DISORDERS OF TISSUE MASS AND CELL DIFFERENTIATION 2

INCREASED TISSUE MASS

An increase in tissue mass is common as an adaptive response to increased work load or increased functional demands.

- **Hypertrophy = an increase in tissue mass due to an increase in cell size**
- **Hyperplasia = an increase in tissue mass due to an increase in cell number**

Although they are distinct processes, **hypertrophy and hyperplasia often occur together** and **may be triggered by the same stimulus**. Accurate distinction is often impossible without microscopic examination of affected tissues.

HYPERTROPHY

- an hypertrophied organ has no new cells, just larger cells

- cell enlargement and increased metabolic activity reflect increased synthesis of structural components with nuclear enlargement, expansion of the cytoplasm and increased numbers and size of cellular organelles (e.g. mitochondria, endoplasmic reticulum and, in muscle cells, myofilaments)

- in most tissues, hypertrophy is probably mediated by growth factors that alter gene expression

- hypertrophy may occur in any tissue but it is seen in its purest form (unaccompanied by hyperplasia) in tissues composed of **permanent cells** (e.g. myocardial fibres)
- hypertrophied permanent cells have enlarged nuclei and a higher DNA content than normal but do not undergo mitotic division

- hypertrophy can be **physiological** or **pathological**

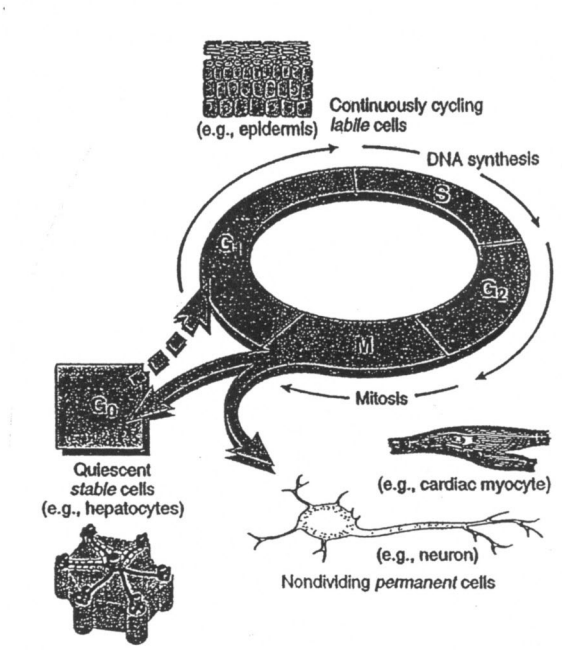
- hypertrophy is a **reversible process**; if the stimulus is removed, the cell size and tissue mass will eventually revert to normal

- hypertrophy is most commonly a response to **increased workload** or **increased hormonal stimulation**

The Cell Cycle and Cell Replicative Potential

Cells are divided into three groups on the basis of their proliferative capacity and stage in the growth cycle. The cell growth cycle consists of **G_1 (pre-synthetic)**, **S (DNA synthesis)**, **G_2 (pre-mitotic)** and **M (mitotic) phases** (Figure 1). Quiescent cells are in **G_0 stage**.

Figure 1



***Reference**:* "Robbins Pathologic Basis of Disease" – R.S. Cotran, V. Kumar and T. Collins, 6th edition, W.B. Saunders Company, 1999

- **Labile cells** = cells that continuously divide throughout life, following the cell cycle from one mitosis to the next. Continual replication allows replacement of cells that are continuously destroyed or lost.

  ***Examples*:** Lymphoid cells and bone marrow haematopoietic cells and cells of surface epithelium (e,g. skin epidermis, mucosa of alimentary tract, transitional epithelium of urinary tract, mucosa of genital tract, ductal mucosa of glands, bile duct mucosa etc.).

  In most of these tissues, regeneration is by division of less differentiated reserve or stem cells.

- **Stable (or quiescent) cells** = cells that usually replicate at only a low rate during adult life but retain the capacity to undergo rapid division in response to various stimuli. Stable cells are considered to be in G_0 phase but can be stimulated to enter G_1.

  ***Examples*:** Parenchymal epithelial cells of virtually all glandular organs (including pancreas, liver, kidneys, and endocrine and salivary glands), vascular endothelial cells, and other mesenchymal cells such as fibrocytes, osteocytes, chondrocytes and smooth myocytes.

- **Permanent cells** = cells that have left the cell cycle and are generally incapable of mitotic division in post-natal life.

