Pathophysiology

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Lecture 2

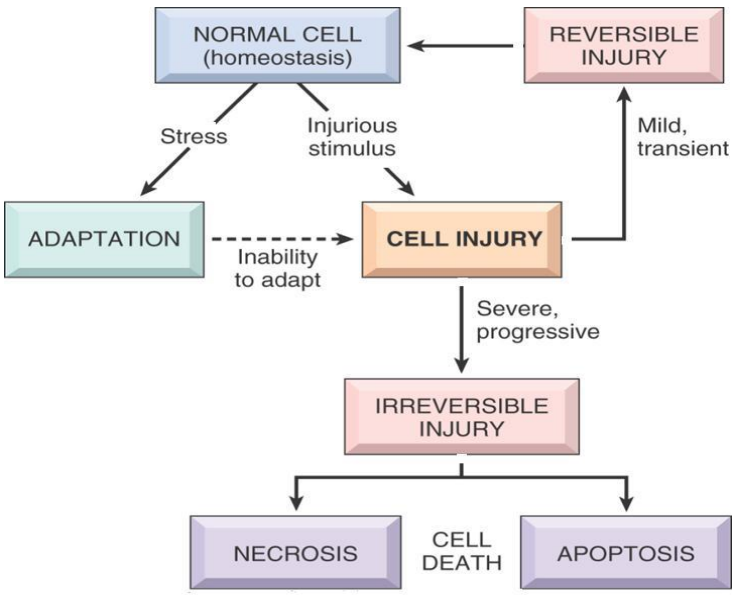
I. Learning objectives

1. **Comprehending the concepts of adaptations: Hyperplasia, Hypertrophy, Atrophy, Metaplasia.**
2. **Comprehending the concepts of Reversible cell injury.**
3. **Comprehending the concepts of Irreversible cell injury.**
4. **Classifying necrosis.**
5. **Compare and differentiate between apoptosis and necrosis.**
6. **Identify common intracellular accumulations: Fat, Hyaline, CA++, Proteins, Glycogen, Pigments.**
7. **Understand aging and differentiate the concepts of preprogrammed death.**

Cells have the ability to maintain their intracellular milieu within a very narrow range of physiologic parameters; that is, they maintain normal homeostasis. As cells encounter physiologic stresses or pathologic stimuli, they can undergo adaptation, achieving a new steady state and preserving viability and function.

Allostasis refers to the idea that ALL of an organism's internal parameters are varied in order to appropriately match them to external stressors, and thus homeostasis is wrong because by their definition, homeostasis required ALL internal parameters to be constant.

The principal adaptive responses are hypertrophy, hyperplasia, atrophy, and metaplasia. If the adaptive capability is exceeded or if the external stress is inherently harmful, cell injury develops.

