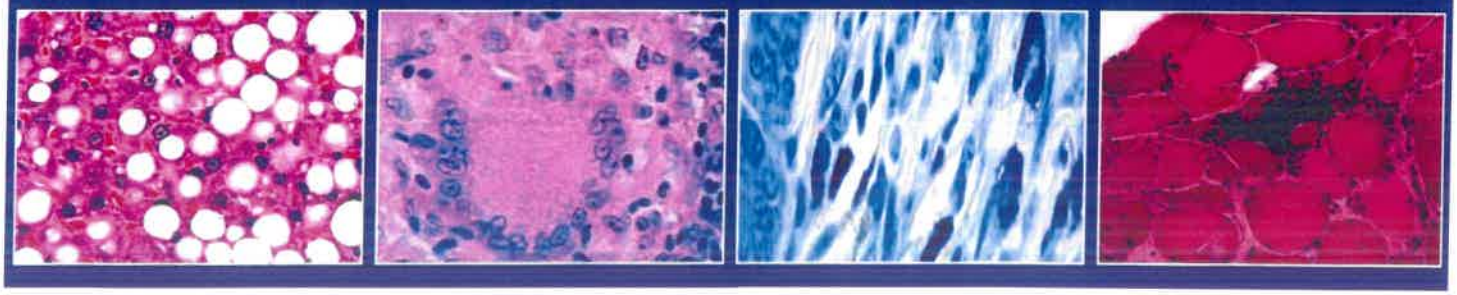
Cerebellum
Get the balance right

Cerebellum Pathology

For the Students
By the Teachers



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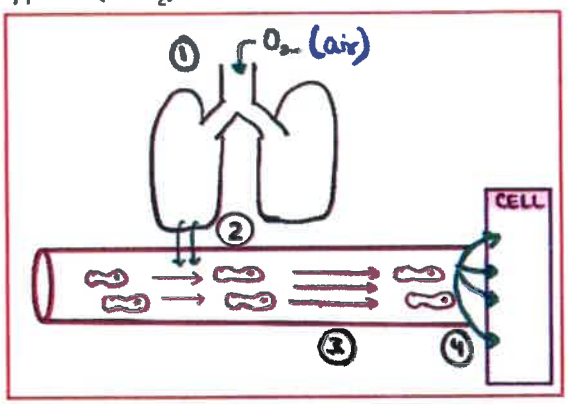
Section 1
Cell Injury

1.1 Chapter

CONCEPTS OF CELL INJURY & REVERSIBLE CELL INJURY

Most common cause of cell injury at the level of cell → Hypoxia ($\downarrow\downarrow O_2$)

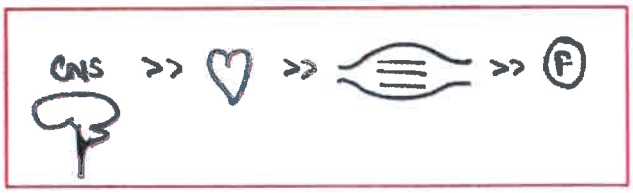


Types of Hypoxia

1.	Hypoxic hypoxia	High altitudes, COPD
2.	Anaemic hypoxia	Anaemia, CO poisoning
3.	Stagnant hypoxia	Ischemia (MC cause), Arterial obstruction >> Venous obstruction
4.	Histotoxic hypoxia	Cyanide poisoning

Sensitivity of different cell for O_2 availability -

CNS (Neurons) >> Cardiac Cells >> Skeletal Muscle fibres >> Fibroblast



Extremely sensitive areas

- All territories of brain
- Subendocardial tissue
- Watershed areas in intestine (Griffith point, splenic flexure etc.)

REVERSIBLE CELL INJURY

- ↓O2 - Mitochondrial activity ↓↓ - Cellular manifestations occur
- 1st organelle affected in reversible cell injury: Mitochondria

A) Cell membrane:

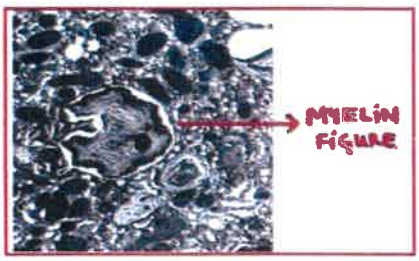
- ATP↓ - Na+ accumulation (as Na+-K+ Pump activity ↓) - ↑water (Hydropic Changes).
- Hydropic change (Cell swelling) is the 1st microscopic change.
- Outpouching occurs - Membrane blebs Formation.
- Fatty changes due to accumulation of Triglycerides in Heart & Liver.

B) Endoplasmic reticulum:

- Due to ↓ ATPs in Cell - ↓ RER activity → ↓ Protein synthesis
- ATP degradation results in ↓ activity of SER - ↑↑ misfolded protein accumulation.

C) Nuclear changes:

- Due to accumulation of Lactic acid & Pyruvic acid - Clumping of chromatin.
- Due to excess H2O in cells, a part of Membrane from cell organelle or cell membrane curling upon itself → Appear as spiral structure known as Myelin Figures.



1.2 Chapter

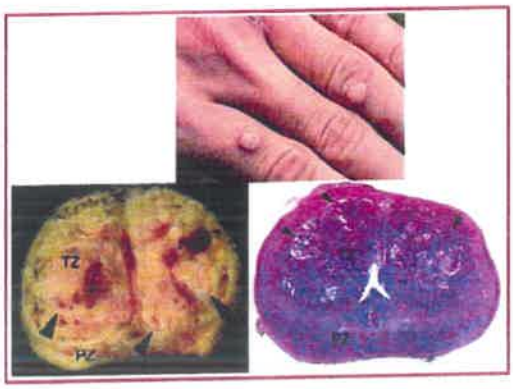
CELLULAR ADAPTATION

1. Hypertrophy
   - Hyper – excessive, trophy – growth
   - Seen in Permanent cells (Muscle cells, Cardiac cells & Neurons)
   - Increase size of cells leads to increase function of cells
   - increased synthesis of structural protein
   - Both physiological & pathological → benign condition.

