Cell growth disturbances (ADAPTIVE DISORDERS or Adaptive disorders of growth)

-Adaptive disorders are the adjustments which the cells make in response to stresses which may be for physiologic needs (physiologic adaptation) or a response to non-lethal pathologic injury (pathologic adaptation).

Types of disorders of growth

1- **Atrophy**

- Atrophy refers to a decreased size of cell with decreased function, as a result of decreased nutrient supply , injury or disuse
- atrophy is not necessarily accompanied by small organ size because its compensated by an increase in connective tissue and adipose tissue or because the hypoplasia .
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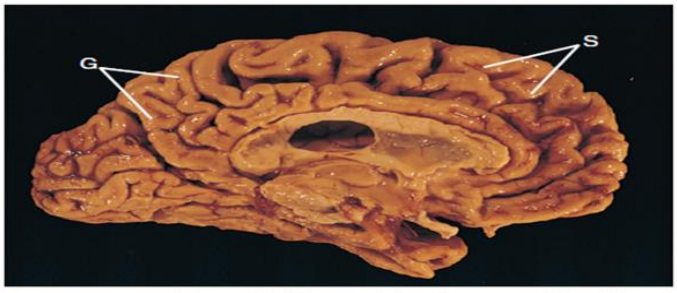
Macroscopic appearance

- The affected organ is small and less weight , pale ,and often shrunken
- The atrophic organ has zigzag vessels and a wrinkled capsule.



Link 2-21 Atrophic Brain. The gyri *(G)* are narrow and the sulci *(S)* are wide

Microscopic appearance

- The cells become smaller in size due to reduction in cell organelles, chiefly mitochondria, myofilaments and endoplasmic reticulum.
- increase in the number of autophagic vacuoles containing debris from degraded organelles. These autophagic vacuoles may persist to form 'residual bodies' in the cell cytoplasm e.g. lipofuscin pigment granules in brown atrophy (have increased lipofuscin Pigment).
- Replacement of the normal tissue of the organ with fibrous or adipose connective tissue .
- decrease in cell number duo to Loss of atrophied cells by apoptosis .

