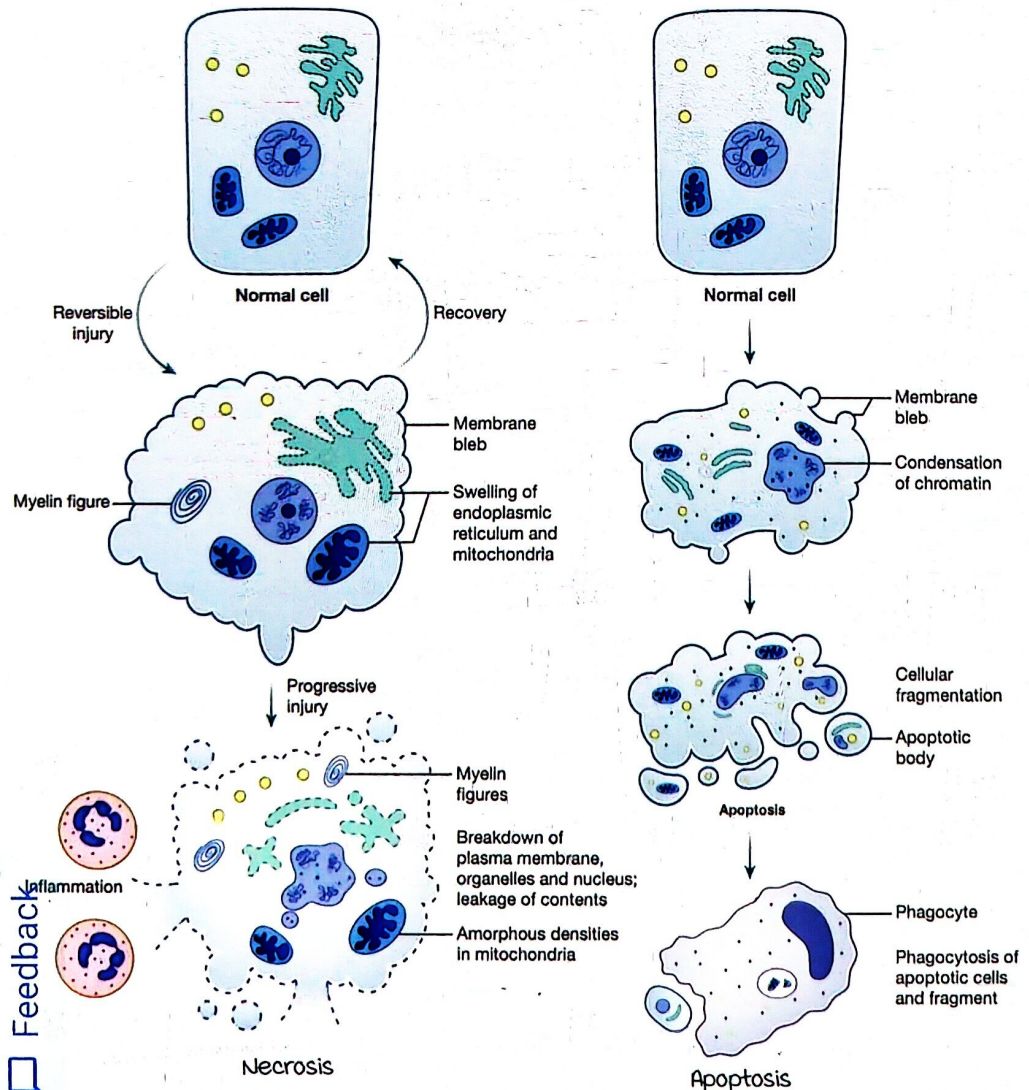
15

Necrosis vs Apoptosis

00:57:35

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

	Necrosis	Apoptosis
Definition	Enzymatic/ischemic process	Genetically programmed cell death
Type of process	Passive process	Active process
Cells involved	Group of cells	Single cell
Occurrence	<ul style="list-style-type: none"> Always pathological Accidental 	<ul style="list-style-type: none"> Physiological/pathological Suicidal
Cell size	Increases	Decreases
Cell membrane	Affected	Intact
Inflammation	Present	Absent
Markers	Absent	Annexin V, CD 95
Polyacrylamide gel electrophoresis (PAGE)/ DNA electrophoresis	Smear pattern (Absent endonuclease)	Step ladder pattern : D/t endonuclease activity ↓ Breaks DNA to fragments



Step ladder pattern in apoptosis

Note :
Effrocytosis :
 Phagocytosis of apoptotic bodies.

