

Pathology

Edition 8.5

Marrow

MARROW

Instructions

- Notes are to be used in conjunction with Marrow videos.

Please note:

- The information in this book has been printed based on the transcript of the Marrow videos. This book has to be used in conjunction with the Marrow videos and not as a standalone material.
- The information contained in this book is for educational purposes only. The content provided is not intended to substitute for professional medical advice, diagnosis or treatment.
- This book cannot be sold separately. It has been made available to only select eligible users who have an active subscription to Marrow videos.
- The text, images, slides, and other materials used in this book have been contributed by the faculty, who are subject matter experts. We have merely reproduced them as video transcripts in this book.
- The notes have been consciously designed in a way that is concise and revisable. To ensure this, we have intentionally added only the most relevant modules and images that are needed for you.
- Reasonable care has been taken to ensure the accuracy of the information provided in this book. Neither the faculty nor Marrow takes any responsibility for any liability or damages resulting from applying the information provided in this book.

All Rights Reserved

No part of this publication shall be reproduced, copied, transmitted, adapted, modified or stored in any form or by any means, electronic, photocopying, recording or otherwise.

©Marrow

//ME901-MPTL

Contents

General Pathology

Cell Adaptations	1
Cell injury • Cell adaptation	
Cell Injury	5
Reversible cell injury • Irreversible cell injury • Free radicals • Misfolded proteins	
Cell Death	10
Necrosis • Apoptosis • Necrosis vs apoptosis • Miscellaneous forms of cell death	
Intracellular Accumulations	18
Intracellular accumulations • Cellular aging • Stains	
Acute Inflammation	25
Features of inflammation • Mechanism of acute inflammation • Leukocyte function defects • Miscellaneous topics	
Chronic Inflammation	32
Cells involved & features • Granulomatous inflammation • Granulomatous disorders • Systemic effects of inflammation	
Mediators of Inflammation	39
Cell derived mediators • Plasma derived mediators	
Wound Healing and Tissue Repair	44
Tissue regeneration and repair • Wound healing • Collagen	
Hemodynamics	50
Hyperaemia and congestion • Thrombosis • Embolism • Infarct	
Neoplasia : Basics	54
Classification • Properties of a tumor • Cell cycle	
Types of Carcinogenesis	59
Radiation carcinogenesis • Chemical carcinogenesis • Microbial carcinogenesis	
Neoplasia : Hallmarks	64
Self sufficiency in growth signals • Insensitivity to growth inhibitory signals • Other mechanisms of neoplasia	
Lab Diagnosis of Cancer	74
Cytology • Biopsy • Immunohistochemistry & frozen section • Miscellaneous	

Tumour Diagnosis	80
Characteristic features of tumours • Different patterns in cancers	
Genetics : Basics & Mendelian Modes	86
Introduction to genetics • Autosomal dominant (AD) disorders • Autosomal recessive (AR) disorders • X-linked recessive (XLR) disorders • Single gene disorders of epigenetic machinery • X-linked dominant (XLD) disorders	
Genetics : Non-Mendelian Modes and Pedigree	94
Non-mendelian modes of inheritance • Pedigree analysis	
Genetics : Chromosomal Disorders	100
Structure and types of chromosomes • Structural abnormalities • Autosomal chromosomal abnormalities • Sex chromosomal abnormalities	
Genetic Disorders - Diagnosis	107
Cytogenetic techniques • Molecular genetic techniques • Miscellaneous topics	
Hypersensitivity Reactions	113
Type 1 hypersensitivity reaction • Type 2 hypersensitivity reactions • Type 3 hypersensitivity reaction • Type 4 hypersensitivity reactions	
Transplant Pathology	117
Types of grafts • Transplantation prerequisites • Graft reactions • Post transplant complications	
Immunodeficiency Disorders	122
Defect in lymphocyte maturation • Defect in lymphocyte activation and function • Systemic disorders • Summary	
Amyloidosis	127
Types • Pathogenesis • Diagnosis	
Hematology	
RBC : Introduction	131
Erythropoiesis • RBC indices • Anemias	
Peripheral Smear Examination	138
Technique and normal findings • Abnormal RBC's • Abnormal WBC's and platelets • Organisms on PS	
Microcytic Hypochromic Anemia	145
Iron deficiency anemia • Anemia of chronic disease • Sideroblastic anemia • Summary	
Megaloblastic Anemia	153
Megaloblastic anemia d/t vit B12 deficiency • Megaloblastic anemia d/t folate deficiency • Pernicious anemia	
Hemolytic Anemia : Part I	158
Classification & clinical presentation • Hereditary spherocytosis (HS) • G6PD deficiency • Sickle cell anemia	

