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Pathology

Doctor 2017 | Medicine | JU

Sheet Slides

DONE BY

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Introduction

Pathology comes from Patho: disease/suffering and Logy: study. Therefore, Pathology is the study of disease.

Pathology is the bridge between basic science and clinical science. It is essential to understand the diseases, signs, symptoms, mechanisms, everything u need to know about the disease and the pathogenesis of the disease which we will be taking in this course.

Extra important information

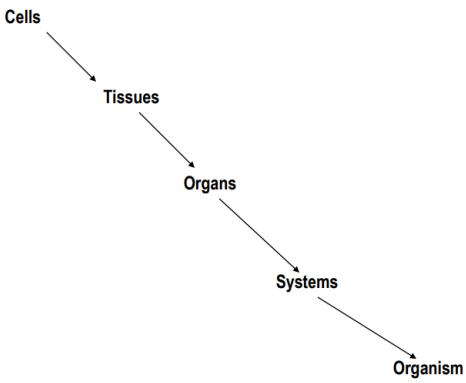
There are **two important terms** we will encounter throughout our study of pathology and medicine and therefore, they must be known:

- **Etiology** refers to the underlying causes and modifying factors that are responsible for the initiation and progression of a disease.
- **Pathogenesis** refers to the mechanisms of development and progression of disease, which account for the cellular and molecular changes that give rise to the specific functional and structural abnormalities that characterize any particular disease.
  - **Conclusion: etiology** refers to why a disease arises, and **pathogenesis** describes how a disease develops.

Pathology is divided into Basic Pathology and Systemic Pathology. This course will cover the basic pathology, which includes the following chapters: Cell injury and Adaptation, Inflammation and Repair, Neoplasia.

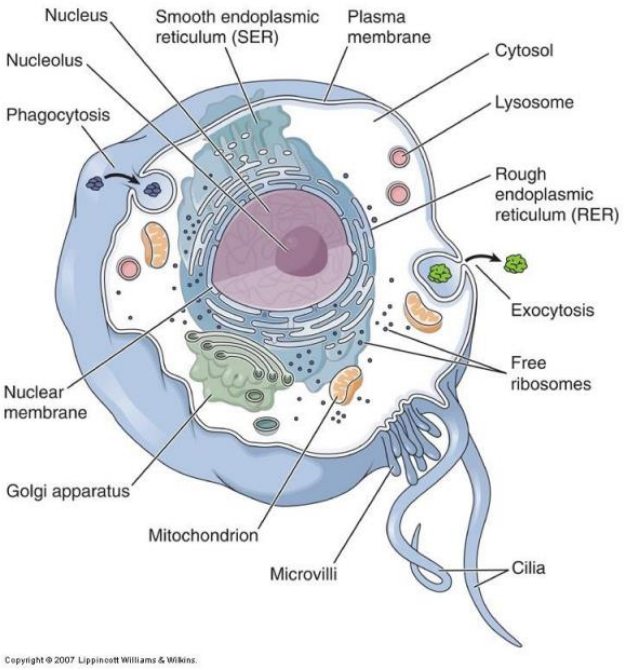
First Chapter: Cell injury, Cell death and Adaptation

- The cell is the basic unit of the human body.
  - A group of cells will form tissues.
  - The group of tissues will form Organs.
  - The group of organs will form Systems.
  - Systems will form the whole organism.



Any disease state will start at the cellular level (morphology or molecular changes in biochemical level in the cell) that's why we will study any changes that occur to the cell after injury.

The cell is composed of:



- Cell membrane that preserves the integrity of the cell which is a very important role.
- Nucleus that contains DNA or chromatin material which plays a major role and has a part in cell injury.
- Cytoplasm that have organelles such as mitochondria (where production of ATP occurs), ribosomes, endoplasmic reticulum, lysosomes which are all essential components affected in the cell injury.

Homeostasis

All normal cells are in homeostasis; which is a state of balance.

Recall from physiology course:

Homeostasis: is the ability of our body to maintain almost constant variables.

Everything in the cell and outside the cell is preserved in a certain range, any deviation from this range due to changes that occurred will cause the cell in that case to adapt.

When we are put under a stress, the first thing we do is try to cope with that stress. The cell does the same thing, it tries to cope with the stress (adaptation) in a way that it remains functional. Furthermore, severe prolonged injury problems such as hypoxia and ischemia cause the cell to lose its ability to adapt and therefore, enters injury phase. The diagram in page 3 summarizes the chapter.

Summary: The cell is in homeostasis. When any deviation occurs, the cell tries to cope with the stress by adaptation. If it fails to adapt, cell injury happens. (Adaptation to stress can progress to cell injury if the stress is not relieved).

