Pathology (Theaory)– 3rd year

Pathology is a science dealing with the study of diseases. **Four important components of pathology are** etiology (causative factors), pathogenesis (mechanism or process by which disease develops), morphology (appearance of cells, tissues or organs) and clinical features.

Cell injury

Disease occurs due to alteration of the functions of tissues or cells at the microscopic level. **The various causes of cell injury include:**

1. **Hypoxia:** It is the **most common cause of cell injury**. It results due to decrease in oxygen supply to the cells.
2. **Physical Agents:** Cell injury may occur due to radiation exposure, pressure, burns, frost bite etc.
3. **Chemical Agents:** Many drugs, poisons and chemicals can result in cell injury.
4. **Infections:** Various infectious agents like bacteria, virus, fungus and parasites etc can cause cell injury.
5. **Immunological reactions:** These include hypersensitivity reactions and autoimmune diseases.
6. **Genetic causes:** Cell injury can also result due to derangement of the genes.

7. **Nutritional imbalance:** Cell injury can result due to deficiency of vitamins, minerals etc.

The response of cells to injurious stimuli depends on a number of variables:

- The nature of the injurious stimulus.
- The duration of action or injury.
- The adaptability of specific cells to injury.

In response to injury, a cell/tissue can have following consequences:

- **Adaptation**: The cell changes its physiological functions in response to an injurious stimulus.
- **Reversible cell injury.**
- **Irreversible cell injury**.

. **Pathologic calcification.**

Reversible Cell Injury: hypoxia is the most common cause of cell injury. Oxygen is an important requirement of mitochondria for the formation of **ATP**. All cellular processes requiring ATP for normal functioning will be affected. Important organelles affected are **cell membranes** (require ATP for functioning of Na+ - K+ pump), **endoplasmic reticulum** (require ATP for protein synthesis) and **nucleus**.

Irreversible Cell Injury: Features of irreversible cell injury include

-- **Damage to cell membrane:** It results due to continued influx of water, loss of membrane phospholipids and loss of protective amino acids (like glycine). Damage to cell membranes result in massive influx of calcium.

-- **Calcium influx:** Massive influx of Ca2+ results in the formation of large flocculent mitochondrial densities and activation of enzymes.

-- **Nuclear changes:** These are the most specific microscopic features of irreversible cell injury. These include: **Pyknosis**, **Karyorrhexis** and **Karyolysis**.

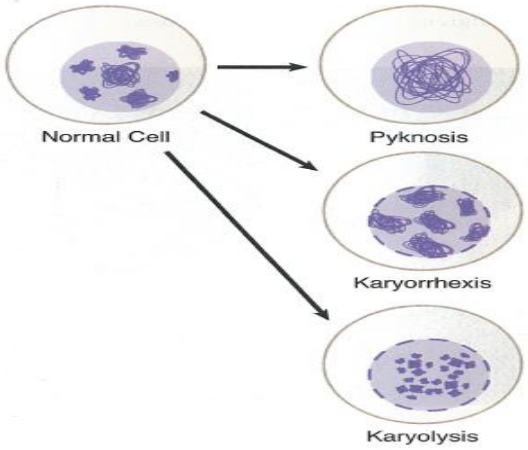

Figure 2-5. Nuclear Changes in Irreversible Cell Injury

The morphologic hallmark of cell death is loss of the nucleus, which occurs via nuclear condensation (pyknosis), fragmentation (karyorrhexis), and dissolution (karyolysis).

The two mechanisms of cell death are necrosis and apoptosis.

Morphology of irreversible cell injury (cell death)

Cell death is a state of irreversible injury. It may occur in the living body as a local or focal change (i.e. autolysis, necrosis and apoptosis) and the changes that follow it (i.e. gangrene and pathologic calcification), or result in end of the life (somatic death).

Autolysis

Autolysis (i.e. *self-digestion*) is disintegration of the cell by its own hydrolytic enzymes liberated from lysosomes. Autolysis can occur in the living body when it is surrounded by inflammatory reaction. Autolysis is *rapid* in some tissues rich in hydrolytic enzymes such as in the pancreas, and gastric mucosa; *intermediate* in tissues like the heart, liver and kidney; and *slow* in fibrous tissue.

If the cell is exposed to continuous injurious stimulus or if the injury is severe, the cells undergo **cell death**. Two main types of cell death: Necrosis and apoptosis.

Necrosis

Necrosis is defined as a localised area of death of tissue followed later by degradation of tissue by hydrolytic enzymes liberated from dead cells; it is invariably accompanied by inflammatory reaction.