Physiological	Pathological
Pregnancy, Puberty or Powerlifting	Cardiac hypertrophy due to HTN or Valvular disease

2. Hyperplasia
   - Increase in number of cells

Physiological	Pathological
Uterus & Breast – pregnancy	Endometrial hyperplasia (Can progress to Cancer)
BM: hemolytic anaemia (↑ erythropoetin)	Prostatic hyperplasia
In case of Liver Donation	HPV (warts etc.)



3. Atrophy
   - Absence of growth
   - Associated with decrease size and decrease function
   - Reversible change, but can increase chances of cancer.
   - 2 pathways responsible for it: Ubiquitin Pathway (via Proteasomes) and Autophagy (Defense mechanism)

Physiological	Pathological
Uterus (Post-parturition)	Disuse atrophy
Fetal development	Denervation atrophy (E.g. Polio)
	Reduced nutrition (Cachexia)
	Ischemic atrophy (E.g. Alzeimer's disease)
	Pressure atrophy (E.g. Kidney stones)

4. Metaplasia
   - Change in nature of cells in presence of stress factor.
   - On stress, change in nature stem cells → metaplasia
   - Benign & reversible in nature
   - Can progress to cancer if not treated or if stress is persistent.

Examples

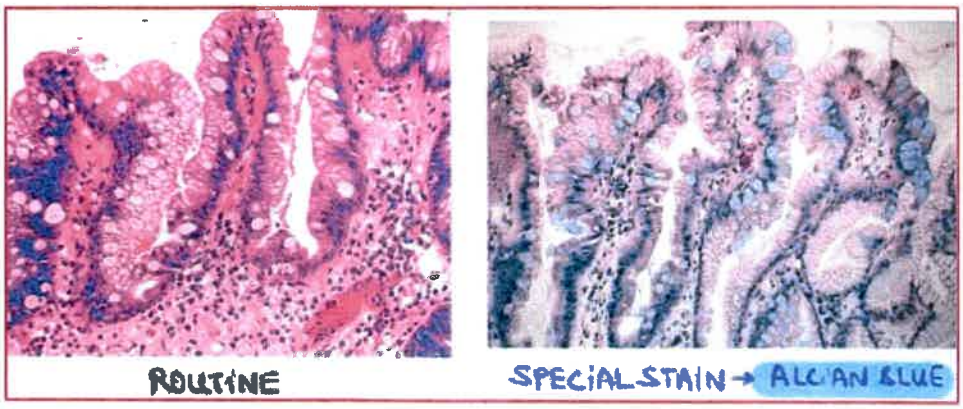
A. Epithelial metaplasia

1. In lungs smoking leads to squamous metaplasia (commonest example).
   - Ciliated columnar ↔ squamous epithelium

- If change persist - squamous cell carcinoma of lungs

2. In the stomach, GERD causes intestinal columnar metaplasia of esophagus (Barrett esophagus) i.e. intestinal columnar cells replace the normal stratified squamous cells of lower esophagus.

[NOTE - Barrett esophagus - Goblet cells have mucin which is identified by Alcian blue stain



3. Urinary bladder: Normal transitional epithelium converted into squamous cells because of Schistosoma infection.
4. Vitamin A deficiency → Squamous epithelium converted to Keratinised Squamous epithelium.

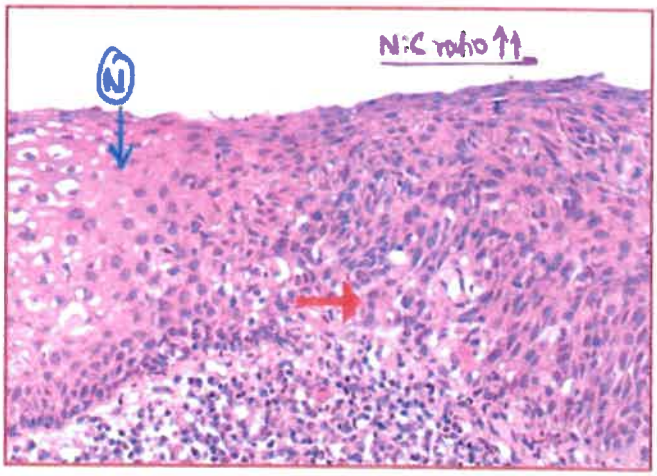
B. Connective tissue metaplasia

Myositis ossificans - after trauma due to haemorrhage the muscle is replaced by bone like tissue.

5. Dysplasia

- Disordered cell growth.
- High chances of Cancer development.
- Due to excessive cell growth → Increased Mitotic figures.

E.g. - HPV infection in cervical epithelium → Mitosis occur throughout the epithelial thickness with altered N:C ratio.



Cell production defects:

- Aplasia - no production of cells. E.g. Unilateral renal agenesis.
- Hypoplasia - Decreased production of cells. E.g. Turner syndrome (Streak gonads).

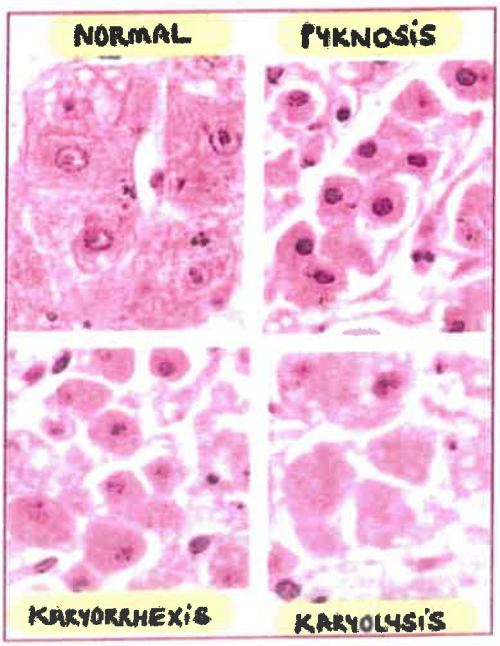
1.3 Chapter

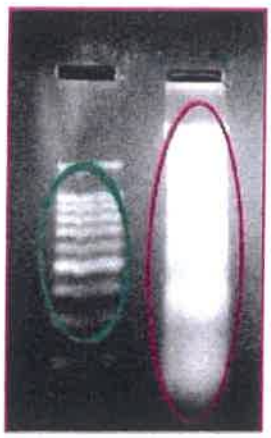
IRREVERSIBLE CELL INJURY

Persistent hypoxia - decrease mitochondrial function → ↓↓↓ ATP leads to ↑↑ Ca^{2+} inside cell.