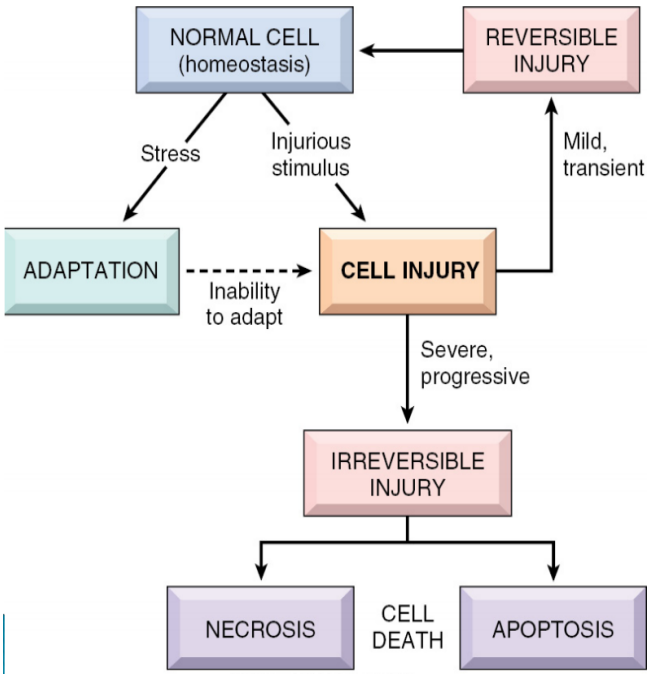
In adaptation: the cell's function may increase, decrease or change completely.

In Cell Injury: the cell loses all its function.

Cell injury can be reversible: Reversible injury is the stage of cell injury at which the deranged function and morphology of the injured cells can return to normal if the damaging stimulus is removed.

If stress continues, reversible injury transforms to irreversible cell injury which is the point of no return, the cell will not return to its normal state and is, unfortunately, dead.

So, irreversible cell injury is cell death and takes two pathways: 1) Necrosis 2) Apoptosis



Adaptation

Note: you will be asked whether the adaptation is physiologic or pathologic.

First thing the cell does when a stress is encountered is changing its size, number or type to cope with this stressful situation. If it can't overcome this stressful situation, it enters cell injury phase.

- Adaptation is divided into 4 types:

1) **Hypertrophy** 2) **Hyperplasia** 3) **Atrophy** 4) **Metaplasia**

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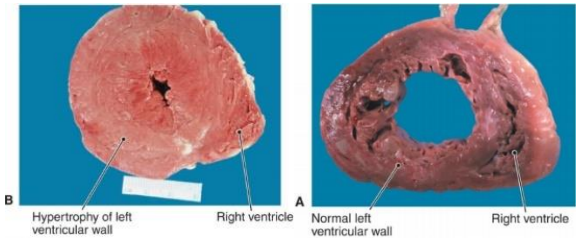
1) Hypertrophy: increasing in cell size and functional capacity.

The cell that can't divide; cannot undergo proliferation, therefore it can only undergo hypertrophy to maintain its function. Increase in size leads to increase in function to withstand the stress.

***Histology**: Remember that the cells that can't proliferate are the cells that are highly specialized*

- Hypertrophy adaptation can be pure or mixed.
  - Pure Hypertrophy: The tissue undergoes hypertrophy only, since it is not capable of proliferation.
  - Mixed Hypertrophy with hyperplasia: which happens in cells that can proliferate; they do hypertrophy and hyperplasia.
- In the mechanism of hypertrophy, the cell gets bigger because the number of structural proteins produced is increased to do more function.
- We can have Physiologic hypertrophy or pathologic hypertrophy.

- Causes of Hypertrophy (driving force): Hormonal stimulations or Increased functional demand.

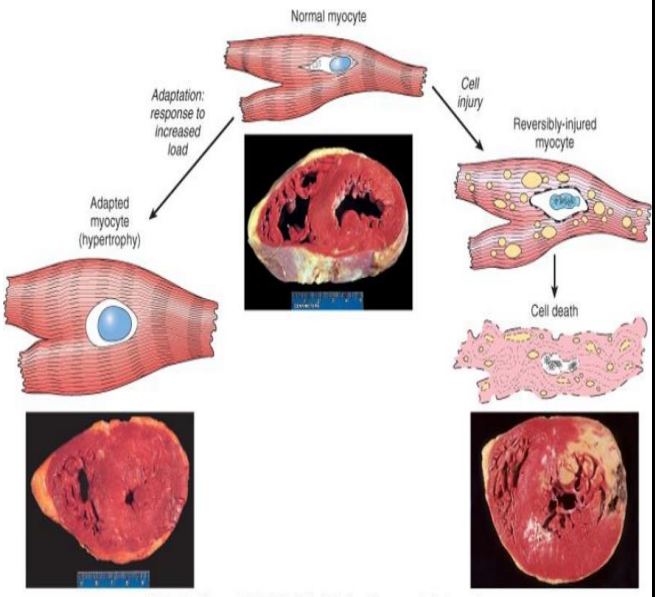


Pathologic

Examples:

a) Increased functional demand

Cardiac hypertrophy due to Hypertension (high vascular resistance in the blood vessels) or Aortic valve stenosis (high resistance in the aortic valve)