Hemolytic Anemia : Part 2	169
Thalassemia • Autoimmune hemolytic anemia • Paroxysmal nocturnal hemoglobinuria	
WBC : Introduction	177
Hematopoiesis • WBC physiology • WBC pathology	
Acute Lymphoblastic Leukemia	183
Features of leukemia • Classification of ALL • Lab diagnosis & management	
Acute Myeloid Leukemia	187
Etiology & clinical presentation • Classification systems • Management • ALL vs AML	
Myeloid Disorders	192
Myeloproliferative neoplasms (MPNs) • Myelodysplastic syndrome (MDS) • Langerhan's cell histiocytosis (LCH) • Bone marrow findings in WBC disorders	
Chronic Leukemia	199
Chronic lymphocytic leukemia (CLL) • Chronic myeloid leukemia (CML) • Summary of acute and chronic leukemias	
Hodgkin's Lymphoma	205
Hodgkin's vs non-hodgkin's lymphoma • Reed Sternberg cell • Types of Hodgkin's lymphoma • Pathogenesis & management	
Non Hodgkin's Lymphoma	209
Lymphoid neoplasms • B cell neoplasms • T cell NHL • Newer peripheral T cell & NK cell neoplasms	
Plasma Cell Disorders	218
Multiple myeloma • Other plasma cell disorders	
Hemostasis : Part 1	223
Mechanism of hemostasis • Tests for hemostasis • Disorders of hemostasis	
Hemostasis : Part 2	229
Hemophilia • Von Willebrand's disease • Microangiopathic hemolytic anemias (MAHAs) • Summary of hemostatic disorders • Thromboelastography	
Blood Banking and Transfusion Medicine	236
Blood groups • Blood banking • Blood transfusion • TRALI vs TACO	
Cardiovascular System	
Blood Vessels : Sclerosis	242
Normal blood vessel • Monckeberg's medial calcific sclerosis • Arteriosclerosis • Atherosclerosis • Aneurysm • Aortic dissection	
Blood Vessels : Vasculitis	248
Classification • Large vessel vasculitis • Medium vessel vasculitis • Small vessel vasculitis	
Vascular Tumors	255
Benign vascular tumors • Kaposi's sarcoma • Malignant vascular tumors	

Cardiovascular System : Part 1	260
Heart failure • Ischemic heart disease	

Cardiovascular System : Part 2	265
Endocarditis • Summary of valvular vegetations • Myocarditis & pericarditis • Cardiomyopathy • Tumors of heart	

Genitourinary System

Kidney : Basics	273
Urine microscopy • Kidney biopsy	

Nephritic Syndromes	279
Post streptococcal glomerulonephritis (PSGN) • Rapidly progressive glomerulonephritis • Other nephritic syndromes	

Nephrotic Syndrome	283
Minimal change disease • FSGS • Genetic basis of nephrotic syndrome • Membranous nephropathy • Membranoproliferative glomerulonephritis (MPGN)	

Renal Involvement in Systemic Diseases	288
Diabetic nephropathy • Lupus nephritis • Renal changes in hypertension • Amyloidosis • Miscellaneous	

Kidney Tumors	292
Benign tumors • Wilm's tumor • Renal cell carcinoma	

Male Genital System : Penis and Prostate	296
Lesions of penis • Prostate • Gleason's score	

Male Genital System : Testis	301
Normal histology • Lesion of testis • Classification of testicular tumors • Germ cell tumors : Seminomatous • Germ cell tumors : Non-seminomatous • Sex cord stromal tumors • Testicular lymphoma	

Female Genital Tract : Vulva, Vagina and Cervix	307
Vulva • Vagina • Cervix • Infections	

Female Genital Tract : Uterus and Endometrium	313
Normal endometrial histology • Endometriosis • Adenomyosis • Endometrial hyperplasia • Endometrial cancer • Myometrium	

Female Genital Tract : Ovaries	318
Ovarian tumors • Surface epithelial tumor • Germ cell tumors • Sex cord stromal tumors • Krukenberg's tumor • Summary of ovarian tumors • Gestational trophoblastic disease	

Gastrointestinal System

Esophagus	326
Overview • Infective esophagitis • Barrett's esophagus • Esophageal cancers	

Stomach	331
Anatomy • Gastritis • Peptic ulcer disease (PUD) • Gastric tumours	
Intestinal Disorders	338
Malabsorption syndromes • Pseudomembranous colitis • Intestinal ulcers • Microvillus inclusion disease	
Inflammatory Bowel Disease	343
Crohn's disease (CD) • Ulcerative colitis (UC) • Clinical presentation of IBD	
Colorectal Polyps and Cancer	348
Colorectal polyps • Colon cancer • Carcinoid tumor	
Liver Pathology : Part 1	354
Normal liver • Jaundice • Cirrhosis • Alcoholic liver disease (ALD) • NASH • Reye's syndrome	
Liver Pathology : Part 2	361
Hemochromatosis • Wilson's disease • α 1 antitrypsin deficiency • Hepatitis • Hepatic tumors • Bile duct disorders • Miscellaneous	
Respiratory System	
Obstructive Lung Diseases	368
Overview • Emphysema • Chronic bronchitis • Bronchial asthma • Bronchiectasis	
Restrictive Lung Diseases	375
Pneumoconiosis • Fibrosing restrictive lung disease • Pulmonary alveolar proteinosis (PAP)	
Granulomas and Infections of Lung	379
Sarcoidosis and hypersensitivity pneumonitis • Tuberculosis • Pneumonia • Miscellaneous	
Lung Tumors	384
Benign lung tumors • Malignant lung tumors • Pleural tumors	
Endocrine System and Breast	
Thyroid : Non-Neoplastic Lesions	390
Anatomy and overview • Hyperthyroidism • Hypothyroidism	
Thyroid Tumors	393
Thyroid cytology • Follicular adenoma • Thyroid malignancy • Lymphoma	
Adrenal Medulla	399
Pheochromocytoma • Neuroblastoma • MEN syndrome (Multiple endocrine neoplasia)	
Pituitary and Parathyroid Gland	403
Pituitary gland • Parathyroid gland	
Breast Pathology : Part 1	408
Breast structure and histology • Inflammatory lesion of breast • Epithelial lesions • Paget's disease • Breast tumors	