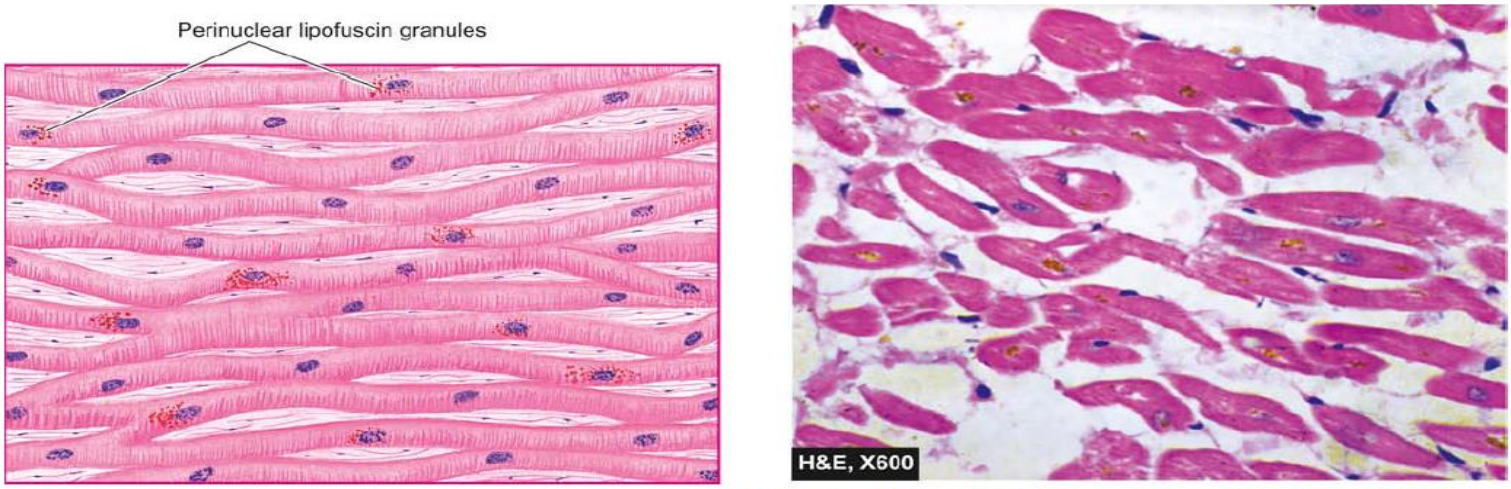


Figure 2.18 Brown atrophy of the heart. The lipofuscin pigment granules are seen in the cytoplasm of the myocardial fibres, especially around the nuclei.

Mechanisms of Atrophy

Decrease in cell size occurs via ubkjuitin-proteosome degradation of the cyloskeleton and autophagy of cellular components.

1. In ubiquitin-proteasome degradation, intermediate filaments of the cytoskeleton are "tagged" with ubiquitin and destroyed by proteosomes.
2. Autophagy of cellular component s involves generation of autophagic vacuoles. These vacuoles fuse with lysosomes whose hydrolytic enzyme s breakdown cellular components.

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Types of atrophy

A-Physiologic atrophy. e.g during fetal development(Some embryonic structures, such as the notochord, undergo atrophy during fetal development), atrophy of some tissue in ageing.

B-Pathologic atrophy .e.g Prolonged diminished functional activity is associated with disuse atrophy of the organ e.g. Wasting of muscles of limb immobilised in cast , Brain(cerebral atrophy or senile atrophy), mainly because of reduced blood supply as a result of atherosclerosis of the carotid artery. Loss of innervation or hormonal stimulation. direct pressure on the tissue cells(Pressure atrophy)

2- Hypertrophy

-Increase in size of the cell due to increased synthesis of in protein synthesis and an increase in the size or number of intracellular organelles.

-Nondividing cells, eg, myocardial fibres , undergo hypertrophy only. Dividing cells (stable cells) undergo both hyperplasia and hypertrophy

- A distinction must be made between pseudo-hypertrophy, which is an increase in the size of the organ as a result of an increase in other tissue, such as fatty tissue or connective tissue, and not the parenchymal tissue of the organ.

- **Types of Hypertrophy**
- 1- **Physiological Hypertrophy :**This occurs due to increased functional demand and stimulation by growth factors and hormones , e.g Hypertrophy of smooth muscle uterus during pregnancy from estrogenic stimulation. skeletal muscle hypertrophy of body builders

, **2. Pathological hypertrophy:e.g .** hypertrophy of urinary bladder muscle in response to urethral obstruction by stones

Mechanisms of Hypertrophy

-Hypertrophy is due to increased synthesis of cellular proteins. Steps involved in biochemical mechanisms of myocardial (cardiac muscle) hypertrophy :

1-Activation of the Signal Transduction Pathways

Various mechanisms involved are:

Physiologic hypertrophy: Increased workload on the myocardium produces mechanical stretch

Pathologic hypertrophy: Growth factors and hypertrophy agonists are involved in pathologic hypertrophy.

Mechanical sensors also stimulate production of growth factors and agonists. They cause increased synthesis of muscle proteins.

