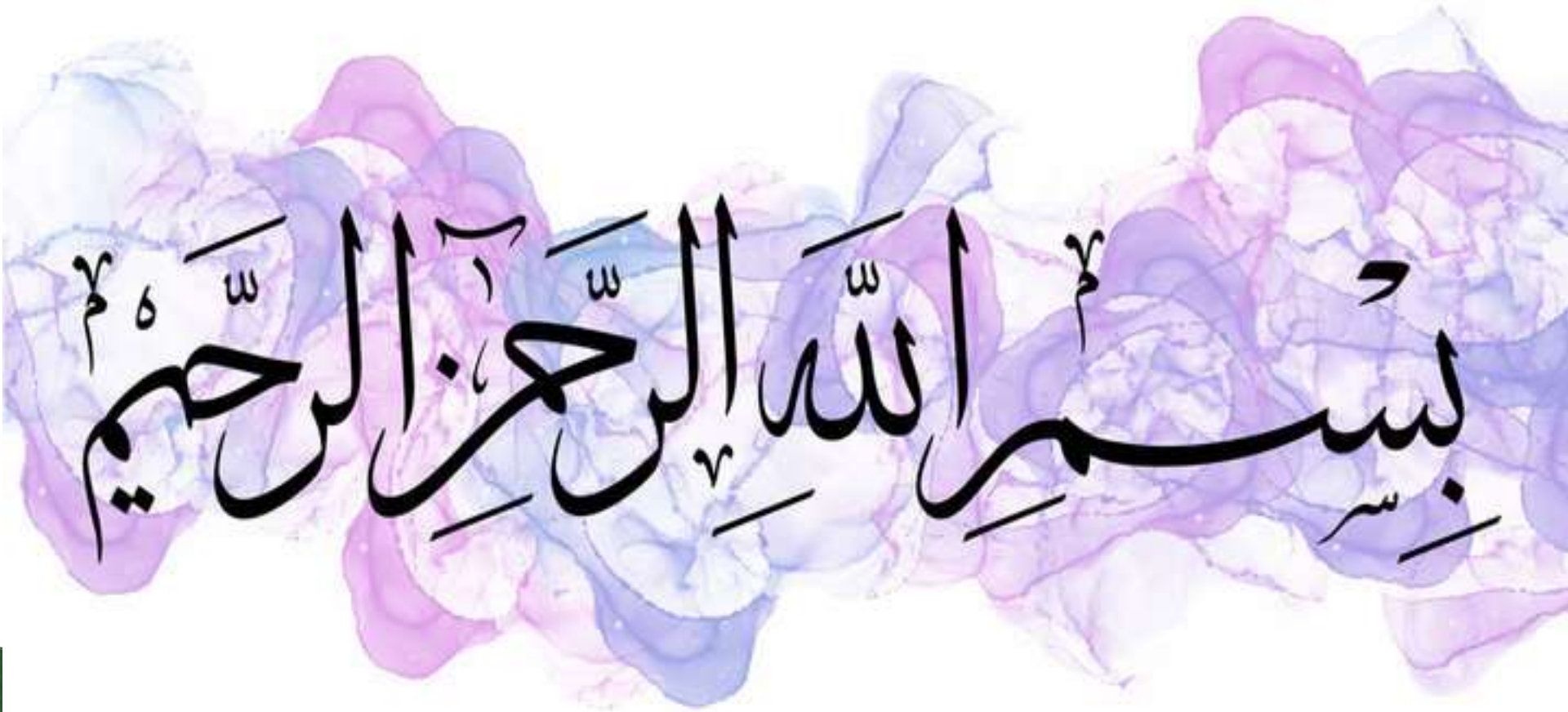
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FOUNDATION MODULE _1

