CELLULAR RESPONSES TO STRESS AND NOXIOUS STIMULI

Cells are actively interact with their environment , constantly adjusting their structure and function to accommodate changing demands and extracellular stresses.

The intracellular milieu of cells is normally tightly regulated such that it remains fairly constant state , this state is referred to as **homeostasis**.

As cells encounter physiologic stresses or potentially injurious conditions, they can undergo **adaptation,** by achieving a new steady state and preserving viability and function.

The principal adaptive responses are ***hypertrophy, hyperplasia, atrophy*** , **and *metaplasia* .**

If the adaptive capability is exceeded or if the external stress is inherently harmful or excessive, ***cell injury*** develops . Within certain limits the cell injury is ***reversible***, and cells return to a stable baseline .

lf the stress is severe, persistent, results in ***irreversible*** *injury* and death of the affected cells. *Cell death* is one of the most crucial events in the evolution of disease in any tissue or organ.

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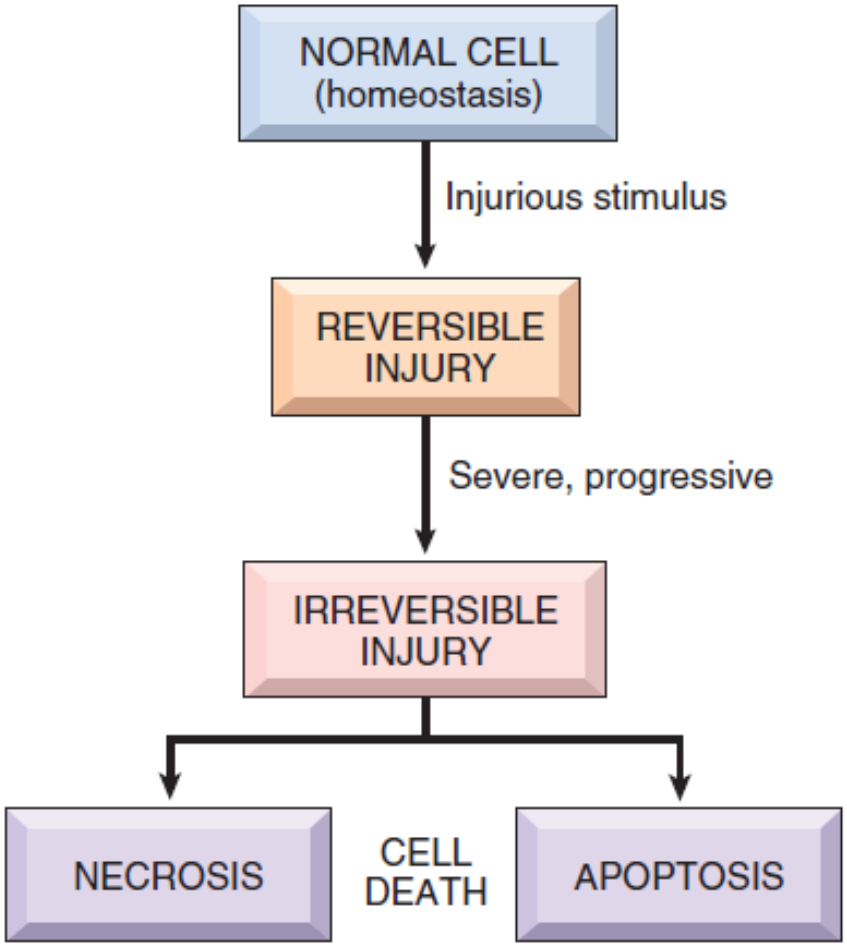


Fig. 2.2 Sequence of reversible cell injury and cell death. Necrosis and apoptosis are the two major pathways of cell death and are discussed in detail later.

CELLULAR ADAPTATIONS TO STRESS

Adaptations are reversible changes in the number, size, phenotype , metabolic activity , or functions of cells in response to changes in their environment .

There two types of Adaptations:-

1- ***Physiologic adaptations*** usually represent responses of cells to normal stimulation by hormones (e.g., the hormone-induced enlargement of the breast and uterus during pregnancy).

2- ***Pathologic adaptations*** are responses of cell to stress that allow cells to modulate their structure and function and thus escape injury .