- Increase calcium causes

1. Mitochondria dysfunction:
   - Mitochondrial/ amorphous densities
   - It leads to further decrease in concentration of ATPs and the cycle continues.
2. Enzymes activation:
   - Lysosomal enzymes → Autolysis (cell death)
   - Phospholipase (Cell membrane damage)
   - Nucleases → Nuclear changes occur:
     1. Nucleic acid condensation - Pyknosis (Ink-dot nucleus)
     2. Nucleic acid material fragment - Karyorrhexis
     3. Complete breakdown of nuclear material - karyolysis (Nucleus disappear)





Smear Pattern

Clinical use

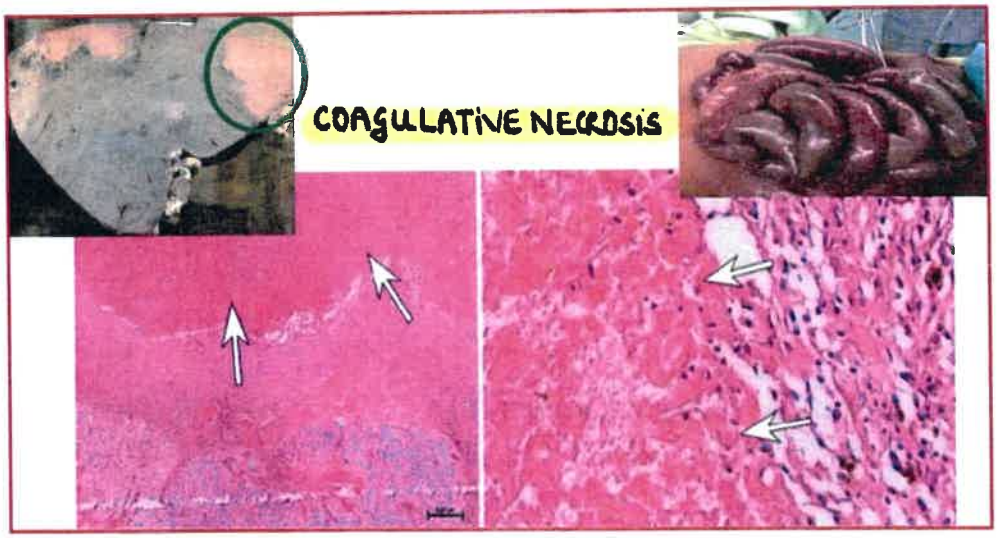
- Reversible cell injury in cardiac tissue is angina
- Irreversible cell injury in cardiac tissue is Myocardial infarction; associated with increased troponins in blood (Use to diagnose Myocardial Infarction)

NECROSIS

- Morphological changes in a tissue after cell death occurs.

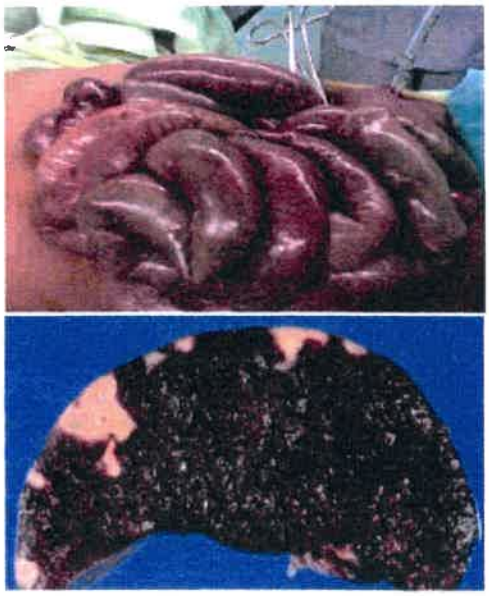
Subtypes of necrosis

1. Coagulative necrosis:
   - Most common type of necrosis.
   - Most common cause - ischemia
   - Seen in all organs of the body except CNS.
   - Neutrophilic infiltration seen in coagulative necrosis.
   - TOMBSTONE APPEARANCE present.
   - Zenker's degeneration → seen in patients of Typhoid.



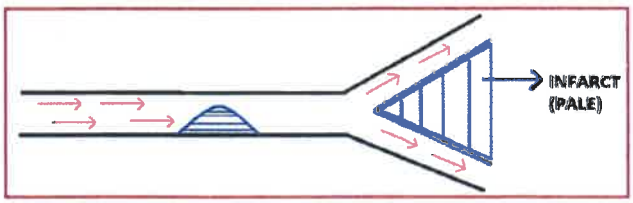
Features seen -

- Increased Eosinophilia
- "Moth eaten" cytoplasm
- Glassy appearance
- Nucleus disappear



Infarct:

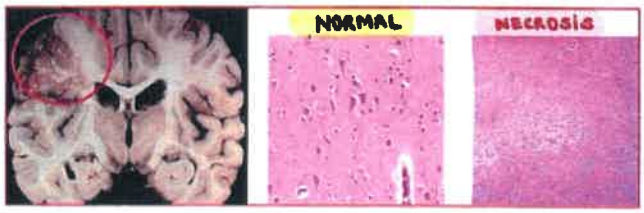
- Localised area formed due to ischemia, usually triangular in shape.
- Apex of infarct is towards the direction of sites of obstructions.



