CELL INJURY

Content

- Introduction
- Cell injury- Definition
- Etiology of cell injury
- Pathogenesis of cell injury
    * Pathogenesis of hypoxic & ischemic injury
        -Reversible cell injury
        -Irreversible cell injury
    * Pathogenesis of chemical injury
    * Pathogenesis of physical injury

Introduction

- Cells are the basic units of tissues, which form organs and systems in the human body. Traditionally, body cells are divided in to two main types: epithelial and mesenchymal cells. In health, the cells remain in accord with each other.
- In 1859, Virchow first published cellular theory of disease, bringing in the concept that diseases occur due to abnormalities at the level of cells.
- In general, cells of the body have inbuilt mechanism to deal with changes in environment to an extent.

Cell injury

- Cell injury is defined as a variety of stresses a cell encounters as a result of changes in its internal and external environment.
- The cellular response to stress may vary and depends upon the following variables:

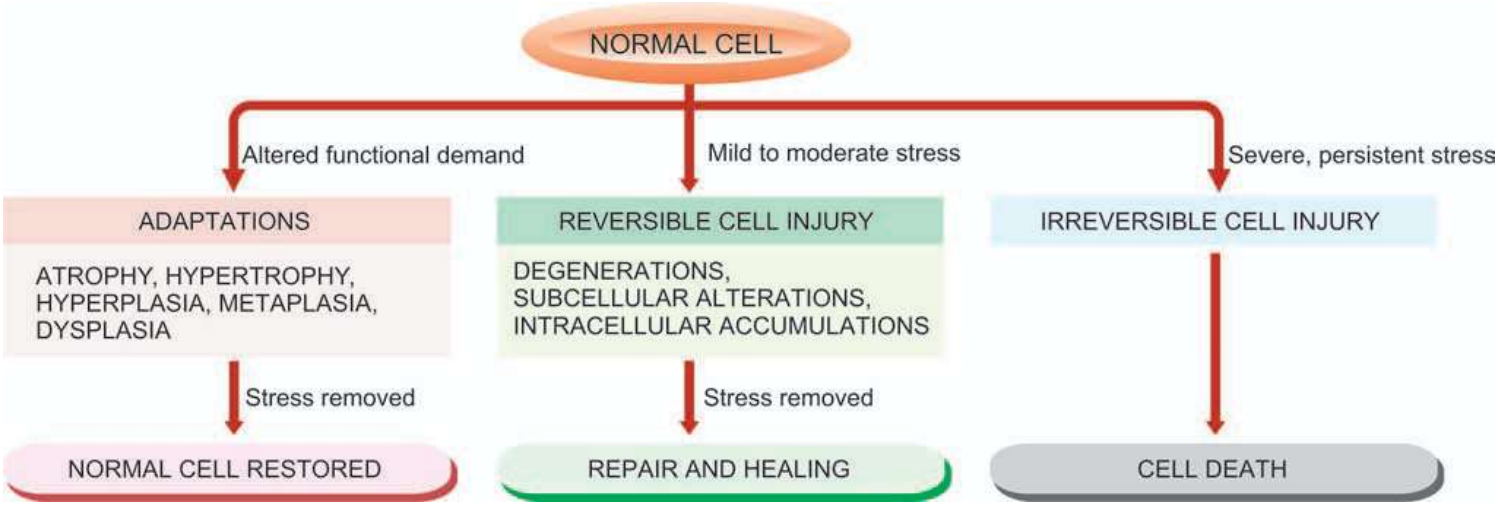
  i) The type of cell and tissue involved.

  ii) Extent and type of cell injury.
- Various forms of cellular responses to cell injury are,

1. When there is increased functional demand, the cell may adapt to the changes which are expressed morphologically and then revert back to normal after the stress is removed(cellular adaptations).

2. When the stress is mild to moderate, the injured cell may recover (reversible cell injury), while when the injury is persistent cell death may occur (irreversible cell injury).

3. The residual effects of reversible cell injury may persist in the cell as evidence of cell injury at subcellular level (subcellular changes), or metabolites may accumulate within the cell (intracellular accumulations).



Etiology of Cell Injury

The cells may be broadly injured by two major ways:

A. By genetic causes

B. By acquired causes

A. Genetic causes

- Developmental defects – error in morphogenesis
- Chromosomal abnormalities
- Mutations

B. Acquired causes

- **HYPOXIA & ISCHEMIA** :

(hypoxia- deficiency in oxygen supply to cells, ischemia – decreased supply of blood to cells due to interruption)

Cells and tissues require oxygen to generate energy and perform metabolic functions. Hypoxia results in failure to carry out these activities by the cells. Hypoxia is the most common cause of cell injury. Hypoxia may result from ischemia.