Feedback

Miscellaneous Forms Of Cell Death

NECROPTOSIS

Programmed necrosis (Combination of necrosis and apoptosis).

mechanism: Stalls on apoptosis → Caspase independent → Ends as necrosis.

mediator: RIPK-1.

morphology: Features of necrosis (↑ Cell size, damaged cell membrane).

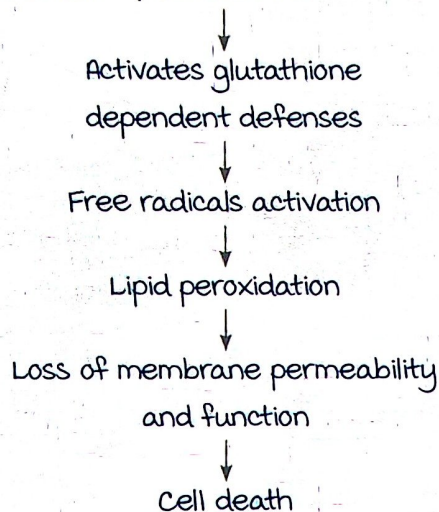
Examples:

- Development of mammalian growth plate.
- Acute pancreatitis.
- Acute steatohepatitis.
- Neurodegenerative disorders.

FERROPTOSIS

Cell death due to ↑ level of Iron (Fe^{2+}).

mechanism: ↑ Level of Iron



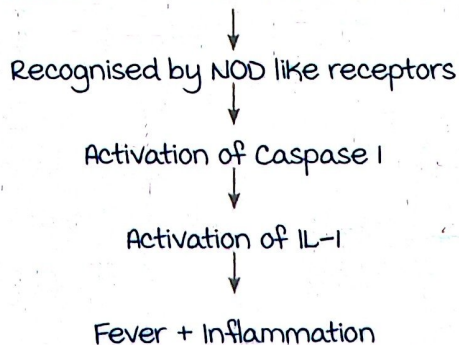
Example:

- Cancer.
- Stroke.
- Neurodegenerative disorders.

PYROPTOSIS

Cell death caused by fever inducing cytokine, IL-1.

mechanism: microbial toxin enters cell



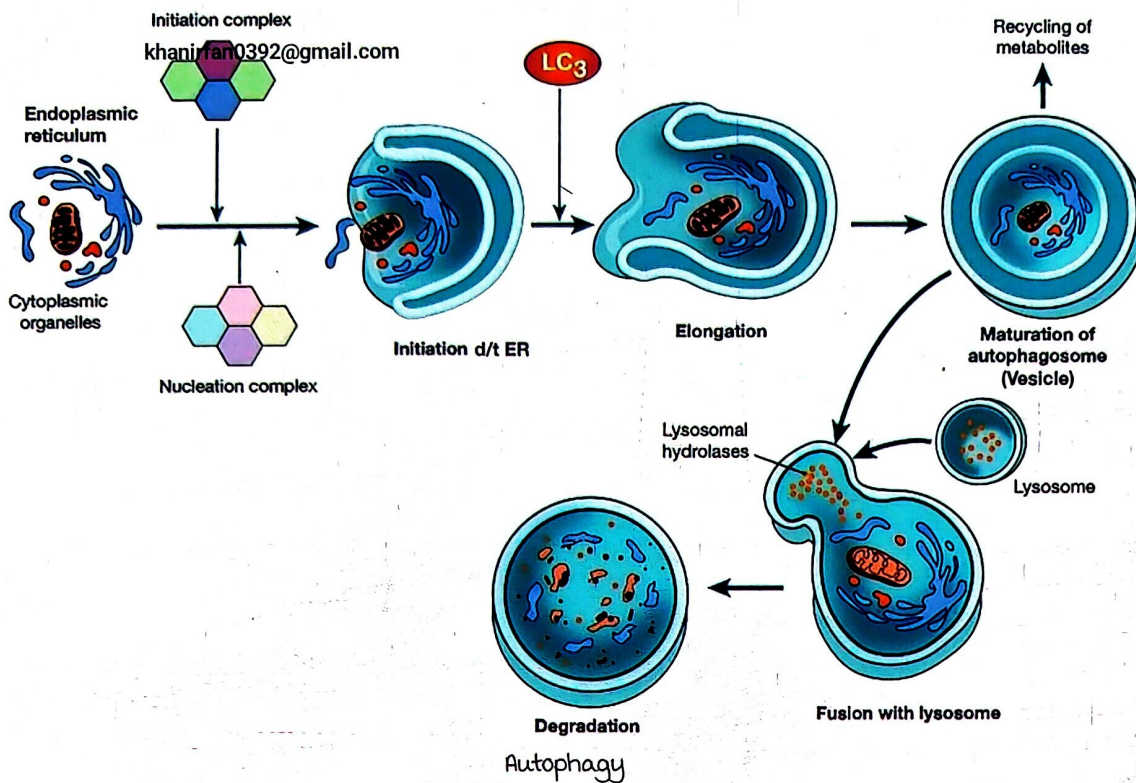
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AUTOPHAGY

