SHEET NO. 1

PATHOLOGY

DOCTOR 2019 | MEDICINE | JU

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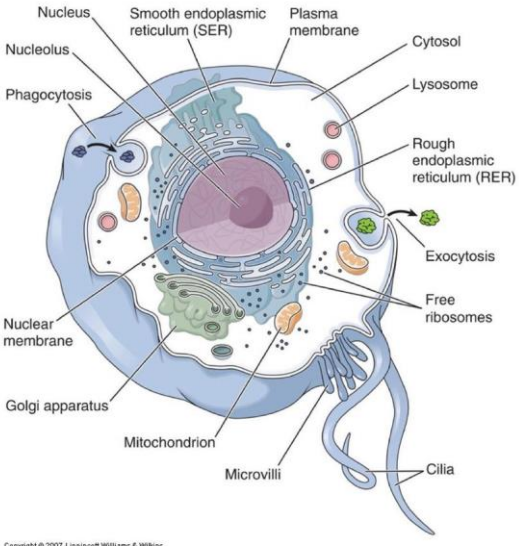
Cell injury, cell death and adaptations (belongs to chapter 2 in Robbins)

- ❖ **Our body is made of the basic unit which is called the cell.**
- ❖ **Cells are composed of different components:**

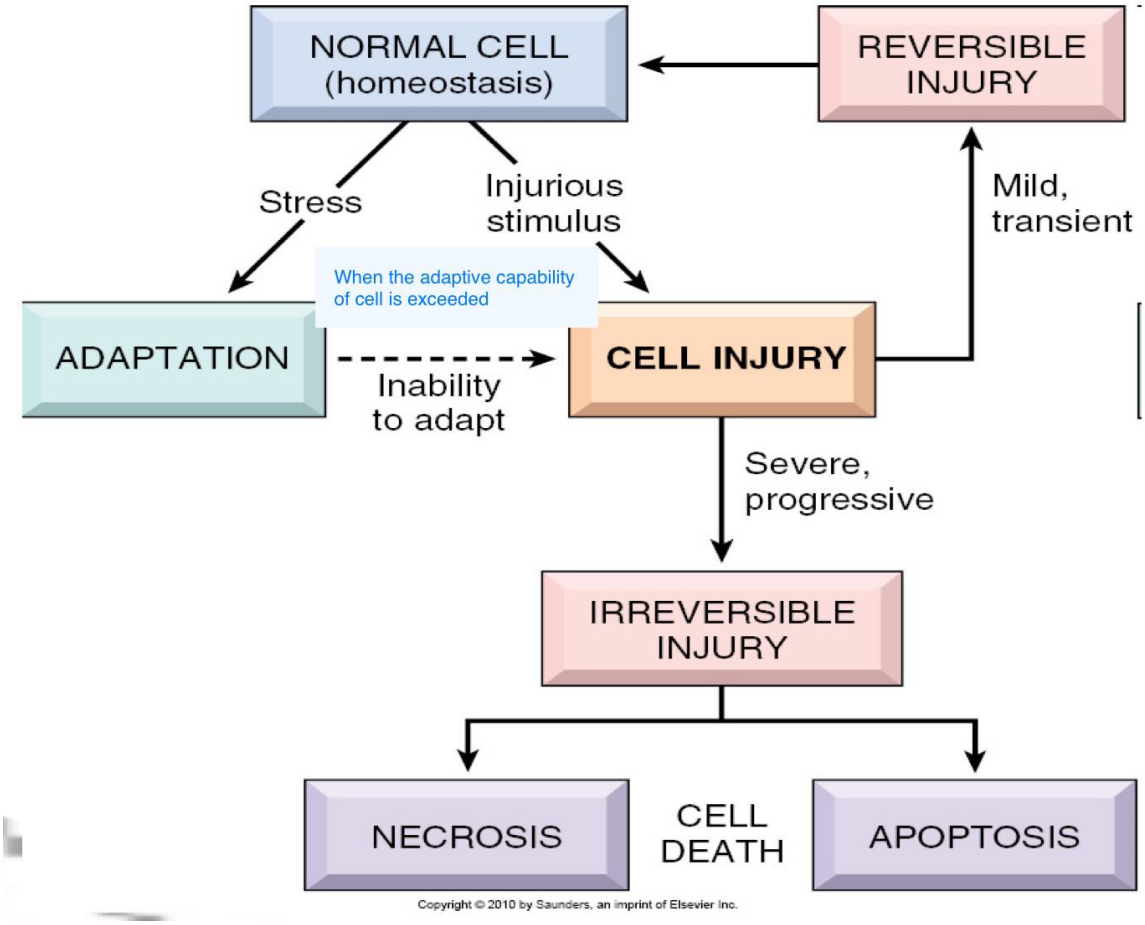
1- **The cell is covered by a cell membrane.**
2- **Nucleus covered with a nuclear membrane.**
3- **Mitochondria ----> energy factory of the cell.**
4- **Ribosomes for protein production.**
5- **Lysosomes contain digestive enzymes.**
And other organelles.