Hypoxia may result from other causes as well e.g. disorders of oxygen-carrying RBCs (e.g. anemia, carbon monoxide poisoning), heart diseases, lung diseases and increased demand of tissues. Due to ↓ Blood Supply, Heart & Lung diseases or Anemia.

- **PHYSICAL AGENTS.**

Physical agents in causation of disease are as under:

mechanical trauma (e.g. road accidents);

thermal trauma (e.g. by heat and cold);

electricity;

radiation (e.g. ultraviolet and ionising); and

rapid changes in atmospheric pressure.

- **CHEMICALS AND DRUGS.**

An ever increasing list of chemical agents and drugs may cause cell injury. Important examples include the following:

chemical poisons such as cyanide, arsenic, mercury;

strong acids and alkalis;

environmental pollutants;

insecticides and pesticides;

Oxygen at high concentrations;

hypertonic glucose and salt;

social agents such as alcohol and narcotic drugs; and

therapeutic administration of drugs.

- **MICROBIAL AGENTS.**

Injuries by microbes include infections caused by bacteria, rickettsiae, viruses, fungi, protozoa, metazoa, and other parasites

- **IMMUNOLOGIC AGENTS.**

Immunity is a ‘double edged sword’—it protects the host against various injurious agents but it may also turn lethal and cause cell injury.

e.g. hypersensitivity reactions, anaphylactic reactions; and autoimmune diseases.

- **NUTRITIONAL DERANGEMENTS.**

A deficiency or an excess of nutrients may result in nutritional imbalances.Nutritional deficiency diseases may be due to overall deficiency of nutrients (e.g. starvation), of protein calorie (e.g.marasmus, kwashiorkor), of minerals (e.g. anaemia), or of trace elements. Nutritional excess is a problem of affluent societies resulting in obesity, atherosclerosis, heart disease and hypertension.

- **AGING:**

Cellular aging or senescence leads to impaired ability of the cells to undergo replication and repair, and ultimately lead to cell death culminating in death of the individual.

- **PSYCHOGENIC DISEASES.**

There are no specific biochemical or morphologic changes in common acquired mental diseases due to mental stress, strain, anxiety, overwork and frustration. However, problems of drug addiction, alcoholism, and smoking result in various organic diseases such as damage, chronic bronchitis, lung cancer, peptic ulcer, hypertension, ischaemic heart disease etc.

- **IATROGENIC CAUSES.**

Although very physician is bound not to do or administer anything that causes harm to the patient, there are some diseases as well as deaths attributed to iatrogenic causes(owing to physician). Examples include occurrence of disease or death due to error in judgment by the physician and untoward effects of administered therapy (drugs, radiation).

- **IDIOPATHIC DISEASES.**

Idiopathic means “of unknown cause”. Finally, although so much is known about the etiology of diseases, there still remain many diseases for which exact cause is undetermined. For example, most common form of hypertension (90%) is idiopathic (or essential) hypertension.

PATHOGENESIS OF CELL INJURY

The following principles apply in pathogenesis of most forms of cell injury by various agents:

Type, duration & severity of injurious agent

- The extent of injury depend upon type (living/non living), duration (how much time it contact to the cell)& severity (how much injurious agent is severe) of stimulus agents.
- Ex. Small dose of chemical toxin or short duration of ischemia causes cell injury, whereas a large dose of same chemical persistent ischemia causes cell death.

Type, status & adaptability of target cell

The type of cell as regards its susceptibility to injury, its nutritional and metabolic status, and adaptation of the cell to hostile environment determine the extent of cell injury e.g. skeletal muscle can withstand hypoxic injury for long-time while cardiac muscle suffers irreversible cell injury after 20-30minutes of persistent ischemia.

Underlying intracellular phenomenon

Essential biochemical phenomena underlie all forms of cell injury are,

i) Mitochondrial damage causing ATP depletion.

ii) Cell membrane damage disturbing the metabolic and trans-membrane exchanges.

iii) Release of toxic free radicals.