Breast Pathology : Part 2

413

Breast carcinoma • Morphological types of breast carcinoma • IHC •
Molecular classification of breast cancer

Skin and Musculoskeletal System

Dermatopathology

420

Normal histology of epidermis • Skin diseases • Skin malignancies •
Bullous disorders of skin

Bone and Soft Tissue Lesions

427

Paget's disease • Bone tumors • Summary • Soft tissue tumors

Nervous System

CNS : Non Neoplastic Lesions

433

Glial cells • Transmissible spongiform encephalopathies (TSE) •
Neurodegenerative disorders • Miscellaneous

CNS Tumors

438

Classification of CNS tumors • Grading of brain tumors • Glial tumors •
Undifferentiated tumors • Meningeal tumors • Schwannoma (acoustic neuroma) •
Primary CNS lymphoma • Syndromes associated with brain tumors

Miscellaneous

Demonstration of Instruments

447

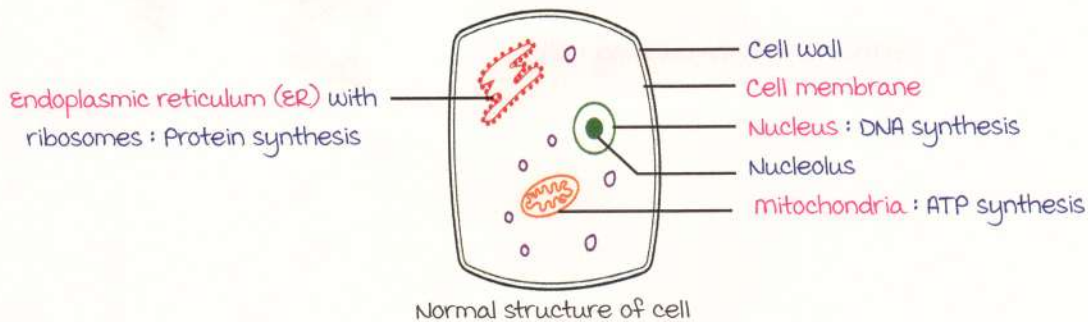
Vacutainers • Bone marrow needles • ESR tubes • Sahli's
hemoglobinometer • Microscope

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

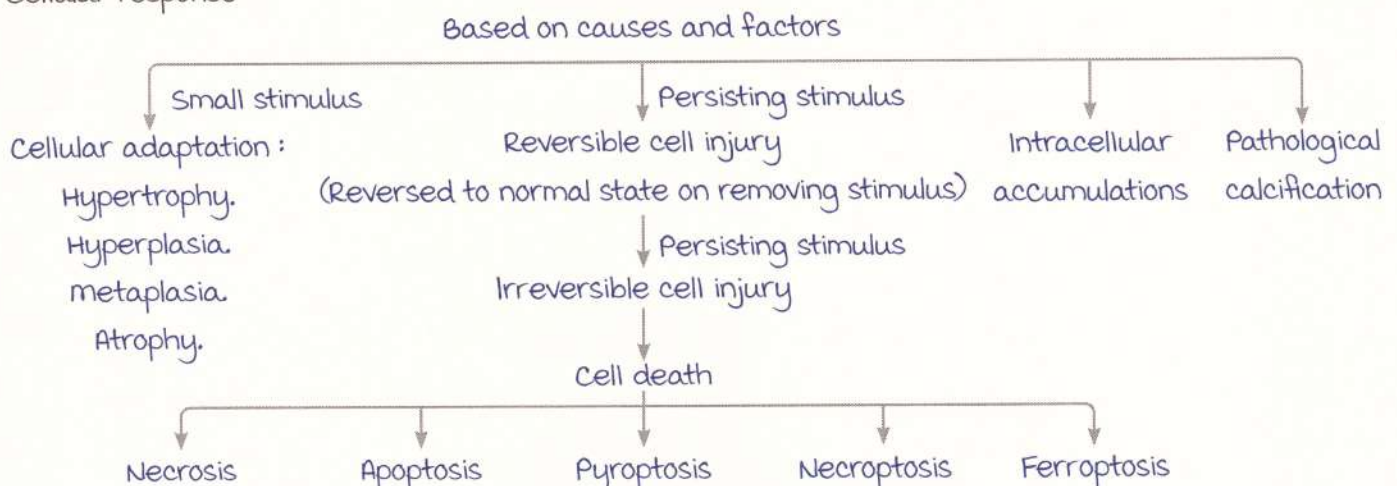
Other agents :

- 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 :



Cell Adaptation

00:14:00

Hypertrophy :

↑ cell size (No ↑ in cell number).

