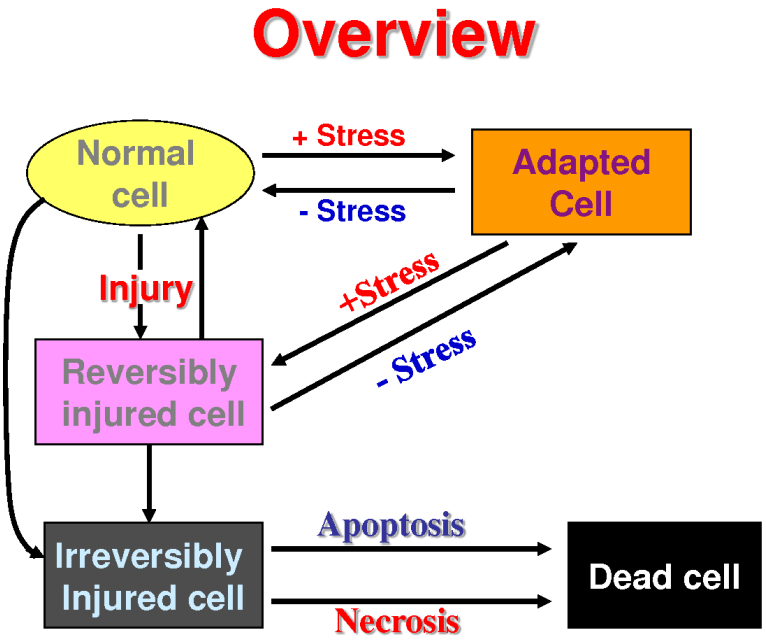
Department of Pathology

GSL 5 Cellular pathology Dr Asawari Sant

Learning outcome : Understand the pathogenesis of cellular injury

Definition and Introduction :

- Cellular injury is defined as a variety of stresses a cell encounters as a result of changes in internal or external environment.
- The cellular response to stress depends on –
    1. Type of cell and tissue involved
    2. Extent and type of cell injury
- Increased functional demand leads to cellular adaptations which revert to normal once stress is removed.
- Moderate stress leads to reversible cell injury, followed by repair and healing.
- Severe stress leads to irreversible cell damage and cell death.



