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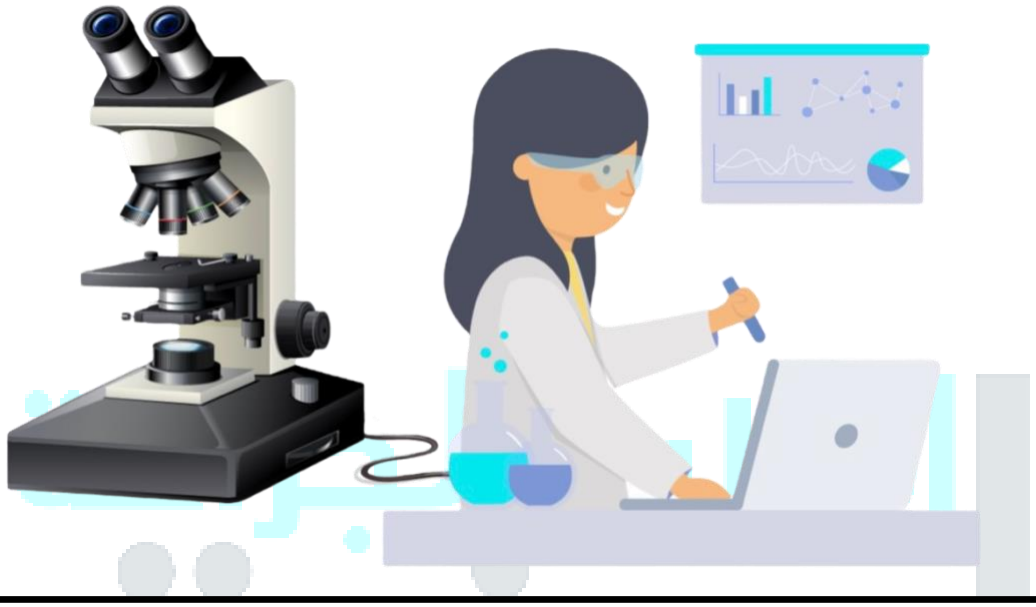
Doctor 2021 - Rouh - medicine - MU