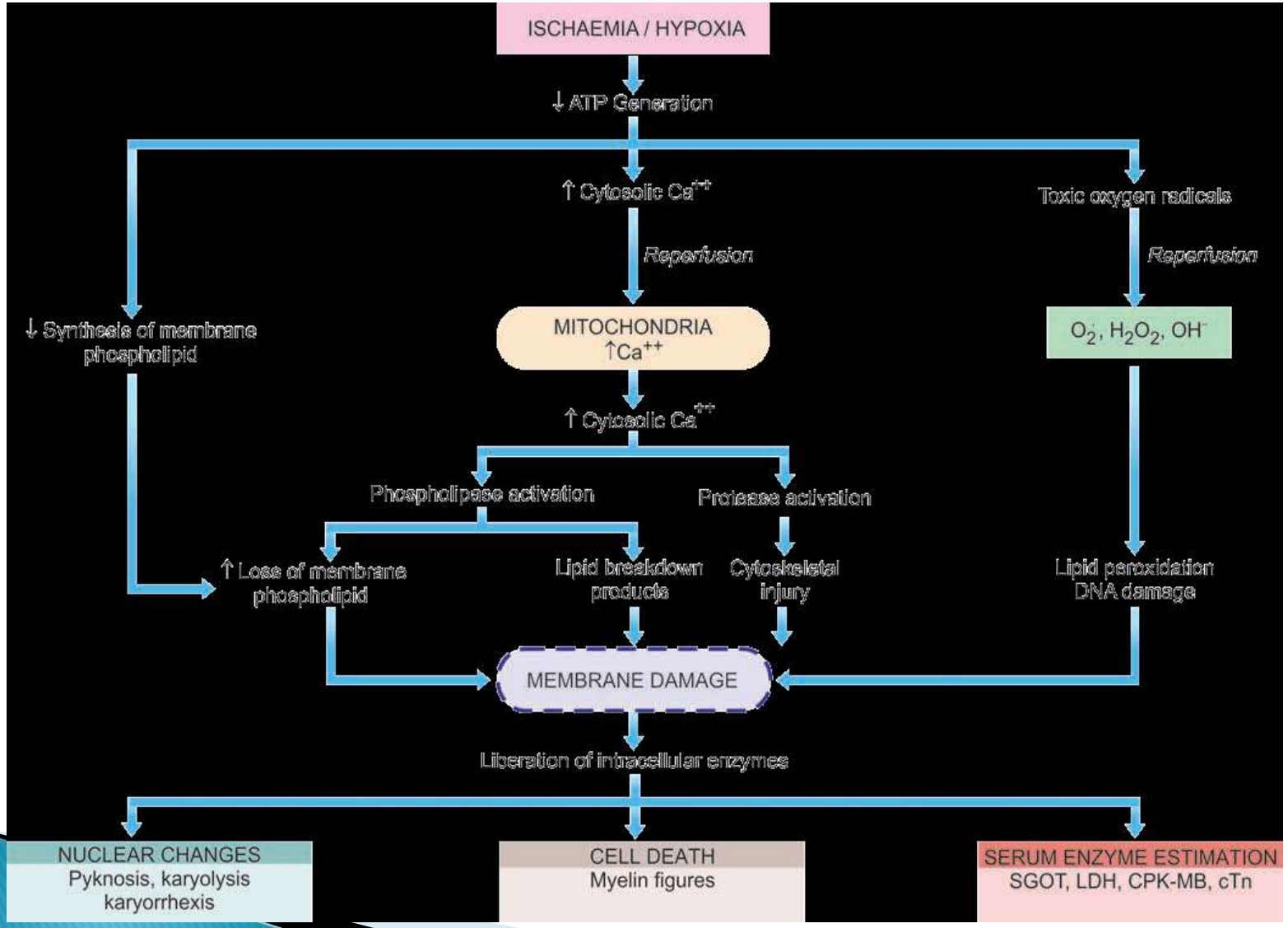
Morphologic consequences

The biochemical changes caused by cell injury are expressed in the form of morphological alterations (ultra structure can be change).

The morphologic changes of reversible cell injury (e.g. hydropic swelling) appear earlier than morphologic alterations in cell death (e.g. in myocardial infarction).

