GENERAL PATHOLOGY
CELL INJURY AND APOPTOSIS

Theory Lecture 2
2023-2024

Homeostasis

In normal conditions, the cells of the body are in equilibrium with their external environment. They maintain their internal machinery in a dynamically stable and steady state called homeostasis.

Cell adaptation

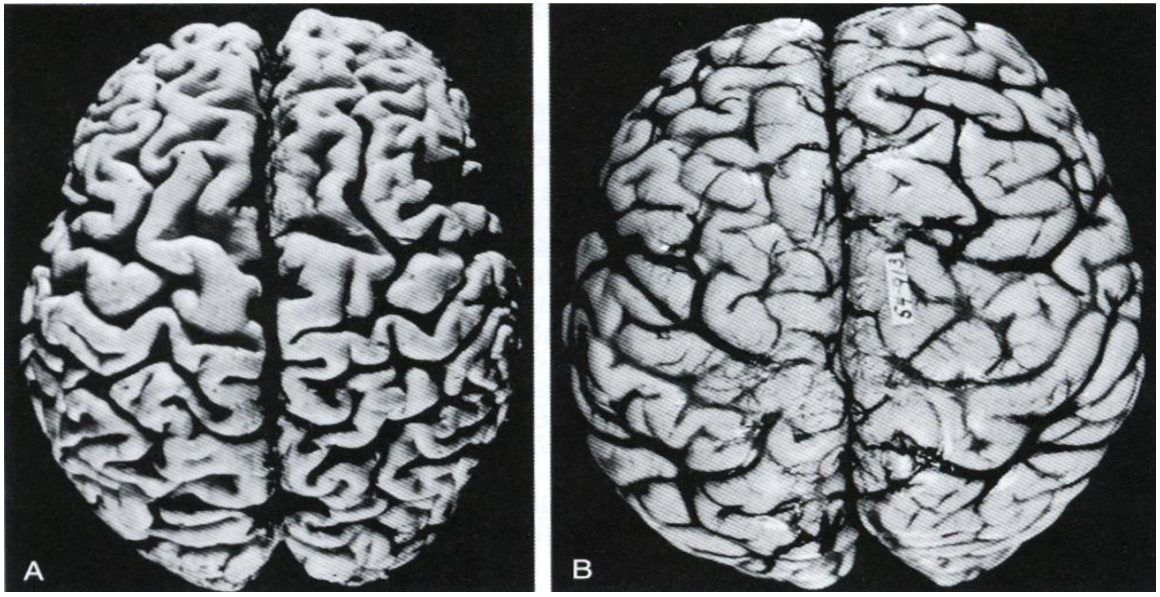
- When this homeostasis is disrupted by external disturbances (stress), changes within the cells occur to counteract with the external disturbances.
- There will be a number of changes, inside the cells, in which a new altered steady state is created. These induced changes are referred to as adaptations.
- The aim of adaptations is to preserve cell viability i.e. prevent cell injury.

Examples of adaptations

1. Hypertrophy of skeletal muscles due to an increase in the size of the individual muscle fibers as in athletes (sport individuals) or heavy mechanical workers.

Examples of adaptations

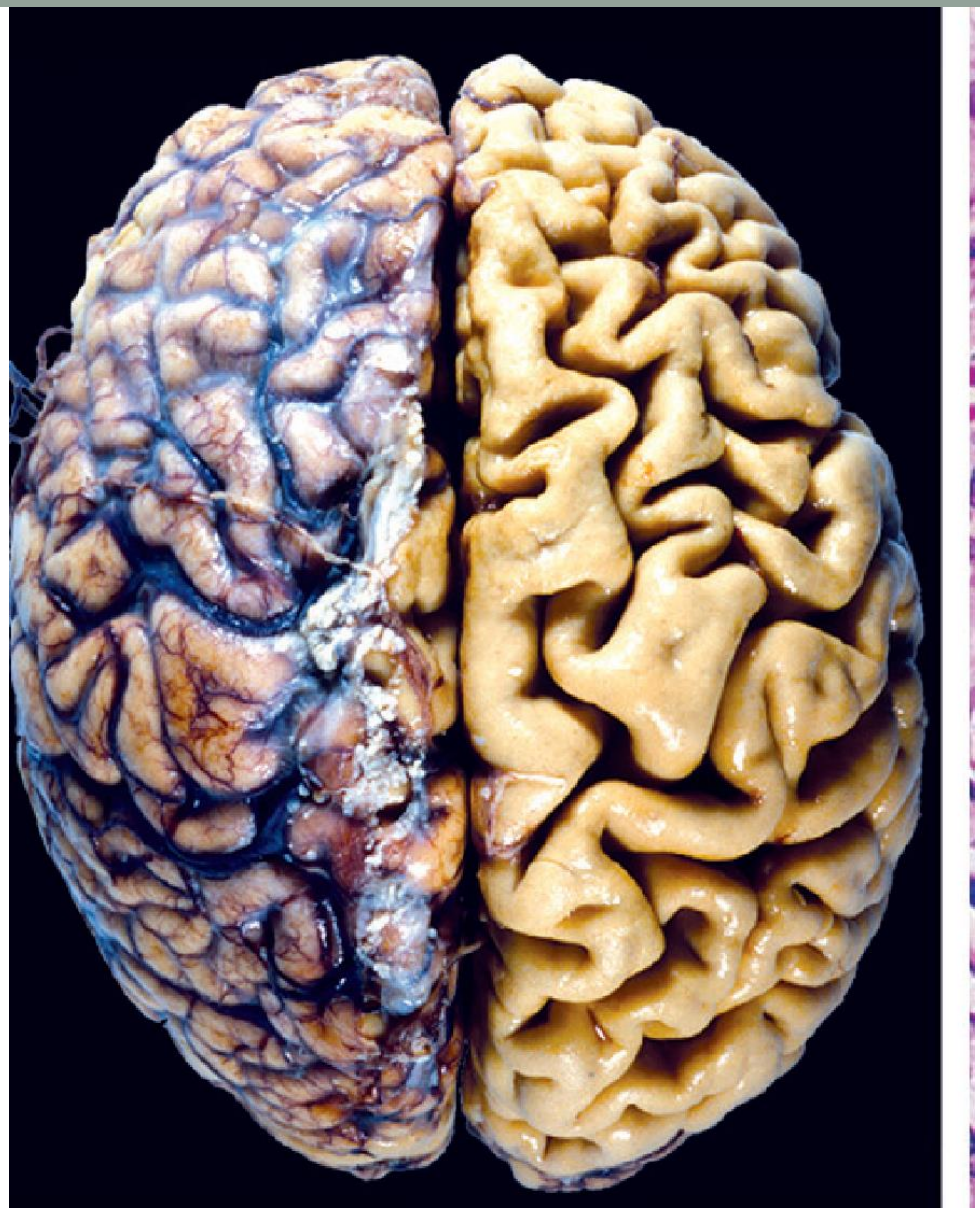
2. Atrophy in which there is a decrease in the size and function of cells and consequently the size of the organ or tissue containing them.