pathology sheet

Lecture 2:Cell injury and necrosis

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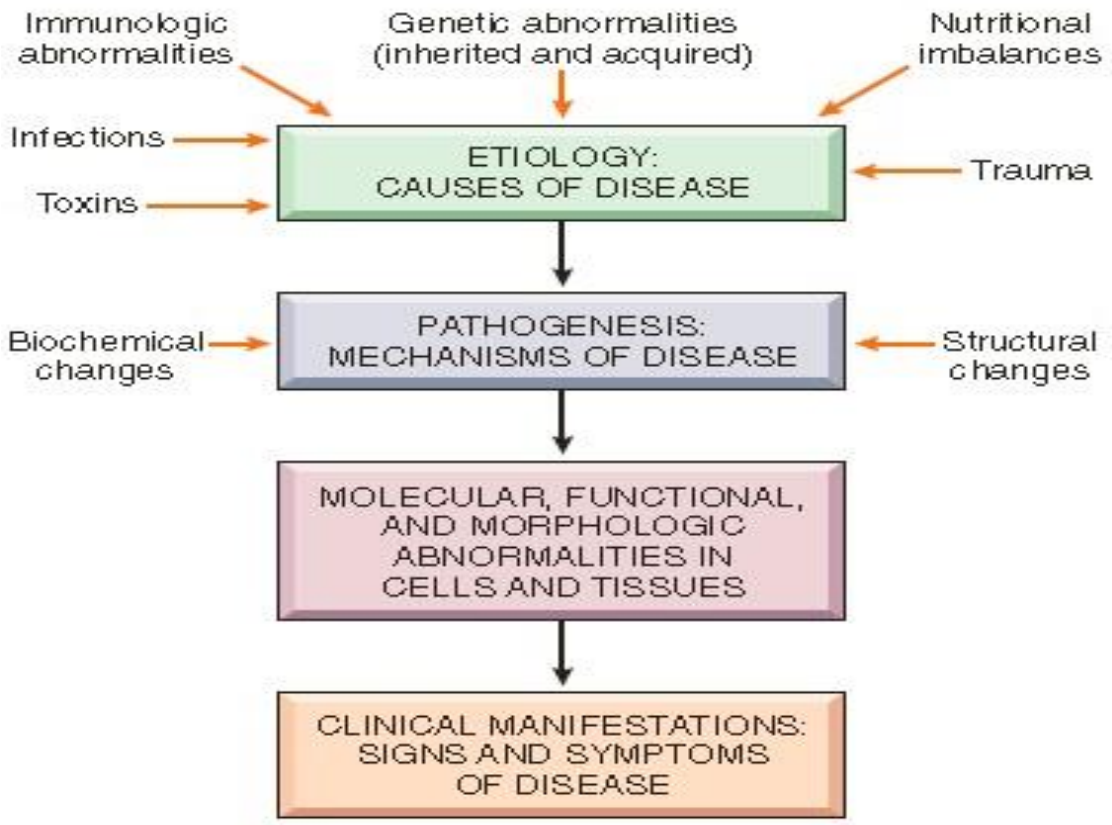
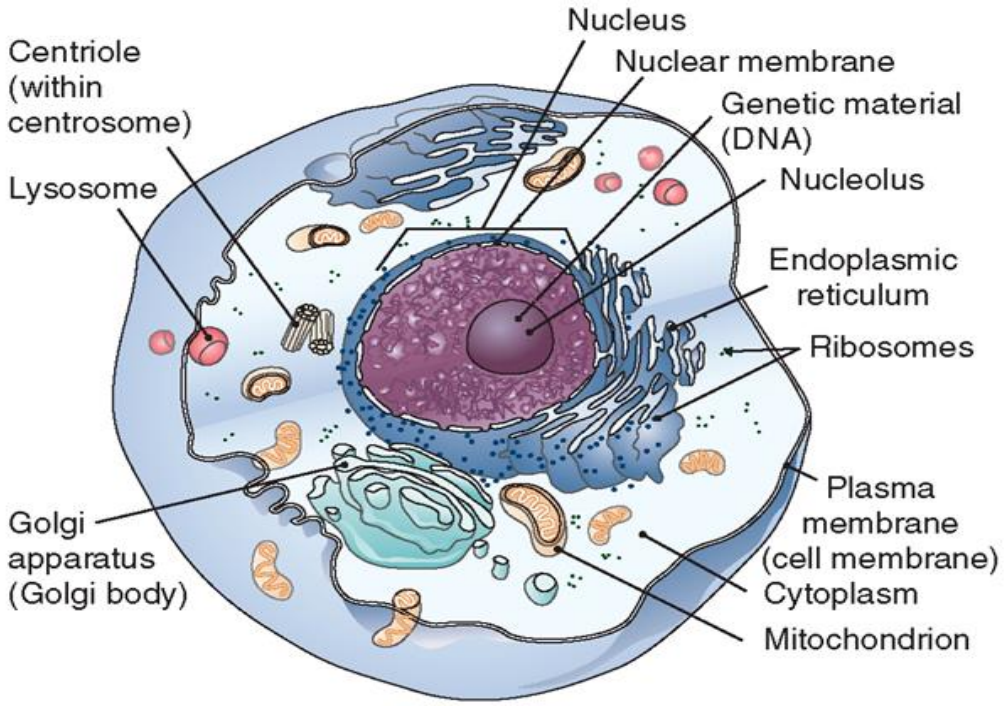

Immunologic abnormalities
Genetic abnormalities (inherited and acquired)
Nutritional imbalances
Infections
Toxins
ETIOLOGY: CAUSES OF DISEASE
Trauma
Biochemical changes
PATHOGENESIS: MECHANISMS OF DISEASE
Structural changes
MOLECULAR, FUNCTIONAL, AND MORPHOLOGIC ABNORMALITIES IN CELLS AND TISSUES
CLINICAL MANIFESTATIONS: SIGNS AND SYMPTOMS OF DISEASE

Normal cell


Nucleus
Nuclear membrane
Centriole (within centrosome)
Genetic material (DNA)
Lysosome
Nucleolus
Endoplasmic reticulum
Ribosomes
Plasma membrane (cell membrane)
Golgi apparatus (Golgi body)
Cytoplasm
Mitochondrion

-Homeostasis.. is maintenance of normal internal environment, such as normal bp, electrolyte level, pH level, etc. any change of such (elevated or lowered) may lead to a disease. Deficiency in vitC increases tendency of bleeding.