Reversible and Irreversible Cell Injury

LGIS

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Motto

Vision; The Dream/Tomorrow

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures

Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

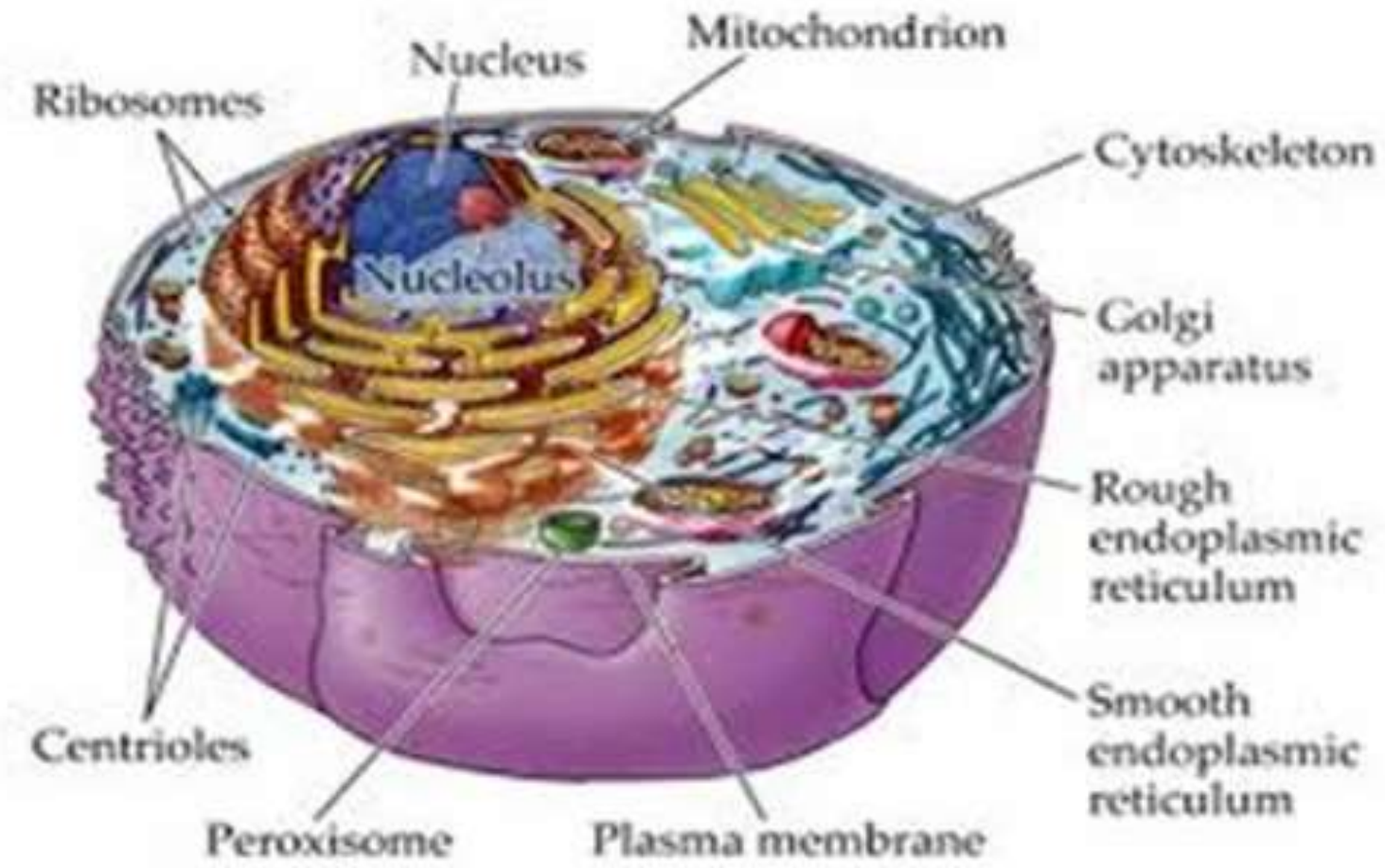
Learning Outcomes

By the end of this session you should be able to:

- Describe mechanism of cell injury
- Explain etiology and pathogenesis of different types of cell injury
- Correlate morphological features of various types of injury with their clinical manifestations

Learning Resources : Robbins & Cotran Pathologic Basis Of Disease 10th Edition

Basic Structure of Cell



CAUSES OF CELL INJURY

Alcohol and Narcotic Drugs

Insecticides and herbicides

Oxygen Deprivation (Hypoxia)

Ischemia: Loss of blood supply to a tissue

Anaemia: Decreased haemoglobin,

Physical Agents

Mechanical trauma.