An atrophied brain of an old man

Normal brain of a young man

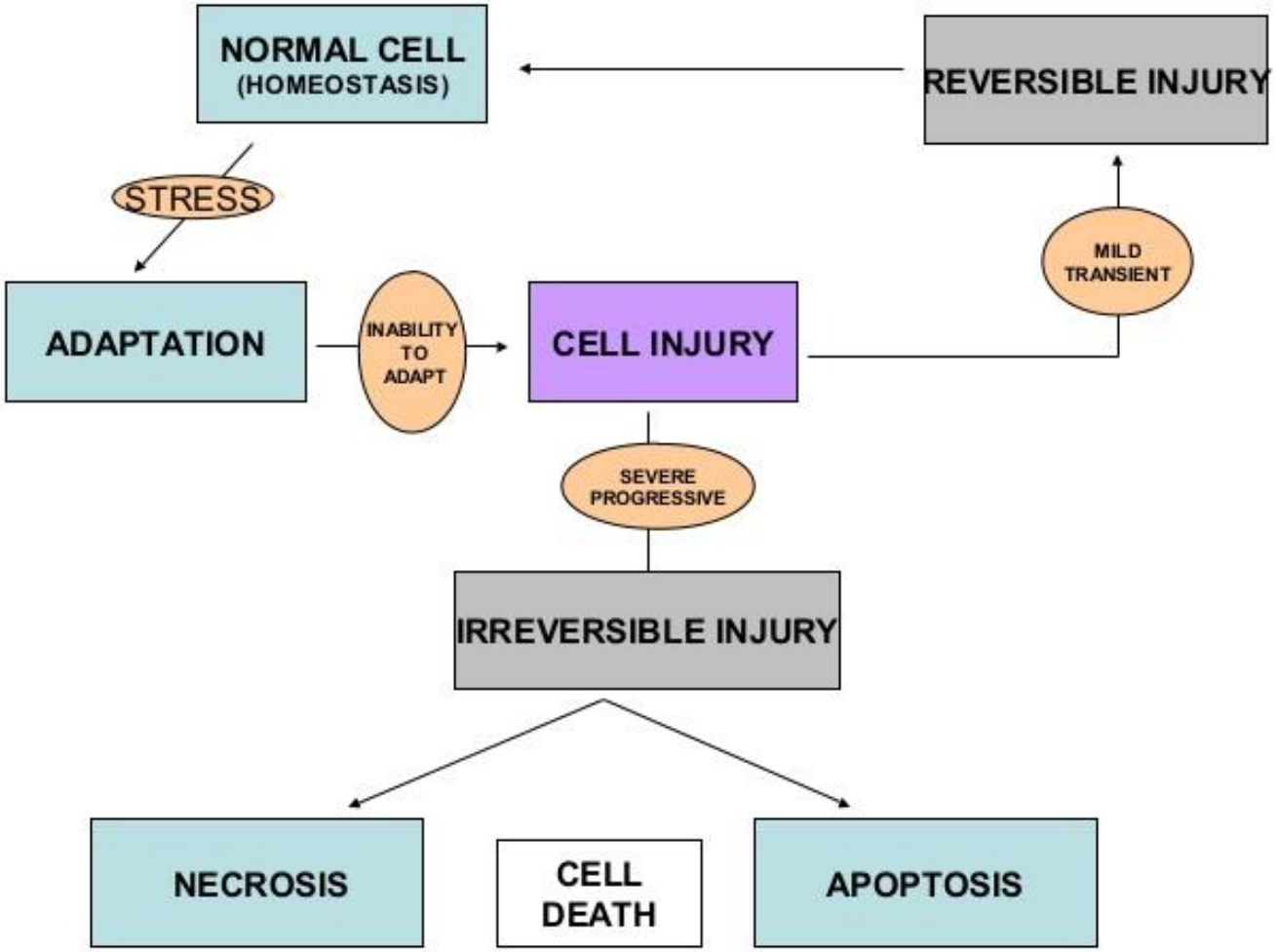
Atrophy associated with Alzheimer's Disease



Cell injury

If the cells fail to adapt under stress, they undergo certain changes called **cell injury**.