- ○ **Cells interact actively with their surrounding environment, so they are constantly changing in order to adjust their structure and function to adapt to changing demand and stress that surrounds each cell.**
- ○ **The intracellular compartments of each cell is kept within a normal range and it is highly regulated to remain constant ---> this is what we called homeostasis.**
- ○ **Every cell lives in its own homeostasis and it will try to keep it.**

-When a cell encounters any increasing demands like physiologic stress or is exposed to any injurious stimuli -----> the cell will undergo changes. The changes either adaptations. However, the adaptive capability is restricted. So when it is exceeded then the cell is involved in a process called cell injury.
It can be first reversible injury. But if the stress or the injurious stimuli is very severe, constant progressive or very rapid, the cell will undergo irreversible injury or what we call cell death.

- ✔ **Irreversible ---> the point of no return. The cell can't go back to normal.**
- ✔ **Reversible ----> the cell can go back to normal when the injury disappears.**



- **Why we study cell injury?**

Because cell injury is crucial and basic element in any disease process.
All diseases in the body will start at first by cell injury. So, we have to study cell injury and the reaction of cells with its surrounding environment whether by first adaptation, second by reversible cell injury, third by irreversible cell injury or what we call it cell death.

- **Adaptations are subdivided into:**

1- **Physiologic adaptations** **(which is a physiologic phenomena that can be a response to any physiologic changes in our body).**
2- **Pathologic adaptations** **(which can result from a disease process).**

- **Forms of adaptation:**

1- **Increase in cell size.**
2- **Increase in number of cells.**
3- **Decrease in cell size.**
4- **Change into another type of cell.**

In these forms of adaptation, the functions of the cell can be changed according to change in cell size, cell number, …. So the functions can be affected (different from the functions of normal cell), but the cell is still functional with different capabilities and still alive.

- **Adaptation to stress can progress to cell injury if the stress is not relieved.**

- **Adaptive mechanisms:**
  1- **Hypertrophy.**
  2- **Hyperplasia.**
  3- **Metaplasia.**
  4- **Atrophy.**

All of these adaptive mechanisms are considered reversible (when the stressful event is relieved, the cell will go back to normal)