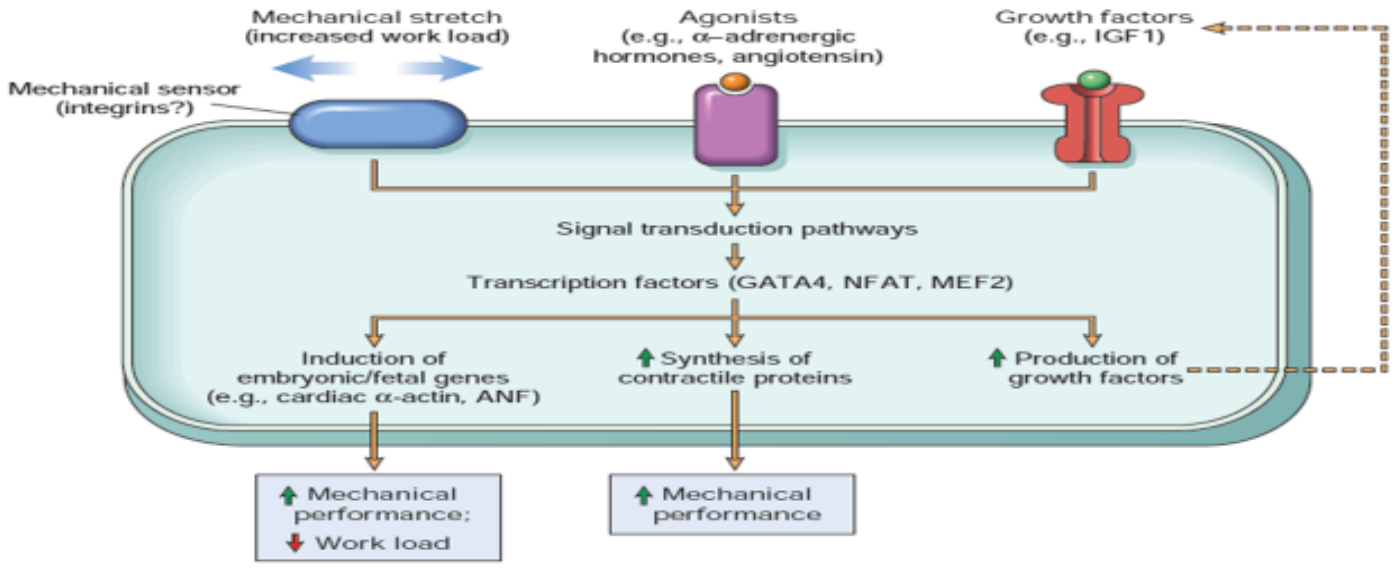
2-Activation of Transcription Factors

Mechanical stretch, growth factors and hypertrophy agonists activate the signal transduction pathways and transcription factors The activated transcription factors results in:

• Increased synthesis of contractile proteins

• Induction of embryonic/fetal genes: Some genes are normally expressed only during early development of embryo and fetus. They are re-expressed in hypertrophied cells.

• Increased production of growth factors.



• **Figure 2-4 Biochemical mechanisms of myocardial hypertrophy. The major known signaling pathways and their functional effects are shown. Mechanical sensors appear to be the major triggers for physiologic hypertrophy, and agonists and growth factors may be more important in pathologic states. ANF, Atrial natriuretic factor; GATA4, transcription factor that binds to DNA sequence GATA; IGF1, insulin-like growth factor; NFAT, nuclear factor activated T cells; MEF2, myocardial enhancing factor 2.**