Or (Maintaining Dynamic state)

Normal cell is nevertheless able to handle physiologic demands, maintaining a healthy steady state called homeostasis.

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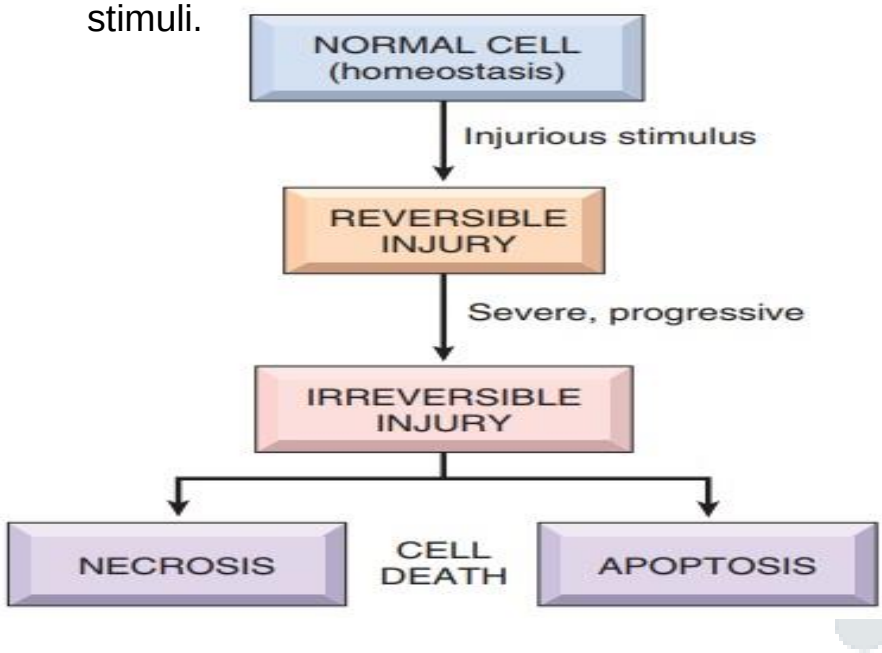
Stages of the cellular response to stress and injurious stimuli.



Causative agent = injurious agent = toxic = stressful agent = insult
Cell injury: molecular and functional alterations due to causative agent

-Adaptations:

Adaptations are reversible functional and structural responses to changes in physiologic states (e.g., pregnancy) (physiologic change, temporary hypertrophy and hyperplasia) and some pathologic stimuli, during which new but altered steady states are achieved, allowing the cell to survive and continue to function.

After injurious stimulus, the normal cell with homeostatic state will progress firstly to adaptation to maintain its function. However, if the injurious stimulus is more severe for longer time, it will become cell injury.
Cell injury: 1. Reversible-→ the cell can return to its normal homeostatic state

2. Irreversible-→ the cell cannot

Adaptation:the first stage after injurious change

-The adaptive response may consist of:

- **an increase in the size (hypertrophy)**
- **functional activity of cells, an increase in cell number (hyperplasia).**
- **a decrease in the size and metabolic activity of cells (atrophy) (people who suffer paralysis their muscles become weak due to denervation to atrophic muscle bundle.**
- **a change in the phenotype of cells (metaplasia) (due to stimulation virus or specific conditions)**

If the stress is eliminated, the cell can return to its original state without having suffered any harmful consequences.

¶×¶ Causes of cell injury:

- **Hypoxia Vs ischemia (most common of reason injury)**
- **Chemical Agents and Drugs**
- **Infectious Agents**
- **Immunologic Reactions**
- **Genetic Abnormalities**
- **Nutritional Imbalances**
- **Physical Agents**

-Hypoxia and ischemia..