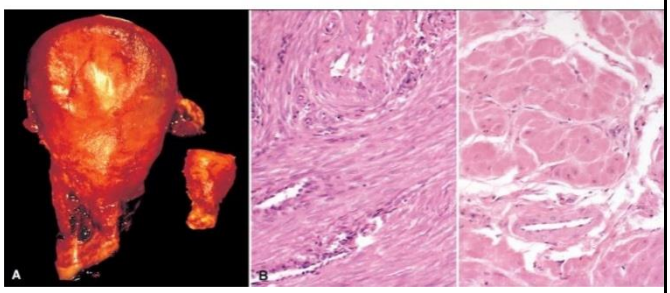


Due to the high resistance, the left side of the heart must pump more blood and needs to push stronger to deal with this resistance and to give powerful contractions. To do that, cardiac myocytes undergo hypertrophy not hyperplasia because cardiac cells cannot divide. When a huge number of cells undergo hypertrophy, the whole organ undergoes hypertrophy (thickened ventricle wall). This is a pathologic hypertrophy.

The problem with hypertrophied cells is that they need more oxygen even if blood supply is normal, with time it will start to suffer from relative ischemia. Degenerative changes occur in the myocardial fibers, and heart failure can develop. **Summary:** With time, people with hypertension will have cardiac hypertrophy adaptation then heart failure (failure of adaptation) since the heart will no longer be able to pump with same power; it will lose its power in contraction.

b) The uterus in pregnancy

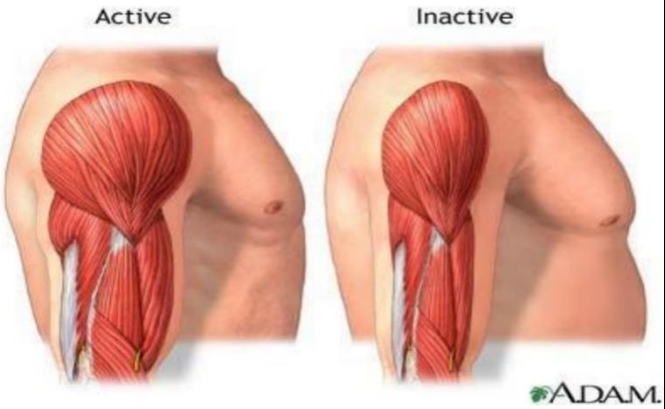
Physiologic



- This is a physiologic hypertrophy because Pregnancy is a physiologic state.
  - The uterus, under the hormonal stimulation of high estrogen levels, will get bigger to accommodate the fetus but here it is mixed; Hypertrophy and hyperplasia because smooth muscles of the myometrium can divide/proliferate.

11:30

c) Skeletal muscles in athletes and body builders

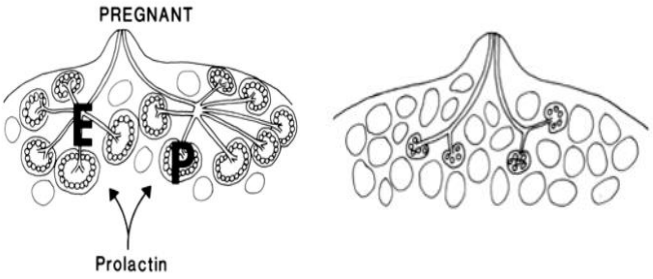


- Another example for physiologic hypertrophy.
  - Increased work load/demand on these muscles will lead to hypertrophy.
  - Skeletal muscles (straited muscles) are like cardiac muscles, they cannot proliferate; They can only undergo pure hypertrophy.

2) Hyperplasia: Increase in the number of cells.

- Pure or mixed with hypertrophy.
- Cells that have proliferative ability undergo this adaptive mechanism.
- It can be physiologic, pathologic or can precede/transform to cancer.

Causes of hyperplasia: increased functional demand, compensatory, injury, infections and Hormonal stimulation like breast and uterus during pregnancy (physiologic hyperplasia) glands in the breast, smooth muscles undergo proliferation, hyperplasia.



Compensatory hyperplasia: cells that take place of cells that are gone for certain reasons.