Extremes of temperature (burns and deep cold)

Chemical Agents and Drugs

Poisons such as Arsenic and Cyanide

Infectious Agents:

Viruses, Bacteria, Fungi, Parasites

Immunologic Reactions:

- Serves as defense against biologic agents Autoimmune diseases,
- Anaphylactic Reactions

Genetic Derangements: Genetic defects may result in pathologic changes as down syndrome

Nutritional Imbalances:

- Protein Calorie Deficiencies
- Vitamin Deficiency

Aging:

Point of No Return

Two phenomena consistently characterize irreversibility :

The inability to **reverse mitochondrial dysfunction** (lack of oxidative phosphorylation and ATP generation) even after resolution of original injury

Profound disturbances in membrane function

Reversible Cell Injury: Morphologic Changes

The two main morphologic correlates of reversible cell injury are:

Cellular Swelling: It is the result of failure of energy dependent ion pumps in the plasma membrane, leading to an inability to maintain ionic and fluid homeostasis.

Fatty Change: It occurs in hypoxic injury and various forms of toxic or metabolic injury.

It is manifested by the appearance of small or large lipid vacuoles in the cytoplasm.

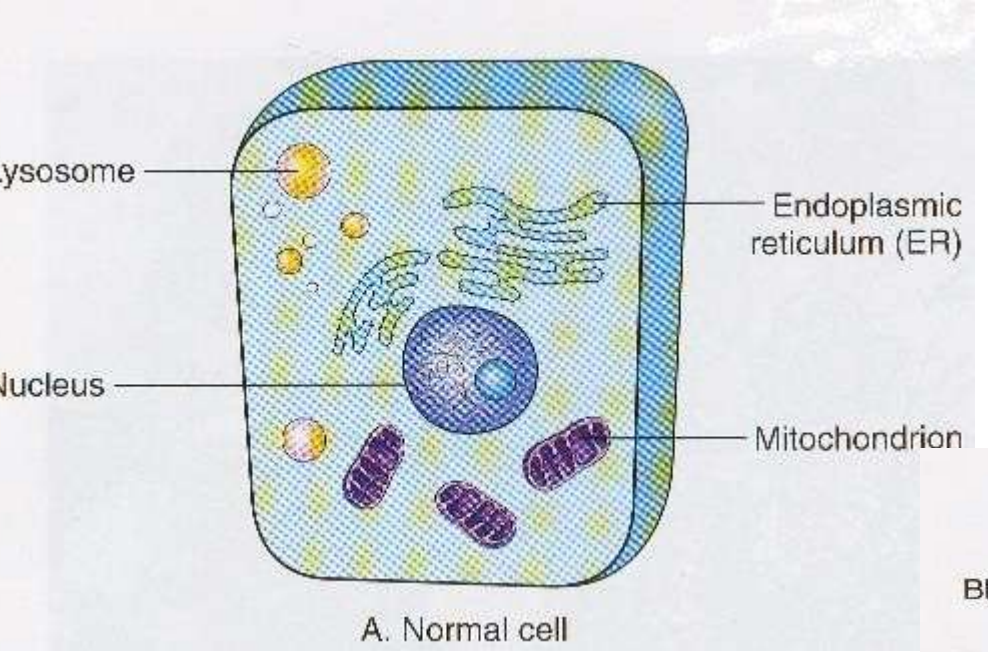
Ultra structural changes of Reversible Cell Injury

CORE SUBJECT

- Blebbing of plasma membrane
  Blunting or distortion of microvilli
  Loosening of intercellular attachments