Adaptations can take several distinct forms :-

Hypertrophy

Is an increase in the size of cells resulting in increase in the size of the organ . In hypertrophy there are no new cells , just the cells are bigger , by containing an increased amount of structural proteins and organelles .

hypertrophy occurs when cells are incapable of dividing or when cells have a limited capacity to divide .

Hypertrophy and hyperplasia can occur together, and both result in an enlarged organ .

Hypertrophy caused either by increased functional demand or by growth factor or hormonal stimulation.

Hypertrophy can be **physiologic** or **pathologic**

- Physiologic hypertrophy :-

Examples

- enlargement of the uterus during pregnancy occurs as a consequence of estrogen-stimulated smooth muscle hypertrophy and smooth muscle hyperplasia

- Enlargement of striated muscle cells in both skeletal muscle and heart due to increased workload in weight lifter and athletes.

- Pathologic hypertrophy :- include the cardiac enlargement that occurs with hypertension or aortic valve disease .

Hyperplasia

an increase in cell number resulting in increase the size of organ or an increase in the number of cells in an organ due to increased proliferation, either of differentiated cells or, less differentiated progenitor cells.

hyperplasia takes place if the tissue contains cell populations capable of replication ; it may occur with hypertrophy and in response to the same stimuli.

hyperplasia is caused by growth factors that are produced by a variety of cell types.

Hyperplasia can be **physiologic** or **pathologic**

- ***physiologic hyperplasia* are :-**

(1) *hormonal hyperplasia*:- exemplified by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy.

(2) *compensatory hyperplasia* :- in which residual tissue grows after removal or loss of part of an organ. For example, when part of a liver is resected.

- ***pathologic hyperplasia*** are caused by excessive hormonal stimulation. For example, endometrial hyperplasia that occurs due to disturbances in the balance between estrogen and progesterone hormones causing abnormal menstrual bleeding .

pathologic hyperplasia constitutes a fertile soil in which cancerous proliferation may eventually arise. Thus, patients with hyperplasia of the endometrium are at increased risk of developing endometrial cancer .

Atrophy

is shrinkage (decrease) in the size of the cell by the loss of cell substance **.**

Atrophy results from **decreased protein synthesis** , **increased protein degradation** in cells and **autophagy** which is the process in which the starved cell eats its own organelles in an attempt to survive .

When a sufficient number of cells is involved, the entire tissue or organ is reduced in size, or atrophic .

Causes of atrophy include:-

1- decreased workload (e.g., immobilization of a limb to permit healing of a fracture).

2- loss of innervations.

3- diminished blood supply .

4- inadequate nutrition .