MORPHOLOGIC FEATURES

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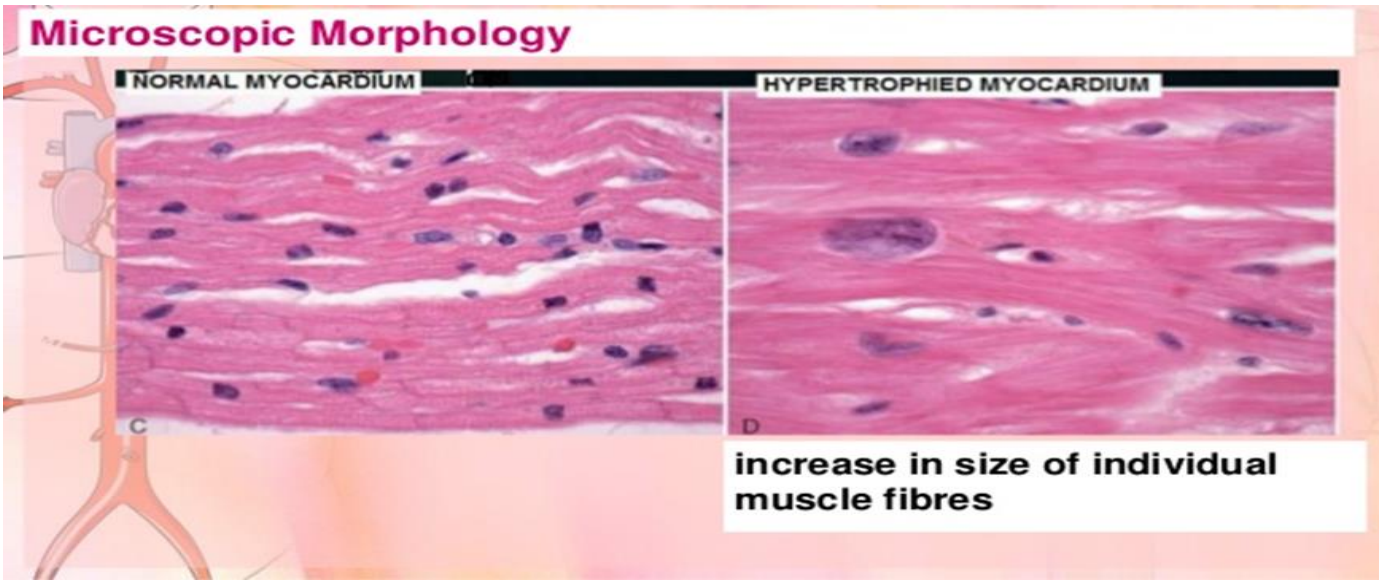
- **Macroscopic appearance**

- The affected organ is enlarged and heavy weight.
- When Hypertrophy is localized, there is a change in the external appearance of the organ in the form of thickenings or nodules.

- **Microscopic appearance**
- Increase in size of the cells as well as the cytoplasm and nuclei
- At ultrastructural level, there is increased synthesis of DNA and RNA, increased protein synthesis and increased number of organelles such as mitochondria, endoplasmic reticulum and myofibrils.



3-Hyperplasia

- Hyperplasia is defined as an increase in the number of cells in an organ or tissue in response to a stimulus

Mechanisms of Hyperplasia

- occurs due to increased recruitment of cells from G0 (resting) phase of the cell cycle to undergo mitosis, when stimulated.

- Production of transcription factors that induce genes encoding growth factors, receptors for growth factors and cell-cycle regulators e.g . • In hormonal hyperplasia, hormones themselves act as growth factors and trigger transcription of genes.

• In compensatory hyperplasia, there is proliferation of remaining cells(is the result of growth factor-driven proliferation of mature cells) and, in some cases, by increased output of new cells from stem cells.

-For instance, after partial hepatectomy growth factors are produced in the liver that engage receptors on the surviving cells and activate signaling pathways that stimulate cell proliferation. But if the proliferative capacity of the liver cells is compromised, as in some forms of hepatitis causing cell injury, hepatocytes can instead regenerate from intrahepatic stem cells.

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Types of hyperplasia

Physiologic Hyperplasia :due to the action of hormones or growth factors occurs in several circumstances. e.g . Hyperplasia of pregnant uterus , Prostatic hyperplasia in old age

Pathologic Hyperplasia:- Most forms of pathologic hyperplasia are caused by excessive hormonal stimulation or excessive effects of growth factors on target cells. e.g. In wound healing, there is formation of granulation tissue due to proliferation of fibroblasts and endothelial cells.

RPHOLOGIC FEATURES

Macroscopic appearance

- increases in size of the affected organ or tissue.
- when Hyperplasia may occur together with hypertrophy in the same organ as in an enlarged prostate, in which case it is difficult to distinguish them by naked eye, but they can be distinguished microscopically

- **Microscopic appearance**
  - increase in the number of cells, and increased mitoses of the cells.

- The number of cells in the affected tissue can be observed by counting the number of cells or rows of cells or observing the appearance of hyperplasia in the form of clusters or thickenings
- When hyperplasia affects the epithelial tissue of the lining ducts, hyperplasia is observed extending in the form of protrusions or folds into the cavity of the canal and may lead to partial or complete closure of the canal.