Examples:

a) Compensatory hyperplasia in liver cells: Physiologic

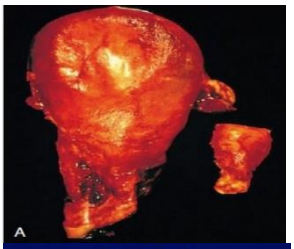
If a patient had Liver tumor or trauma and we had to remove a part of the liver, the rest of liver cells have the ability of proliferation to regain its normal size after a period of time. Which is called **compensatory hyperplasia.**

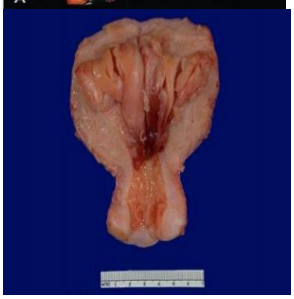
❖ If the tissue is capable of proliferation and there is an increased demand it will proliferate, undergo hyperplasia.

b) Injury: cut wound; we must have proliferation and hyperplasia of the Fibroblasts to be able to close that wound.

c)**Warts caused by Human Papillomavirus (HPV):** Proliferation/hyperplasia of the keratinocytes in the skin (pathologic hyperplasia).

d) **Another example is Endometrium** which can have hyperplasia as a pathological condition due to excessive estrogen as a pathologic state (hormonal stimulation) for **different reasons**:





1) Patient is taking drugs that contain estrogen.

2) Patient has anovulatory cycles; So, estrogen keeps functioning unopposed by progesterone, estrogen causes proliferation in endometrial glands.

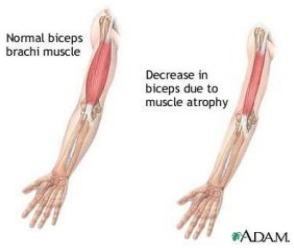
3) Patient has tumor producing estrogen; Estrogen affects endometrium, leads to endometrial hyperplasia.

- This is pathologic but reversible. However, if it stays untreated it can turn to endometrial cancer.

e) Breast gland hyperplasia: pregnancy and lactation: Hormonal stimulation, physiologic.

3) Atrophy

- Shrinkage; decrease in cell size and cell function (atrophic cells can still function).
- Mechanism is the opposite of hypertrophy's mechanism:
  - Protein synthesis decreases.
  - Protein degradation increases
  - And sometimes another mechanism called autophagy occurs:
    Autophagy; the cell starts to eat itself; its own organelles and proteins in order to cope well with the new conditions and preserve the function.
- **Causes**: Decreased demand, ischemia (cells shrink due to reduced blood supply), disuse, aging, lack of nerve or hormonal stimulation, chronic inflammation.
- Remember in all adaptive mechanisms, when the stress is no longer present, it goes back to its normal condition.



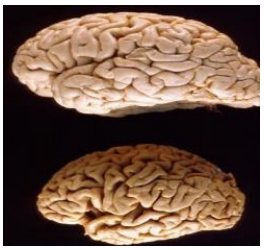
Examples

a) Decreased demand/Disuse: Bone fracture

Immobilization of fracture, So the patient stops using the muscle (as you broke an arm bone you can't move your hand) after you remove your

cast/splint, the arm will be thinner than the other one because you didn't use your muscle. (muscle atrophy)

Brain atrophy due to brain ischemia or



Notice that loss of brain substance narrows the gyri and widens the sulci

b) Aging. During aging, cells undergo atrophy/shrinkage.

c) Lack of nerve stimulations.

Cut wound or injury to one of the nerves that supply skeletal muscles. (loss of innervation) Therefore, skeletal muscles that are supplied by this nerve will undergo atrophy.

d) Lack of hormonal stimulations: Endometrium after menopause

Estrogen is the driving force for proliferation, therefore, when estrogen levels decrease after menopause, endometrium undergoes atrophy (Endometrial atrophy).

This is a physiologic atrophy.

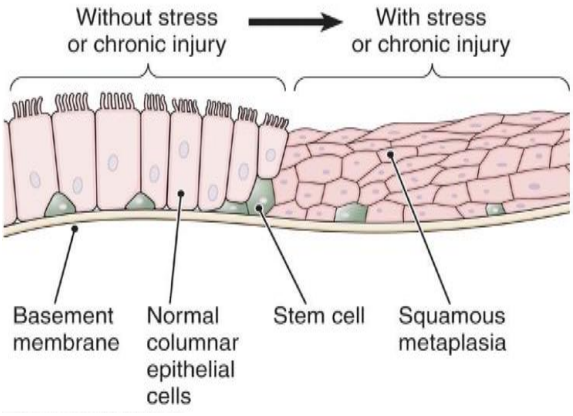
4) Metaplasia: the last adaptive mechanism.