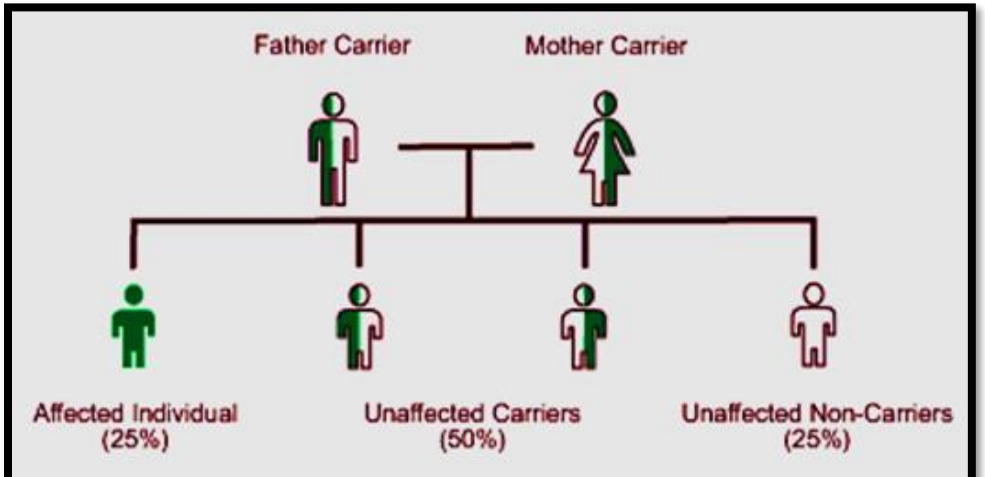
Cell injury


NORMAL CELL
(HOMEOSTASIS)
REVERSIBLE INJURY
STRESS
MILD
TRANSIENT
ADAPTATION
INABILITY
TO
ADAPT
CELL INJURY
SEVERE
PROGRESSIVE
IRREVERSIBLE INJURY
NECROSIS
CELL
DEATH
APOPTOSIS

Causes of cell injury

A. Genetic causes

A genetic disorder or disease is a condition caused by abnormalities in genes or chromosomes.



Causes of cell injury

B. Acquired causes

1. **Nutritional imbalances**

a. **Deficiencies** such as deficiency of **proteins**, **vitamins** and **elements essential** for specific metabolic processes.

b. Excesses such as excess of **lipids** and **carbohydrates**.

2. Hypoxia The term “hypoxia” refers to a **decrease in oxygen supply** to the cells. It leads to **cessation** of the **oxidative respiration** of the cells.

Causes of cell injury

3. Physical factors such as trauma (mechanical injury), extreme heat, deep cold, electricity and radiation.

4. Chemical factors such as:

Strong acids and alkalis, poisons (arsenic or cyanide), insecticides, etc.

5. Infectious agents including viruses, bacteria, fungi and parasites.

Factors influencing the severity of cell injury

1. Type, duration and severity of the injurious agent.
2. Type of the affected cells:

A. The neurons are highly susceptible to ischemic damage. They undergo irreversible damage when deprived of oxygen (by ischemia) for 3-4 minutes.

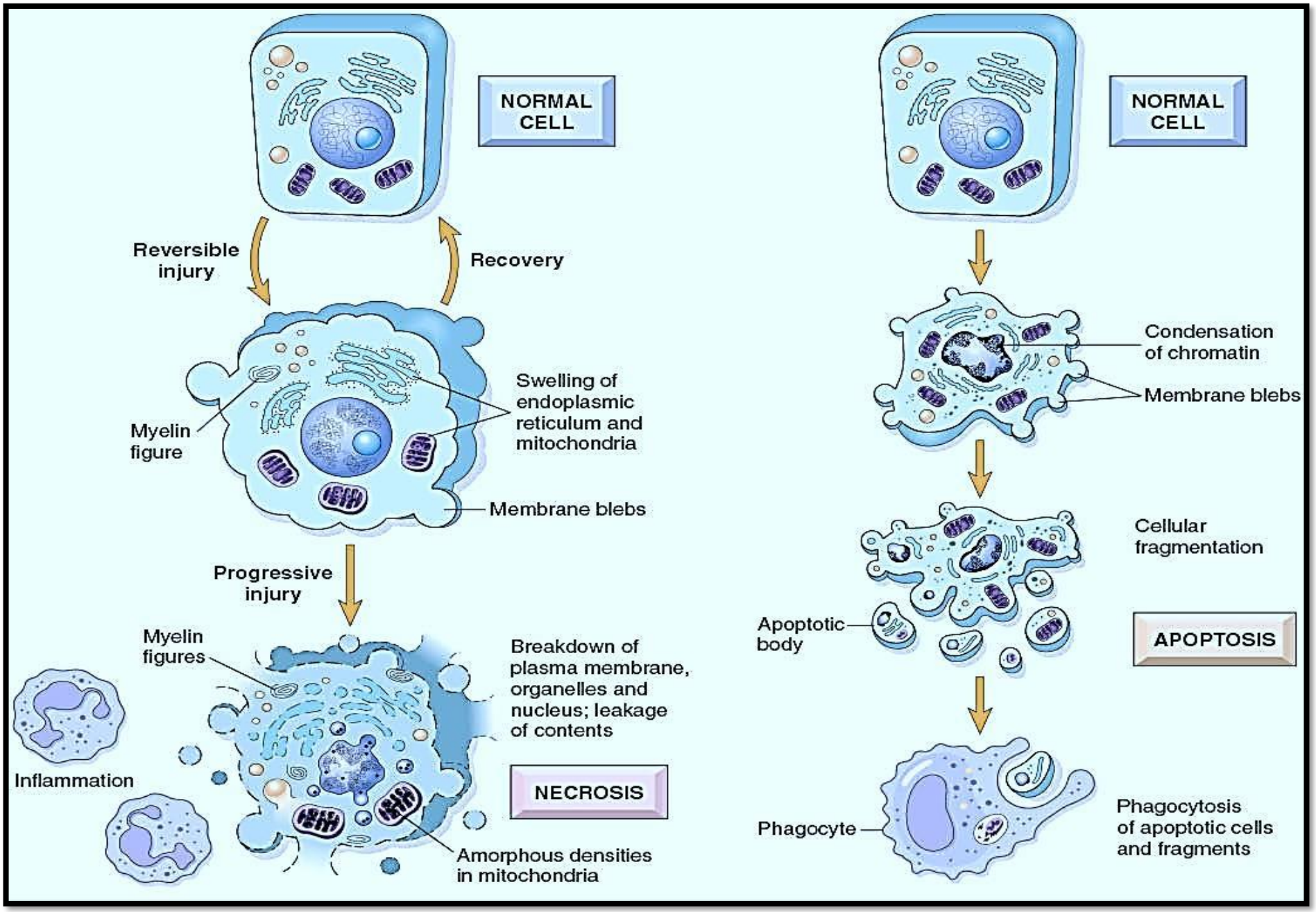
B. Myocardial cells and hepatocytes are of intermediate susceptibility to ischemic damage (20-30 minutes).