Hypertrophy

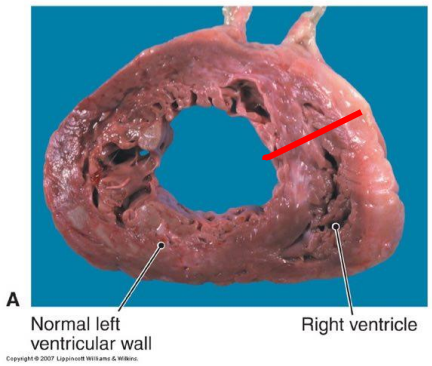
- **Increased in cell size and functional capacity -----> because when you increase cell size, the function of the cell will increase so the net result is increase in the organ size.**
- **Hypertrophy can be:**
  1- **Pure: in organs or cells that have a limited capacity to divide, so they can't go hyperplasia. They only undergo hypertrophy. Examples: cardiac muscles & skeletal muscles.**
  2- **Mixed: in cells or tissues that can divide, so they can undergo hypertrophy and hyperplasia. Example: smooth muscles of uterus.**
- **The mechanism of hypertrophy is by increase the production of structural proteins and organelles.**
- **Hypertrophy can be physiologic or pathologic.**
- **The causes of hypertrophy:**
  1- **Hormonal stimulation.**
  2- **Growth factor stimulation.**
  3- **Increased functional demand.**

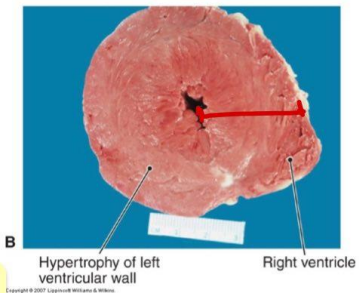
EXAMPLES:

- **The most common example on pathologic hypertrophy is the hypertrophy of the cardiac muscles as a response to hypertension or aortic valve stenosis.**
  - **When the demand increases on the heart, the cardiac muscle cells will start to adapt to increase the force of contraction by hypertrophy. So, the net result is an increase in the size of the heart. The heart has a capacity to this adaptation. So if the adaptation reaches a limit -----> the cardiac muscles will undergo cell injury (HOW?) the thickened heart will need more blood supply which can't be sustained, so the cells will start to degenerate and**

the cell injury will take place, so those patients after a while have heart failure for example.

- **The mechanism here is by increasing functional demand. Sometimes, growth factor stimulation.**

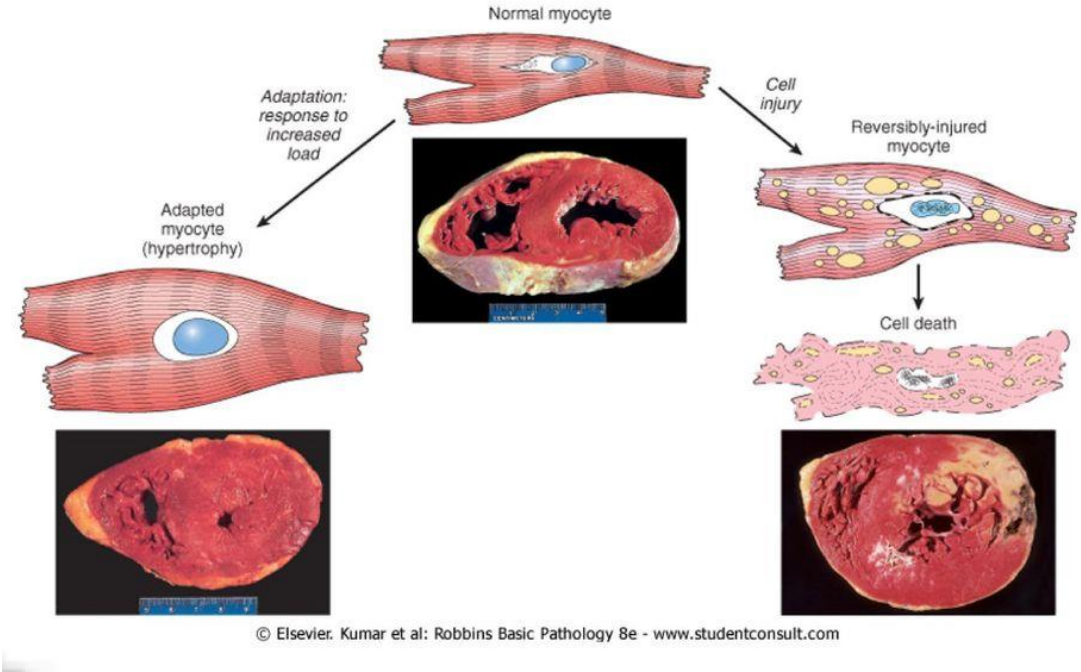




First image: the normal heart.