Metaplasia is a change from one cell type to another. New cell type copes better with stress but functions less. It is a reversible mechanism. Mechanism: Altered stem cell differentiation. However, this persistent change increases risk of cancer.

Examples

a) Simple example is what happens to smokers in their bronchial airways. The lining cells in bronchial airways are ciliated columnar pseudostratified epithelium or respiratory epithelium. Recall cilia is very important in clearance of any particles that enter along with air. pseudostratified cells can produce mucus which is also very important and has a protective role.

Columnar mucosa, very functional, can't handle smoking so the stem cells differentiate to another type, squamous epithelium, which is less functional in protection role. The transformation doesn't happen to the mature cell.



The transformation happens in the level of stem cells to give squamous cells instead of columnar cells, which is better in opposing the stress, but it cannot stop the particles or dust that enter the airway. This is reversible. **However,** if it stays it can

transform to dysplasia, accumulate mutations, and converts to cancer/squamous cell carcinoma. 20:30

b) Gastro Esophageal Reflux Disease (GERD)

The lining of esophagus is squamous cells. When Acidic secretions of the stomach go back to esophagus it affects the cells and eventually cells in that area change from squamous epithelium to intestinal (or gastric) type epithelium. Therefore, the function of the squamous epithelium is lost but the new epithelium can handle and withstand the acidity. This is reversible. However, it can transform to esophageal adenocarcinoma.

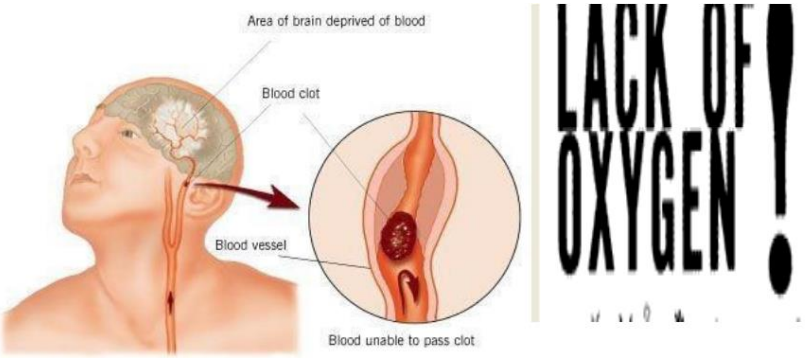
c)Vitamin A deficiency.

Vitamin A is important in differentiation of epithelial cells like leading to differentiated ciliated epithelial cells in airways. Therefore, vitamin A deficiency may cause squamous metaplasia. All adaptive mechanisms are reversable unless it is mutated then it can convert to a cancer.

Cell injury

If the stress is severe, prolonged and the cell cannot do adaptation, it enters cell injury.

Causes of Cell injury



1) Oxygen deprivation

- **Hypoxia and ischemia**

Hypoxia: which refers to oxygen deficiency

Ischemia: reduced blood supply; an inadequate blood supply to an organ or part of the body.

Most common cause of hypoxia is **ischemia.**

No blood (blood carries oxygen), tissue hypoxia occurs. Oxygen is essential for oxidative phosphorylation which is important to cell function and to produce ATP.

Not always hypoxia is related to ischemia, there are other causes that can prevent oxygenation of the blood such as:

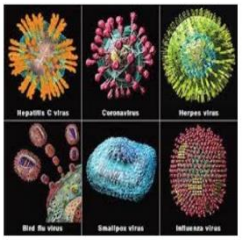
Problems in oxygenation of the blood like obstructive pulmonary diseases in smokers and pneumonia, Anemia: low oxygen carrying capacity.

2) Toxins, chemical agents



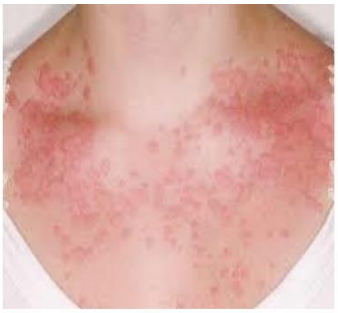
Potentially toxic agents are encountered daily in the environment; these include air pollutants, insecticides, CO, cigarette smoke, ethanol and drugs especially when used excessively or inappropriately. Innocuous chemicals such as glucose (sugar), salt, water and oxygen can be toxic and lead to injury especially when used in large amounts.

3) Infectious agents

All types of disease-causing pathogens including viruses, protozoa, parasites, bacteria, fungi and worms.

4) Immunologic reactions



- Allergic reactions (like eczema) against environmental substances like dust and excessive or chronic immune responses to microbes.
- Autoimmune reactions (like Autoimmune hepatitis) against one's own tissues.