Red infarct	White infarct
Found in organs with loose connective tissues.	Found in an organ with end arterial blood supply.
Found in organs with dual blood supply like lungs or liver.	Particularly in solid organs. E.g. Heart, kidney
Venous occlusion	Arterial occlusion
Dual blood supply	Single blood supply (Solid organs)
Reperfusion injury	No reperfusion

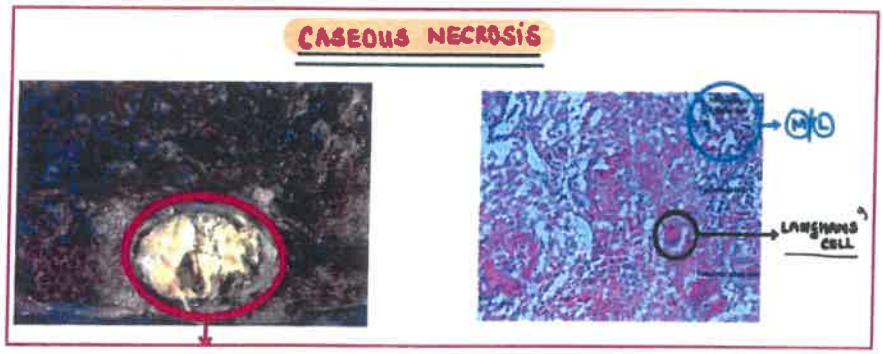
2. Liquefactive necrosis (aka Colliquative necrosis)

Hydrolytic enzyme activation leads to damage to tissue structure. Seen with CNS ischemia and pyogenic infections (eg Staph aureus infection)



3. Caseous necrosis:

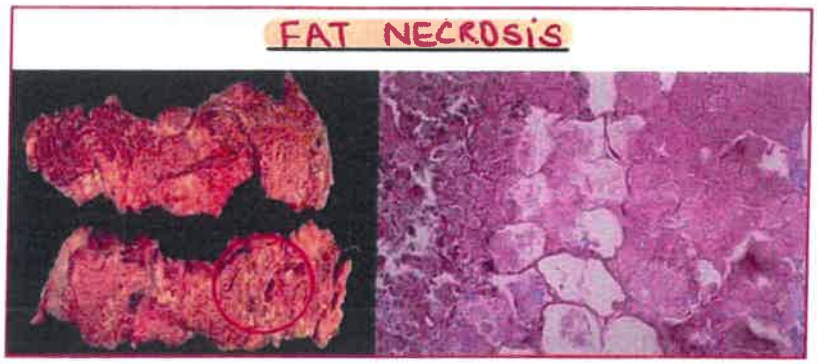
- It is like cheese-like necrotic material.
- Combination of Coagulative necrosis + Liquefactive necrosis, but coagulative necrosis is the most predominant contributor.
- Found in Tuberculosis (due to Mycolic acid), fungal infection like (histoplasmosis, coccidioidomycosis = valley fever) & syphilis.



- Granulomatous reaction is present.
- Macrophages (form Granuloma) & lymphocytes infiltration seen.
- Langerhans giant cells are associated with tubercular focus.

4. Fat necrosis:

- Found in organs with excess fats (Non-enzymatic) or with increased concentration of lipases (Enzymatic).
- Found in injury to breast tissue or injury to omentum tissue and pancreatitis.



Acute pancreatitis

- Gallstones or alcohol → Lipase activation → lipids broken down into fatty acid.
- With Ca^{2+}, Fat can form Chalk-like deposits.
- Fatty acid combines with Ca^{2+} → Serum Ca^{2+} level drops & it is an important prognostic factor to know the severity of pancreatitis.

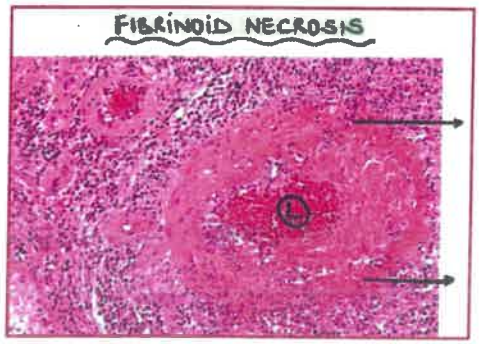
In Pancreatitis: 2 types of necrosis

1) Pancreas - Liquefactive necrosis.

2) Peri pancreatic fat - Fat necrosis.

5. Fibrinoid Necrosis:

Endothelial cell injury leads to immune complex formation, damage to endothelial cells and deposition of plasma protein in the vessels wall. Seen in



- Malignant hypertension
- Aschoff body in Rheumatic heart disease.
- Preeclampsia in pregnant females.
- Immune complex disorder (or Type 3 hypersensitivity reaction)

6. Gangrene

Dry gangrene	Wet gangrene	Gas gangrene
Ischemia (↓↓ blood supply)	Ischemia + secondary infection	Sub type of wet gangrene
Coagulative necrosis	Liquefactive necrosis	Seen with Clostridium welchii (Clostridium perfringens)

1.4 Chapter

APOPTOSIS

- Caspase dependent programmed cell growth.
- Caspase → Cysteine containing protease enzyme which break down the targeted protein at the site of aspartic acid.
- It is controlled by genes and it affects a single or a small group of cells.

Pro apoptotic genes (BH1-3)	Anti-apoptotic genes	Apoptosis initiators or Sensors
BAK Gene	BCL-2 Gene (Most Important)	BIM Gene
BAX Gene	BCL XL Gene	BAD Gene
p53 Gene	MCL1 Gene	PUMA Gene
Glucocorticoids	Sex (Love) Steroids	NOXA Gene