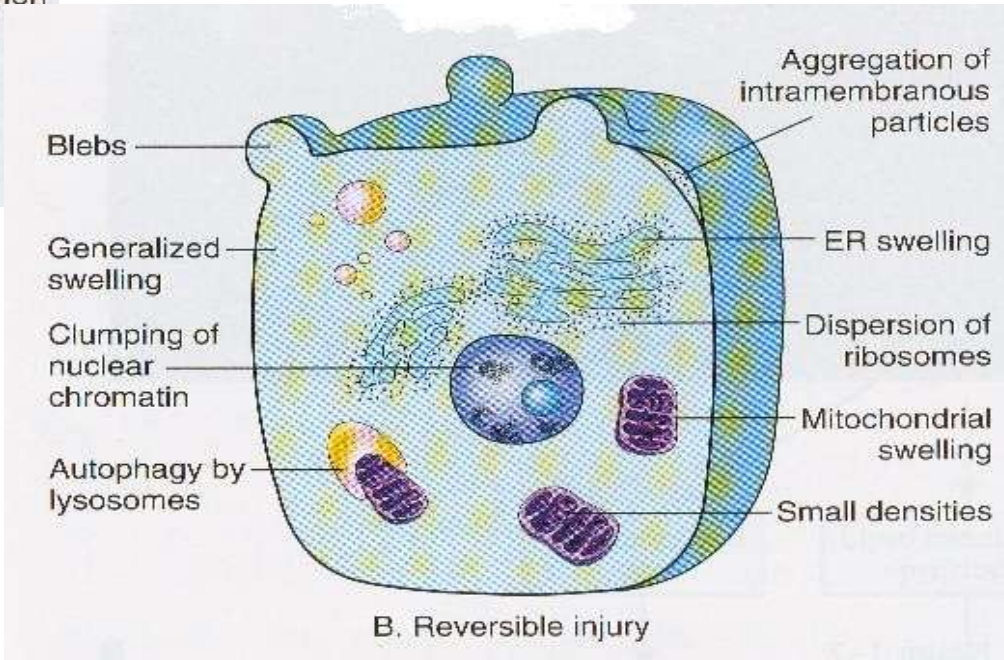
- Swelling and appearance of phospholipid – rich amorphous sdensities in mitochondria
- Dilation of endoplasmic reticulum
- Detachment of ribosomes
- Nuclear alterations with clumping of chromatin

NORMAL CELL



A. Normal cell

REVERSIBLE CELL INJURY



B. Reversible injury

Necrosis

Sum of the morphologic changes that follow cell death in a living tissue or organism'.

Two mechanisms are involved in necrosis:

Enzymatic digestion of cells by catalytic enzymes

(i) Autolysis: Catalytic enzymes derived from the lysosomes of dead cells.

(ii) Heterolysis: Catalytic enzyme derived from lysosomes of immigrant leucocytes.

_Denaturation of Proteins

Types of Necrosis

Several distinct types of necrosis are recognized:

- **Coagulative Necrosis**
- **Liquefactive Necrosis**
- **Caseous Necrosis**
- **Gangrenous Necrosis**
- **Fibrinoid Necrosis**
- **Fat Necrosis**

MorphologicChanges in Necrosis

Changes in Cytoplasm

- Increased Eosinophilia: It is due to:
- Loss of normal basophilia imparted by RNA
- Cell will assume a **glassy homogenous appearance** . Due to digestion of cytoplasmic organelles by enzymes, the **cytoplasm will appear vacuolated** and appear moth- eaten

Calcification of dead cell may occur

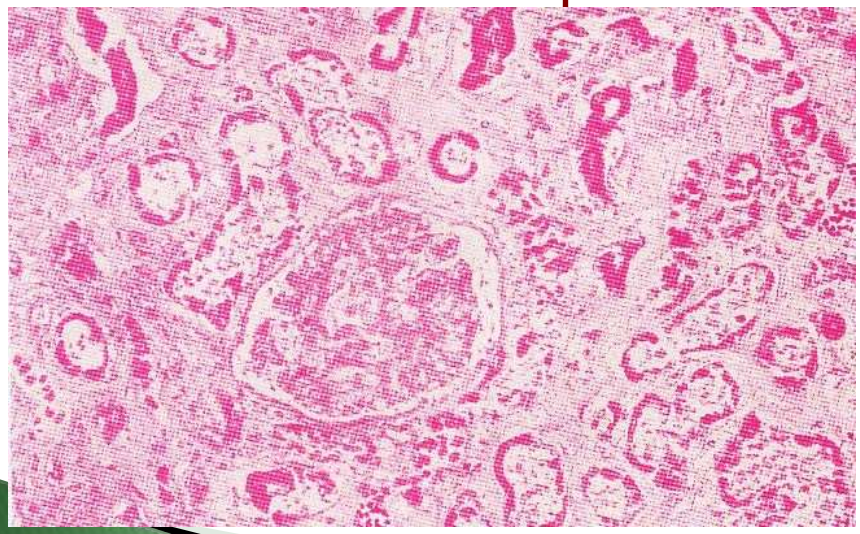
Changes in Nucleus

- Pyknosis: Shrinkage of nucleus
- Karyolysis: Dissolution of nucleus
- Karyorrhexis: Fragmentation of nucleus

Copulative Necrosis

Coagulative Necrosis is the most common type of necrosis. The process of coagulative necrosis, with preservation of the general tissue architecture is characteristic of hypoxic death of cells (due to lack of blood supply) in all tissues except brain

The pathogenesis of coagulative necrosis is denaturation of proteins.