Pathogenesis of ischemic and hypoxic injury

Sequence of events in the pathogenesis of reversible and irreversible cell injury caused by hypoxia/ischaemia



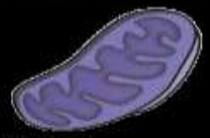
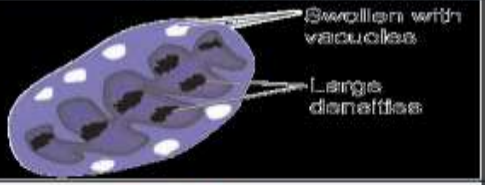
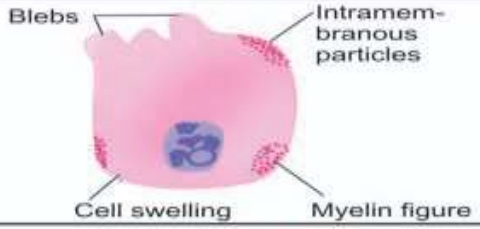
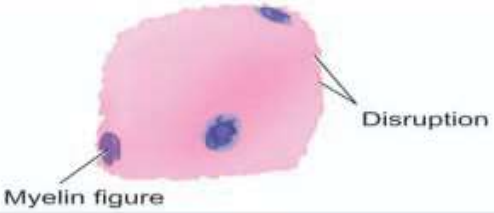
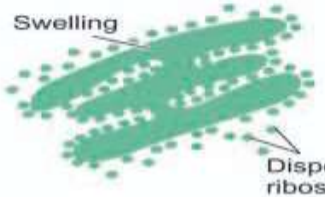
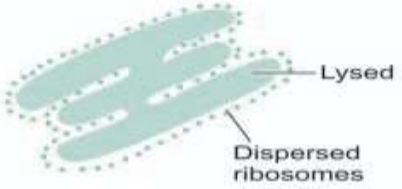
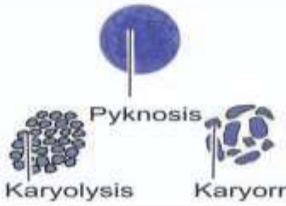
Ischaemia and hypoxia are the most common forms of cell injury. Although underlying intracellular mechanisms and ultrastructural changes involved in reversible and irreversible cell injury by hypoxia and ischaemia depending upon extent of hypoxia and type of cells involved, they are a continuation of the process.

REVERSIBLE CELL INJURY.

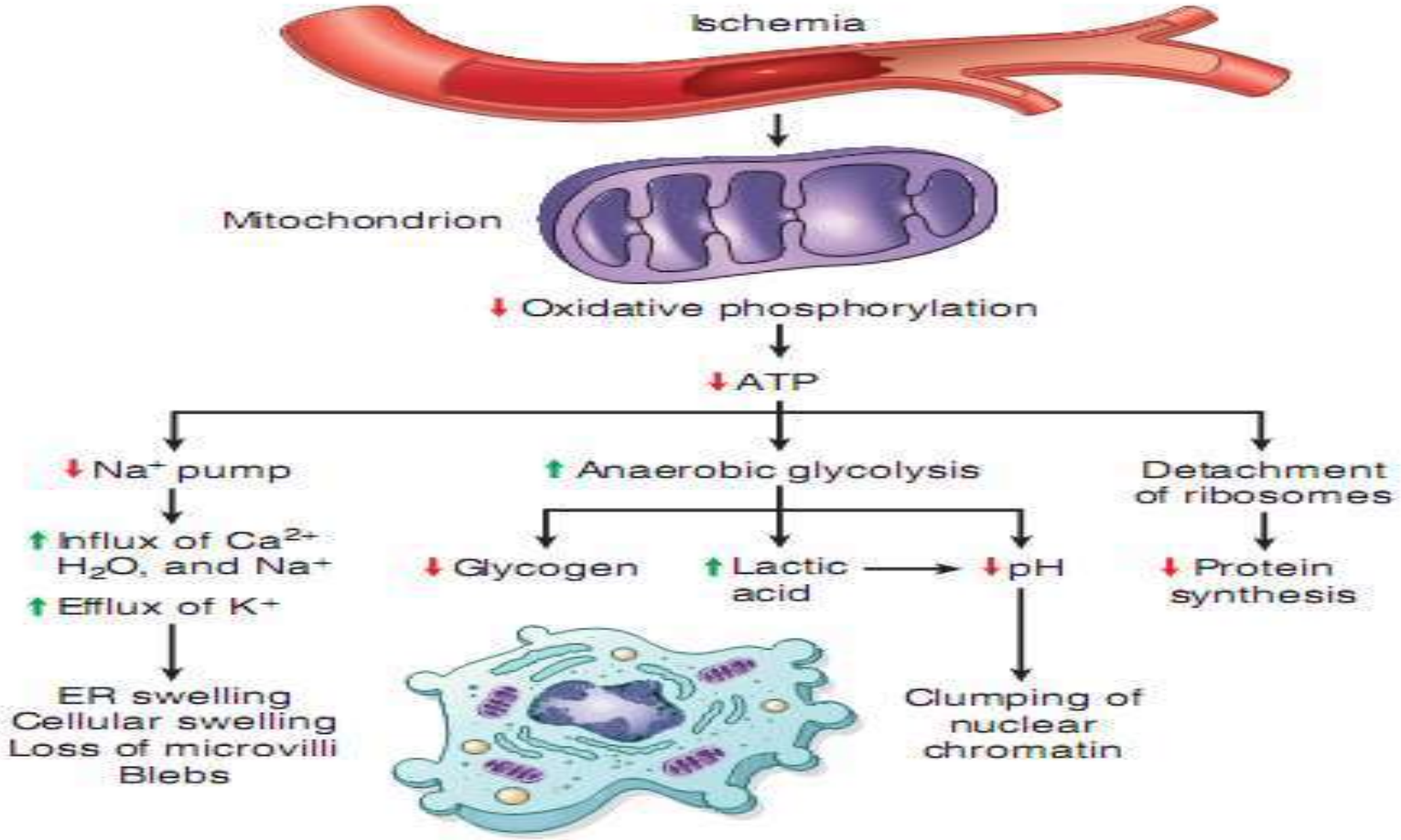
If the ischaemia or hypoxia is of short duration, the effects may be reversible on rapid restoration of circulation. The sequential biochemical and ultrastructural changes in reversible cell injury are as under**:**