- Pathologic hyperplasia can progress to cancer
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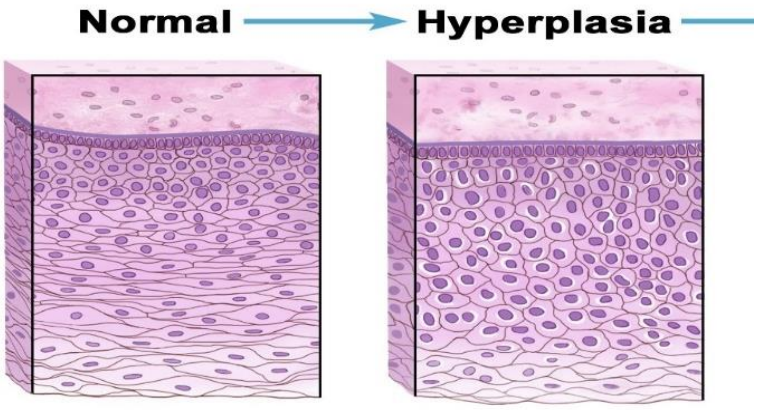
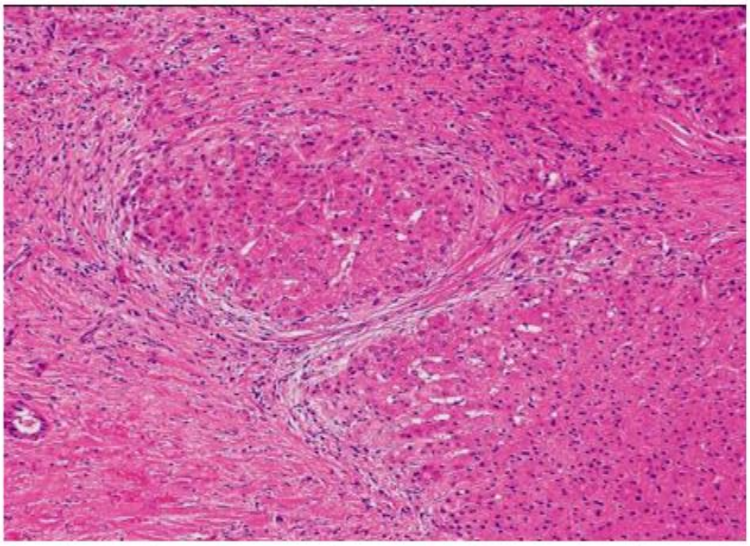
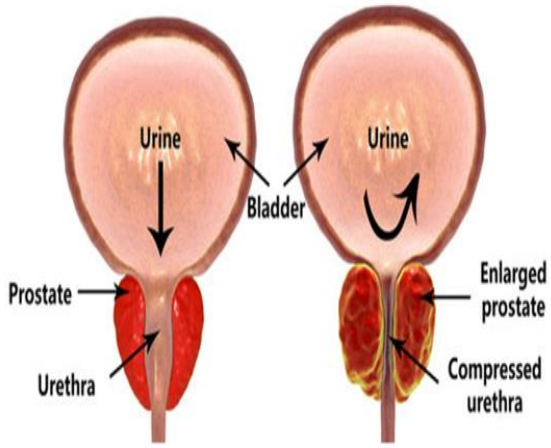




• Focal nodular hyperplasia :Central portion of nodular hyperplasia showing the interphase between the fibrous scar and the hepatocytic nodules



Benign prostatic hyperplasia : A-normal prostate , B- enlarged prostate

4-Metaplasia

- Metaplasia is defined as a reversible change of epithelial or mesenchymal adult cells to another type of adult epithelial or mesenchymal cells, usually in response to chronic irritation **or** stimuli, and often reverts back to normal on removal of stimulus. However, if the stimulus persists for a long time, epithelial metaplasia may progress to dysplasia and further into cancer.