+ most common causes of injury. (most common injurious agent)

+Hypoxia: Oxygen deficiency: Hypo(decreased) oxia (oxygen)

Ischemia, anemia, lung disease, CO

+Ischemia: reduce blood supply: arterial obstruction

-Chemical Agents and Drugs :

Decreased vitD leads rickets in children; in adults osteomalacia and later osteoporosis. If glucose increases more than the normal range, it will lead to hyperosmolar state. If oxygen increases abnormally, it will lead to O2 intoxication; also drug overdose; also insecticide; also cigarettes, alcohol. Formalin is a cancerous substance.

-The list of chemicals that may produce cell injury defies compilation.

-Simple chemicals such as glucose or salt in hypertonic concentrations may cause cell injury directly or by deranging electrolyte and fluid balance in cells. Even oxygen at high concentrations is toxic.

-Trace amounts of poisons, such as arsenic, cyanide, or mercury, may damage sufficient numbers of cells within minutes or hours to cause death.

- Other potentially injurious substances are our daily companions: environmental pollutants, insecticides, and herbicides; industrial and occupational hazards, such as carbon monoxide and asbestos; recreational drugs such as alcohol; and the ever increasing variety of therapeutic drugs, many of which have toxic side effects.

-Infectious Agents.

- *These agents range from submicroscopic viruses to tapeworms several feet in length. In between are rickettsiae, bacteria, fungi, and higher forms of parasites. + tapeworms and prions, misfolded proteins in brain that lead to Creutzfeldt–Jakob disease*

-Immunologic Reactions

Could be primary or secondary. Primary: the immune system attacks itself (autoimmune) against internal antigen, such as Hashimoto's thyroiditis in which antibodies attack follicular cells in thyroid leading to decreased amount of thyroxine and the patient's manifestation will be hypothyroidism and Hashimoto's disease (common in female).

- ***-The immune system serves an essential function in defense***
- ***against infectious pathogens, but immune reactions may***
- ***also cause cell injury.***
- ***-Injurious reactions to endogenous self antigens or external agents, such as viruses and environmental substances.***

-Nutritional shortages: ***in developing countries***

- ***- Nutritional imbalances continue to be major causes of cell injury. Vitamins deficiency leads to weight loss***
- ***Anorexia nervosa (A psychiatric disease particularly in females leads to weight loss)***
- ***-Obesity.***
- ***-In addition to the problems of undernutrition and overnutrition (Hyperlipidemia → high cholesterol →myocardial infraction).***

-Genetic Abnormalities

- ***genetic aberrations as extreme as an extra chromosome, as in Down syndrome, or as subtle as a single base pair substitution leading to an amino acid substitution, as in sickle cell anemia.***
- ***Genetic defects may cause cell injury because of deficient protein function, such as enzyme defects in inborn errors of metabolism, or accumulation of damaged DNA or misfolded proteins (such as Alzheimer's, and amyloidosis) , both of which trigger cell death when they are beyond repair.***
  Any genetic alteration will finally lead to protein or enzyme deficiency (cell injury)

-Physical Agents

- ***Physical agents capable of causing cell injury include mechanical trauma, extremes of temperature (burns and deep cold), sudden changes in atmospheric pressure, radiation, and electric shock. Lead to cell injury***

(¬°¬) The Progression of Cell Injury and Death

- If the limits of adaptive responses are exceeded or if cells are exposed to damaging insults, deprived of critical nutrients, or compromised by mutations that affect essential cellular functions, a sequence of events follows that is termed cell injury.

-Cell injury is reversible up to a point, but if the injurious stimulus is persistent or severe, the cell suffers irreversible injury and ultimately undergoes cell death.

- Adaptation, reversible injury, and cell death may be stages of progressive impairment following different types of insults.

If the injurious agent persists, or increases in concentration, or is not mild (moderate to severe), or leads to damage to cells, the cell starts the

process of cell injury, or time. For example, Tuberculosis (TB) is a chronic infection.

2- Duration. 3-types of injurious agent

-REVERSIBLE Cell injury (cell may return to normal state)

Reversible cell injury is characterized by functional and structural alterations in early stages or mild forms of injury, which are correctable if the damaging stimulus is removed.

Two features are consistently seen in reversibly injured cells.