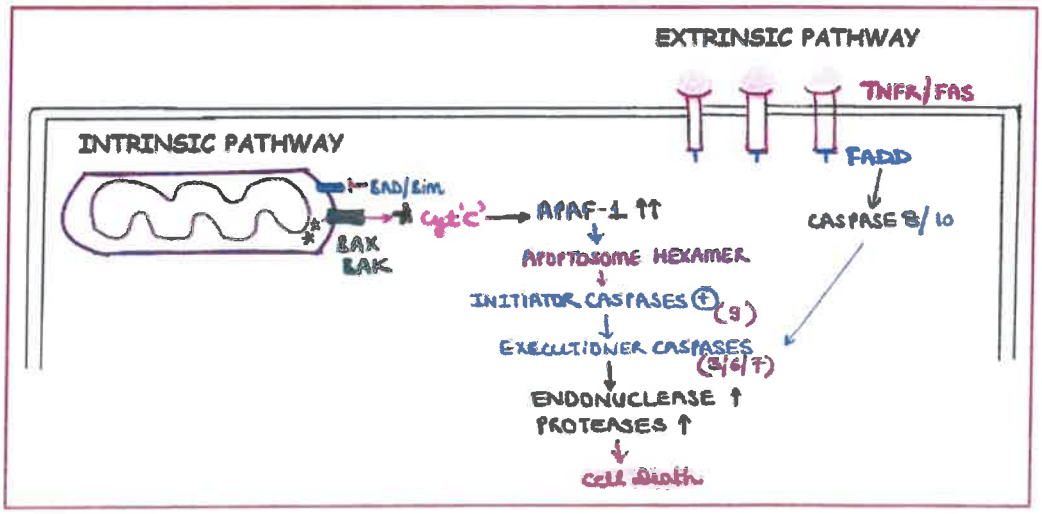
- BCL-2 → act as Gatekeeper of mitochondria and prevent outward movement of cyt-C, Underactivity of BCL-2 and overactivity of BAX & BAX causes Cyt-c leakage leading to apoptosis.

Physiological apoptosis

- Embryogenesis
- Hormones dependent Involution like Breast tissue and Endometrial cells.
- Removal of tail cells present in developing foetuses.
- End of Immune response
- Elimination of Self reactive cells
- Separation of fingers due to death of cells present between fingers, if apoptosis fails to occur fingers will not separate resulting in a condition known as syndactyly.

Pathological apoptosis

- DNA damage
- Viral infection of hepatitis - councilman body
- Accumulation of misfolded proteins - Alzheimer's, Parkinson disease
- Duct obstruction → Atrophy



APAF - Apoptosis activating factor

TNFR - Tumour Necrosis Factor Receptor

FADD - FAS Associated Death Domain

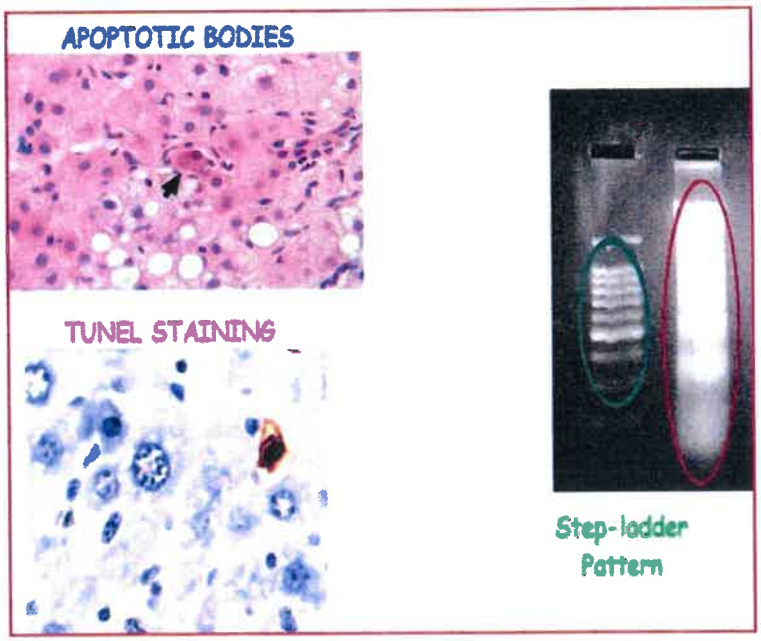
- CTL (Cytotoxic T-Lymphocytes) [CD8 cells] → on activation, release Perforin/ Granzyme and activate Caspases.
- FLIP protein - inhibits the activation of Caspase 8 → Procaspase 8 is not activated to Caspase 8.
- Neurons have Apoptosis Initiating factor instead of APAF, which directly activates Caspases.

Clinical Importance

- BCL 2 overexpression - B Cell Lymphoma
- P53 underactivity - Li Fraumeni Syndrome
- Fas - FasL defect → ALP (Autoimmune Lympho-Proliferative) syndrome with features

Salient features of apoptosis

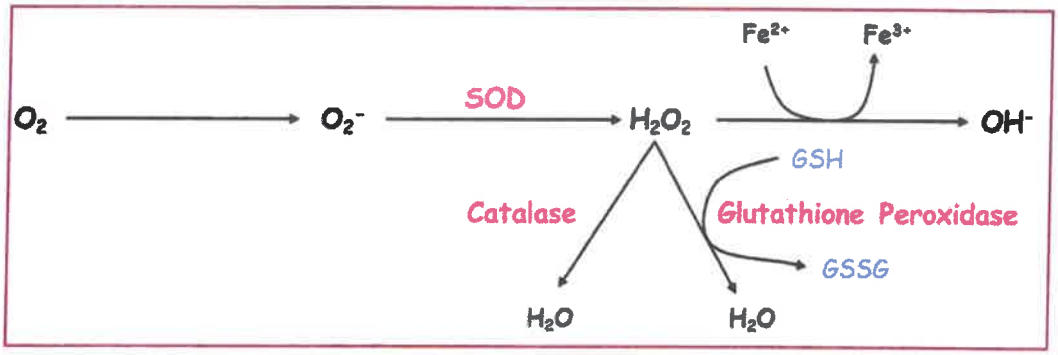
- Cell size decrease
- Chromatin condensation (HALLMARK)
- Inflammation ABSENT
- Gel electrophoresis → Step Ladder Pattern
- TUNEL technique/Staining - attach specifically to the 3' end.
- Efferocytosis → Rapid Phagocytosis via Phosphatidylserine, C1q and Thrombospondin.
- Stains - Annexin V, DAPi



1.5 Chapter

FREE RADICAL INJURY

- Free radical have an unpaired electron → Lipid peroxidation (Autocatalytic reaction)
- Free radical → Attack Cell membrane, Nucleic acid and denaturation of Proteins



- Lipofuscin - golden brown color and indicate Free Radical Injury.
- SOD mutation - associated with increased risk of ALS (Amyotrophic Lateral Sclerosis).