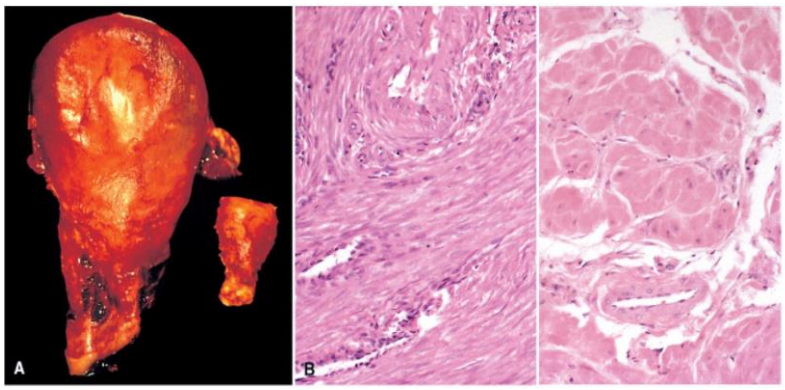
Second image: heart hypertrophy.

Look at the thickness of myocardium of the left ventricle.



***Cell death like in ischemia or myocardial infarction.**

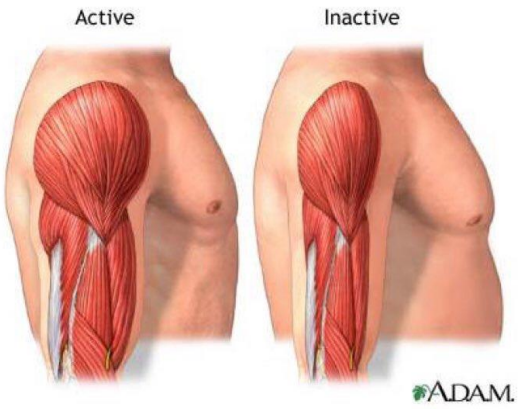
- **The smooth muscles of uterus can undergo hypertrophy and hyperplasia in response to estrogenic stimulation during pregnancy ---> physiologic adaptive mechanism.**
  It is reversible ----> after pregnancy when estrogen goes back to normal, these enlarged muscles will go back to normal size and the newly formed muscles due to hyperplasia will disappear.



This is the normal appearance of smooth muscle cells (spindle in shape)

This is the hypertrophied smooth muscle cells during pregnancy.

- **Skeletal muscles of athlete(physiologic): the skeletal muscle will adapt due to this increased demand by hypertrophy. That's why you will find the muscles of the bodybuilders and the athletes are enlarged.**

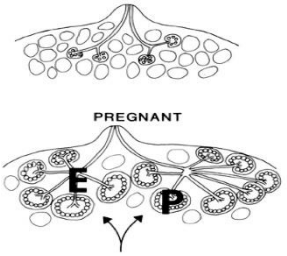


Hyperplasia

- **Increase in the number of cells with a correspondent increase in the size of the organ.**
- **Tissues that can undergo hyperplasia are the tissues that have proliferative ability.**
  Skeletal muscles & cardiac muscles don't have the ability to divide, so they can only undergo hypertrophy.
- **Hyperplasia can be pure or mixed.**
- **Hyperplasia can be physiologic or pathologic.**
- **Physiologic hyperplasia due to:**
  1- **Hormonal stimulation.**
  2- **Compensatory.**

  Examples:

  1- **Hyperplasia of the breast glandular tissue in puberty and pregnancy (in preparation to lactation).**

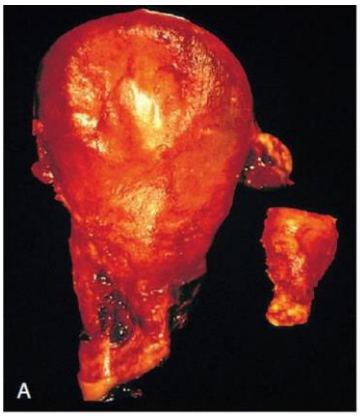
  There is increase in the number of glands.