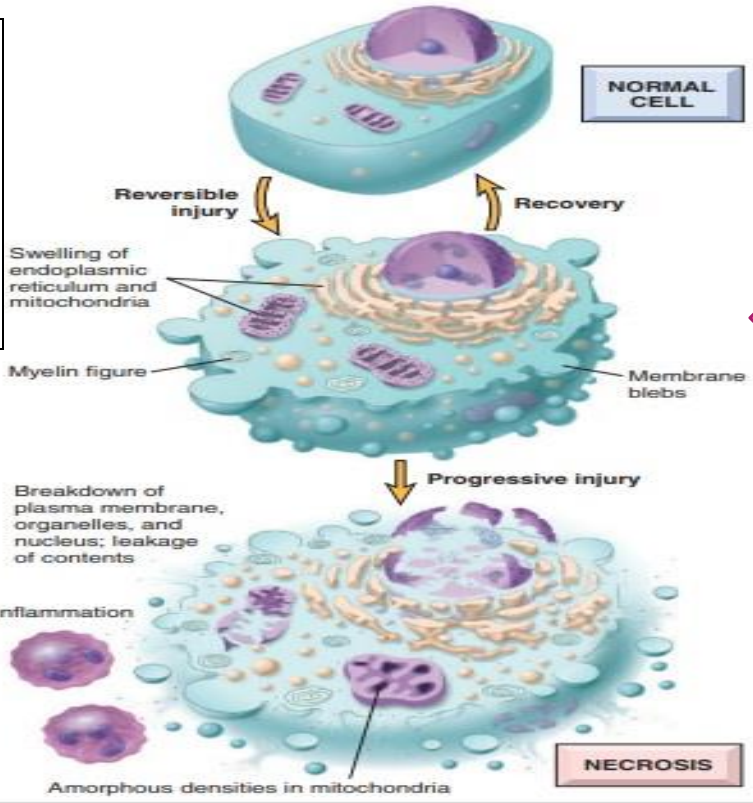
- ***Early alterations in reversible injury include generalized swelling of the cell***
- ***Fatty change.(liver, heart)***

-Two main morphological abnormalities in reversible cell injury;

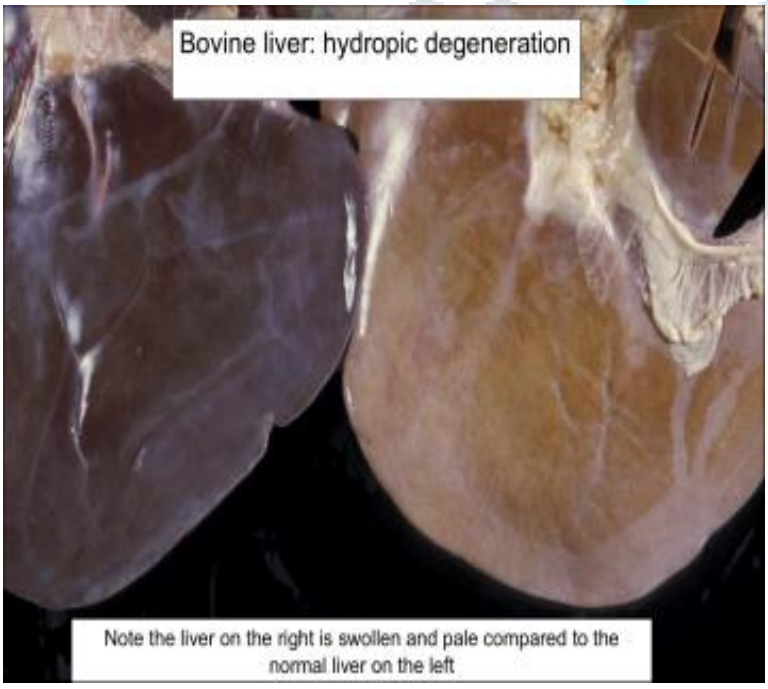
1. Cellular Swelling:

- ***Results from failure of the sodium potassium pump (energy-dependent ion pumps) due to ATP depletion.(increase H2O in the cell)***
- ***It is reversible***
- ***Gross > microscope***
- ***Gross: pallor, ↑ turgor, ↑ weight.***
- ***Microscopy: small clear vacuoles within the cytoplasm (hydropic change or vacuolar degeneration)***
- ***The organelles within the cells are also swollen.***