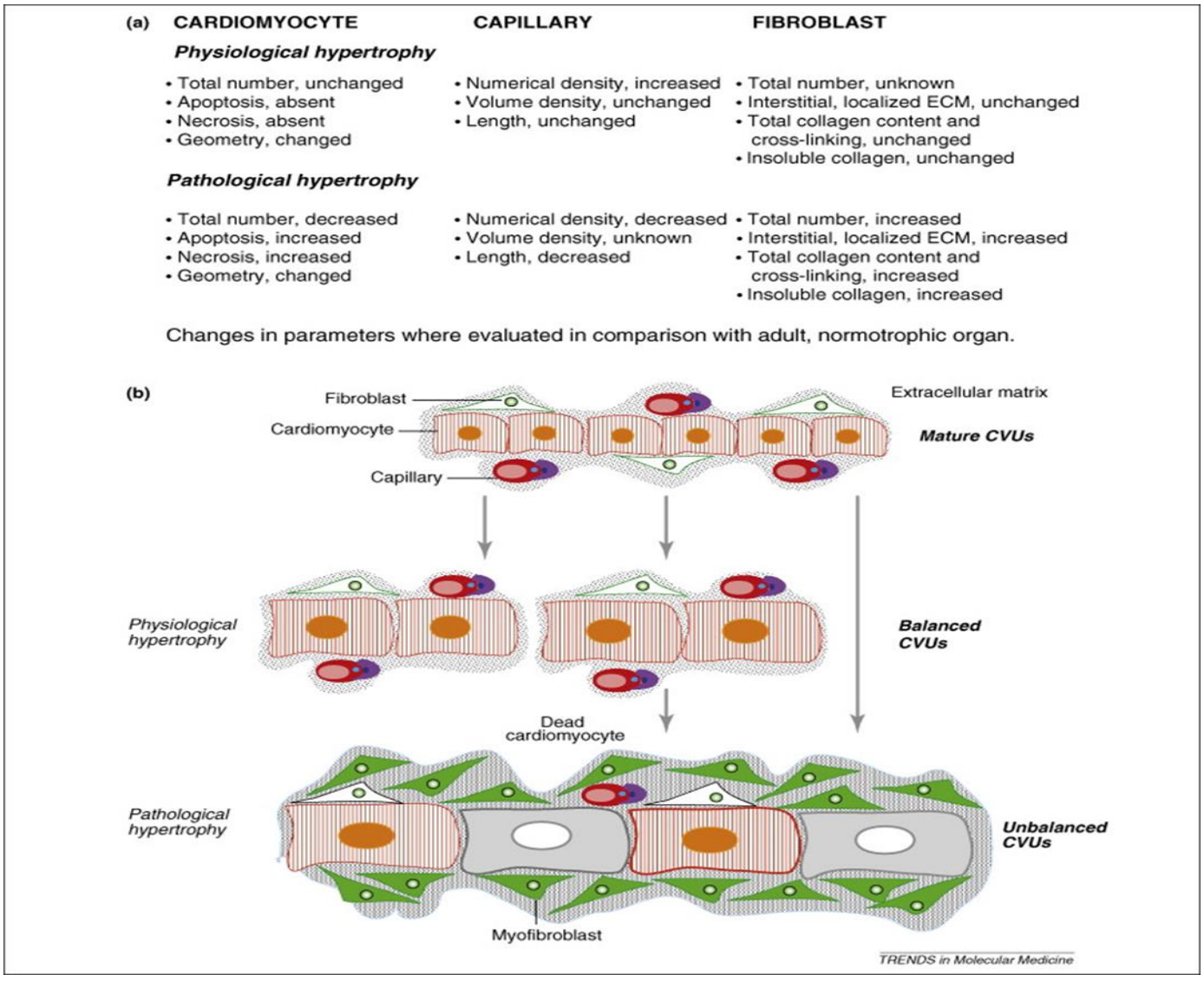


Adaptations *are reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to changes in their environment.*
It is of two types: -

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

2- Pathologic adaptations are responses to stress that allow cells to modulate their structure and function and thus escape injury. Such 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 pure hypertrophy there are no new cells, just bigger cells, enlarged by an increased amount of structural proteins and organelles. Hypertrophy can be physiologic or pathologic and is caused either by increased functional demand or by specific hormonal stimulation. The striated muscle cells in both the skeletal muscle and the heart can undergo only hypertrophy in response to increased demand because in the adult they have limited capacity to divide. Therefore, the avid weightlifter can develop a rippled physique only by hypertrophy of individual skeletal muscle cells induced by an increased workload. Examples of **pathologic** cellular hypertrophy include the cardiac enlargement that occurs with hypertension or aortic valve disease.

The mechanisms driving cardiac hypertrophy involve at least two types of signals:

I- **Mechanical triggers**, such as stretch.

II- **Trophic triggers**, such as activation of **α- adrenergic receptors**.