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

- Cell kills itself to help the organism survive a nutrient deprived state.



markers :

- **LC3** : For autophagy.
- **ATG16L1** : ATG involved in development of Crohn's disease.

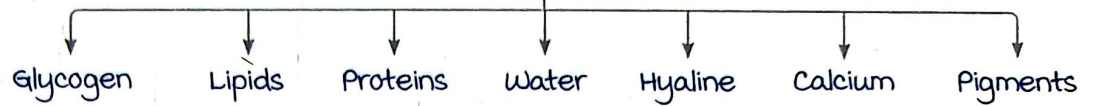
----- Active space -----

INTRACELLULAR ACCUMULATIONS

Intracellular Accumulations

00:00:30

Substances deposited inside cell in response to cell injury :



GLYCOGEN

Clinical Conditions :

1. Glycogen Storage Disorders.
2. Tumors : Clear cell Renal Cell Carcinoma.
3. Severe diabetic nephropathy : **Armani Ebstein lesions**
Glycogen deposition in Proximal Convoluted Tubules as clear vacuoles.

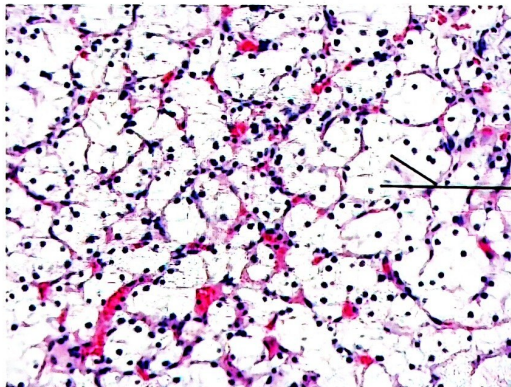
microscopy : Clear vacuoles (D/t dissolution in aqueous mixture).

Special stain : **Periodic Acid Schiff (PAS)**.

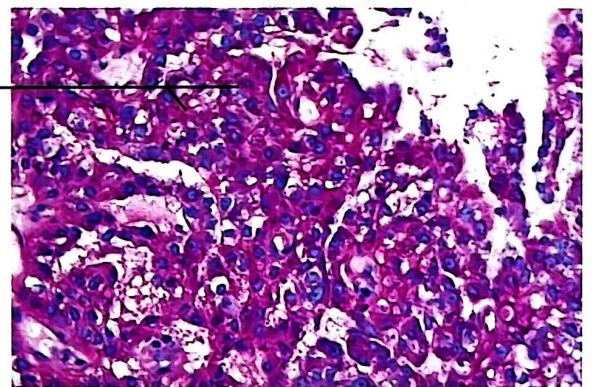
Note : PAS positive substances

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- Fungi.
- Lymphoblasts.
- Basement membrane (can differentiate invasive and insitu cancer).