C. Skeletal muscles, the epidermis of the skin and fibroblasts are of low susceptibility to ischemia (many hours).

Types of cell injury

The affected cells may recover from the injury (reversible) or may die (irreversible).

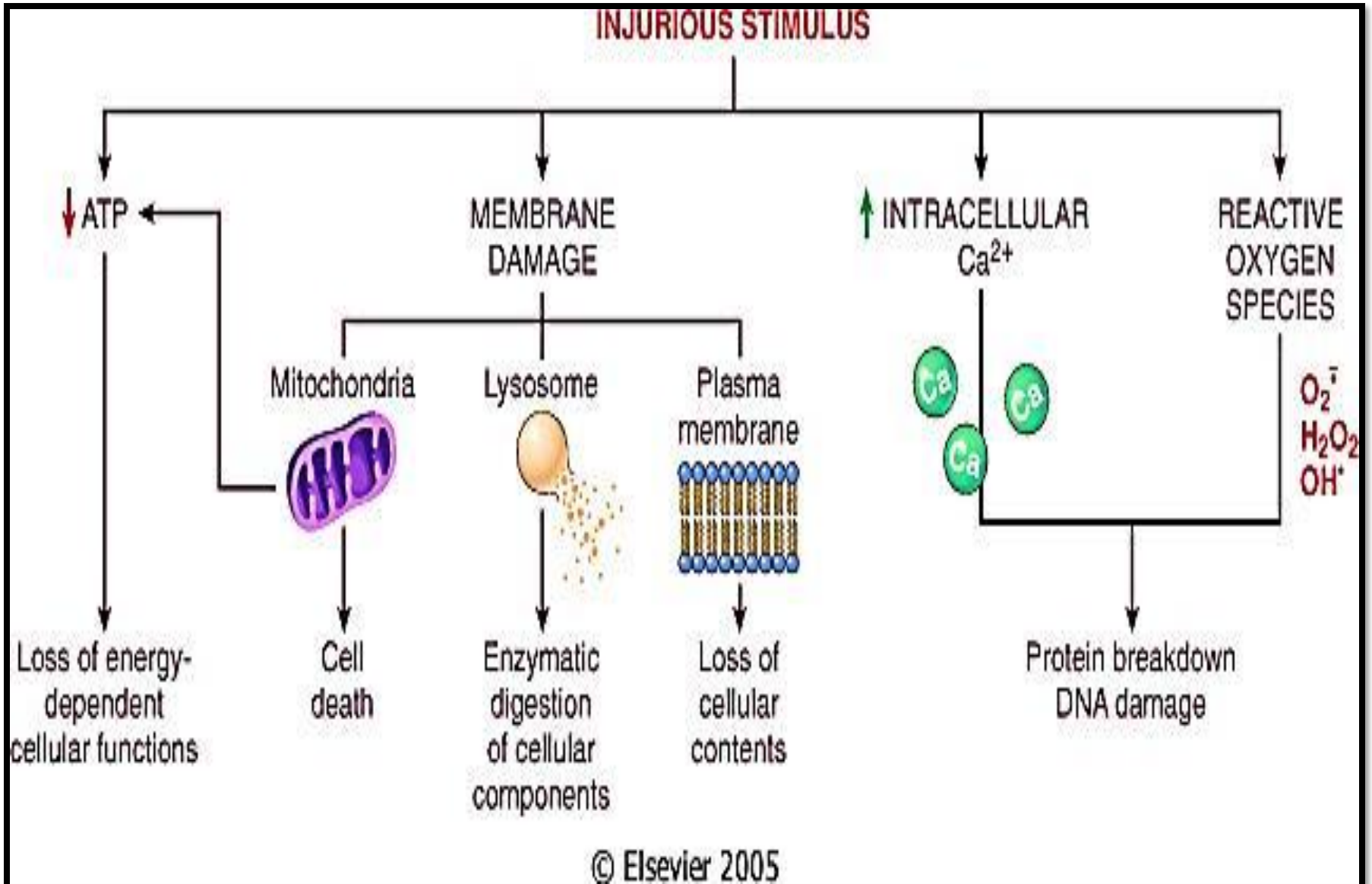
1. **Reversible cell injury:** occur when the injurious stimulus was removed, the cell will return to normal state.
2. **Irreversible cell injury:** persistent or excessive injury causes the cell to pass the point of no return into cell death.