These stimuli turn on signal transduction pathways that lead to

1- The induction of a number of genes, which in turn

2- Stimulate synthesis of numerous cellular proteins, including

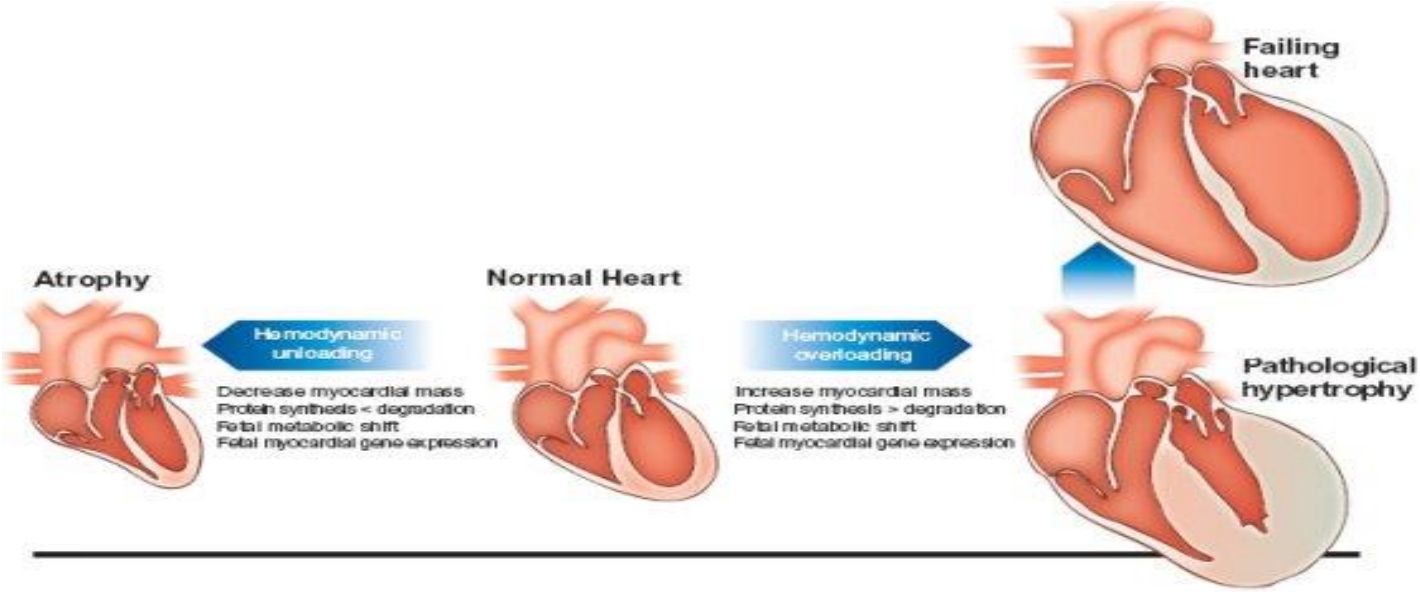
a- Growth factors.

b-Structural proteins.

3- There will be increased **vasculature to adequately supply** the enlarged fibers with nutrients.

4- The mitochondria will increase the supply adenosine triphosphate(ATP).

5- The biosynthetic machinery also will provide the contractile proteins or other cytoskeletal elements.



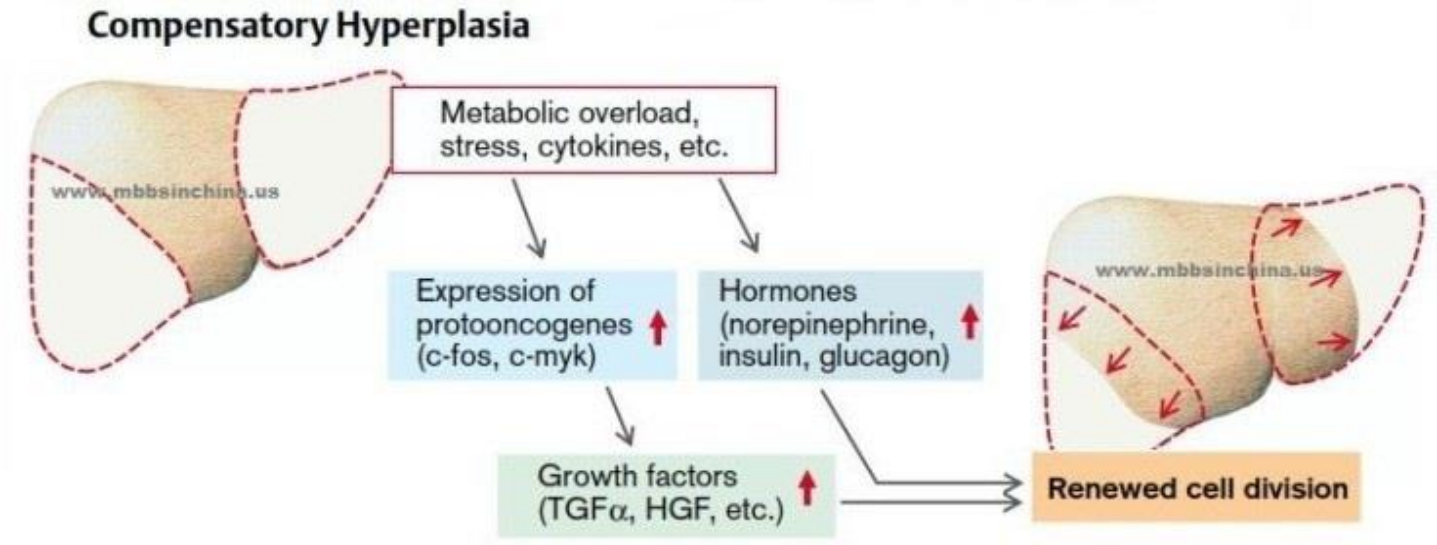
Hyperplasia *is characterized by an increase in cell number.*
It takes place if the cell population is capable of replication; it may occur with hypertrophy and often in response to the same stimuli. Hyperplasia can be physiologic or pathologic.