Types of cell injury

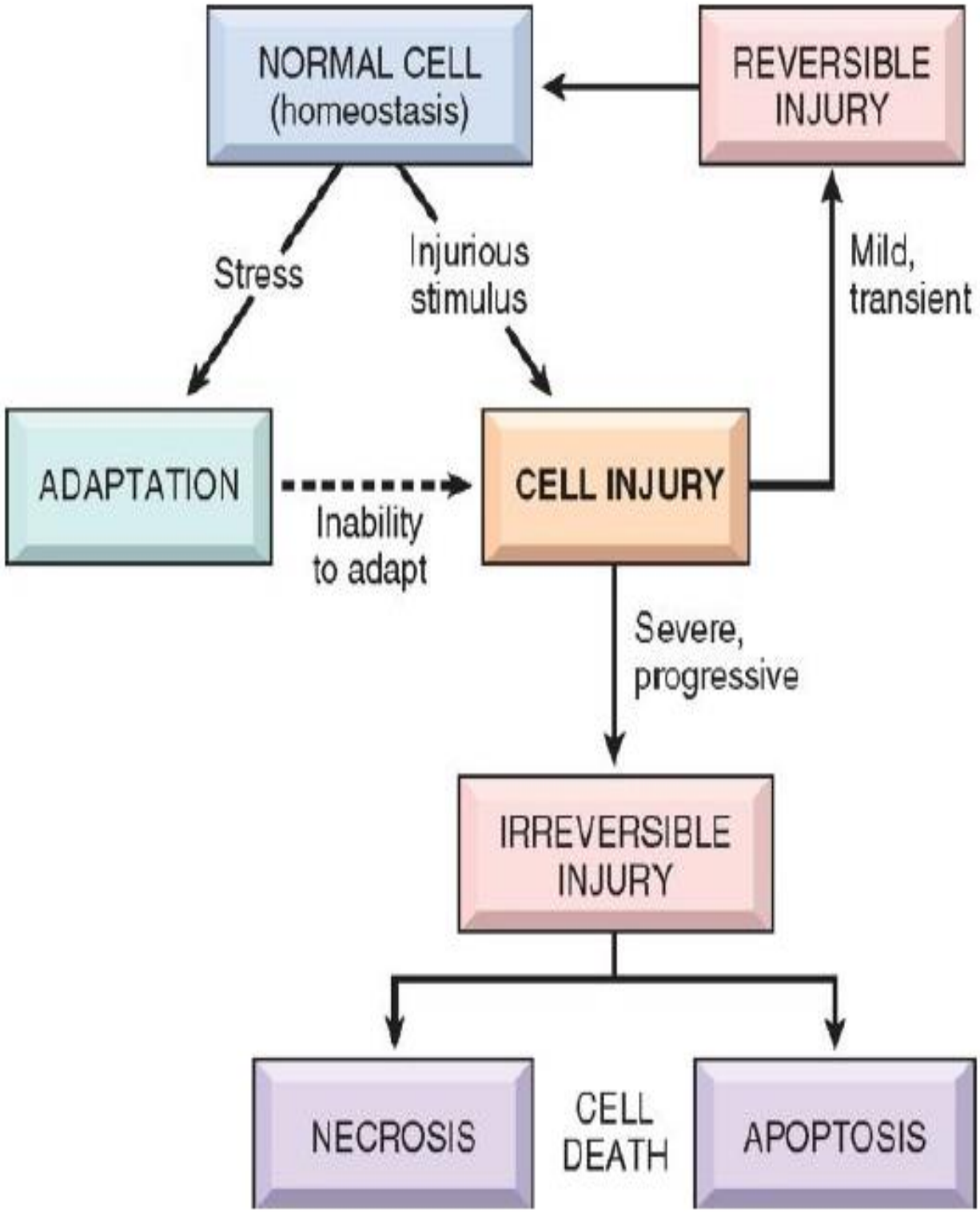
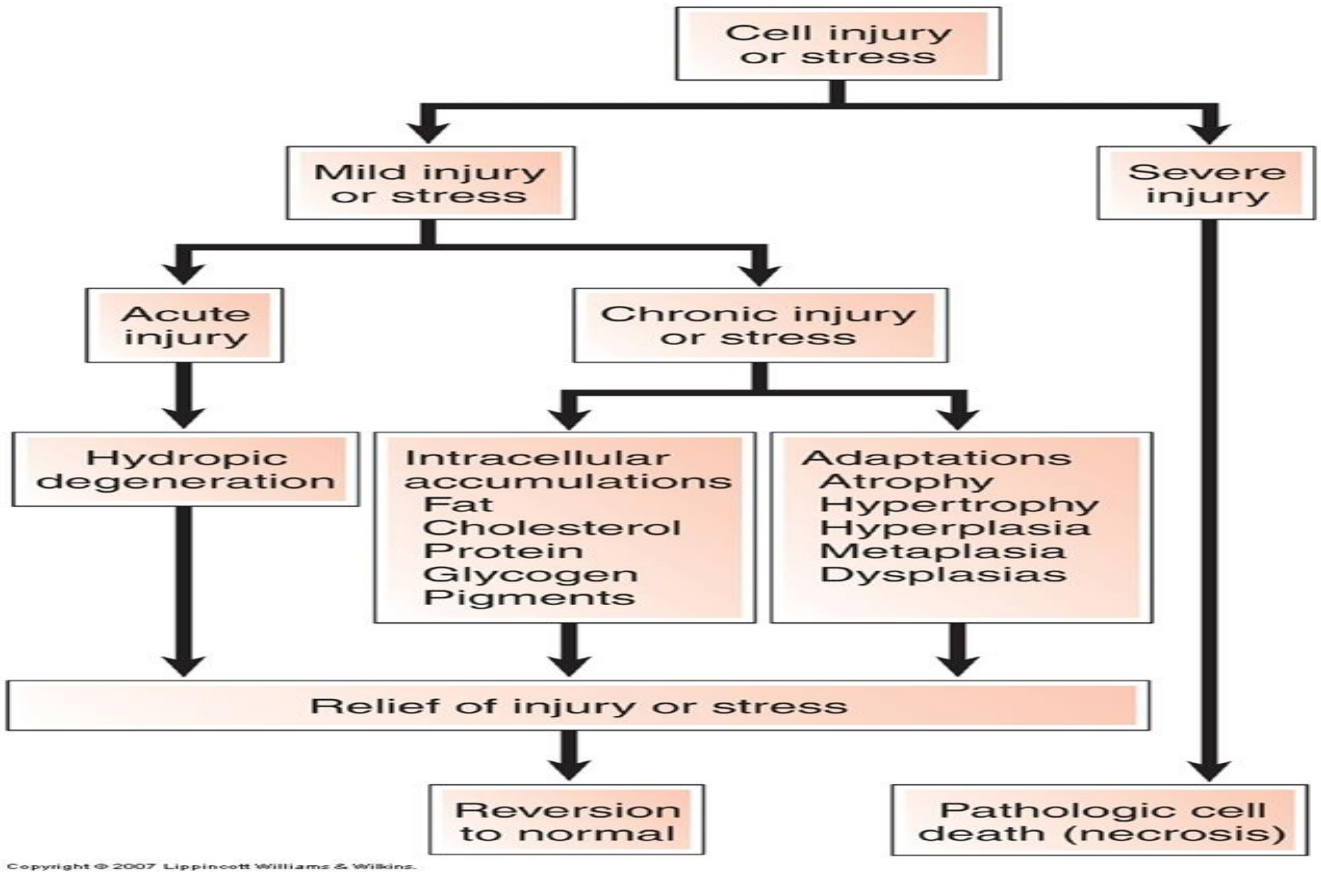