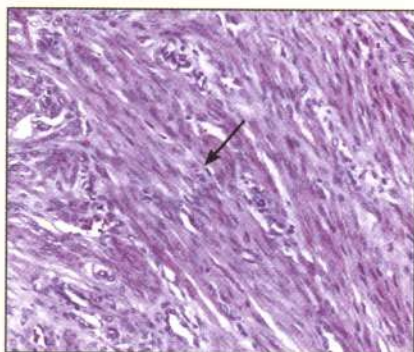
mechanism :

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

Examples :

Physiological :

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



Normal myometrial 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 :

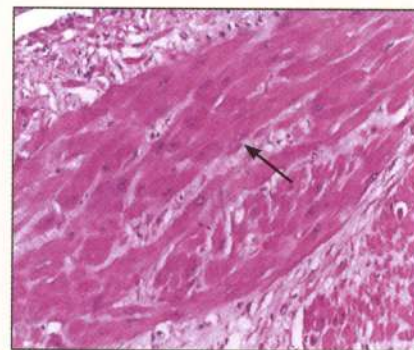
- Breast during puberty
- uterus during pregnancy.



Hypertrophy + hyperplasia of gravid uterus

Pathological :

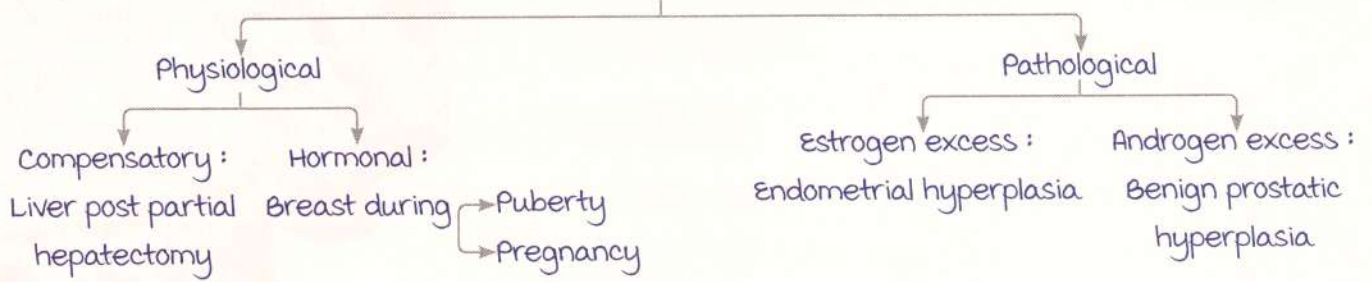
- Left ventricular hypertrophy (Hypertension → ↑ work load).
- Bladder obstruction by stone → Proximal area hypertrophy.



↑ size of smooth muscle cells

Examples :

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



Partial Hepatectomy



Healthy liver



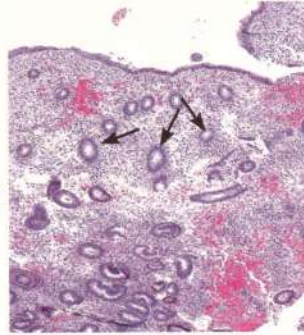
15 days

Regenerating liver

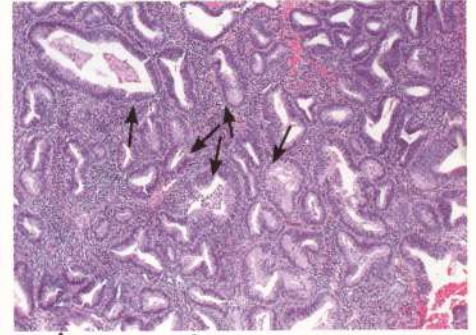


complete
mass recovery

Hyperplasia of liver



Normal endometrium



↑ number of endometrial glands

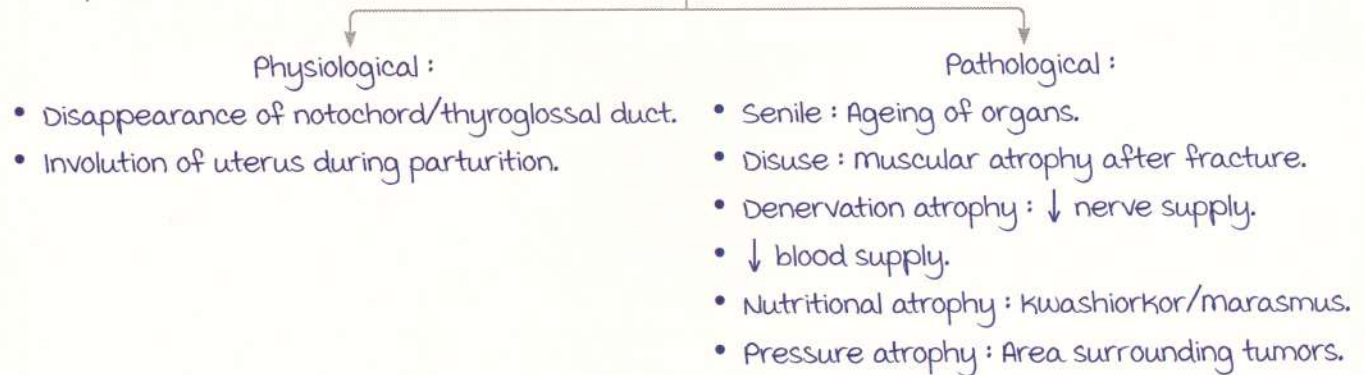
Atrophy :

↓ cell size, ↓ cell number.

mechanism :

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

Examples :



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

metaplasia :

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

mechanism :