- **Macroscopic and microscopic appearance**
- Metaplasia cannot be seen by naked eye
- Tissue transformation can be diagnosed by observing the presence of tissue in a misplaced position or the transformation may be local, i.e. transformed cells can be seen beside the normal cells

Types of Metaplasia

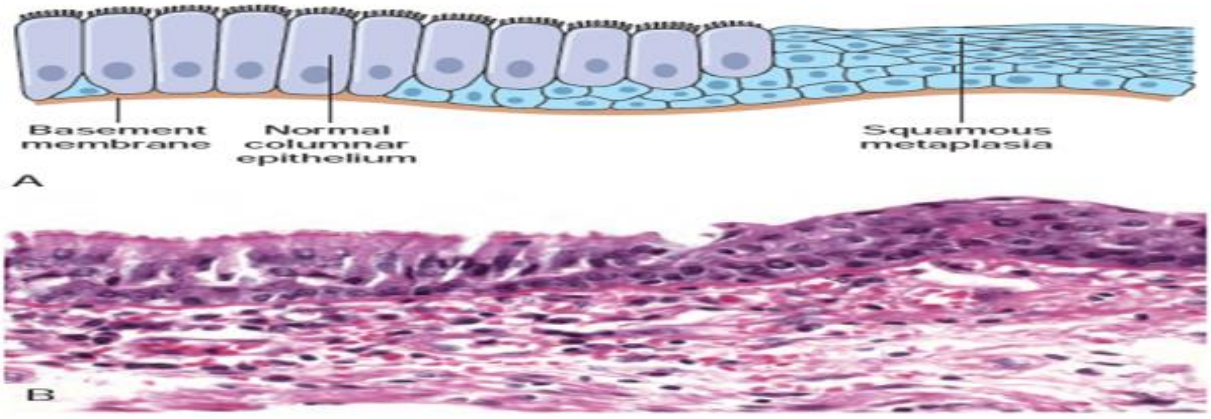
- Metaplasia named by the cell which replaces. e.g. squamous metaplasia.

Epithelial Metaplasia

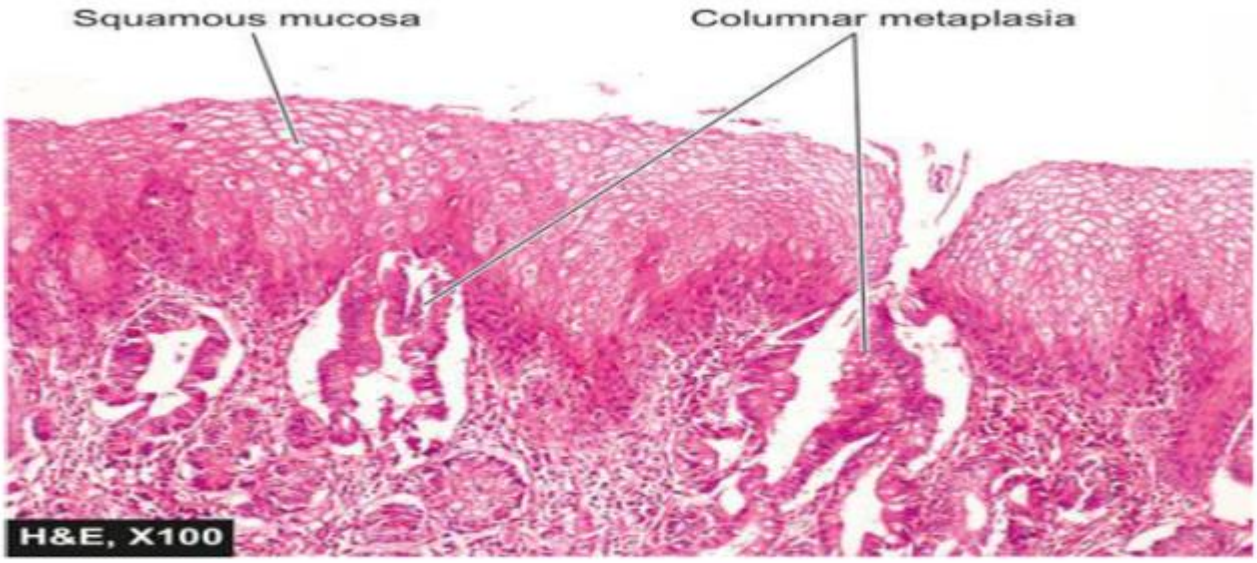
- **1. Squamous metaplasia. e.g.**In bronchus (normally lined by pseudostratified columnar ciliated epithelium) in response to chronic irritation(cigarette smoking) and vitamin-A deficiency. replaced by stratified squamous epithelial cells.