1. **Decreased generation of cellular ATP: Damage by ischaemia *versus* hypoxia from other causes.**
2. **Intracellular lactic acidosis:Nuclear clumping.**
3. **Damage to plasma membrane pumps: Hydropic swelling and other membrane changes.**
   - *Failure of sodium-potassium pump.*
   - *Failure of calcium pump*
4. **Reduced protein synthesis: Dispersed ribosomes.**

.

ORGANELLES IN NORMAL CELL	A, REVERSIBLE CELL INJURY	B, IRREVERSIBLE CELL INJURY
 1. MITOCHONDRIA		
 2. MEMBRANES		
 3. RER AND RIBOSOMES		
 4. LYSOSOMES		
 5. CYTOSKELETON		
 6. NUCLEUS		

ATP DEPLETION



IRREVERSIBLE CELL INJURY

Continuation of ischaemia or hypoxia results in irreversible damage to the structure and function of the cell (cell death). The stage at which this *point of no return or irreversibility* is reached from reversible cell injury is unclear but the sequence of events is a continuation of reversibly injured cell.

Two essential phenomena distinguish irreversible from reversible cell injury**:**

- Inability of the cell to reverse *mitochondrial dysfunction* on reperfusion or reoxygenation.
- *Disturbance in cell membrane function* in general, and in plasma membrane in particular.

In addition, there is further reduction in ATP, continued depletion of proteins, reduced intracellular pH, and leakage of lysosomal enzymes into the cytoplasm. These biochemical changes have effects on the ultrastructural components of the cell**:**

1. Calcium influx: Mitochondrial damage

Mitochondrial Damage:

Mitochondria are important targets for all types of injury, including hypoxia and toxins.

Mitochondrial changes are seen as vacuoles in the mitochondria and deposit of amorphous calcium salts in mitochondrial matrix.

Mitochondria can be damaged by :

- A- Increases of cytosolic Ca2+
- B- Oxidative stress
- C- Breakdown of phospholipids, and by
- D- Lipid breakdown products.

Mitochondrial damage results in the formation of a high-conductance channel, called mitochondrial permeability transition, present in the inner mitochondrial membrane.

In the initial phase it is reversible but once mitochondrial permeability transition is irreversble it becomes a deathblow to the cell. Mitochondrial damage can also be associated with leakage of cytochrome *c* into the cytosol.

2. Activated phospholipases: Membrane damage.

Damage to membrane function in general, and plasma membrane in particular, is the most important event in irreversible cell injury in ischaemia.

As a result of sustained ischaemia, there is increased cytosolic influx of calcium in the cell. Increased calcium activates endogenous *phospholipases*.