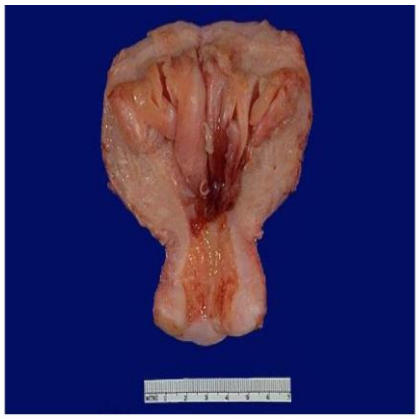
  2- **Compensatory hyperplasia of the liver after partial resection of the liver. Sometimes a part of the liver is removed in cases of trauma and hepatic tumors. The remaining cells of the liver will produce some growth factors that will stimulate the proliferation of hepatocytes to retain the normal pre resection size of the liver. This is a peculiar ability of the liver cells to restore the normal size of the liver.**

- **Pathologic hyperplasia:**
  1- **Excessive hormonal stimulation.**
  2- **Viral infections.**

  Examples:

  1- **Endometrial hyperplasia, estrogen induced.**
  EXPLANATION: endometrial hyperplasia is driven by continuous estrogenic stimulation. Continuous estrogenic stimulation in these females can lead to endometrial hyperplasia. If this endometrial hyperplasia persists or not treated, it can transform at some point into the endometrial carcinoma. It can also happen even in pre-menopausal women due to estrogenic stimulation.





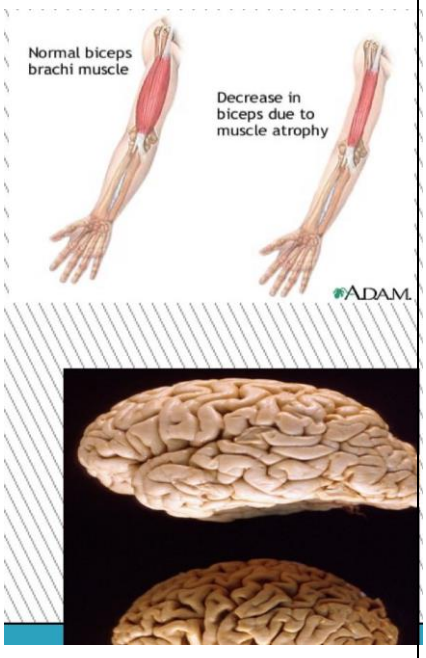
The uterus is transected from the middle. Notice the endometrial hyperplasia.

2- **Benign prostatic hyperplasia, androgen induced.**
   The prostate glands in elderly males can undergo hyperplasia caused by hyper androgenic stimulation leads to enlargement of the prostate gland.
3- **Warts (HPV).**

- **Pathologic hyperplasia constitutes a fertile soil in which cancers may eventually arise.**