. **2- Columnar metaplasia .e.g .**Barrett esophagus Metaplasia in lower esophageal mucosa from stratified squamous epithelium to columnar epithelium with goblet cells and May progress to Cancer glandular adenocarcinoma.

3**- Mesothelium metaplasia**: transformation of simple squamous epithelial tissue in mesothelium into cuboidal or columnar epithelial tissue such as that which occurs in the peritoneum in endometriosis.



Metaplasia of columnar to squamous epithelium. A, Schematic diagram. B, Metaplasia of columnar epithelium *(left)* to squamous epithelium *(right)* in a bronchus.



- Columnar metaplasia oesophagus (Barrett's oesophagus). Part of the oesophagus which is normally lined by squamous epithelium undergoes metaplastic change to columnar epithelium of intestinal type.

Connective Tissue Metaplasia or MESENCHYMAL METAPLASIA

- there is transformation of one adult type of mesenchymal tissue to another. The examples are as under:

1. Osseous metaplasia is formation of bone at sites of tissue injury .e.g. In scar of chronic inflammation

2. Cartilaginous metaplasia In healing of fractures.

3- Myeloid metaplasia is proliferation of hematopoietic tissue at sites other than the bone marrow, such as the liver and spleen.

Mechanisms of Metaplasia

- Metaplasia does not result from a change in the phenotype of an already differentiated cell type; instead it is the result of a reprogramming of stem cells (i.e. undifferentiated mesenchymal cells) that are known to exist in normal tissues, or of undifferentiated mesenchymal cells present in connective tissue**.**
- In a metaplastic change The differentiation of stem cells to a particular lineage or new pathway is brought about by signals generated by cytokines, growth factors, and extracellular matrix components in the cells' environment.

5-Dysplasia

-change in the shape, size and direction of cells in the tissue Usually occurs in epithelial tissue only , due to chronic irritation or prolonged inflammation and Arises from longstanding pathologic hyperplasia or metaplasia.

-may be reversible (at least in its early stage) On removal of the inciting stimulus, the changes may disappear.
-More severe dysplasia is known to progress to carcinoma in situ(cancer confined to layers superficial to basement membrane) and invasive carcinoma.

Macroscopic appearance

- Dysplasia cannot be distinguished by naked eye.

- **Microscopic appearance**

- occurs most often in epithelial cells. Epithelial dysplasia is characterised by cellular proliferation and cytologic changes as under:
1. altered nuclear size and nuclear shape (Cellular pleomorphism). And Large hyperchromatic nuclei(Nuclear hyperchromatism) as increased basophilia on staining with haematoxylin.

2. Loss of polarity or of orientation of cells with respect to one another (*architectural disorientation*).Or Loss of basal polarity i.e. nuclei lying away from basement Membrane