TABLE 1-1 -- Cellular Responses to Injury

Nature of Injurious Stimulus	Cellular Response
ALTERED PHYSIOLOGICAL STIMULI; SOME NONLETHAL INJURIOUS STIMULI	**CELLULAR ADAPTATIONS**
• Increased demand, increased stimulation (e.g., by growth factors, hormones) • Decreased nutrients, decreased stimulation • Chronic irritation (physical or chemical)	• Hyperplasia, hypertrophy • Atrophy • Metaplasia
REDUCED OXYGEN SUPPLY; CHEMICAL INJURY; MICROBIAL INFECTION	**CELL INJURY**
• Acute and transient • Progressive and severe (including DNA damage)	• Acute reversible injury Cellular swelling fatty change • Irreversible injury → cell death Necrosis Apoptosis
METABOLIC ALTERATIONS, GENETIC OR ACQUIRED; CHRONIC INJURY	**INTRACELLULAR ACCUMULATIONS; CALCIFICATION**
CUMULATIVE SUBLETHAL INJURY OVER LONG LIFE SPAN	**CELLULAR AGING**



- **Causes of cell injury**

- Hypoxia and free-radical injury
- Physical agents (heat, cold, radiation, trauma)
- Chemical agents and drugs
- Infectious organisms
- Immunologic reactions
- Genetic derangements
- Nutritional imbalances
- Neoplasms
- Ageing