The two types of 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**, that is, hyperplasia that occurs when a portion of the tissue is removed or diseased. For example, when a liver is partially resected, mitotic activity in the remaining cells begins as early as 12 hours later, eventually restoring the liver to its normal weight.

The stimuli for hyperplasia in this setting are **polypeptide growth factors** produced by remnant hepatocytes as well as non-parenchymal cells in the liver.

After restoration of the liver mass, cell proliferation is "turned off" by various **growth inhibitors.**

Pathologic hyperplasia *is caused by excessive hormonal or growth factor stimulation*.



For example, after a normal menstrual period there is a burst of uterine epithelial proliferation that is normally tightly regulated by stimulation through pituitary hormones and ovarian estrogen and by **inhibition through progesterone**. However, if the balance between estrogen and progesterone is disturbed,

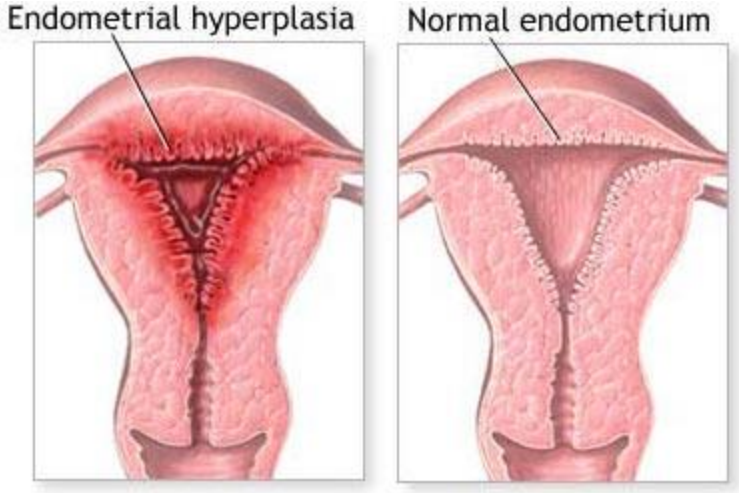
endometrial hyperplasia ensues, a common cause of abnormal menstrual bleeding.

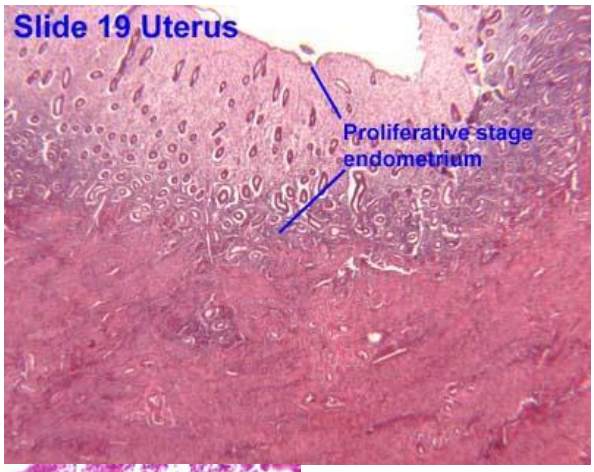
Hyperplasia is also an important response of connective tissue cells in wound healing, in which proliferating fibroblasts and blood vessels aid in repair.