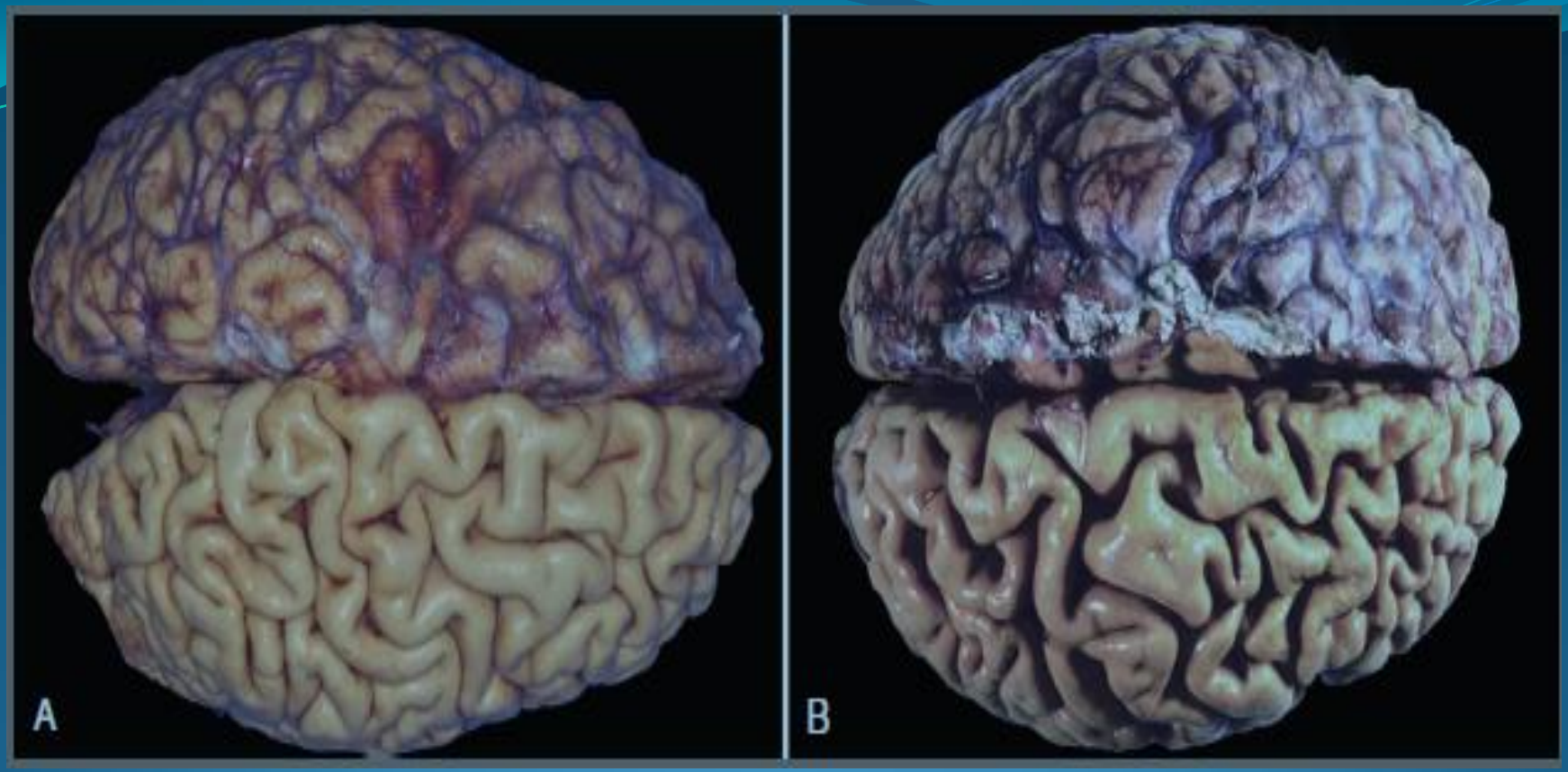
5- loss of endocrine stimulation .

6- aging (senile atrophy).

Types of atrophy

- physiologic atrophy (e.g., the loss of hormone stimulation in menopause and decrease the size of uterus after parturition)

- pathologic atrophy (e.g., denervation , atrophy of brain in old man).



A, Normal brain of a young adult. **B,** Atrophy of the brain in an 82-year-old man narrowing of the gyri and widens the sulci. (aging or senile atrophy).

Metaplasia

Metaplasia is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type. In this type of cellular adaptation, cells which is sensitive to a particular stress are replaced by other cell type better able to withstand to this stress .

Metaplasia may result in reduced functions or increased propensity for malignant transformation

There are to types of metaplasia:-

-Epithelial Metaplasia is exemplified by

1- The normal ciliated columnar epithelial cells of the trachea and bronchi are replaced by stratified squamous epithelial cells which able to survive the noxious chemicals in cigarette smoke .

2- the normal stratified squamous epithelium of the lower esophagus replaced by gastric or intestinal-type columnar epithelium in chronic gastric reflux .

- Mesenchymal Metaplasia For example, bone is occasionally formed in soft tissues, particularly in foci of injury .

CELL INJURY

Cell injury results when cells are exposed to severe stress that they are not able to adapt or when cells are exposed to inherently damaging agents or when cells suffer from intrinsic abnormalities . Injury may progress through a **reversible stage** and **culminate in Irreversible cell injury (cell death)** .

- **Reversible cell injury**. Occur when the injurious agent is mild and shortlived . Functional and morphologic changes are **reversible** if the damaging stimulus is removed. although there may be structural and functional abnormalities , the injury has not progressed to membrane damage and nuclear dissolution.
- **Irreversible cell injury (Cell death.)** With continuing damage, the injury becomes irreversible, at which time the cell cannot recover and it dies.