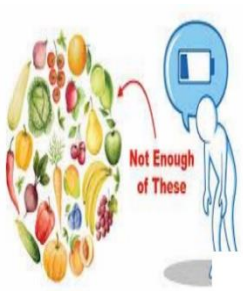
In all these situations, immune responses elicit inflammatory reactions, which are often the cause of damage to cells and tissues.

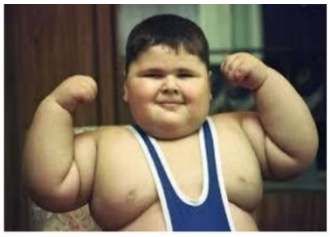
5) Genetic factors/abnormalities


- Starting from those at the level of chromosomes which leads to pathologic changes as conspicuous as the congenital malformations associated with Down syndrome or as subtle as the single amino acid substitution in hemoglobin giving rise to sickle cell anemia.

- Genetic defects may cause cell injury as a consequence of deficiency of functional proteins, such as enzymes in inborn errors of metabolism, or accumulation of damaged DNA or misfolded proteins, both of which trigger cell death when they are beyond repair.

6) Nutritional imbalances

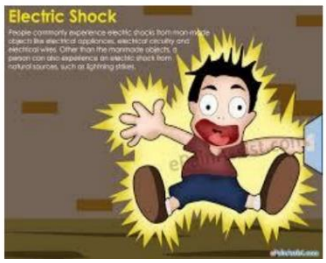




Protein-calorie insufficiency and vitamin deficiencies are major causes to cell injury

On the other hand, Excessive nutrition can cause obesity which is an underlying factor in many diseases.

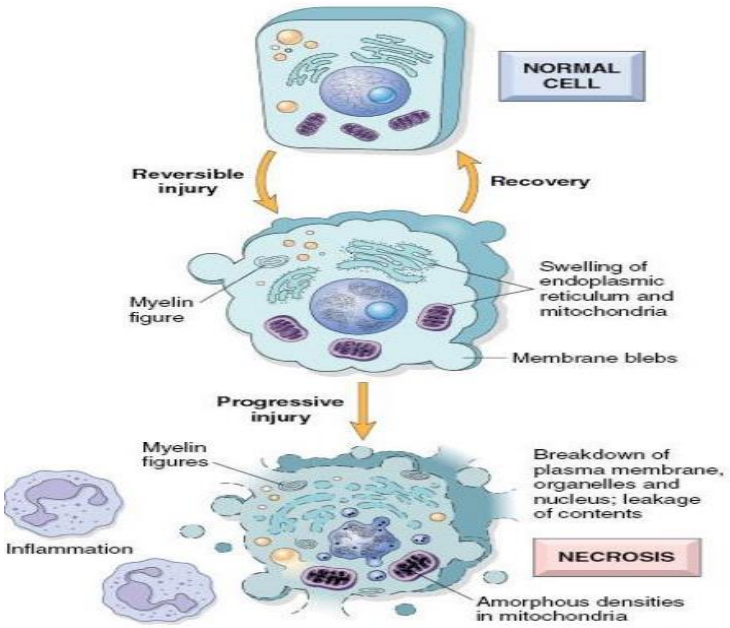
7) Physical agents

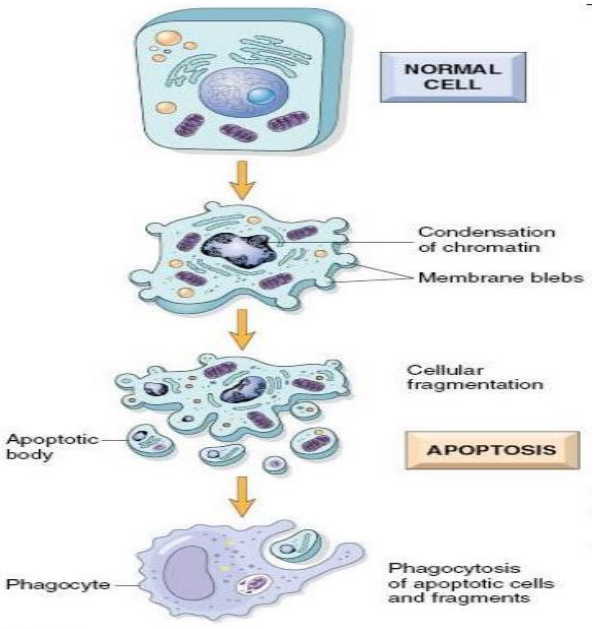


like trauma, sudden changes in temperature (excessive heat, excessive cold), electric shocks and sudden changes in atmospheric pressure.

8) Aging

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





What is the difference between normal (adaptation) and reversible cell injury?