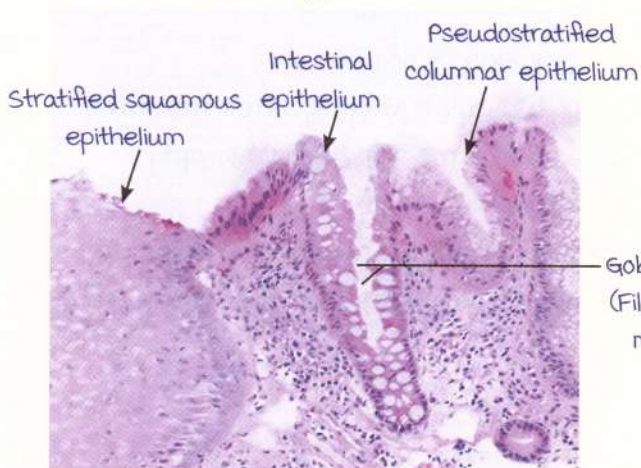
- Reprogramming of stem cells.
- Risk factor : **vitamin A deficiency**.

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 (CLO) :

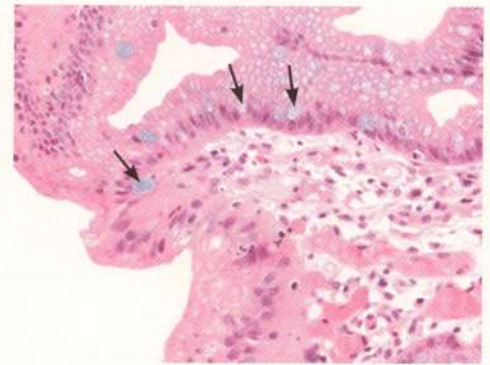
- Stratified squamous epithelium $\xrightleftharpoons[\text{On treatment}]{\text{GERD/Risk factors}}$ Columnar epithelium.
- Histopathological remark (H&E) :
 - **Intestinal metaplasia**.
 - **Goblet cells** present.
- Risk factor for **adenocarcinoma** of esophagus.
- Special staining : **Alcian blue**/mucicarmine (Stains mucin inside goblet cells).

3. myositis ossificans : muscle → Bone.

Goblet cells
(Filled with
mucin)

Glands

Esophageal biopsy : Barrett's esophagus



Alcian blue stained goblet cells

CELL INJURY

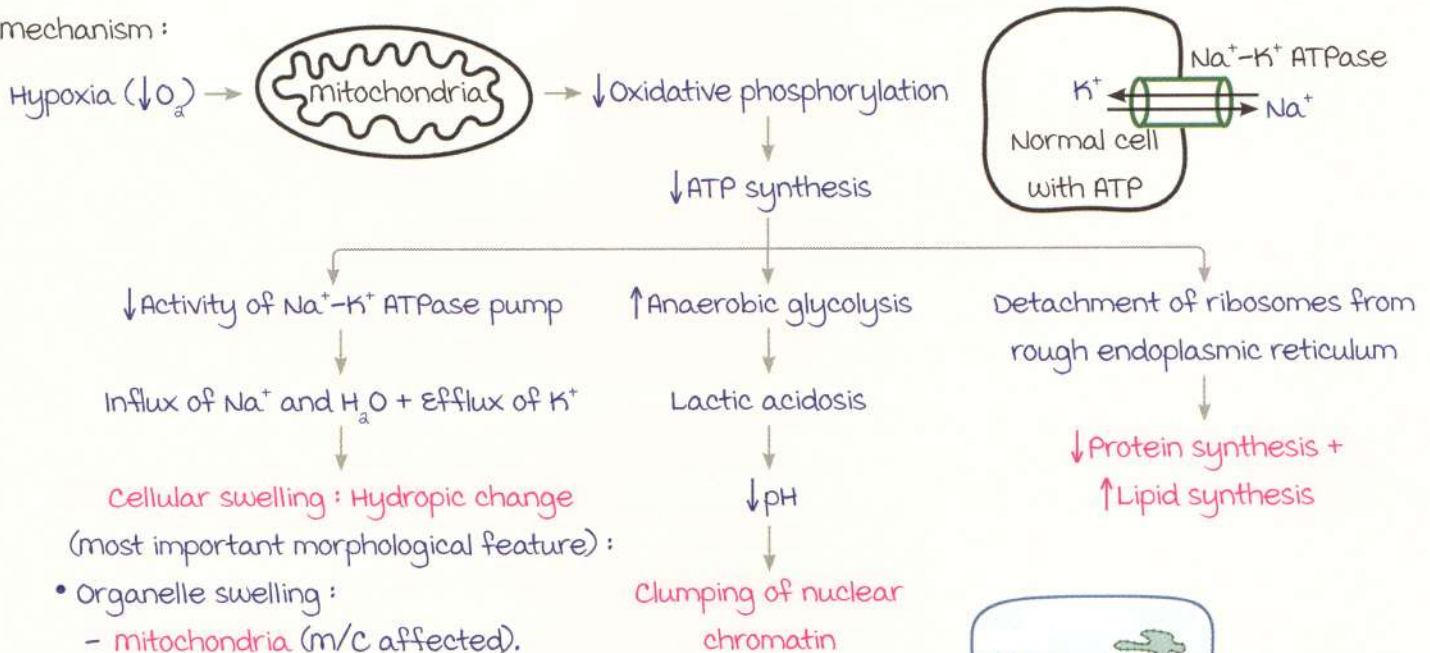
----- Active space -----



Reversible Cell Injury

00:01:10

mechanism:

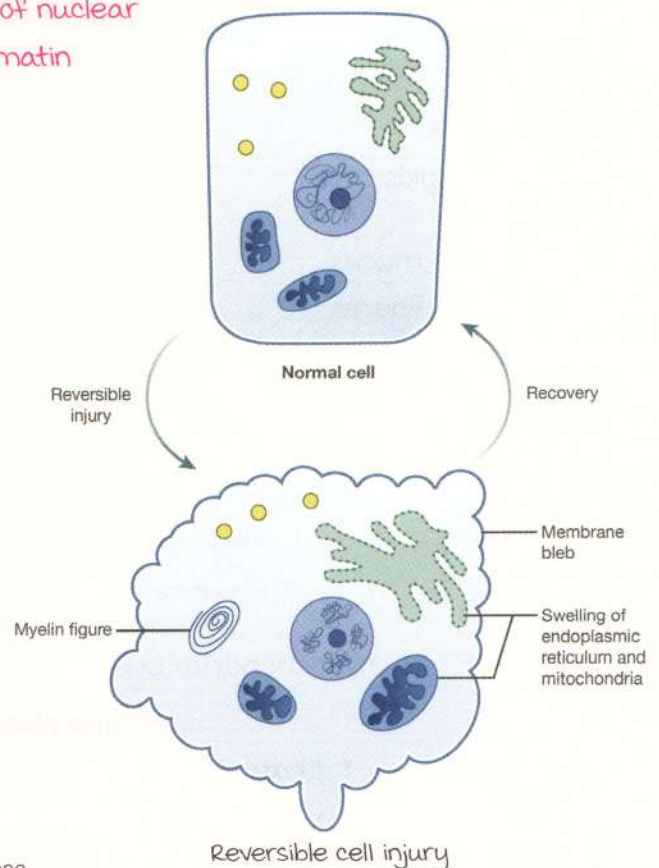


- Organelle swelling:
 - mitochondria (m/c affected).
 - Endoplasmic reticulum.
- membrane blebs.
- myelin figures:
 - Seen in reversible < irreversible cell injury.
 - Produced d/t plasma membrane damage.
 - Composition: Phospholipids + Ca^{2+} .

Note:

mitochondria:

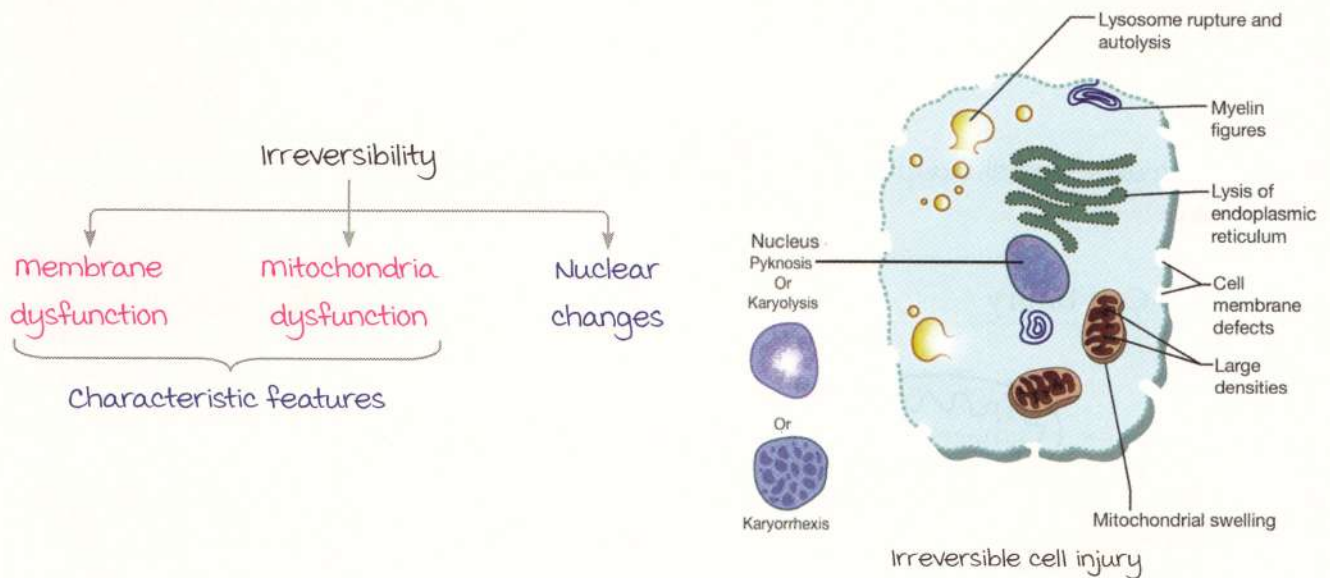
- most important organelle affected in: Reversible cell injury, apoptosis.
- Calcification (earliest appearance).