CAUSES OF CELL INJURY

1- Oxygen Deprivation

Hypoxia, or oxygen deficiency is an extremely important and common cause of cell injury and death. Hypoxia should be distinguished from *ischemia,* which is a loss of blood supply in a tissue due to impeded arterial flow or reduced venous drainage. While ischemia is the most common cause of hypoxia, oxygen deficiency can also result from inadequate oxygenation of the blood, as in pneumonia, or from reduction in the oxygen- carrying capacity of the blood, as in blood loss anemia or carbon monoxide (CO) poisoning. (CO forms a stable complex with hemoglobin that prevents oxygen binding).

2- **Chemical Agents**

are encountered daily in the environment as air pollutants, insecticides, CO, asbestos, cigarette smoke, ethanol, and drugs . Even innocuous substances, such as glucose, salt, water and oxygen, can be toxic.

3 -Infectious Agents

All types of disease-causing pathogens, including viruses, bacteria, fungi, and protozoans, injure cells.

4- Immunologic Reactions

Although the immune system defends the body against pathogenic microbes, immune reactions can also result in cell and tissue injury. Examples include autoimmune reactions against one's own tissues and allergic reactions against environmental substances in genetically susceptible individuals .

5- Genetic defects

Genetic defects can result in pathologic changes as the congenital malformations associated with **Down syndrome** or in the single amino acid substitution in hemoglobin S giving rise to **sickle cell anemia** .

6-Nutritional Imbalances

Protein–calorie insufficiency remains a major cause of cell injury. Vitamin deficiencies are not uncommon even in developed countries .

Excessive dietary intake may result in obesity and also is an important factor in many diseases, such as type 2 diabetes mellitus and atherosclerosis .

7- Physical Agents

Trauma, extremes of temperatures, radiation, electric shock, and sudden changes in atmospheric pressure all have wide-ranging effects on cells.

8- Aging

Cellular senescence results in a diminished ability of cells to respond to stress and, eventually, the death of cells and of the organism .

MECHANISM OF CELL INJURY

- The cellular response to injurious stimuli depends on the type of injury, its duration, and its severity .
- The consequences of an injurious stimulus also depend on the type, status , adaptability, and genetic makeup of the injured cell.
- Cell injury results from functional and biochemical abnormalities in one or more of several essential cellular components .

The most important targets of injurious stimuli are:-

(1) mitochondria , the sites of ATP generation .

(2) cell membranes, on which the ionic and osmotic homeostasis of the cell and its organelles depends .

(3) protein synthesis (ribosome).

(4) the cytoskeleton (microtubules and various filaments).

(5) the genetic apparatus of the cell (nuclear DNA).

1- ATP Depletion

ATP, the energy store of cells, is produced mainly by oxidative phosphorylation of adenosine diphosphate (ADP) during reduction of oxygen in the electron transport system of mitochondria .

In addition, the glycolytic pathway can generate ATP in the absence of oxygen using glucose derived either from the circulation or from the hydrolysis of intracellular glycogen.

The major causes of ATP depletion are

1.reduced supply of oxygen and nutrients,

2.mitochondrial damage, and

3.the actions of some toxins (e.g., cyanide).

The ATP is required for all processes within the cell, include membrane transport, protein synthesis etc. depletion of ATP to less than 5% -10% of normal levels has widespread effect on many cellular systems .

2- Damage to Mitochondria

Mitochondria are the cell's suppliers of life-sustaining energy in the form of ATP, but they are also critical players in cell injury and death.

Mitochondria can be damaged by increases of cytosolic Ca^{2}, reactive oxygen species, and oxygen deprivation, and toxins .

1.The formation of a channel in the mitochondrial membrane, called the **permeability transition pore**. The opening of this channel leads to the loss of mitochondrial membrane potential and PH changes, resulting in failure of oxidative phosphorylation and progressive depletion of ATP, culminating in necrosis of the cells.

2.Increase permeability of the mitochondrial membrane may result in leakage of cytochrome c (the major protein involved in electron transport) that are capable for activating apoptotic pathways .

3- Influx of Calcium

Cytosolic free calcium concentrations that are as much as 10,000 times lower than the concentration of extracellular calcium or of sequestered intracellular mitochondrial and ER calcium.