Examples of Free Radicals Injury

- Radiation injury: Ionizing radiation falls on water and releases hydroxyl (OH-) radical
- Oxidative stress: Involved in gradual aging, cancer, and inflammation.
- Reperfusion injury
- Transitional metals in excess (Iron in hemochromatosis, Copper in Wilson's disease)
- Respiratory burst - for the killing of pathogens.
- Chemicals:
- 1. Carbon Tetrachloride used in dry cleaning factories (CCl_4) → upon metabolism, it forms CCl_3^- → causes Centrilobular Necrosis known as Fatty Change.
- 2. Paracetamol poisoning causes Liver damage → N-acetyl Cysteine use as an antidote which replenishes GSH (reduced Glutathione) stores and neutralizes free radicals.

ANTI-OXIDANTS

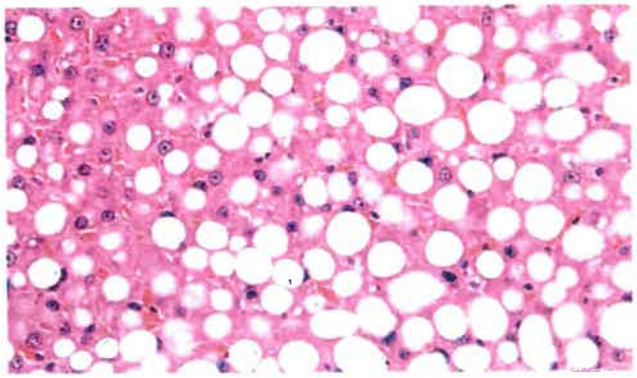
- Enzymes - Superoxide Dismutase, catalase & glutathione peroxidase.
- Vitamins - Vit A, Vit C, Vit E. (Vit C- strongest, Vit E - fat soluble)
- Metals binding proteins like ceruloplasmin and transferrin

Note - High GSSG:GSH ratio is an indicator of high oxidative stress in a cell.

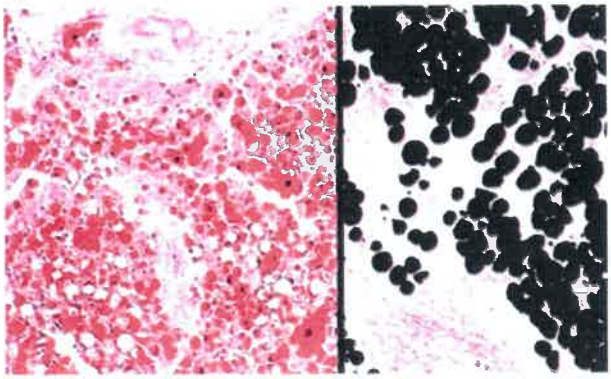
1.6 Chapter

INTRACELLULAR ACCUMULATIONS

1. Lipid Accumulation
   A. Fatty changes/Steatosis
      - Predominant organ - Liver
      - 2 types -
         I. Macrovesicular → Nucleus pushed to the periphery.
         II. Microvesicular → Nucleus not displaced.



- Seen in cases of Diabetes mellitus, obesity, altered lipid metabolism etc.
- Frozen Section - Advantage → No loss of Fat during tissue processing.
- Machine use → Cryostat
- Stain use - Oil Red 'O' (Most commonly used - Red stain) & Sudan black 'B' (Black stain).

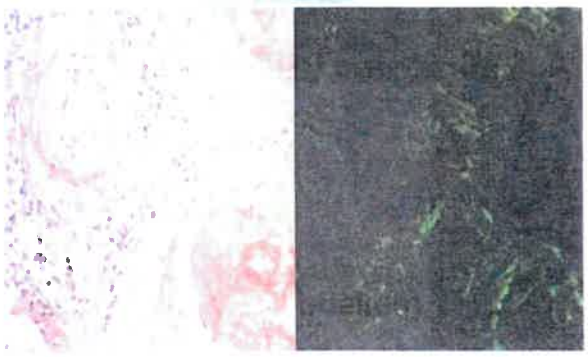


B. Cholesterol Deposition
   - Xanthelasma - deposition of cholesterol in and around the eye (in subcutaneous tissue)
   - Atherosclerosis - Deposition over vessel wall.
   - Niemann Pick's disease Type 'C' - Deposition inside tissue.
   - Cholesterolosis - Deposition of cholesterol in lamina propria of gallbladder.

* Niemann Pick's Disease
* Cholesterolosis

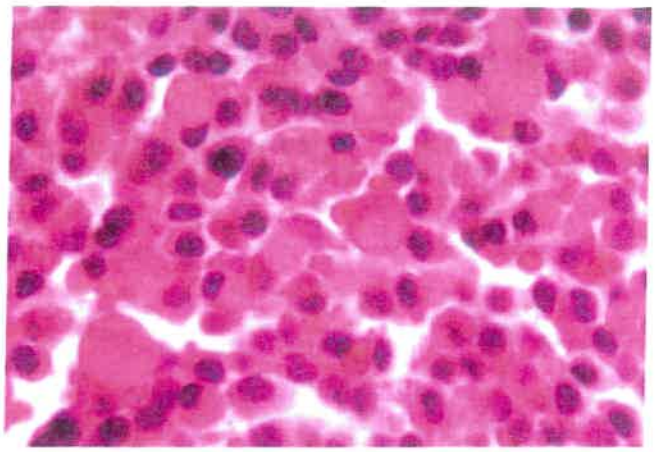
2. Proteins accumulation
   A. Amyloid
      - Stain - Congo Red → Pink/Red appearance
      - Under Plane Polarised Light - Apple Green Birefringence.