Necrosis can be caused by various agents such as hypoxia, chemical and physical agents, microbial agents, immunological injury, etc. Based on etiology and morphologic appearance, there are5 types of necrosis: coagulative, liquefaction (colliquative), caseous, fat, and fibrinoid necrosis.

Apoptosis

Apoptosis is a form of 'coordinated and internally programmed cell death' having significance in a variety of physiologic and pathologic conditions . When the cell is not needed, pathway of cell death is activated ('cell suicide'). Unlike necrosis, apoptosis is not accompanied by any inflammation and collateral tissue damage.

Changes after cell death

Two types of pathologic changes may superimpose following cell injury: **gangrene** (after necrosis) and **pathologic calcification**.

Gangrene

Gangrene is necrosis of tissue associated with superadded putrefaction, most often following coagulative necrosis due to ischaemia (e.g. in gangrene of the bowel, gangrene of limb).

On the other hand, gangrenous or necrotising inflammation is characterised primarily by inflammation provoked by virulent bacteria resulting in massive tissue necrosis.

There are 2 main types of gangrene—**dry** and **wet**, and a variant of wet gangrene called **gas gangrene**. In all types of gangrene, necrosis undergoes liquefaction by the action of putrefactive bacteria.

Pathologic calcification

Deposition of calcium salts in tissues other than osteoid or enamel is called pathologic or heterotopic calcification.

Two distinct types of pathologic calcification are recognised:

1- **Dystrophic calcification**: is characterised by deposition of calcium salts in dead or degenerated tissues with normal calcium metabolism and normal serum calcium level.

2-**Metastatic calcification**: occurs in apparently normal tissues and is associated with deranged calcium metabolism and hypercalcaemia.

Adaptations

Cellular adaptations are reversible changes in size, number, phenotype, metabolic activity or function of cells in response to changes in the environment.

Physiological:

Response to normal stimulation by hormones or endogenous chemical mediators.

Pathological:

Response to environmental stress, which helps them to escape from injury.

Physiologic and pathologic adaptations occur by following processes :

- **Decreasing or increasing their size** i.e. atrophy and hypertrophy respectively, or by increasing their number i.e. hyperplasia .

-**Changing the pathway of phenotypic differentiation of cells** i.e. metaplasia and dysplasia .

In general, the adaptive responses are reversible on withdrawal of stimulus. However, if the irritant stimulus persists for long time, the cell may not be able to survive and may either die or progress further e.g. cell death may occur in sustained atrophy; dysplasia may progress into carcinoma in situ.

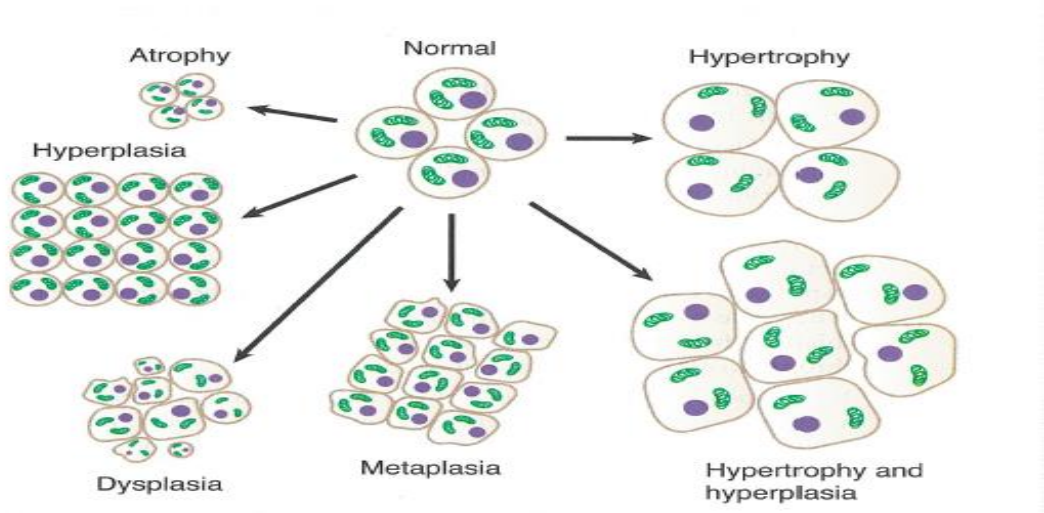

Figure 2-7. Cellular Adaptive Responses to Cell Injury