Ischemia and certain toxins cause an increase in cytosolic calcium concentration, initially because of release of Ca^{2+} from the intracellular stores, and later resulting from increased influx across the plasma membrane. *Increased cytosolic Ca^{2+} activates a number of enzymes*, with potentially deleterious cellular effects .These enzymes include phospholipases (which cause membrane damage), proteases (which break down both membrane and cytoskeletal proteins), endonucleases (which are responsible for DNA), and adenosine triphosphatases (ATPases ; thereby hastening ATP depletion).

4- Accumulation of Oxygen-Derived Free Radicals

Free radicals are chemical compounds with a single unpaired electron in an outer orbital. Such chemical states are unstable and readily react with inorganic and organic chemicals; when generated in cells they attack nucleic acids as well as cellular proteins and lipids.

Reactive oxygen species (ROS) are a type of oxygen derived free radical . are produced normally in cells during mitochonderial respiration and energy generation, but they are removed by cellular defense systems . When their production increase or the defense systems are ineffective, the result is excess of these free radicals, leading to a condition called **oxidative stress**.

Cell injury caused by free radicals include ischemia reperfusion injury , chemical and radiation injury , toxicity from oxygen and other gases, cellular aging , microbial killing by phagocytic cells , and tissue injury caused by inflammatory cells.

5- Defects in Membrane Permeability

The most important membranes that damaged during cell injury are the mitochondrial membrane, the plasma membrane, and membranes of lysosomes.

loss of selective membrane permeability leading to in intracellular accumulation of sodium and efflux of potassium, causing cell swelling.

The plasma membrane can be damaged by ischemia , microbial toxins , lytic complement components , and a variety of physical and chemical agents .

6-Damage to DNA and Proteins

Cells have mechanisms that repair damage to DNA, but if this damage is too severe to be corrected (e.g., after radiation injury), the cell initiates its suicide program and dies by apoptosis. Also accumulation of folded proteins, which may result from inherited mutations cause apoptosis .

REVERSIBLE CELL INJURY

1- Intracellular edema (Cellular swelling)

Also known as **cloudy swelling or hydropic degeneration or vacuolar degeneration** its accumulation of water in cell due to failure of energy –dependent ion pumps in the plasma membrane, leading to an inability to maintain ionic gradients across the membranes i.e. there is influx of sodium (with water) into the cell and departure of the potassium out . Its commonest and earliest form of cell injury.

Etiology (causes)

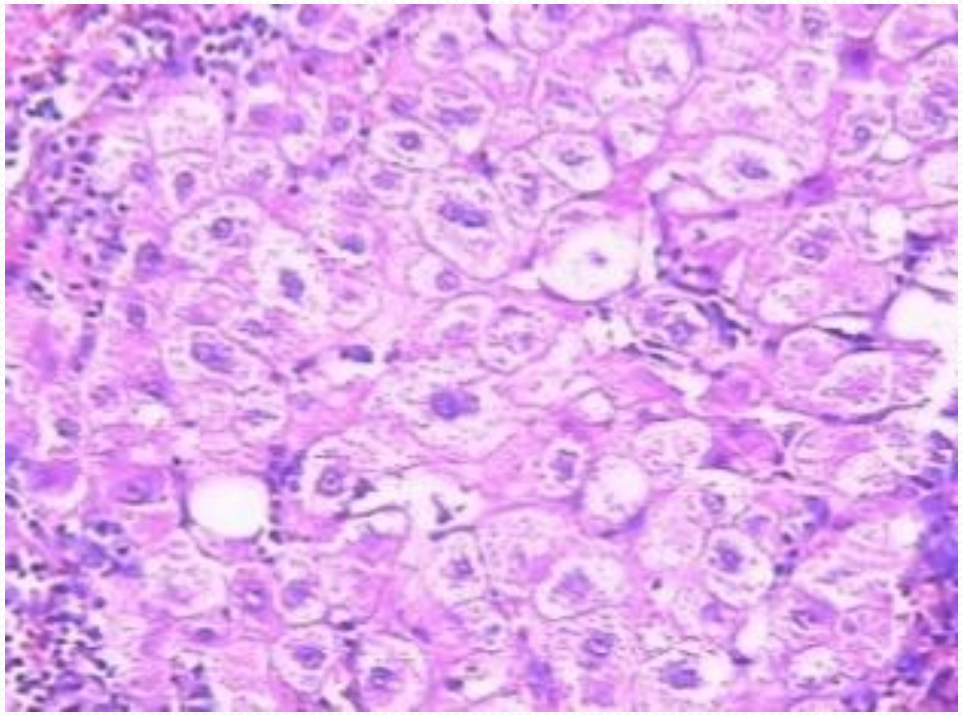
- Bacterial toxins
- Chemical
- Poisons
- Burns
- High fever