These in turn degrade membrane phospholipids progressively which are the main constituent of the lipid bilayer membrane. Besides, there is also decreased replacement-synthesis of membrane phospholipids due to reduced ATP. Other lytic enzyme which is activated is *ATPase* which causes further depletion of ATP.

Continuation of ischemia → Increases cytosolic calcium influx → Activation of phospholipases → Degradation of membrane phospholipids

3. Intracellular proteases: Cytoskeletal damage

The normal cytoskeleton of the cell (microfilaments, microtubules and intermediate filaments) which anchors the cell membrane is damaged due to degradation by activated intracellular proteases or by physical effect of cell swelling producing irreversible cell membrane injury.

4. Activated endonucleases: Nuclear damage

The nucleoproteins are damaged by the activated lysosomal enzymes such as proteases and endonucleases. Irreversible damage to the nucleus can be in three forms:

i) *Pyknosis:* Condensation and clumping of nucleus which becomes dark basophilic.

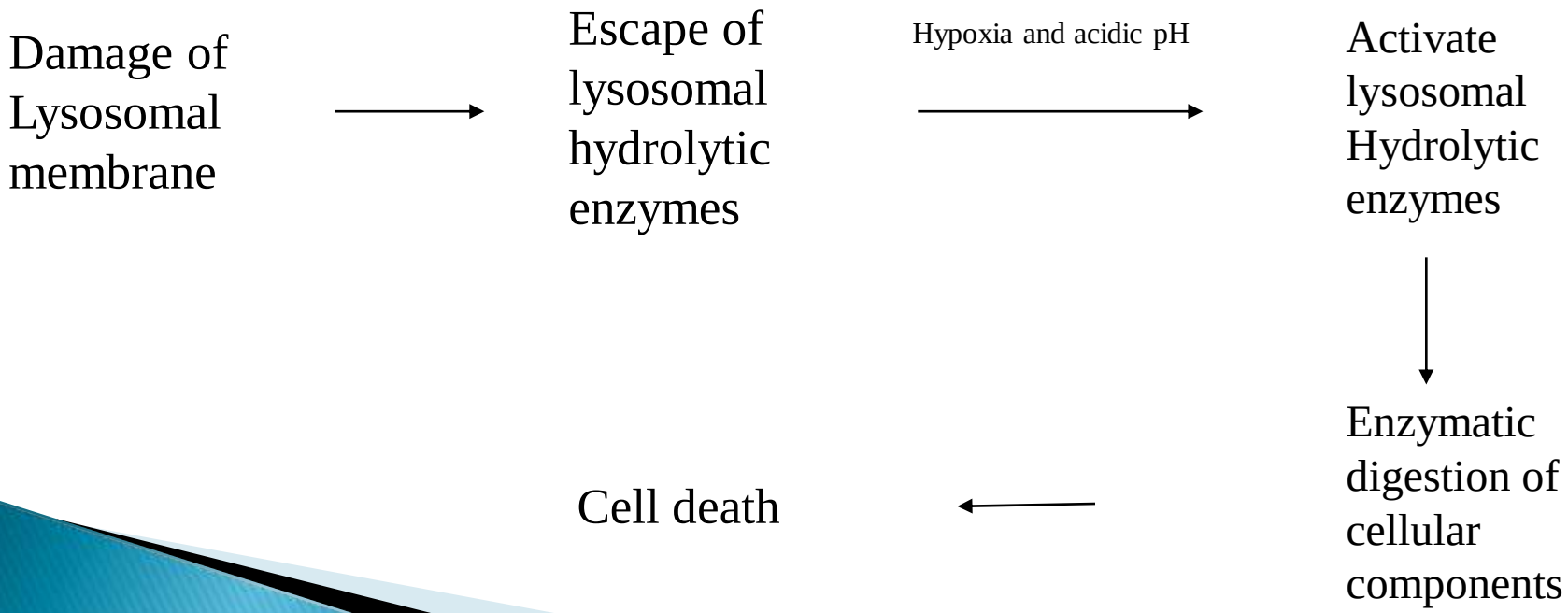
ii) *Karyorrhexis:* Nuclear fragmentation in to small bits dispersed in the cytoplasm.

iii) *Karyolysis:* Dissolution of the nucleus.

5. Lysosomal hydrolytic enzymes: Lysosomal damage, cell death and phagocytosis.

The lysosomal membranes are damaged and result in escape of lysosomal hydrolytic enzymes. These enzymes are activated due to lack of oxygen in the cell and acidic pH.