In reversible cell injury, the cell has bigger size, cellular swelling. Moreover, the cell in reversible injury is not functional but still alive (unlike in adaptation, there is stress, but the cell stays functional). Cell being unable to function means no ATP production which is needed in the sodium potassium pump. Instead of getting sodium out, sodium enters the cell because the pump cannot function without Autopodium takes water with it. Therefore, it swells until it ruptures. If it ruptures, we enter the irreversible cell injury phase.

Hypertrophy and injury/swelling

In hypertrophy, the cell is still functional and what causes its size to increase is the increasing amounts of structural proteins. On the other hand, in cell injury the cell swells because of the excessive amounts of water entering the cell along with sodium and the cell in this case is non-functional.

Changes that happen to the cell can be seen by:

1)**Naked eye**, changes that can be seen on the whole organ, they often take time to be seen since functional changes happens then morphological changes appear.

2)**Light microscope.**

3)**Electron microscope.**

Ultra-structural changes that happens to the cell, mitochondria, nucleus, ribosomes and endoplasmic reticulum **cannot** be seen through a light microscope but can be seen through an electron microscope. 31:25

Hallmarks of reversible injury

- Can be seen by electron microscope.
- Plasma membrane alterations (blebbing, blunting. BUT, it is still intact since the cell didn't explode yet).
- Mitochondrial change (swelling and appearance of densities);
- Dilation of ER.
- Nuclear clumping of chromatin. (clumped, very dark)

- Cytoplasmic myelin figures appear.

➢ Myelin: a lipid material. The membrane of the cell is made of phospholipids. When the cell is injured, denaturation of proteins and degradation of lipids would occur. Therefore, they enter the cells and undergo precipitation in the form of myelin figures, lipid droplets.

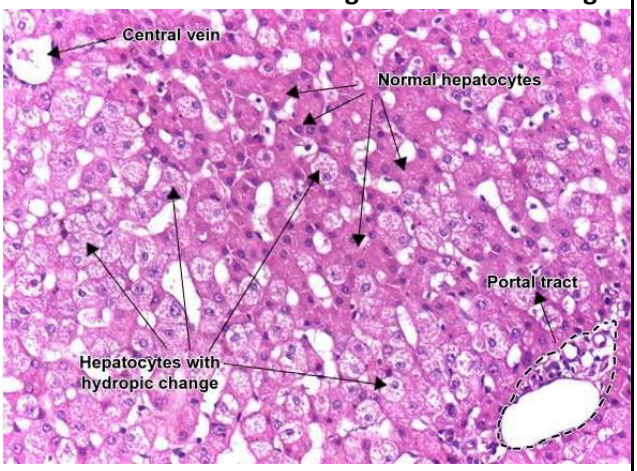
- Changes that can be seen in light microscope. It depends on the type of tissue that was injured, but most important changes are:

1) Hydropic change; cells are swollen due to accumulation of water inside it.

This is a section of the liver. Cells are swollen, they look like a bubble (water is not stained by hematoxylin and eosin)

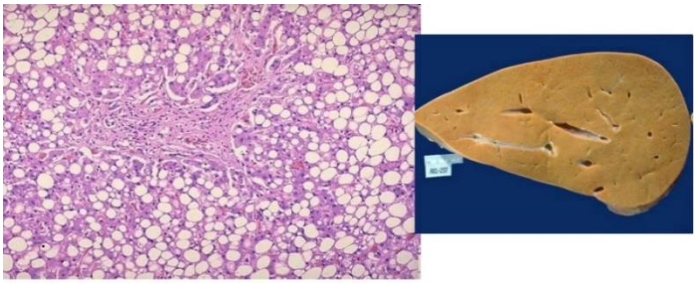
Don't worry about that, the doctor said they will not put a slide of electron microscope and ask about it. You just have to know that cells are swollen.

Reversible damage – cellular swelling



2) Fatty changes due to deposition of fatty droplets in the cell (example: liver cell). Liver cells replaced by fatty droplets which is an indication for injury.