PATHOGENESIS OF CELL INJURY

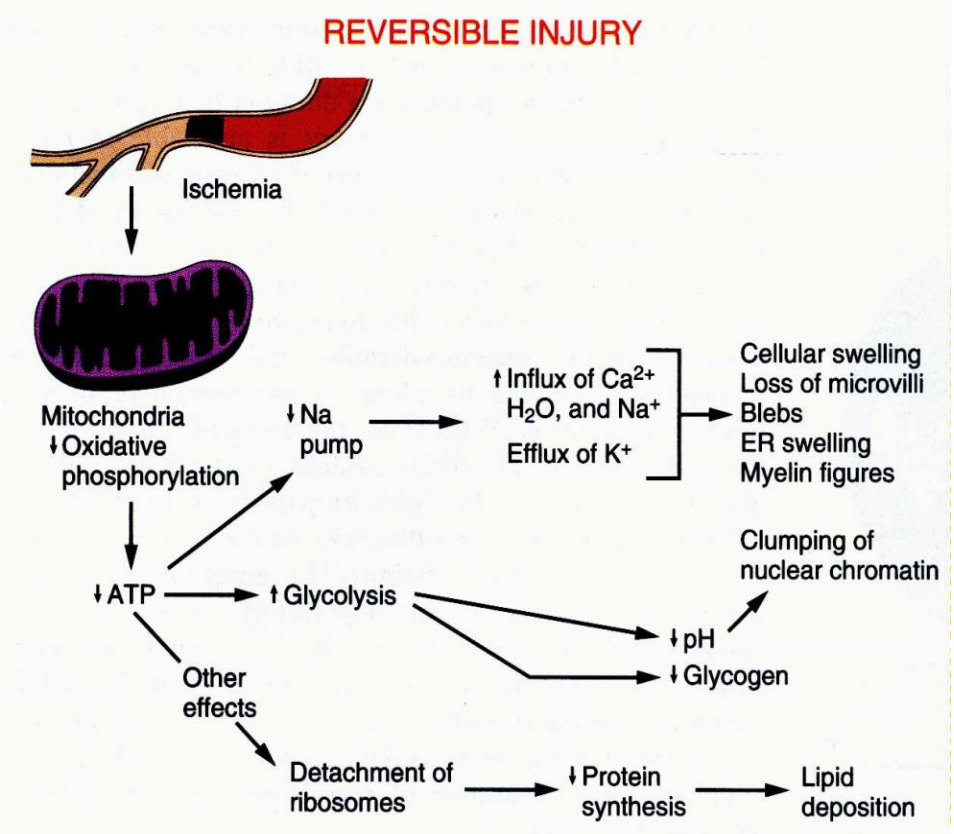
- Reversible cell injury is caused by decreased generation of cellular ATP, reduced intracellular pH, damage to plasma membrane sodium pump and reduced protein synthesis. All these lead to ultrastructural and functional changes which injure cells.

- Irreversible cell injury is caused by mitochondrial dysfunction, membrane damage and release of hydrolytic enzymes.

MECHANISMSOF CELL INJURY :