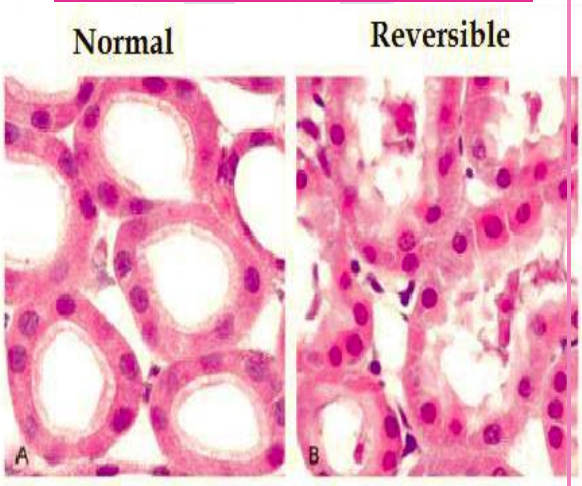
Blebs filled with water due to ATP depletion



Reversible injury



Reversible: displaced mucousa swollen, numerous vacuoles.



-Two main morphological abnormalities in reversible cell injury;

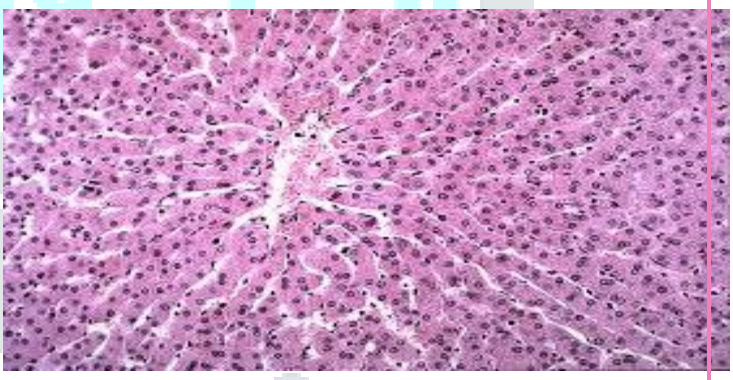
2. Fatty change:

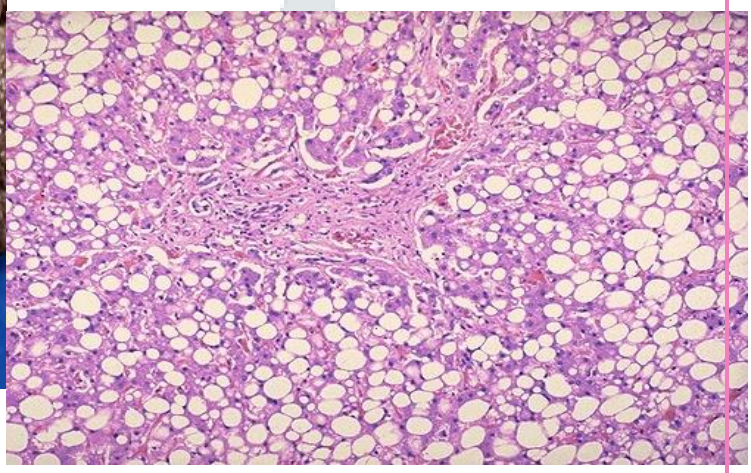
- **Occurs mainly in hypoxic injury and in toxic and metabolic injury.**
- **Microscopy: lipid (triglyceride) vacuoles in the cytoplasm**
- **Seen mainly in organs that involved in fat metabolism like Hepatocytes (LIVER) and myocardial cells (HEART)**
- **It is reversible.**

All injurious agents lead to ATP depletion, fever for example.

Fatty: always yellowish (grossly, macroscopically) associated with people who drink alcohol and diabetic. It is reversible.