NORMAL CELL
Reversible injury
Recovery
Myelin figure
Swelling of endoplasmic reticulum and mitochondria
Membrane blebs
Progressive injury
Myelin figures
Breakdown of plasma membrane, organelles and nucleus; leakage of contents
Inflammation
NECROSIS
Amorphous densities in mitochondria
NORMAL CELL
Condensation of chromatin
Membrane blebs
Cellular fragmentation
Apoptotic body
APOPTOSIS
Phagocyte
Phagocytosis of apoptotic cells and fragments

Reversible cell injury

Mild forms of injury, the functional and morphologic changes are reversible, if the damaging stimulus is removed the cells will return to normal morphological and functional state.

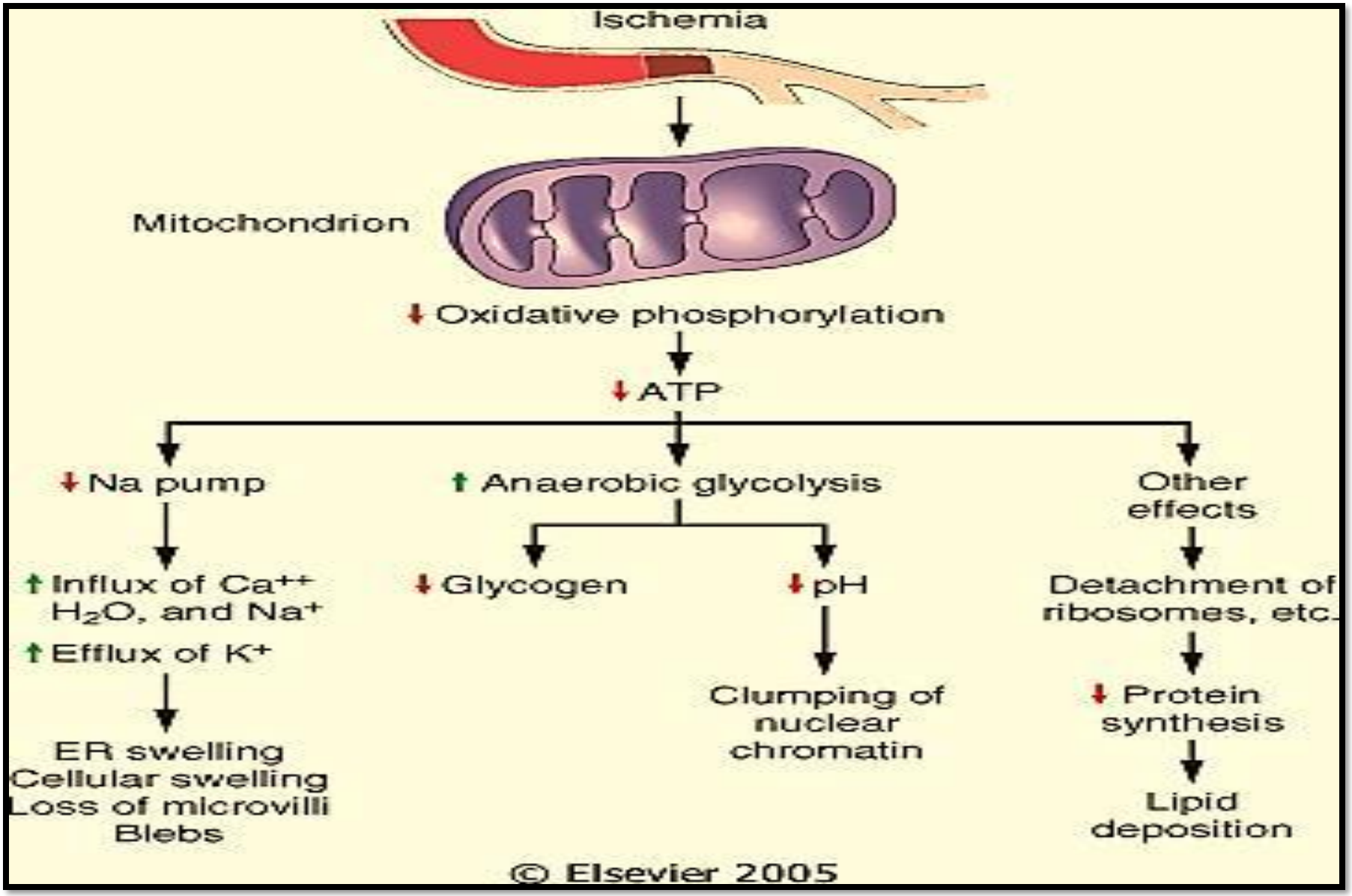
Targets of the injurious agent



Mechanism of ischemia-induced reversible cell injury

1. Ischemia leads to hypoxia, and this in turn results in reduction of the available ATP.
2. Increase in anaerobic glycolysis that leads to increase in the concentration of the intracellular lactic acid.
3. The activity of plasma membrane ATP-dependent sodium pumps is reduced. The result is swelling of the cell.