1. Hypoxia - Ischemia Model
2. Increased cytoplasmic calcium
3. Generation of reactive oxygen species

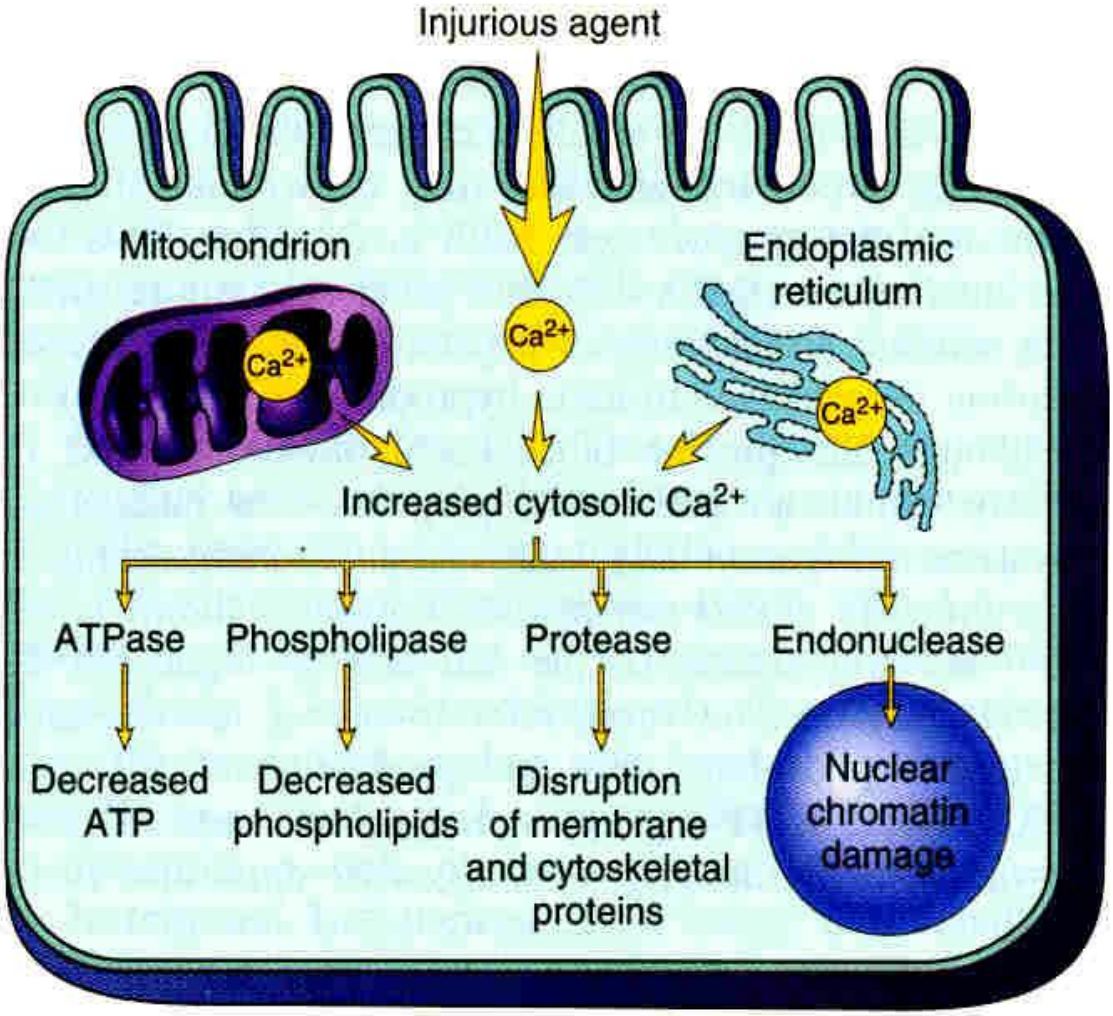
1. HYPOXIA ISCHEMIA MODEL



ISCHEMIA REPERFUSION INJURY :

When the period of ischemia is of short duration, reperfusion with resupply of oxygen restores the structural and functional state of the injured cell .When ischemia is of long duration, then rather than restoration of structure and function of the cell, reperfusion paradoxically deteriorates the already injured cell due to generation of oxygen derived free radicals. Longer periods of ischemia cause irreversible cell injury by itself.

2.INCREASED CYTOPLASMIC CALCIUM



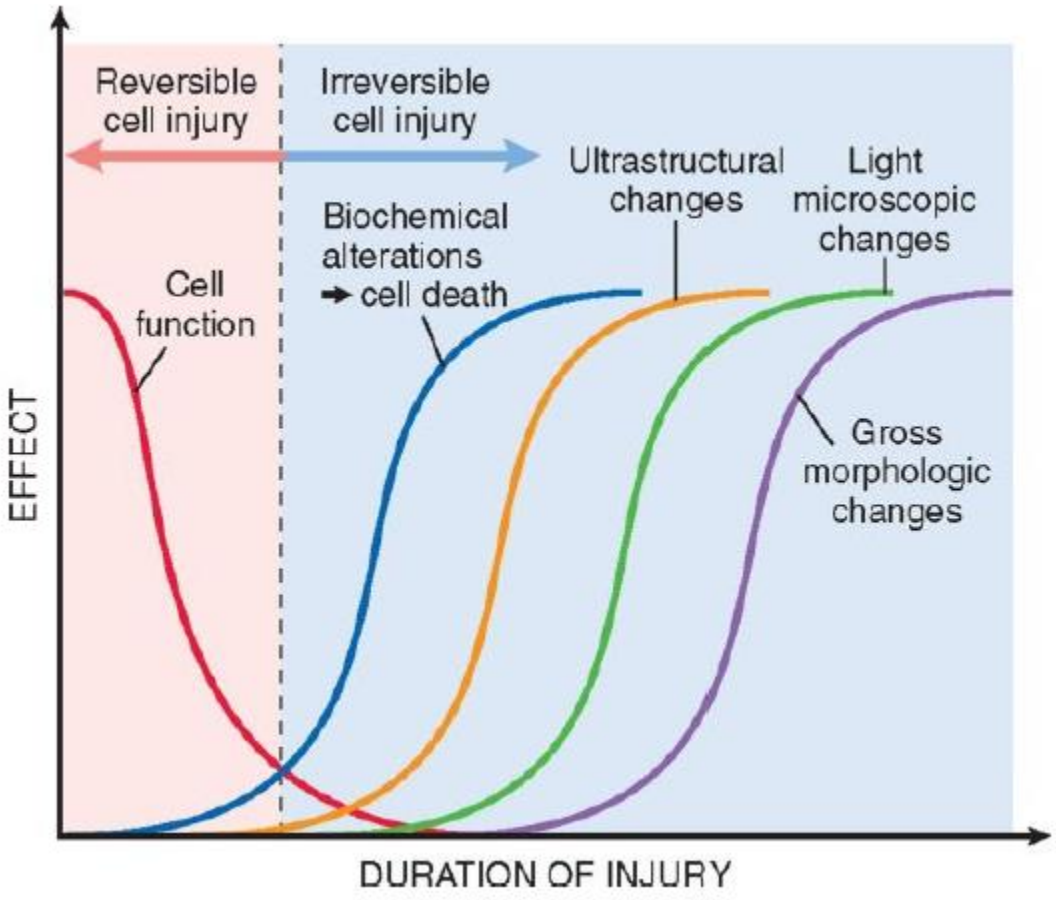
3.REACTIVE OXYGEN SPECIES [ROS]

- Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen. Examples include oxygen ions and peroxides. ROS are formed as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis. However, during times of environmental stress (e.g., UV or heat exposure), ROS levels can increase dramatically. This may result in significant damage to cell structures. Cumulatively, this is known as oxidative stress. ROS are also generated by exogenous sources such as ionizing radiation.
- Highly reactive, unstable chemicals
- Associated with cell injury

Free radical generation occurs by

- Absorption of irradiation
  - E.g. OH•, and H•
- Endogenous normal metabolic reactions especially in neutrophils during inflammation
  - E.g. O_2^-•, and H_2O_2
- Transition metals
  - E.g. Fe^{+++} which donate or accept free electrons
- Nitrous oxide
  - an important paracrine-type mediator that helps regulate vascular pressure
- Toxins
  - e.g. carbon tetrachloride or drug metabolism

Sequential development of biochemical and morphologic changes in cell injury.



REVERSIBLE CELL INJURY

- Also called non lethal injury or retrogressive changes

- Examples –

1.Cellular swelling [cloudy swelling , hydropic change , or vacuolar degeneration]

Commonest and earliest form of cell injury
Etiology : Bacterial toxins , chemicals , poisons , burns , high fever , hypotonic saline or glucose
Pathogenesis : Impaired regulation of intracellular volume
[Na and water enter cells and K leaves]

- Gross – enlarged organ [kidney, liver, heart muscle]
- Cut surface – opaque , bulging
- Microscopy – cells are swollen, microvasculature is compressed.
- Small vacuoles of clear fluid due to distended cisternae of ER
- Ultrastructure – Detachment of polysomes , mitochondrial swelling , blebs on plasma membrane , loss of nucleolar fibrils

2. Hyaline change :

- Hyaline is a descriptive histologic term for glassy, homogenous, eosinophilic appearance of material in H & E and does not refer to any specific substance.

- ***Intracellular hyaline*** – mainly seen in epithelial cells
- Egs – Hyaline droplets in PCT due to excessive reabsorption of proteins
- Hyaline degeneration of voluntary muscle
  [Zenker's degeneration seen in rectus abdominis in typhoid]
- Mallory's hyaline – aggregates of intermediate filaments in hepatocytes in Alcoholic liver disease
- Viral hyaline inclusions – nuclear or cytoplasmic
- Russel's bodies – Immunoglobulins in plasma cells

- ***Extracellular hyaline*** -
- Mainly seen in connective tissues
- Hyaline degeneration in leiomyomas
- Old scars get hyalinised
- Hyaline arteriosclerosis in kidney
- Corpora amylacea
- Hyalinised glomeruli in CGN

3.Mucoid change

- ACCUMULATION OF MUCIN –

- Epithelial mucin is PAS & AB positive.

EG : Catarrhal inflammation of mucus membranes of GIT
Mucocele of oral cavity or gall bladder
Cystic fibrosis of pancreas

- Connective tissue mucin is PAS negative AB positive colloidal iron positive.

EG : Mucoid degeneration of tumours , Myxedema , ganglion

• NECROSIS

- **Definition :** Localized death of cells or tissues occurring in the midst of living tissue , and surrounded by inflammatory response .
- Spectrum of morphological changes that follow cell death in living tissues , largely resulting from the progressive degradative action of enzymes on the lethally injured cell .