PROTEINS



B. Russel bodies

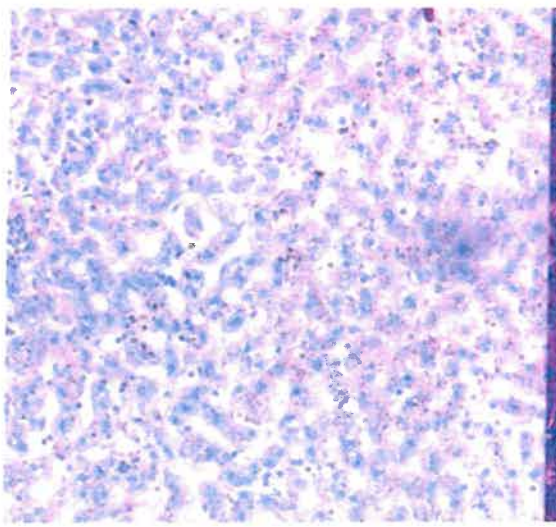
- Overactive cell → Increase Endoplasmic Reticulum activity → Dilatation of Endoplasmic Reticulum



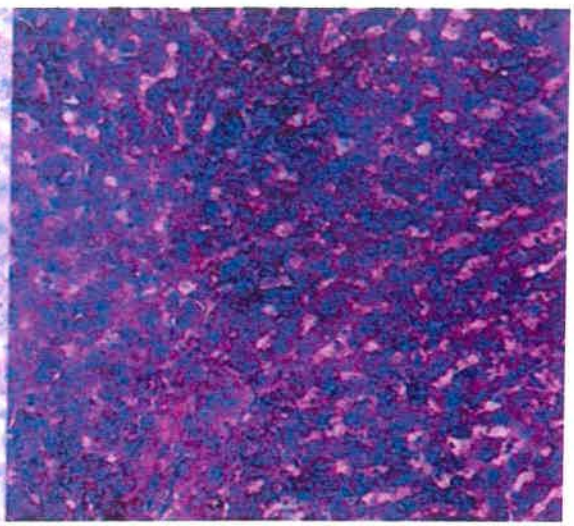
C. Intermediate filaments

3. Glycogen Accumulation

- It washed off with water during tissue processing.
- Absolute alcohol → use as a Fixative for Glycogen for staining.
- Stain → PAS (Per Acid Schiff) reagent.
- To differentiate - Use Diastase treated and not treated sections along with PAS staining.



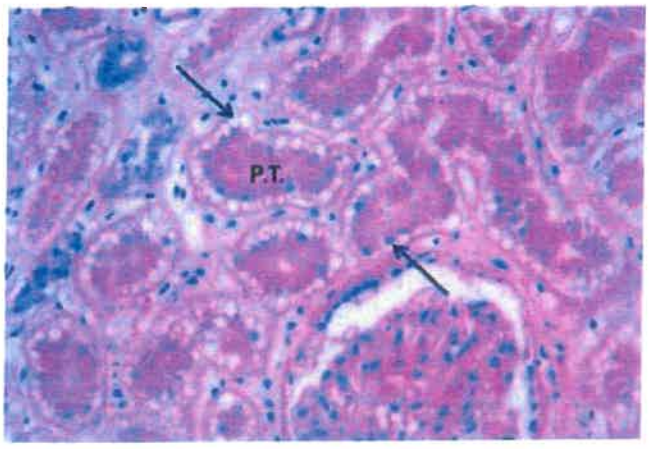
Diastase treated + PAS staining



PAS staining only

- Conditions in which Glycogen accumulations present - Von-Gierke Disease & Diabetes mellitus (Armanni Ebstein cells)

ARMANNI EBSTEIN CELLS

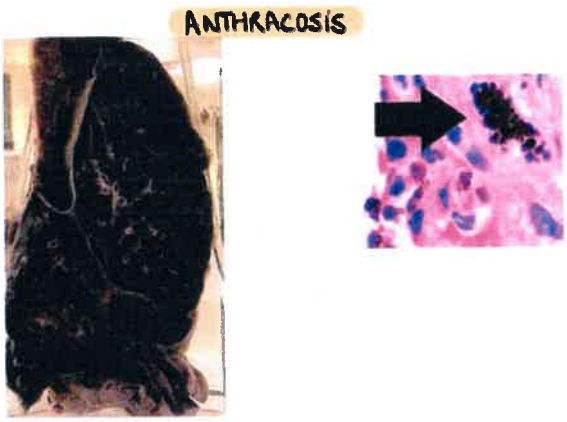


4. Pigmentations

A. Exogenous Pigments

A.1. Anthracosis

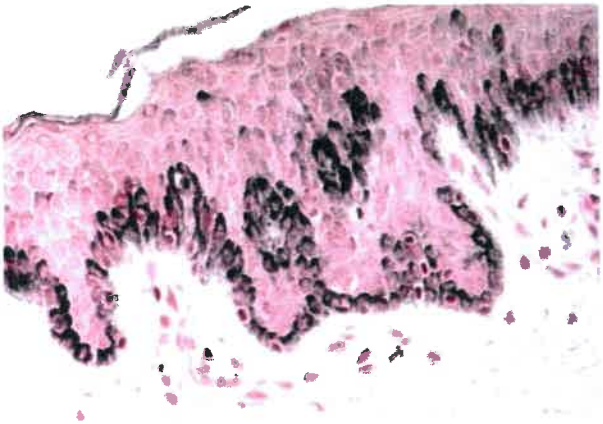
- Deposition of carbon in lung tissue; more in case of smokers
- In coal miners → called Coal Workers Pneumoconiosis



A.2. Tattooing - Deposition of pigments/ Chemicals in skin and Dermal macrophages.

B. Endogenous Pigments

B.1. Melanin:



✳ Masoon Fontana Stain

✳ Schmorl's Stain

- Present at dermo-epidermal junction
- Stain via either Masson Fontana or Schmorl's stain.