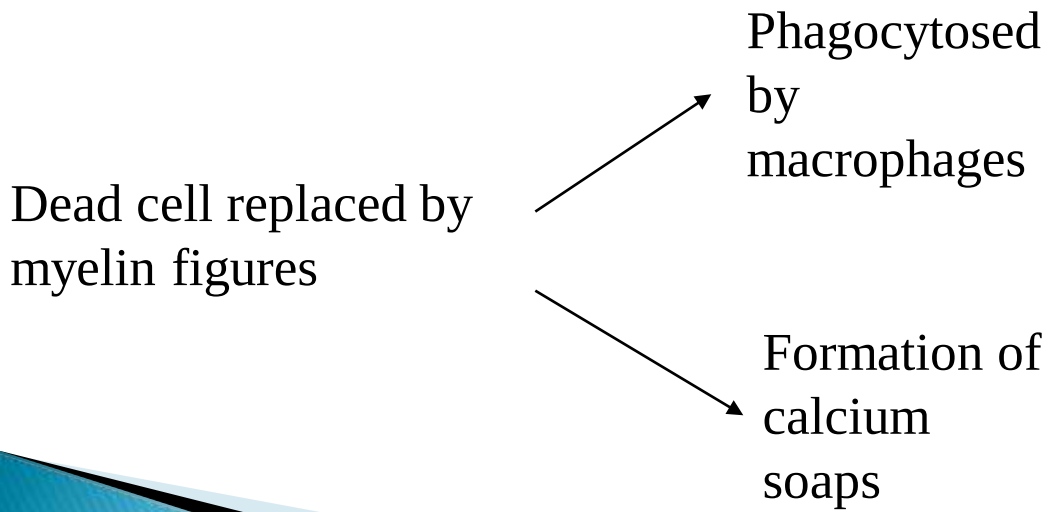
These hydrolytic enzymes (hydrolase, RNAase, DNAase, protease, glycosidase, phosphatase, lipase, amylase, cathepsin etc) which on activation bring about enzymatic digestion of cellular components and hence cell death.



The dead cell is eventually replaced by masses of phospholipids called *myelin figures* which are either phagocytosed by macrophages or there may be formation of calcium soaps.

Liberated enzymes just mentioned leak across the abnormally permeable cell membrane into the serum, the estimation of which may be used as clinical parameters of cell death.

For example, in myocardial infarction, estimation of elevated SGOT, LDH, isoenzyme of creatine kinase (CK-MB), and more recently cardiac troponins (cTn) are useful guides for death of heart muscle.



Pathogenesis of Chemical Injury

Chemicals induce cell injury by one of the two mechanisms:

- by direct cytotoxicity, or
- by conversion of chemical into reactive metabolites.

Direct cytotoxic effects

Some chemicals combine with components of the cell and produce direct cytotoxicity without requiring metabolic activation. The cytotoxic damage is usually greatest to cells which are involved in the metabolism of such chemicals

e.g. in mercuric chloride poisoning, the greatest damage occurs to cells of the alimentary tract where it is absorbed and kidney where it is excreted.

Conversion to reactive toxic metabolites

This mechanism involves metabolic activation to yield toxin that interacts with the target cells. The target cells in this group of chemicals may not be the same cell that metabolised the toxin.

e.g. toxic liver necrosis caused by carbon tetrachloride (CCl_4), acetaminophen (commonly used analgesic and antipyretic) and bromobenzene.

Cell injury by CCl_4 is classic example of an industrial toxin (earlier used in drycleaning industry) that is metabolized by P450 enzyme in the liver cells. CCl_4 is converted into a highly toxic free radical and it cause profound liver injury.

Pathogenesis of Physical Injury

Injuries caused by mechanical force are of medicolegal significance. But they may lead to a state of shock. Radiation injury to human by accidental or therapeutic exposure is of importance in treatment of persons with malignant tumours as well as may have carcinogenic influences.

Killing of cells by ionising radiation is the result of direct formation of hydroxyl radicals from radiolysis of water. These hydroxyl radicals damage the cell membrane as well as may interact with DNA of the target cell.

In proliferating cells, there is inhibition of DNA replication and eventual cell death by apoptosis (e.g. epithelial cells). In non proliferating cells there is no effect of inhibition of DNA synthesis and in these cells there is cell membrane damage followed by cell death by necrosis (e.g. neurons).