Types of necrosis :

- **Coagulative necrosis**
  - **Proteins denature and aggregate rather than degrade**
  - **Dry gangrene**

- **Liquefactive necrosis**
  - **Enzymatic digestion of cellular components**
  - **Wet gangrene**

- **Caseous necrosis**
  - **End result of tuberculous infections, granuloma**

- **Fatty necrosis**
  - **End result of pancreatic lipases digesting fat cells resulting in calcium soaps**

- **Fibrinoid necrosis**
  - **Ag-Ab complexes and fibrin accumulate in arteries or other vessels**

- **Gangrene**

- ***Definition:*** necrosis of tissue with superadded putrefaction giving the tissues a black, foul smelling appearance.

Types of gangrene :

1. Dry gangrene
2. Wet gangrene
3. Gas gangrene

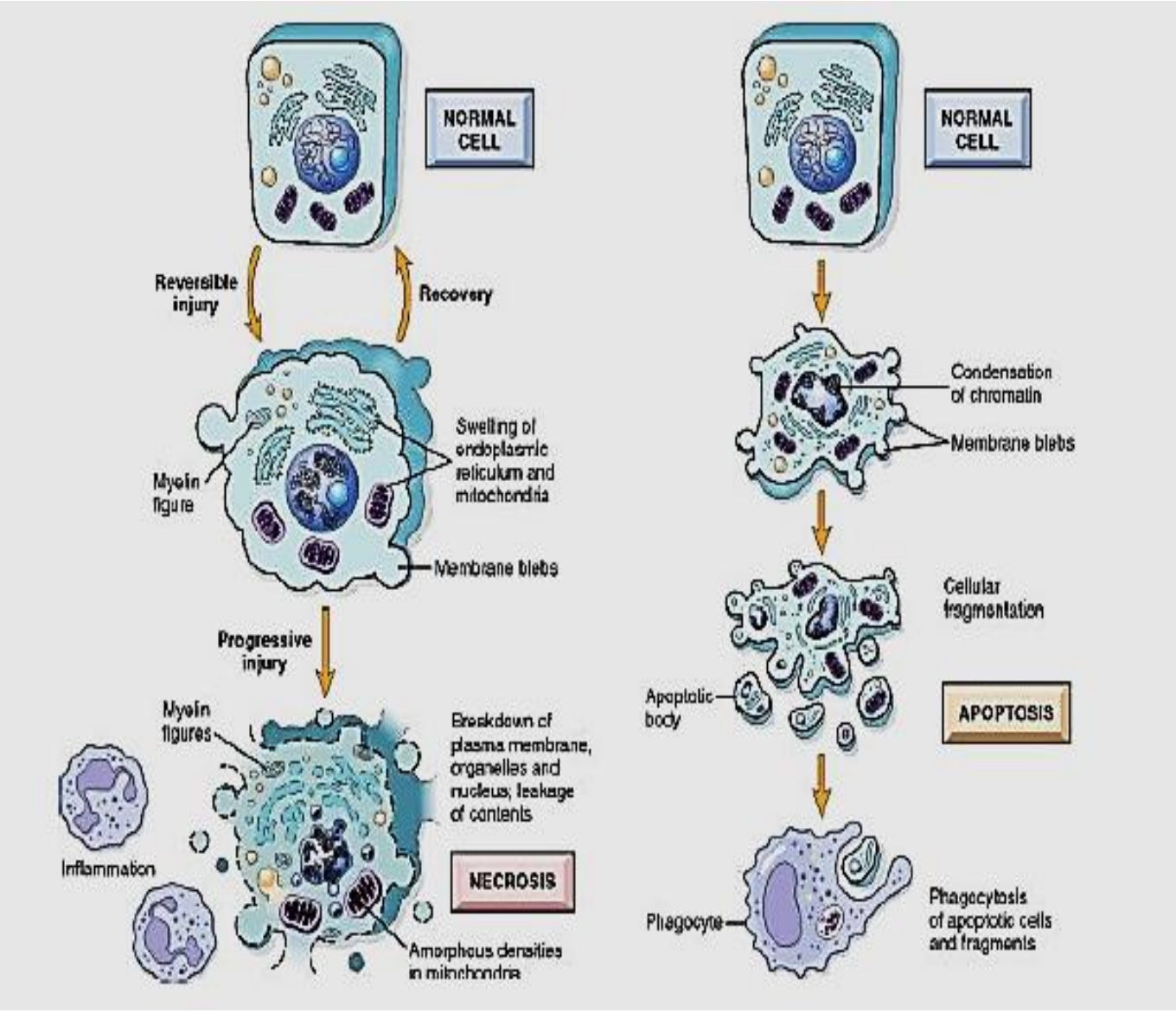
APOPTOSIS : PROGRAMMED CELL DEATH

Apoptosis is a peculiar well controlled individual cell death that is caspase mediated and leads to fragmentation of the cell and organelles into numerous small buds, which are then engulfed by macrophages without surrounding inflammation.

AUTOPHAGY :

The process by which cells digest parts of their own cytoplasm/ organelles.

Schematic illustration of the morphologic changes in cell injury culminating in necrosis or apoptosis.



Differential features of apoptosis and necrosis	
Apoptosis	**Necrosis**
Affects single cells	Affects groups of neighboring cells
No inflammatory response	Significant inflammatory response
Cell shrinkage	Cell swelling
Membrane blebbing but integrity maintained	Loss of membrane integrity
Increased mitochondria membrane permeability, release of proapoptotic proteins and formation of apoptotic bodies	Organelle swelling and lysosomal leakage
Chromatin condensation and non-random DNA fragmentation	Random degradation of DNA
Apoptotic bodies ingested by neighboring cells	Lysed cells ingested by macrophages

INTRACELLULAR ACCUMULATIONS:

- Accumulation of constituents of normal cell metabolism produced in excess
  - eg lipids , carbohydrates , proteins
- Accumulation of abnormal substances
  - eg storage disorders or inborn errors of metabolism
- Accumulation of endogenous or exogenous pigments