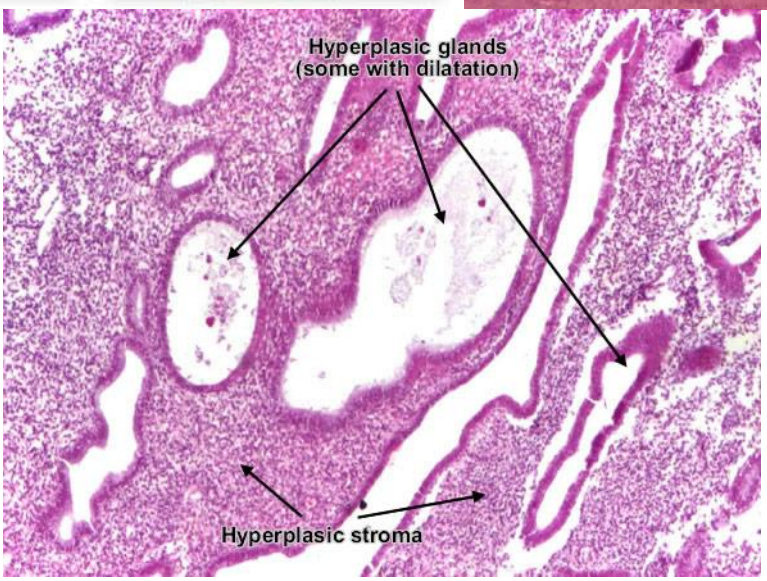
The hyperplastic process **remains controlled; if hormonal or growth factor stimulation abates, the hyperplasia disappears**.

It is this sensitivity to normal regulatory control mechanisms that distinguishes benign pathologic hyperplasia from cancer, in which the growth control mechanisms become dysregulated or ineffective.

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, and certain papillomavirus infections predispose to cervical cancers.







Even with the increase in cell number still there is no loss in the architecture (Important).

Atrophy *Shrinkage in the size of the cell by the loss of cell substance.*

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

It results from:

1- Decreased protein synthesis. Protein synthesis decreases because of reduced metabolic activity.

2- Increased protein degradation in cells. The degradation of cellular proteins occurs mainly by the ubiquitin-proteasome pathway.

In many situations, atrophy is also accompanied by increased autophagy, with resulting increases in the number of autophagic vacuoles. Autophagy ("self-eating") is the process in which the starved cell eats its own components in an attempt to find nutrients and survive.

Causes of atrophy include:

A) **Decreased workload** (e.g., immobilization of a limb to permit healing of a fracture).

B) **Loss of innervation**.

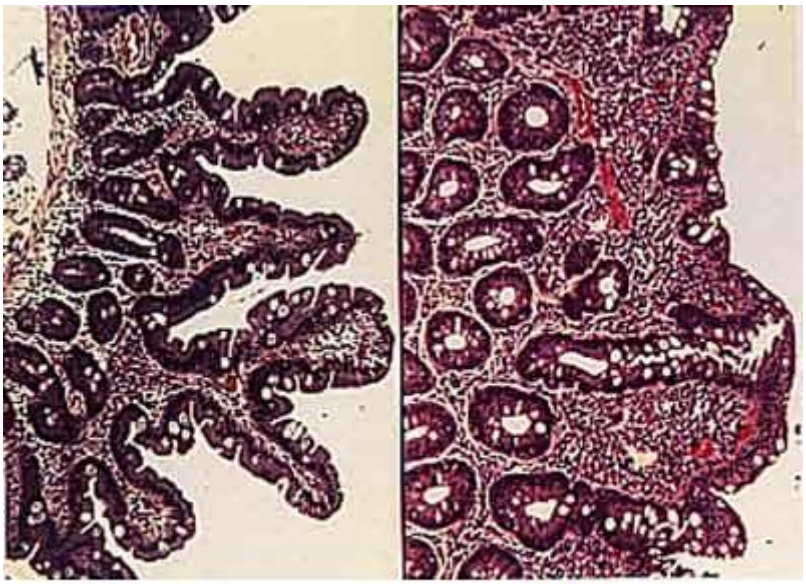
C) **Diminished blood supply**.

D) **Inadequate nutrition**.

E) **Loss of endocrine stimulation**.

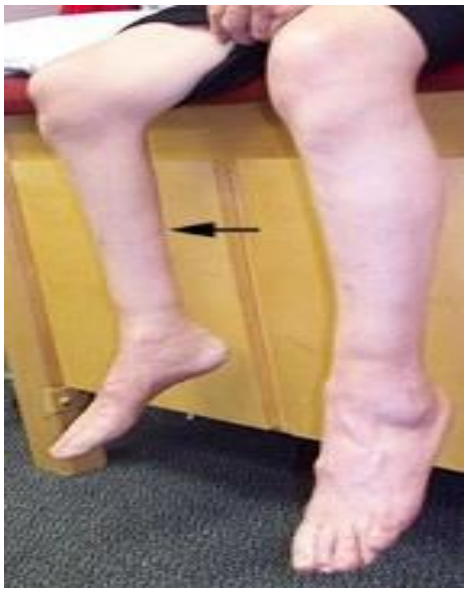
F) **Aging** (senile atrophy).