Reversible damage – fatty change

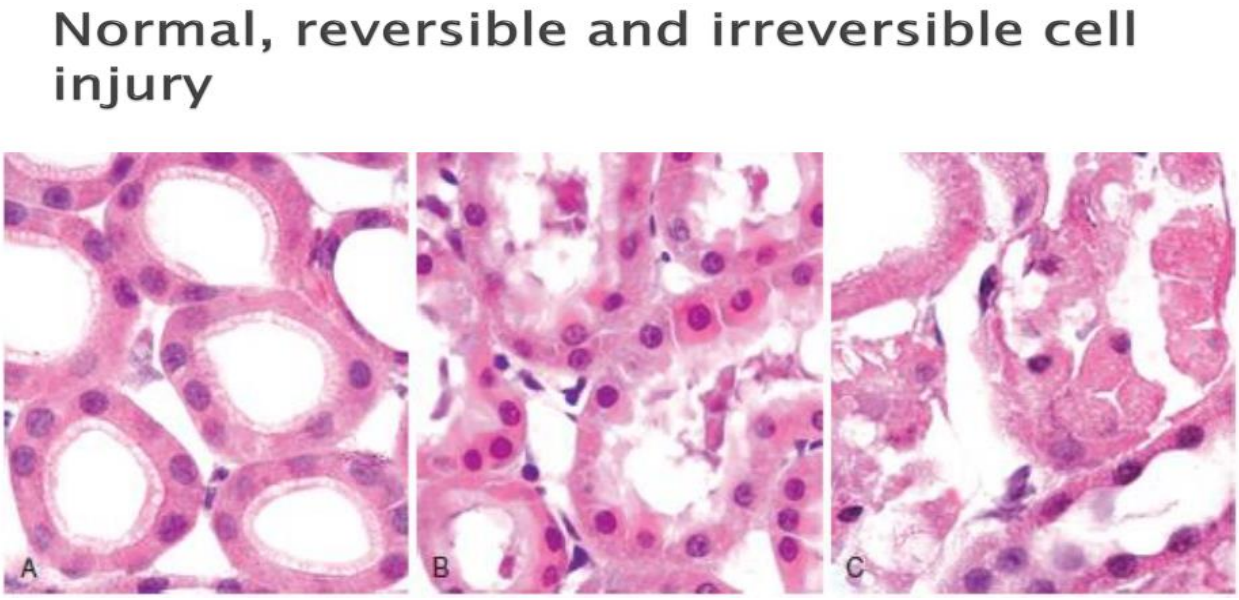


Hallmarks of irreversible injury (Necrosis)

❖ In irreversible injury all changes that we see in reversible injury exist but they are more severe hallmarks and have additional changes:

- Profound disturbances in membrane function (the membrane is discontinuous, integrity distorted and therefore, the components (enzymes, mitochondria) will leak out to the surroundings.
- Profound mitochondrial injury. (not functional, no ATP production)
- Increased cytoplasmic eosinophilia.
- Marked dilatation of ER, mitochondria.

- Mitochondrial densities.
- More myelin figures.
- Nuclear changes: unlike the intact chromatin material in reversible injury, in irreversible injury we have nuclear changes (on chromatin material) that can take 3 forms that don't have a particular sequence:
  - **Pyknosis:** shrinkage of nucleus, very dark, similar to what happens to the nucleus in reversible cell injury.
  - **Karyolysis:** nuclear material will start to fade due to digestion by DNase enzyme (Deoxyribonuclease).
  - **Karyorrhexis:** fragmentation of nuclear material.



The picture shown above is a section of T-tubules in the kidney. Morphologic changes in reversible and irreversible cell injury (necrosis).

(A) Normal kidney tubules with viable epithelial cells. (nucleus and cytoplasm present, tubules intact).

(B) Early (reversible) ischemic injury showing surface blebs, increased eosinophilia of cytoplasm, and swelling of occasional cells. (nucleus is still present and very dark but cells are bigger in size).

(C) Necrotic (irreversible) injury of epithelial cells, with loss of nuclei and fragmentation of cells and leakage of contents. (cells are ruptured that we can't identify the membrane).

Clinical implications

Everything we said so far about cell injury is very beneficial and has clinical implications. Leakage of intracellular proteins through the damaged cell membrane and ultimately into the circulation provides a means of detecting tissue-specific necrosis using blood or serum samples. **Examples:**

1) If we suspect a patient to have hepatitis: If we really have cell injury, death of cells, we expect liver enzymes to exit the cell and enter the blood and therefore, we can examine them using certain laboratory investigations.

2) Cardiac muscle injury, people that have myocardial infarction (MI).

MI cardiac muscle cells also have enzymes. These enzymes, after cell death, will leak out to the blood. That's why when they suspect a patient to have MI, they immediately test for cardiac enzymes in the blood.

- Recall that cell injury can be reversible or irreversible. Irreversible cell injury or cell death can take **two pathways**:

Necrosis is almost always pathologic

1) Necrosis (irreversible cell injury leads to inflammation in the area): we explained its hallmarks previously. Brief recap: cell is swollen, nuclear changes (Pkynosis, Karyolysis and Karyorrhexis) plasma membrane integrity is distorted; enzymes and cellular contents will leak outside and therefore the body will try to get rid of them by inflammatory cells, eg: macrophages to clean the area and engulf the cells and enzymes.

2) Apoptosis: programmed cell death, lacks inflammation, isn't necessarily pathologic. The following table will be explained in next lectures when we explain apoptosis. 40:00

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic; means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA and protein damage

DNA, deoxyribonucleic acid.