Mechanism of cell injury due to ischemia

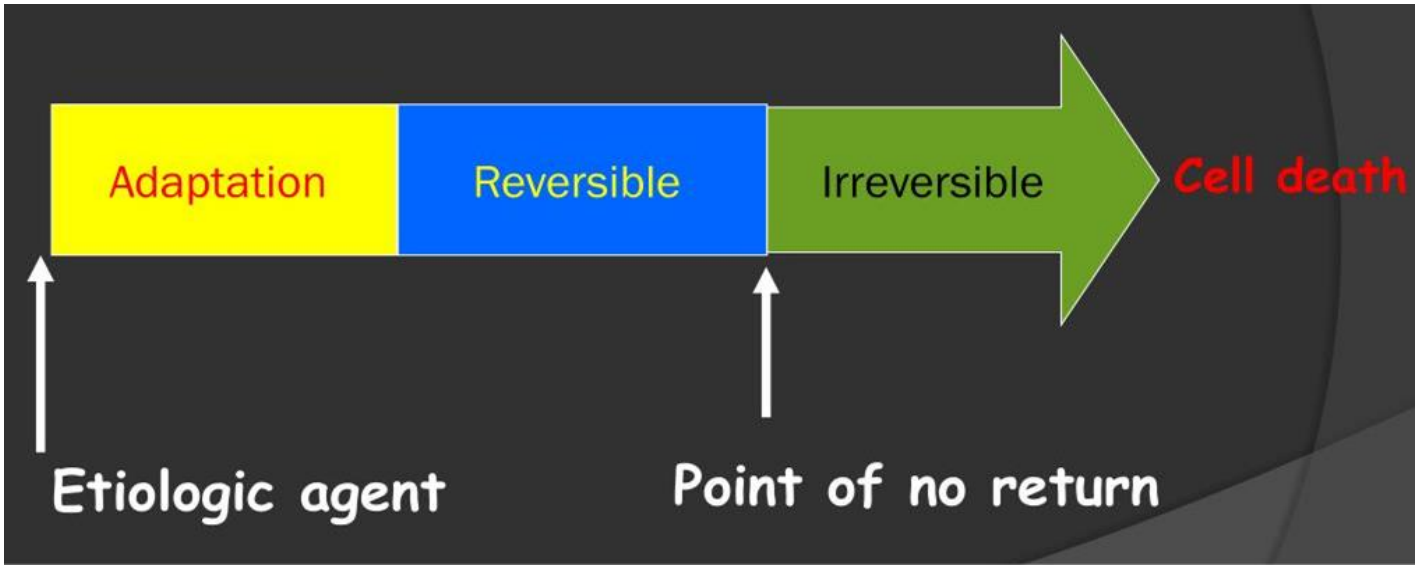


Irreversible cell injury

It is a type of cell injury which occurs when the injurious agent severe and persists. In this case, the cell reaches the maximum limit of its ability to adapt and even after removing the injurious agents the cell not returned to normal structure and function.

Point of no return

It is the precise moment of **transition** from **reversible** to **irreversible cell injury**. At this point, **no adaptation** can save the cell and the **progression to cell death** is inevitable (unavoidable).



Mechanism of irreversible cell injury (cellular alterations seen in irreversible cell injury):

1. Extensive damage to the plasma membranes.

2. Vacuolization of the mitochondria.

3.The lysosomes leak their hydrolytic enzymes into the cytoplasm. Activation of these enzymes leads to enzymatic digestion of cell components.

4.The point of no return is reached when the cell nucleus is damaged beyond repair.

Patterns of reversible (sub-lethal) cell injury

The accumulation includes:

1. Water (Cellular swelling)
2. Triglycerides (Fatty change)
3. Protein (Hyaline change and amyloidosis)
4. Glycogen (Glycogen degeneration)
5. Mucopolysaccharide (Mucoid Degeneration).

1. Cellular swelling (Cloudy swelling)

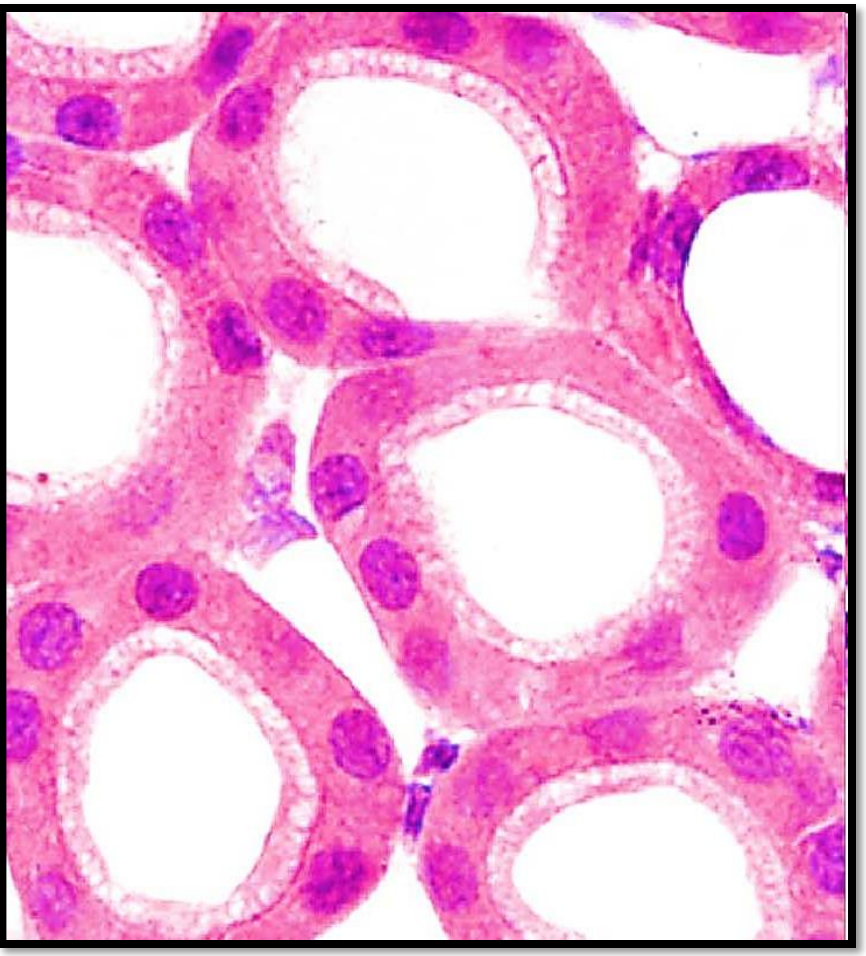
It is an early pathological change characterized by accumulation of water within the cytoplasm of the affected cells. It can be seen in many examples of reversible cell injury.