Clear Cell RCC



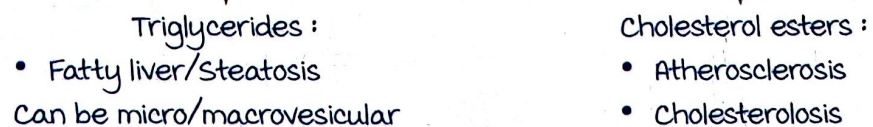
PAS Positivity

Bright pink & magenta
Clear vacuoles d/t glycogen

LIPID/FATS

Clinical Conditions :

D/t accumulation of





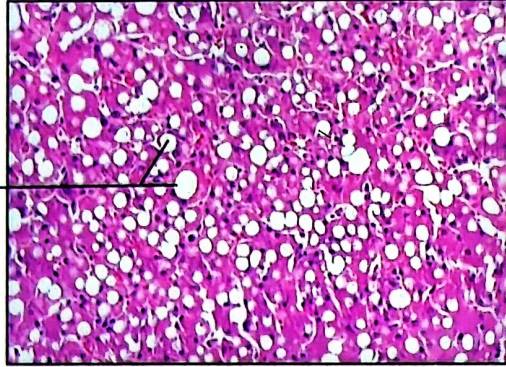
khanirfan0392@gmail.com

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

microscopy : Clear vacuoles.

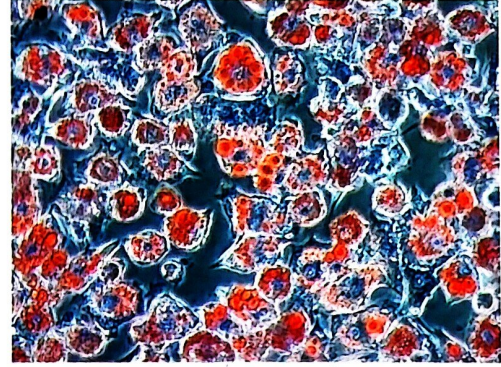
Special Stain :

- Oil Red O.
- Sudan Black.



vacuoles composed of lipids/fat

Liver Biopsy : Steatosis

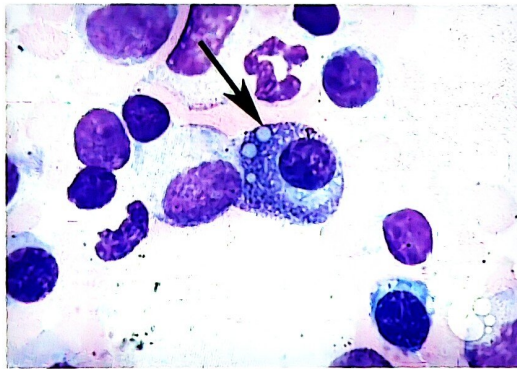


Oil Red O Staining of lipids

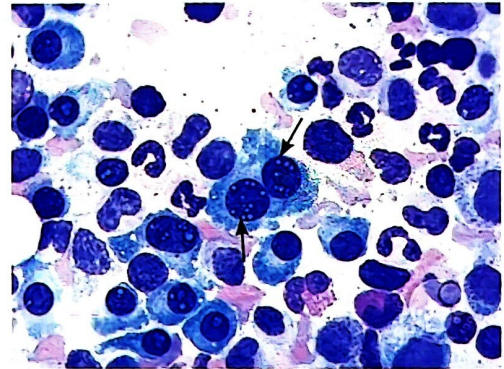
PROTEINS

Clinical Conditions :

1. multiple myeloma : Deposition of abnormal immunoglobulins



Russel bodies : Intracytoplasmic inclusion



Dutcher bodies : Intranuclear inclusion

2. Kidney diseases : Reabsorption droplets.

microscopy : Eosinophilic, granular.

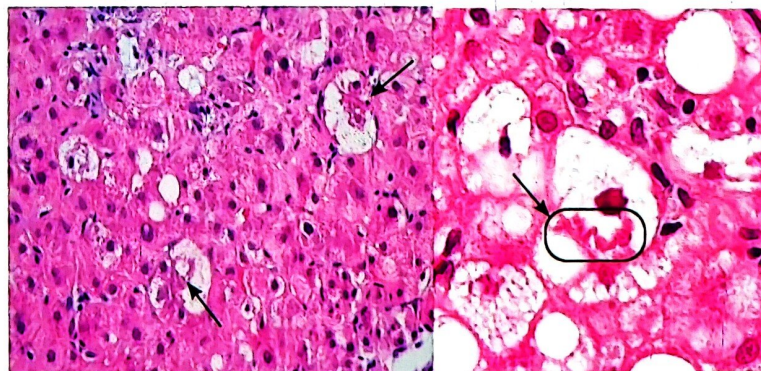
HYALINE

microscopy :

Homogenous Pink.

Types:

- Intracellular : mallery Hyaline Body.
- Extracellular



Liver Biopsy : mallery Denk Bodies

Feedback