Gross Appearance

the organ is swollen with rounded edges ;increased in volume and weight ; and imparts pallor . It is important to distinguish hydropic degeneration from hypertrophy or hyperplasia .

Microscopic Appearance

there are small, clear vacuoles within the cytoplasm; these represent distended segment of the endoplasmic reticulum ER .



2- Fatty change (steatosis)

Fatty changes is manifested by the appearance triglyceride containing of lipid vacuoles in the cytoplasm. It is principally encountered in cells participating in fat metabolism (e.g.hepatocytes)

Causes

1- toxins,

2- protein malnutrition

3-diabetes mellitus,

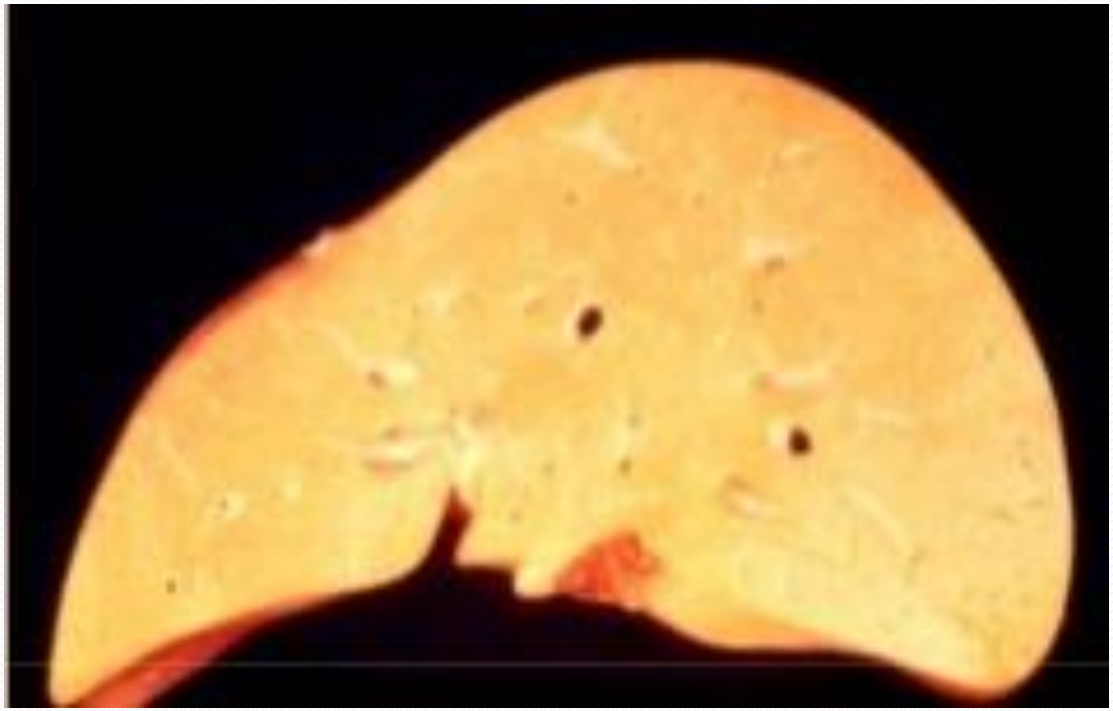
4-obesity.

4- Alcohol abuse

5- diabetes associated with obesity

Gross appearance

The organ becomes large ;yellow ; soft ; and greasy.



Microscopic appearance

Fatty change appear as clear vacuoles in cytoplasm of cell which push the nucleus to the periphery of cell.