Part of kidney deprived of its blood supply. **caogulative necrosis** Cellular and nuclear detail has been Lost. The ghost outline of a glomerulus can be seen in the centre, with remnants of tubule elsewhere

Liquefactive Necrosis

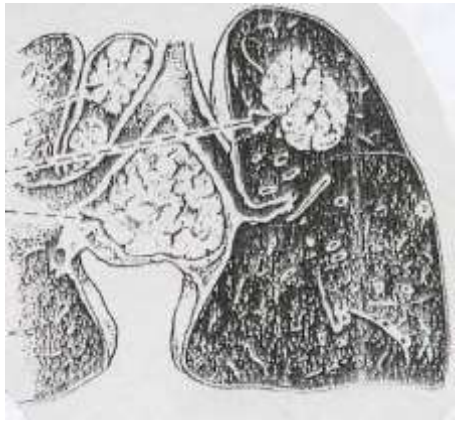
Liquefactive Necrosis is characteristically seen in:

- Hypoxic death of cells within **the central nervous system**
- ,Bacterial or occasionally fungal infections.
- Liquefaction completely digests the dead cells.
- The end result is transformation of the tissue into a liquid viscous mass.
- If the process had been initiated by acute inflammation, the material is frequently creamy yellow because of the presence of dead white cells and is called pus.

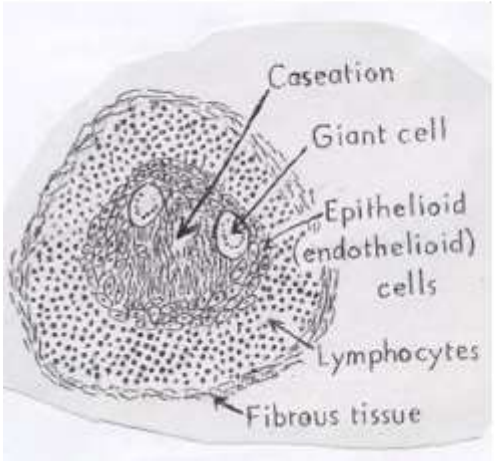
Caseous Necrosis

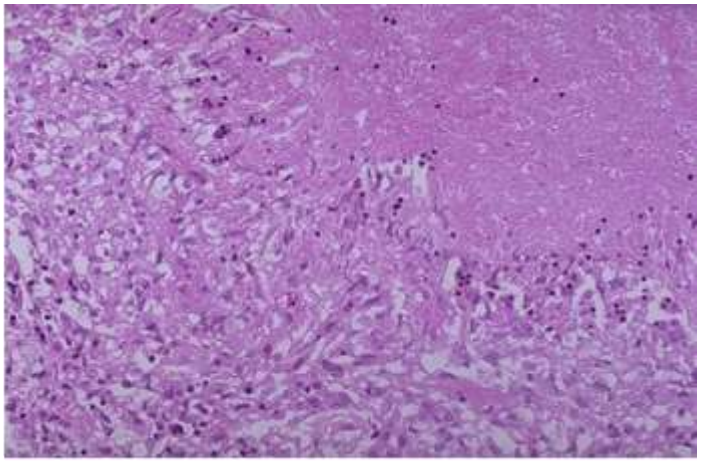
The term caseous is derived from gross appearance of tissue (white and cheesy)

- **Microscopic Appearance**: The necrotic focus appears as amorphous granular debris composed of fragmented, coagulated cells and granular debris enclosed within a inflammatory border known as **Granulomatous Reaction"**



Gross Appearance of Caseous necrosis: Foci of caseous necrosis in Tuberculosis of Lung