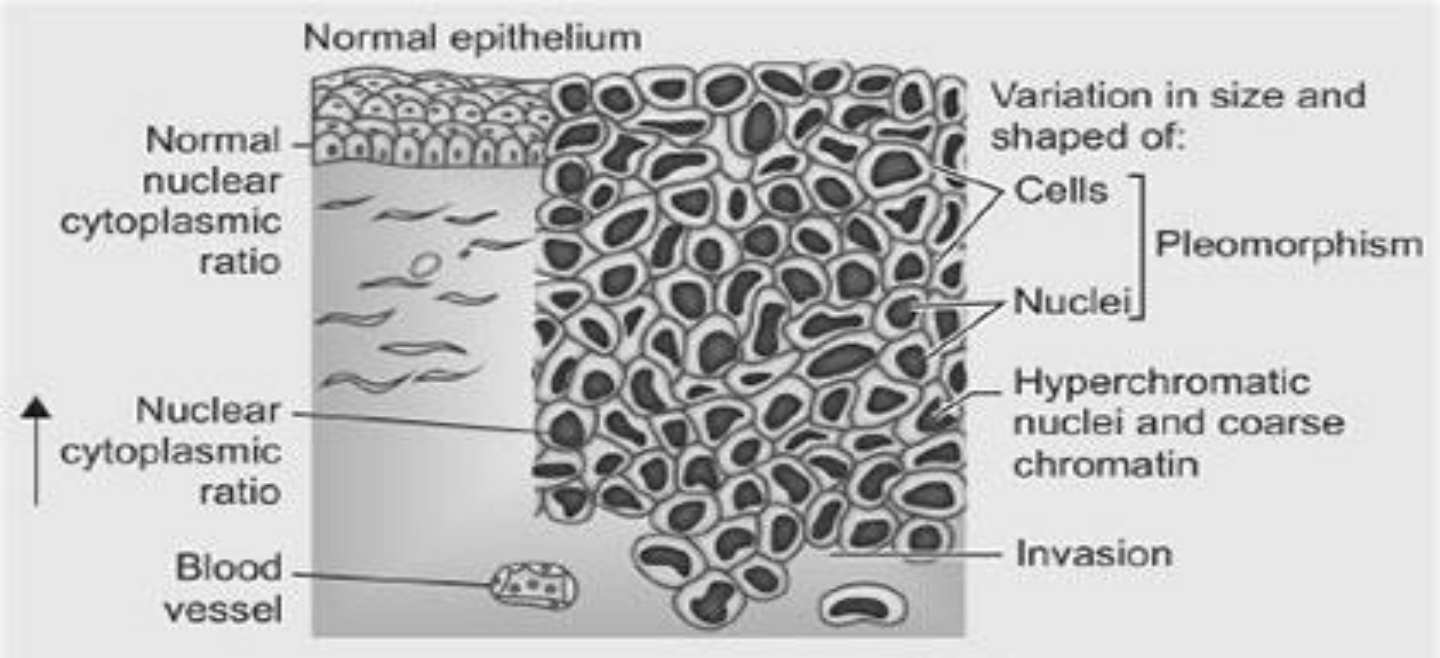
3. Increased number of layers of epithelial cells and Disorderly arrangement of cells from basal layer to the surface layer as in stratified squamous epithelium.
4. Increased nuclear-to -cytoplasmic ratio
5. Increased cell mitotic activity.

Classification of dysplasia:

(1) Mild, (2) moderate, and (3) severe depending on the thickness of epithelium involved by the dysplastic cells.

- Mild-to-moderate dysplastic changes, which do not involve the entire thickness of epithelium may be reversible, if the cause is removed. Thus, dysplasia not progress to cancer.

- Once the tumor cells breach the basement membrane, the tumor is said to be invasive



6-Aplasia

- Aplasia is organ as failed to develop beyond its most primitive form. Duo to Failure of cell production during embryogenesis.

- agenesis is Complete absence of an organ due to absence of the primordial tissue, due to failure of **cell** production.
- - Example: In lung aplasia, the tissue only contains rudimentary ducts and connective tissue and failure to development to kidney

7-Hypoplasia

- Hypoplasia is a **decrease in cell production and** Primordial tissue develops incompletely. Examples: microcephaly (small brain) , unusual position of the organ , such as cryptorchidism, which is the failure of the testicle to descend into the scrotum and remain in the abdominal cavity, which leads to hypoplasia and its size is small

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