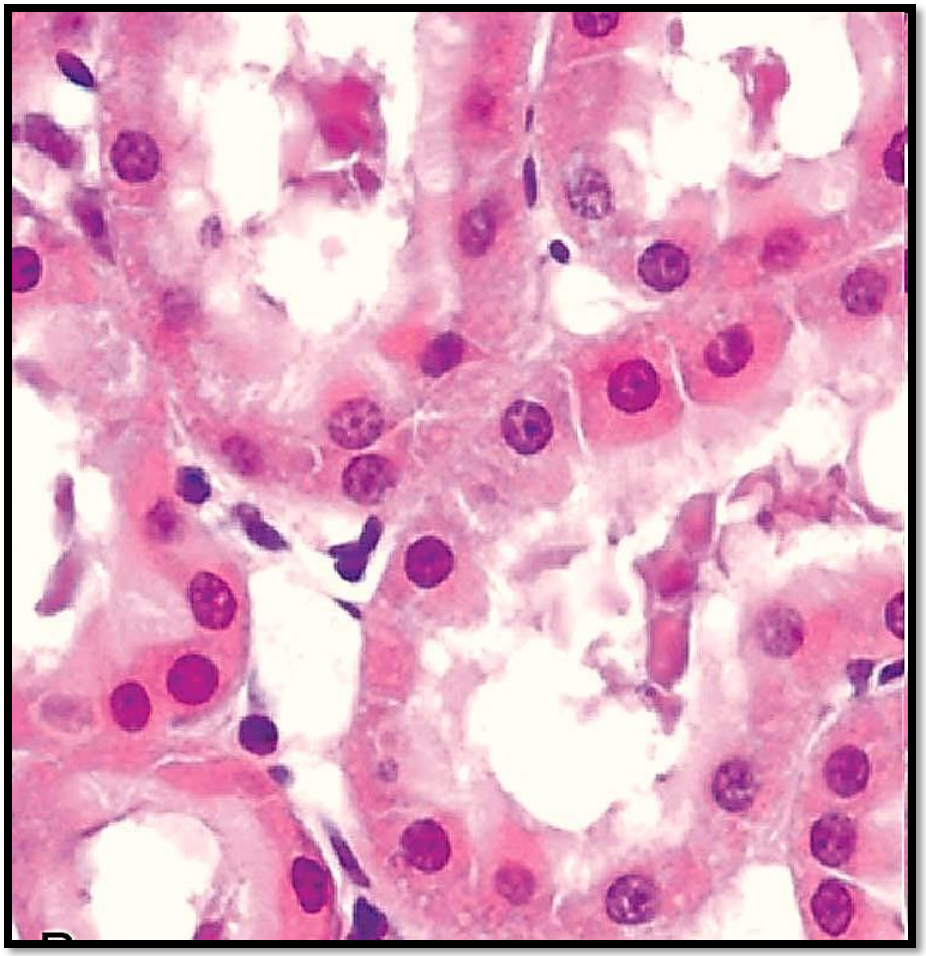
Morphologic features: Grossly, the affected organ such as kidney, liver, pancreas, or heart muscle is enlarged due to swelling. The cut surface bulges outward and is slightly opaque.

Microscopically, it is characterized by the following features:

A. Increase in the size of the cell with pallor of the cytoplasm (cloudy swelling).

B. Small clear vacuoles are seen in the cells and hence the term vacuolar degeneration.



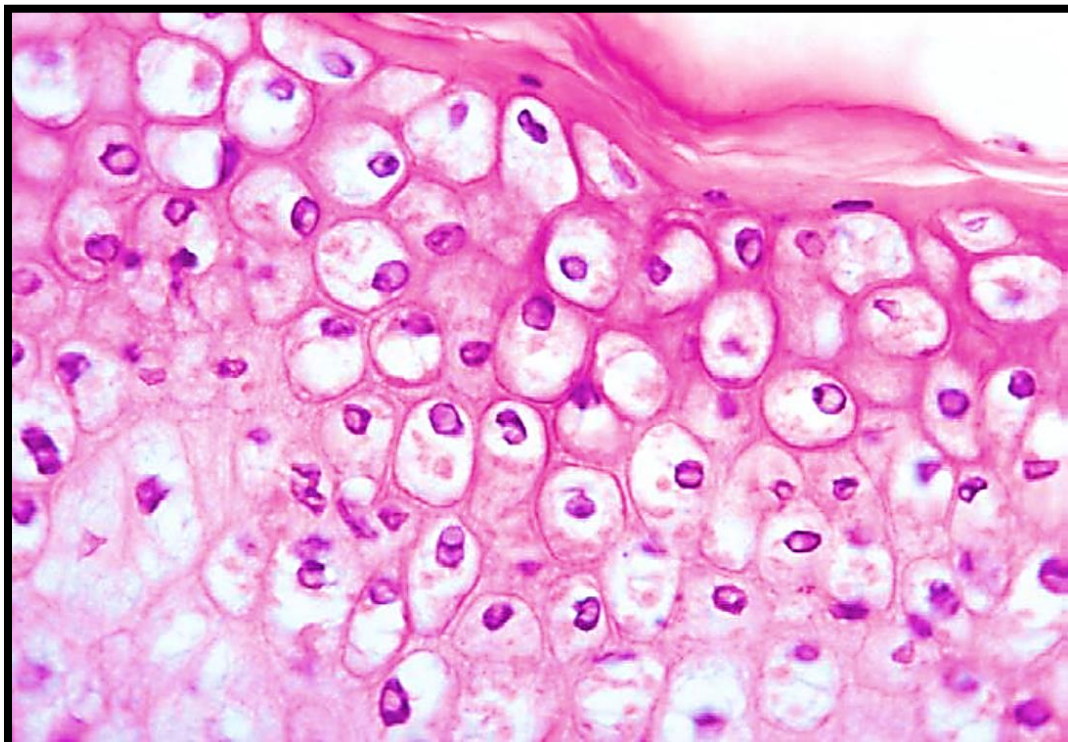


Normal Kidney

Kidney swelling

2. Hydropic degeneration

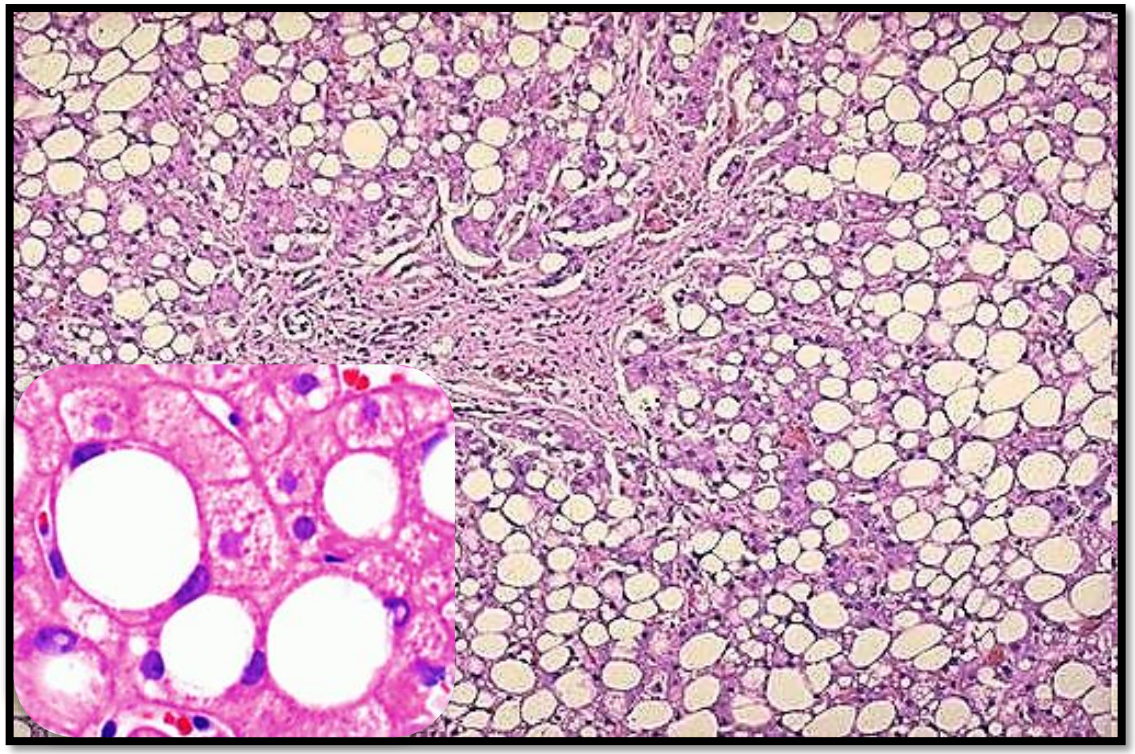
This term is used to describe a more severe condition of cellular swelling characterized by formation of clear vacuoles within the cytoplasm of the affected cells due to continuous accumulation of water.



3. Fatty change (Fatty degeneration)

- This term refers to abnormal accumulation of fat (Triglycerides) within the cytoplasm of parenchymal cells such as those of the liver, heart, and kidney.
- It is an example of reversible (non-lethal) cell injury and is often seen in the liver because of the central role of this organ in fat metabolism.
- In the liver, fatty change may be secondary to alcoholism, diabetes mellitus, malnutrition, obesity, or poisonings.

Reversible damage – fatty change



Fatty metamorphosis (fatty change) of the liver in which deranged lipoprotein transport from injury (most often alcoholism) leads to accumulation of lipid in the cytoplasm of hepatocytes.

Organ:

Liver

Lesion:

1. Presence of clear vacuoles within cytoplasm of the hepatocytes in which the nuclei are generally in normal central situation (A).
2. Periodic acid-Schiff (PAS) reaction shows purplish pink coloration of the vacuoles (B).

Diagnosis:

Glycogen accumulation