Microscopic Appearance of Caseation Necrosis: Characteristic Tubercle showing central necrosis, along with epithelioid cells, multinucleated Giant cells and lymphocytes

Gangrenous Necrosis

- Gangrene is massive necrosis (Caused by acute ischemia or severe bacterial infection) followed by putrefaction

- Gangrene is a special type of necrosis, in which **bacterial infection** is superimposed on **coagulative necrosis** and coagulative necrosis is modified by the liquefactive action of the bacteria

Fat necrosis

Fat Necrosis may be due to:

Direct Trauma to adipose tissue and extracellular liberation of fat. The result may be a palpable mass, particularly at a superficial site such as the breast

Enzymatic lysis of fat due to release of Lipases In Acute Pancreatitis there is release of pancreatic lipase. As a result, fat cells have their stored fat split into fatty acids, which then combine with calcium to precipitate out as white soaps.

Fat Necrosis Pancreas

Cellular injury to the pancreatic acini leads to release of powerful enzymes which damage fat by the production of soaps (combination of calcium salts with fat' ;fat saponification), and these appear grossly as the soft Chalky white areas seen in this cu surface

Fibrinoid Necrosis

Fibrinoid Necrosis is a type of **Connective Tissue Necrosis**

- It is seen particularly in conditions where there is Deposition of Antigen – Antibody Complexes .
- The important examples are Autoimmune Disorders like Systemic Lupus Erythematosus, Rheumatic Fever and Polyartirtis Nodosa.

In these conditions the media and smooth muscles of vessel wall are involved

Differences Between Different Types of Necrosis

COAGULATIVE NECROSIS	LIQUEFACTIVE NECROSIS	CASEOUS NECROSIS	FAT NECROSIS	FIBRINOID NECROSIS
Occurs due to ischemia	Occurs due to ischemia	Occurs due to granuloma-tous disease	Occurs due to trauma or enzymatic fat injury	Due to vascular inflammation
In various tissues	In Brain	In any tissue	In Pancreas and Breast	Around Blood Vessels
Tissue architecture preserved	Architecture destroyed	Cheesy material; Architecture disturbed	Architecture distorted	Architecture not much affected
Involves denaturation of protein & lysosomal enzymes	Denaturation of Proteins & Autolysis	Caseation	Rupture of Fat cells	Accumulation of Fibrinoid material
COAGULATIVE NECROSIS	LIQUEFACTIVE NECROSIS	CASEOUS NECROSIS	FAT NECROSIS	FIBRINOID NECROSS

Apoptosis

- Designed to eliminate unwanted host cells through activation of coordinated, internally programmed series of events
- Affected by a dedicated set of gene products.
- It is a disassembly of cellular components
- to eliminate unwanted cells, during embryogenesis and in various **physiologic processes**.

Stage 1 (Dying Process):

Active metabolic changes in the cell cause cytoplasmic and nuclear condensation and nuclear membrane is intact.

Cell disintegrates into multiple Apoptotic Bodies each surrounded by a part of plasma membrane.

Stage 2 (Elimination Process):

Apoptotic bodies are phagocytosed by surrounding cells ,e.g., liver cells, tumour cells.

This is followed by rapid digestion.

The surrounding cells move together to fill the vacant space leaving virtually no evidence of the process.

Pathogenesis of Apoptosis

Results from action of "caspases" which are activated ,lead to endonuclease digestion of DNA and disintegration of the cell skeleton.

Activation through Death Factor (Fas Ligand): The is by signaling through membrane proteins such as Fas or TNF receptor intracellular death domain.

Release of Cytochrome – C from the Mitochondria:

The second pathway is via the release of Cytochrome – C from mitochondria .

Cytochrome – C binds to Apaf – 1 which then activates caspases.

Apoptosis specific Gene

- Gene that stimulates Apoptosis e.g, *bax – gene*
- APOPTOSIS INHIBITING GENE
  - Gene that blocks apoptosis
  - e.g, bcl - gene

Physiologic and Pathologic Apoptosis conditions

- The programmed destruction of cells during embryogenesis.
- Hormone dependent involution in the adults
- Cell depletion in proliferating cell population
- Cell death in tumours.
- Death of neutrophils during an acute inflammatory response.
- Deletion of B and T lymphocytes after cytokine depletio

Morphologic changes in Apoptosis

MORPHOLOGIC CHANGES IN APOPTOSIS

Cell Shrinkage:

- Cell is smaller in size;
- Cytoplasm is dense; organelles are tightly packed.