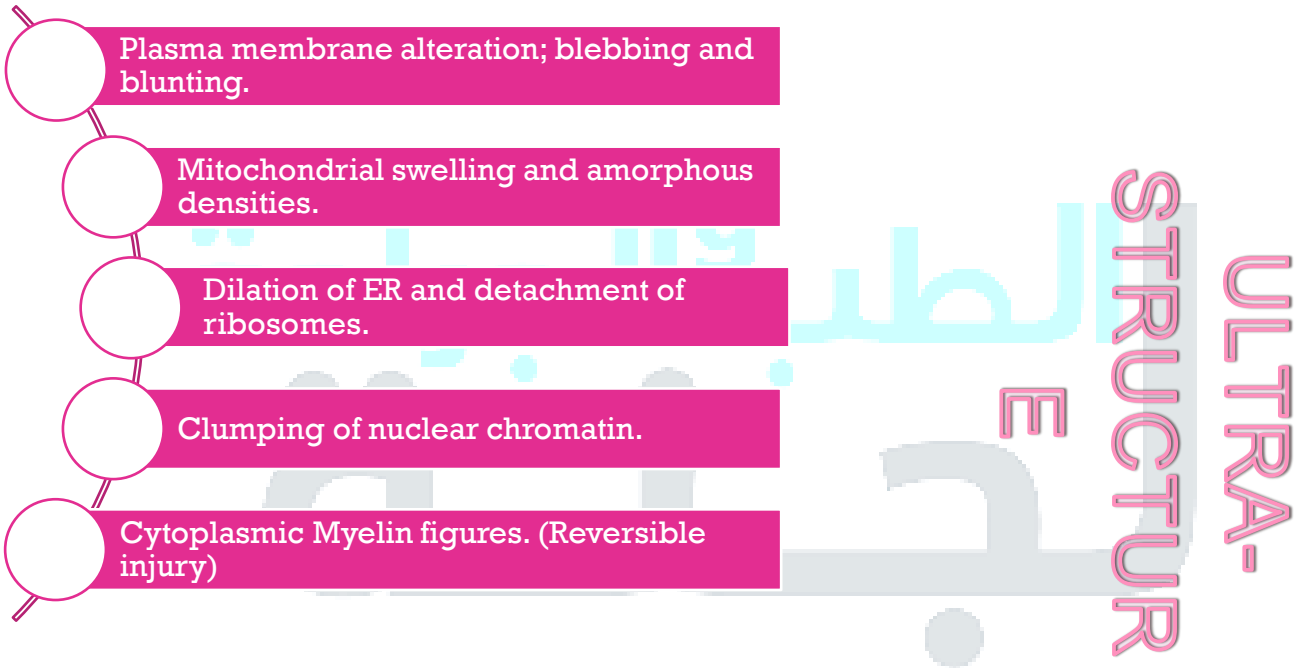
Normal





Morphological changes : gross: fatty liver, microscopically: numerous vacuoles filled with lipid. Clinical manifestation: diabetic patient, high liver function.

All organelles of cell are swollen (1+2+3), and clumping of chromatin and Myelin figures (4+5) are associated in cell injury



-IRREVERSIBLE Cell injury:

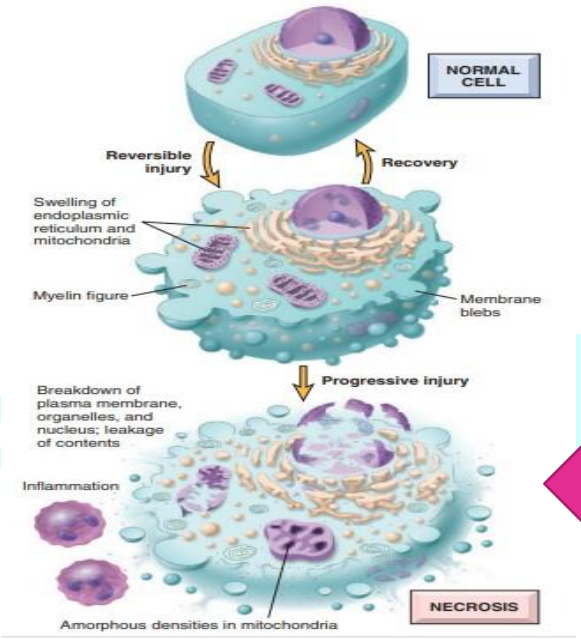
+ if the stress is severe, persistent, or rapid in onset. + leads to damage to cells

+ injured cells pass a nebulous "point of no return" and undergo cell death.