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

Irreversible Cell Injury

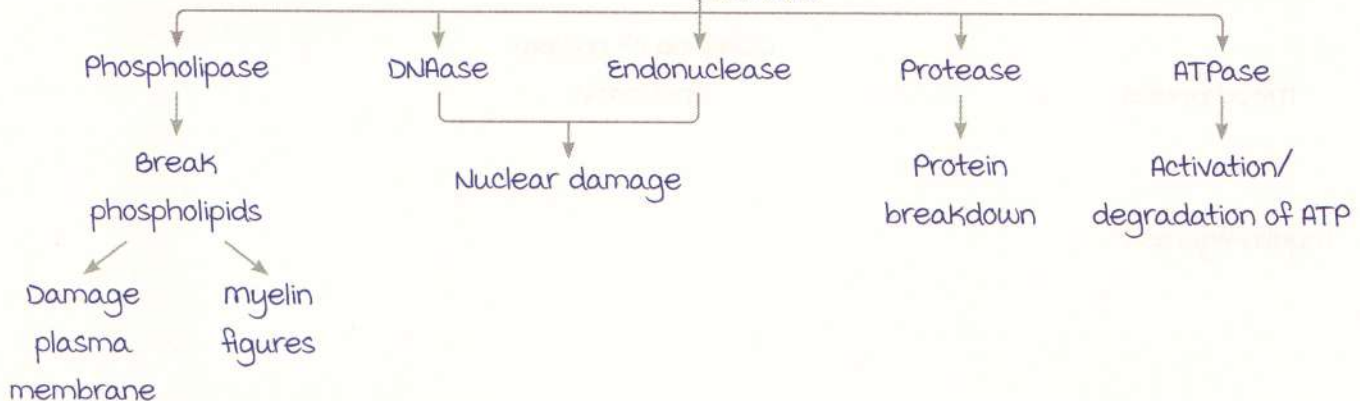
00:12:10

**membrane Dysfunction :**

mechanism :

- Cell membrane : Loss of selective permeability → Completely permeable.
- Organelles membrane :

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



Clinical applications :

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

mitochondrial Dysfunction :

Large, flocculent, amorphous densities in mitochondria :

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

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 $\rightarrow$ Release high energy $\rightarrow$ Damage cells.

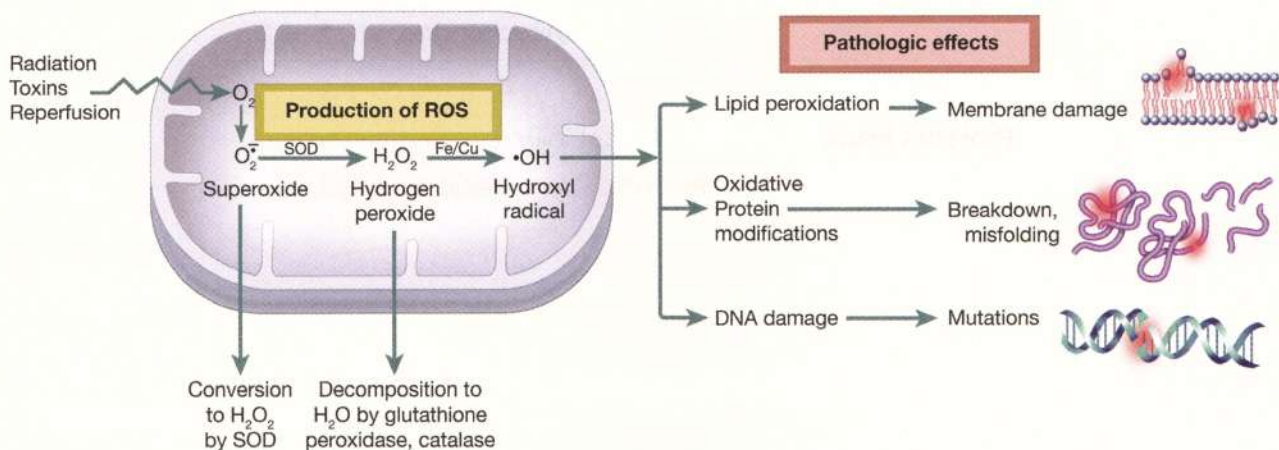
Examples :

- $\text{OH}^\cdot$ (Hydroxyl) : most potent.
- $\text{O}_2^\cdot$ (Superoxide).
- H_2O_2 (Hydrogen peroxide).
- $\text{ONOO}^\cdot$ (Peroxynitrite) : Phagocytosis in O_2 -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.

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

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

- $\downarrow \text{Fe}^{2+}$ in body d/t :

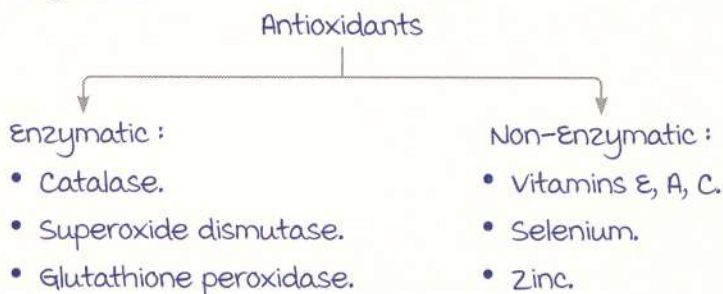
- $\text{Fe}^{3+} \gg \text{Fe}^{2+}$ in vivo.

- 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 & Targets :

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

Importance of SOD-1 :

- Protects brain from free radical injury.
- mutation of SOD-1 → Amyotrophic Lateral Sclerosis.