Atrophy

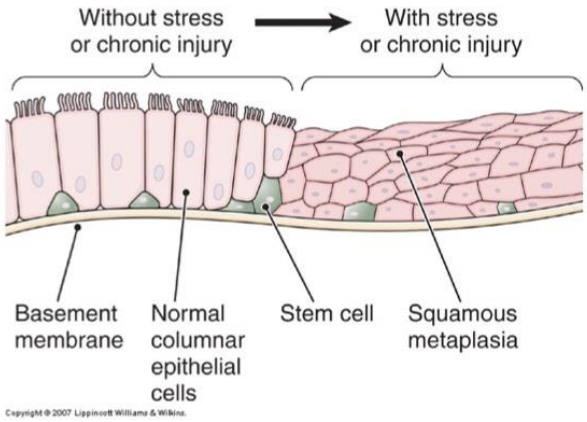
- **Decreased cell size with the correspondent decrease in cell function.**
- **Atrophic cell can still function, but at the minimum.**
- **Mechanisms of cell atrophy:**
  1- **Decrease protein synthesis.**
  2- **Increase protein degradation.**
  3- **Increase in cell autophagy (the newly adaptive cells will eat its own organelles to generate energy).**
- **Causes of cell atrophy:**
  1- **Decreased workload (immobilization of a limb after fracture).**
  2- **Loss of innervation (when you cut a nerve).**
  3- **Diminished blood supply (like in ischemia for example).**
  4- **Inadequate nutrition.**
  5- **Loss of endocrine stimulation.**
     It can be physiologic (patients after menopause have normally decreased levels of estrogen in the blood, so they will develop endometrial atrophy) or pathologic.
  6- **Aging (senile atrophy) --->of the brain the gyri shrunken, and the sulci increased in size.**



- **Physiologic**
  Loss of hormone stimulation in menopause (endometrial atrophy).
- **Pathologic**
  1- **Denervation injury.**
  2- **Chronic ischemia (like the skin of lower limb in patients who have arteriosclerosis or diabetes).**

Metaplasia

- **Change from one cell type to another (reversible)**
- **Reprogramming of stem cells to give us a new type of cells, NOT differentiated cells.**



Normally, the bronchial is lined by ciliated pseudostratified respiratory epithelium generated by stem cells.
If the epithelium is exposed to stress, stem cells give squamous epithelium.

- **Persistent change increases risk of cancer**
- **New cell type copes better with stress but function less.**
- **Causes:**
  1- **Smoking**
  2- **Vitamin A deficiency ---> Vitamin A is needed for normal epithelial differentiation; deficiency leads to squamous metaplasia of the bronchi.**
  3- **GERD (Gastroesophageal reflux disease) -----> in these patients, the normal lining of the esophagus is squamous epithelium, but when the patient has continuous reflux of gastric acidic content to the lower part of the esophagus, the squamous epithelium will change into glandular epithelium that can bear acidity, but its protection to the esophagus is less. The patient might have esophageal carcinoma if metaplasia persisted.**

Ischemia ----> loss of blood supply which can lead to hypoxia.
Hypoxia: loss of oxygen supply which can be caused by ischemia or other causes like for example respiratory diseases.

Causes of cell injury

✔ Oxygen Deprivation (Hypoxia Vs ischemia)

- **ischemia mostly is the result of occlusion of an artery by a thrombus or a blood clot, if it happened in the cerebral vessels, it could lead to O2 deprivation in the brain, or in the heart and causes myocardial infraction.**
- **The main mechanism of ischemia in causing cell injury is the lack of blood supply which leads to lack of oxygen supply (oxygen is needed by all cells in their metabolism and their energy production).**
- **No oxygen ----> cell injury.**
- **Other reasons for O2 deprivation are pulmonary diseases such as pulmonary hypertension, emphysema and obstructive pulmonary diseases.**

✔ Chemical Agents

- **Like sugar, drugs, Pesticides and insecticides.**

✔ Infectious Agents

- **Such as viruses, bacteria, protozoa, parasites and worms.**

✔ Immunologic Reactions

- **Autoimmune, allergic, microbes.**
- **allergic conditions such as: rhinitis, conjunctivitis and eczema.**

✔ Genetic Factors

- **Starting from chromosomal abnormalities such as: down Syndrome ending with single gene defects that lead to abnormal enzymatic activity.**
- **It also could lead to some diseases such as certain types of anemia.**

✔ Nutritional Imbalances

- **Whether from under nutrition or malnutrition by not getting enough of certain types of food, or from excess nutrition by getting excess food, which leads to obesity and its associated diseases.**

✔ Physical Agents

- **Such as: Trauma, extremes of temperature and Electric shock.**

✔ Aging