-Irreversible injury: three phenomena

Although there are no definitive morphologic or biochemical correlates of irreversibility, it is consistently characterized by three phenomena:

- **the *inability to restore mitochondrial function* even after resolution of the original injury. Consequence of irreversible: necrosis, reversible: return to the normal, or if the injurious stimulus is severe, it will become irreversible, thus, necrosis.**
- **the *loss of structure and functions of the plasma membrane and intracellular membranes***
- **and the *loss of DNA and chromatin structural integrity*.**

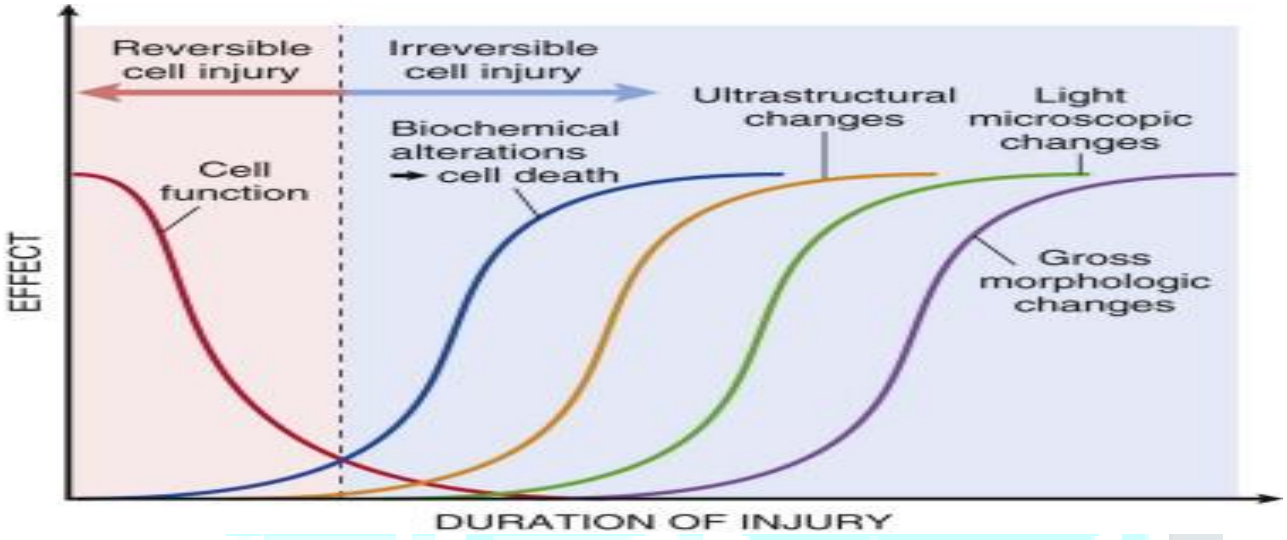


Irreversi

After irreversible

First change is biochemical and loss of function -Cellular function may be lost long before cell death occurs, and that the morphologic changes of cell injury (or death) lag far behind loss of function and viability . For example, celiac disease, in which gluten (the injurious agent) stimulates destruction of microvilli in small intestines. This results in long term the anemia, due to malabsorption of food by villi because they are lost.

¥×¥ Sequential development of biochemical and morphologic changes in cell injury. Cells may become rapidly nonfunctional after the onset of injury, although they may still be viable, with potentially reversible damage; a longer duration of injury may lead to irreversible damage and cell death. Note that irreversible biochemical alterations may cause cell death, and typically this precedes ultrastructural, light microscopic, and grossly visible morphologic changes.



Thrombi are most common cause of MI (myocardial infraction), they make arterial obstruction and this makes ischemia (loss of blood supply), and this makes ATP depletion, then reversible injury, then if blood supply returns, it will not undergo irreversible (it will compensate). If ischemia persists, the cell will undergo irreversible injury. After 1-2 mins, troponin goes out of cells to blood circulation, we then take biopsy, if troponin is positive, then MI is confirmed.

-When cells are injured they die by different mechanisms, depending on the nature and severity of the insult.

المرءُ لا يصِلُ بجُهده، أنت تبذِلُ جهدَك ثمَّ يفتحُ اللهُ عليك.

ـ د حاتم الأنصاري.