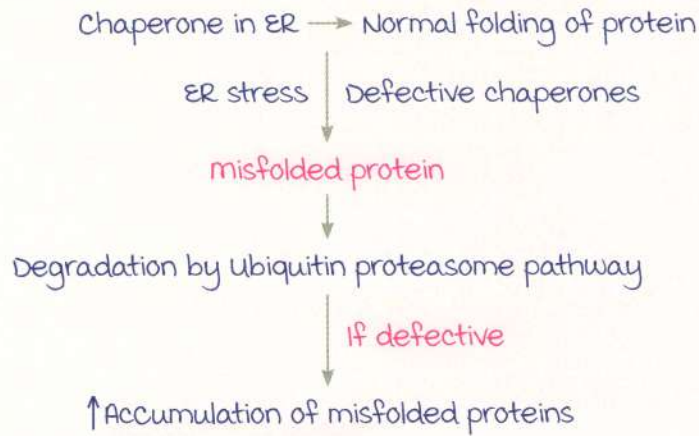
Misfolded Proteins

00:35:35

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

mechanism :

----- 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

CELL DEATH

mechanisms of cell death :

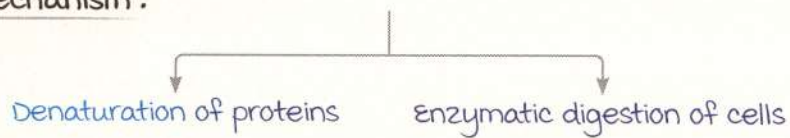
- Necrosis.
- Necroptosis.
- Pyroptosis.
- Ferroptosis.
- Apoptosis.
- Autophagy.

Necrosis

00:01:45

- Accidental death of multiple cells : **Always pathological.**

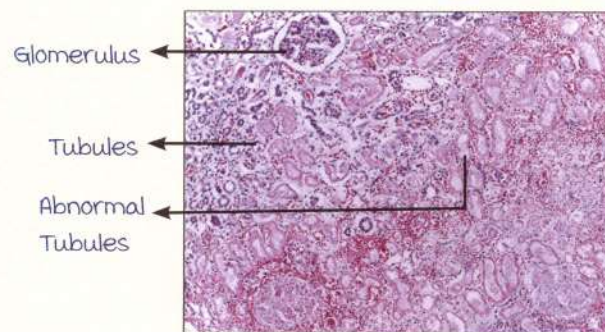
mechanism :



Irreversible cell injury : Damage to plasma membrane

↓
Leakage of cellular contents

↓
↑ Inflammatory infiltrate to clean debris



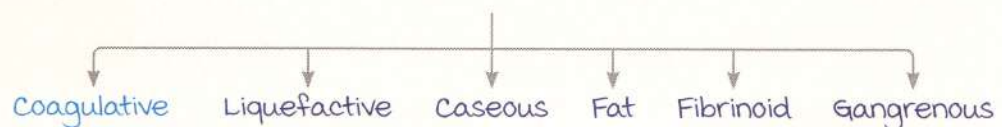
Kidney biopsy : Necrosis on HPE

morphology :

On HPE :

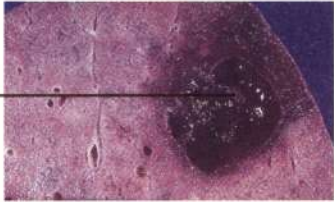
1. Densely eosinophilic cells : D/t loss of cytoplasmic RNA.
2. more glassy/shiny appearance : D/t loss of glycogen.
3. moth-eaten appearance : D/t digestion of organelles by lysosomes.

Types :



Coagulative 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	• Infarct of all solid organs except brain : - Heart (m/c affected) - Liver - Kidney - 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.

Examples :

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



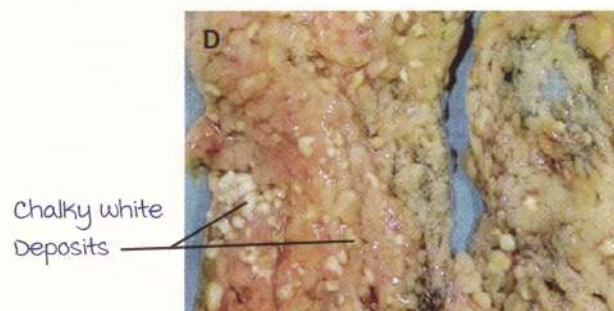
Gross specimen of lung

Fat necrosis :

Types	Examples
Traumatic	Breast
Enzymatic	• Omentum • Pancreas • mesentery

D/D : Breast cancer.

morphology : Chalky white deposits.



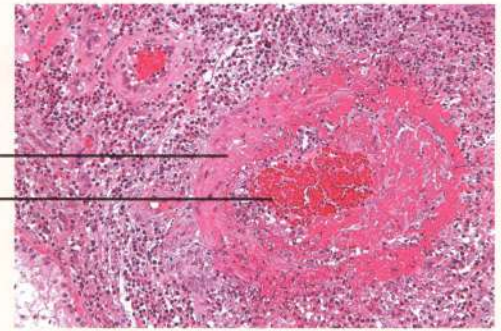
Gross specimen of intestine

----- Active space ----- Fibrinoid necrosis :

- morphology : Fibrin like (Pink coloured).
- Pathology : Type II, III hypersensitivity reactions (HSN).
- D/t immune complex deposition.
- Examples :
 - **Aschoff nodules** : Pathognomonic of rheumatic heart disease.
 - Polyarteritis Nodosa (PAN) : Type III 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.

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).