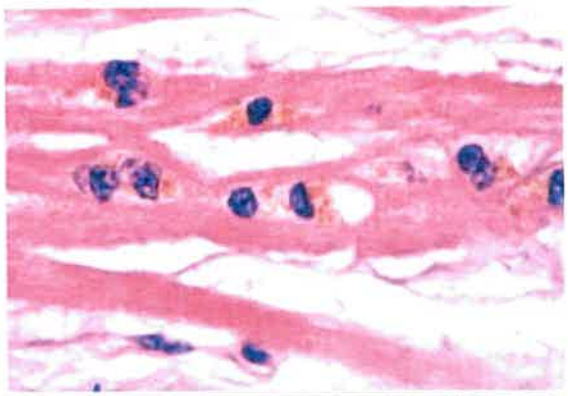
Alkaptonuria - Black pigmentation due to melanin.

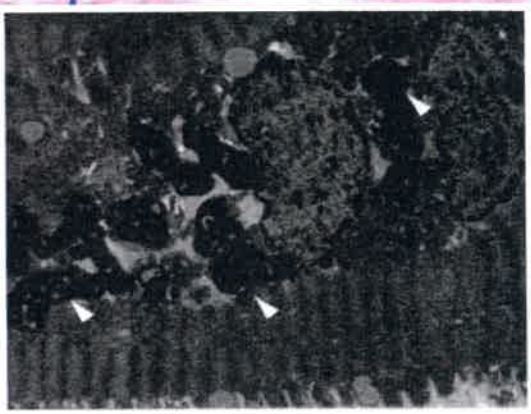
Melanosis coli - due to Chronic use of Laxatives (senna)

B.2. Lipofuscin:

- Lipid derived pigment → due to Lipid peroxidation.
- Indicator of free radical injury: lipofuscin
- Lipochrome: golden brown colour, peri nuclear in location & deposited in lysosomes.
- Seen in ageing / Protein Energy Malnutrition/ Cancer Cachexia.
- Maximum lipofuscin depositions seen in heart & liver.

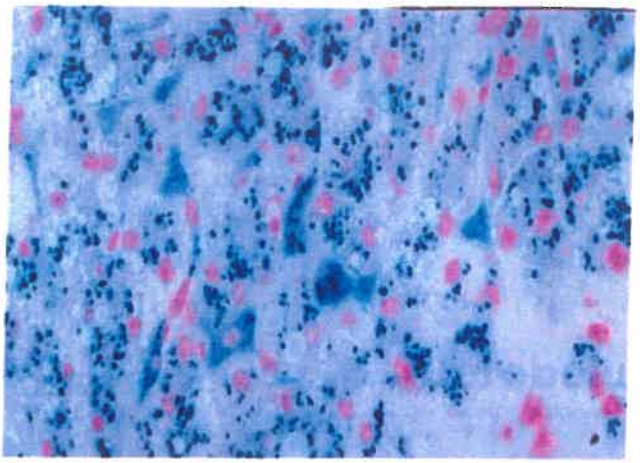
- Ageing is due to:
  1. DNA damage but defective DNA helicase → Premature ageing called WERNER syndrome.
  2. Decreased Telomere length in 60-70 cell cycles (Hay flick's Limit).
  3. Free radical injury (most important) → decrease by decrease calorie intake by 25-30% and increase Sirtuins intake (Red wine)





B.3. Hemosiderin (Iron deposition):

- Due to Ferritin (Increase hemosiderin formation)
- Staining → Prussian blue stain (Perl's reaction), Purple/Dark blue colour.
- E.g. of Iron overload - Hemochromatosis, repeated Blood Transfusion (like in thalassemia), chronic hemolytic anaemia.



B.4. Calcification (Calcium deposition):

Dystrophic calcification	Metastatic calcification
• Dead / degenerated tissue	• Normal / living tissue affected
• Serum calcium normal	• Serum calcium increased (Hypercalcemia)
• Usually localised	• Usually diffuse (MC organelle is Mitochondria)
Association - RATTO • Rheumatic Heart disease • Atherosclerosis • Tuberculosis • Tumours • MOnckeberg's Sclerosis • Infections like CMV and schistosomiasis	Association - (Hypercalcemia, Hyperphosphatemia, ↑ Vit. D activity) • PTH - Parathyroid Adenoma (↑ Ca^{2+}) • PTHrp releasing tumour (↑ Ca^{2+}) • Chronic Kidney Disease (↑ PO_4^-) • Primary hypoparathyroidism (↑ PO_4^-) • Sarcoidosis, William's Syndrome (↑ Vit. D) • Paget's Disease, Multiple Myeloma etc. • Milk-Alkali syndrome, Aluminium toxicity

Tumours having Dystrophic calcification (Mnemonic - MOST PG)

M - Meningioma, Mesothelioma

O - Ovary (Serous cystadenoma)

S - Salivary gland tumour

T - Thyroid (Papillary thyroid cancer)

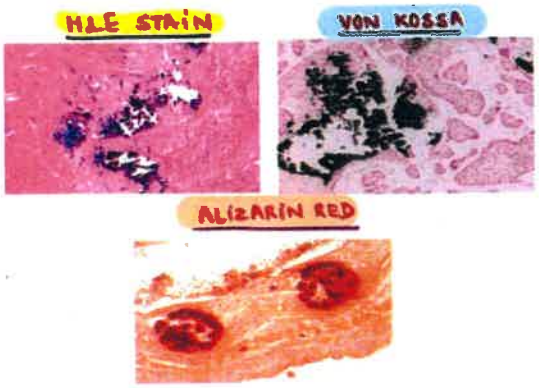
P - Prolactinoma

G - Glucagonoma

Metastatic Calcification:

Tissues with highest risk (Alkaline media)

- Lungs (Most common)
- Kidneys (Deposited more in Basement membrane than Mitochondria)
- Stomach
- Systemic Artery & Pulmonary veins
- Most unlikely tissue - Parathyroid gland
- Tetracycline Labelling Index (due to high affinity with Ca^{+2}) → Bone remodelling time.



Special stain:

- Von Kossa → Black colour
- Alizarin Red → Red colour, stain even a small amount of Ca^{+2} present in the tissue.

Special Bodies:

1. Schaumann bodies - seen in Sarcoidosis
2. Psammoma bodies - Dystrophic calcification, seen in Papillary thyroid cancer, Meningioma, Mesothelioma etc
3. Asbestos Bodies - In Asbestosis