Endogenous pigments :
Hemosiderin , Hemozoin , Bilirubin , Melanin , Lipofuscin

Exogenous pigments :
Inhaled , Ingested or Injected . Eg : Carbon , Tattoo ink , silver etc

PATHOLOGICAL CALCIFICATION :

DYSTROPHIC CALCIFICATION :

Deposition of calcium in dead or degenerated tissue.
Calcium metabolism is normal.
Serum calcium levels are normal.
Two phases –
initiation and propagation.
Calcium is attracted by released membrane phosphates.

EXAMPLES

- Dead tissue – caseous necrosis , liquefaction necrosis in chronic abscess , Fat necrosis in pancreas or breast , Infarcts , venous thrombi [phleboliths], hematomas , Dead parasites
  [hydatid cyst , toxoplasma] , Breast cancer .
- Degenerating tissue = Dense old scars , Atheromas , Monckeberg's sclerosis , Stroma of tumours like fibroids , meningioma [psammoma bodies] , epidermal or pilar cysts
- Senile calcinosis of costal , tracheal or bronchial cartilages .
- Calcinosis cutis

METASTATIC CALCIFICATION

- Deposits of calcium in normal tissue
- Calcium metabolism is deranged
- Serum calcium levels are high
- Alkaline pH favors precipitation of calcium
- Kidneys [nephrocalcinosis] , lungs , stomach , blood vessels , cornea

ETIOLOGY :

- Excessive mobilisation of calcium from bone – hyperparathyroidism , bone destructive lesions , prolonged immobilisation
- Excessive absorption of calcium from gut – hypervitaminosis D , milk alkali syndrome , hypercalcemia of infancy

QUESTIONS :

1. Enumerate the causes of cell injury.
2. Describe the main pathogenetic mechanisms of cellular injury.
3. Describe the changes of reversible cell injury with relevant examples.
4. Define necrosis, apoptosis and autophagy.
5. Classify necrosis and give descriptions of different types of necrosis with appropriate examples.
6. Define and classify gangrene. Give examples of each type.
7. Give examples of intracellular accumulations.
8. Name some endogenous pigments which accumulate in cells.
9. Give examples of dystrophic calcification.
10. Give examples of metastatic calcification.

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