Although some of these stimuli are physiologic (e.g., the loss of hormone stimulation in menopause) and others pathologic (e.g., denervation), the fundamental cellular changes are identical. They represent a retreat by the cell to a smaller size at which survival is still possible; a new equilibrium is achieved between cell size and diminished blood supply, nutrition, or trophic stimulation.



Normal Atrophy

Intestinal villus in celiac disease

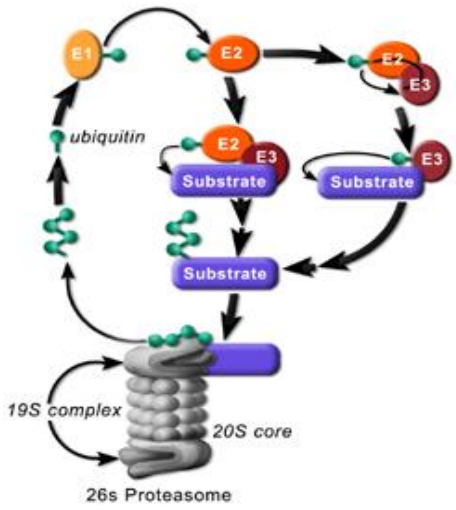


Ubiquitin Proteasome System program

A multicomponent system that identifies and degrades unwanted proteins in the cytoplasm of all cells.

The ubiquitination system functions in cellular processes, by:

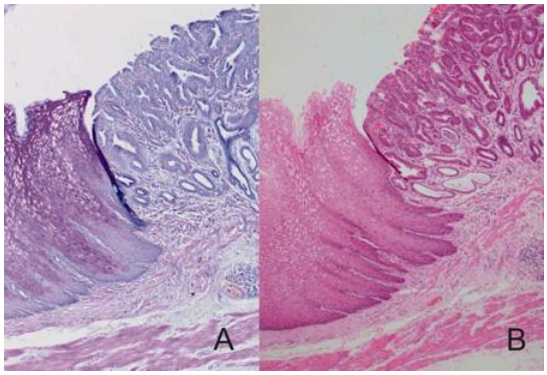
1) Antigen processing.
2) Apoptosis.
3) Biogenesis of organelles.
4) Cell cycle and division.
5) DNA transcription and repair.
6) Differentiation and development.
7) Immune response and inflammation.
8) Neural and muscular degeneration.
9) Morphogenesis of neural networks.
10) Ribosome biogenesis.
11) Viral infection.
12) Response to stress and extracellular modulators.
13) Modulation of cell surface receptors, ion channels and the secretory pathway.

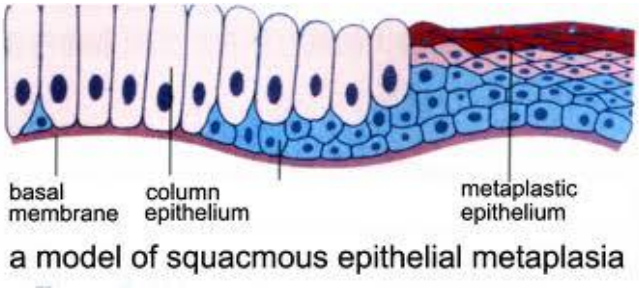


Metaplasia *is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.*

In this type of cellular adaptation, cells sensitive to a particular stress are replaced by other cell types better able to withstand the adverse environment. Metaplasia is thought to arise by genetic "reprogramming" of stem cells rather than transdifferentiation of already differentiated cells.

Epithelial metaplasia is exemplified by the squamous change that occurs in the respiratory epithelium in habitual cigarette smokers. The normal ciliated columnar epithelial cells of the trachea and bronchi are focally or widely replaced by stratified squamous epithelial cells.





a model of squacmous epithelial metaplasia

Although the metaplastic squamous epithelium has survival advantages, important protective mechanisms are lost, such as mucus secretion and ciliary clearance of particulate matter.

Epithelial metaplasia is therefore a double-edged sword; moreover, the influences that induce metaplastic transformation, if persistent, may predispose to malignant transformation of the epithelium. In fact, in a common form of lung cancer, squamous metaplasia of the respiratory epithelium often coexists with cancers composed of malignant squamous cells.

Dysplasia: - *An alteration in cell growth resulting in cells that differ in size, shape, and appearance, often as a result of chronic irritation.* There is loss in the architecture (normal cell arrangement), it could lead to **Neoplasia**