Chromatin Condensation:

- Chromatin aggregates peripherally, under the nuclear membrane;nucleusmay break in fragments
- Formation of cytoplasmic blebs and apoptotic bodies.
- Phagocytosis of apoptotic bodies by adjacent healthy cells.

Comparison of cell death by Apoptosis & Necrosis

FEATURE	**APOPTOSIS** **Cell Suicide**	**NECROSIS** **Cell Homicide**
Induction	**May be induced by physiological or pathological stimuli**	**Invariably due to pathological injury**
Extent	**Single cells**	**Cell groups**
Biochemical events	**(I) Energy- dependent fragmentation of DNA by endogenous endonucleases** **(ii) Lysosomes intact**	**(i) Impairment or cessation of ion homeostasis** **(ii) Lysosomes leak lytic enzymes**
Cell membrane integrity	**Maintained**	**Lost**
Morphology	**Cell fragmentation to form apoptotic bodies**	**Cell swelling and lysis**
Inflammatory	**None**	**Usual**

Pharmacological Agents

- **Role of Drugs in Cell Injury**
- Direct toxic effects: e.g., acetaminophen overdose causing liver cell necrosis
- Free Radical Generation
- Certain drugs (e.g., doxorubicin) generate free radicals, leading to oxidative stress and cell damage
- **Drug-Induced Apoptosis**
- Example: Chemotherapeutic agents inducing apoptosis in cancer cells
- Protective Drugs Against Cell Injury
- Antioxidants: Prevent damage caused by free radicals (e.g., Vitamin C, Vitamin E)

AI in diagnosis of Cell Injury

Digital Pathology with AI Algorithms

AI-powered software analyzes histopathological slides for cellular injury.

Example: Identifying necrosis or apoptosis in liver biopsy samples for hepatitis. Eg PathAI

Predictive Toxicology Models

AI tools predict drug-induced liver injury (DILI) using patient data and drug profiles.

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AI in Laboratory Medicine

Automated detection of cellular injury markers in blood or urine tests.

Example: AI-assisted analysis of troponin levels for myocardial injury detection.

Bioethics

- **Informed Consent** Ensures the patient understands the nature of MI, potential risks, and available diagnostic and treatment options.
- **Beneficence** (Acting in the Patient's Best Interest)Prompt diagnosis via ECG, cardiac biomarkers, and imaging reduces complications and improves survival.
- **Non-Maleficence** (Do No Harm)Avoiding unnecessary delays, misdiagnosis, or incorrect treatments minimizes harm.
- **Justice** (Fairness in Healthcare)Equal access to diagnostic tools and timely intervention ensures ethical and equitable patient care.

Cellular and molecular mechanisms of cell damage and cell death in ischemia–reperfusion injury in organ transplantation Molecular Biology Reports

Review
Published: 29 March 2024
Volume 51, article number 473, (2024)

- **Key Mechanisms:and summary of article**
- **Ischemia**: Hypoxia disrupts mitochondrial function, causing edema.
- **Reperfusion**: Excess oxygen produces ROS, leading to oxidative damage and inflammation.
- **Outcomes**:
- **Moderate IRI**: Reversible cell dysfunction.
- **Severe IRI**: Cell death via pathways like apoptosis, necrosis, ferroptosis, and pyroptosis.
- **Clinical Relevance**: Targeting these mechanisms can enhance transplant success

EOLA

- A 45-year- male with chronic alcohol use presents with severe epigastric pain radiating to the back, nausea, and vomiting. Vitals: BP 90/60 mmHg. Labs: Amylase 980 U/L, Lipase 1400 U/L, ALT 210 U/L, Calcium 7.8 mg/dL, BUN 32 mg/dL. CT shows pancreatic edema and peripancreatic fat stranding. **What confirms the diagnosis of acute pancreatitis?**
- A) CT scan findings
  B) Lipase/amylase elevation + typical symptoms
  C) Serum calcium and BUN levels
  D) Right upper quadrant ultrasound
  E) MRCP for biliary obstruction