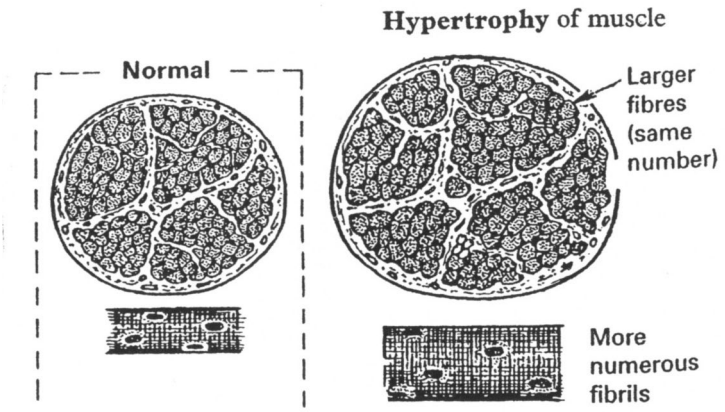
  ***Examples*:** Neurons and cardiac myocytes (the latter can replicate in the first few weeks of post-natal life).

Examples of Physiological Hypertrophy

Increased Workload

- e.g. well-developed musculature and large heart of racing greyhounds, heart enlargement in athletes; increased muscle mass in weight lifters (Figure 2)

Figure 2



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

- e.g. increased bone and tendon density with sustained exercise

- e.g. if part of an organ or one of a pair of organs is lost or dysfunctional, the surviving tissue or the contralateral organ may undergo **compensatory hypertrophy**

- e.g. high protein diets promote renal hypertrophy in order to excrete the additional nitrogenous wastes

- e.g. high protein and energy diets promote hypertrophy of exocrine pancreatic cells

Increased Hormonal Stimulation

- e.g. body weight differences between males and females in part reflect testosterone-stimulated hypertrophy of skeletal muscles

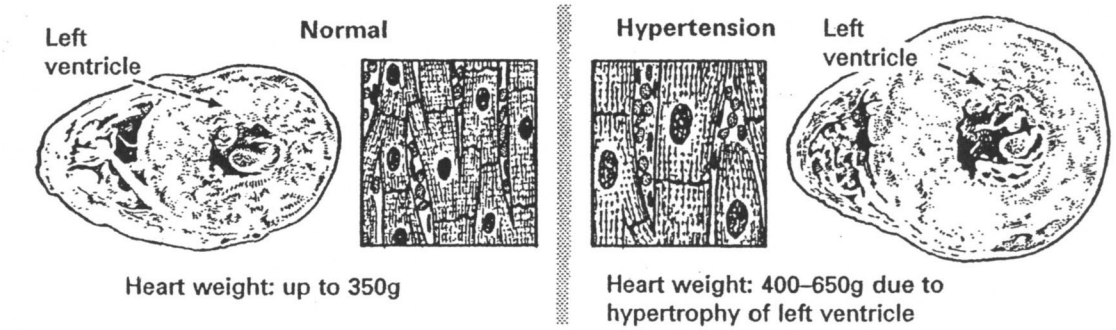
- e.g. hypertrophy of uterine smooth myocytes under the influence of oestrogenic hormones during pregnancy

Examples of Pathological Hypertrophy

Increased Workload

- e.g. compensatory myocardial hypertrophy in response to chronic haemodynamic (blood volume or pressure) overload, as seen in subaortic stenosis, pulmonic stenosis, faulty heart valves, systemic or pulmonary hypertension, congenital cardiac septal defects etc. (Figure 3)

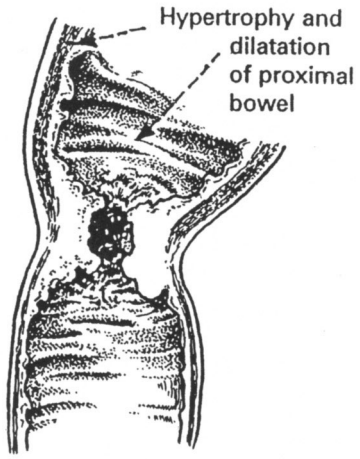
Figure 3



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

- e.g. smooth muscle hypertrophy of the intestine proximal to an obstruction (Figure 4)

Figure 4



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

- e.g. smooth muscle hypertrophy of the urinary bladder in response to chronic partial obstruction of urinary outflow

- e.g. hypertrophy of airway smooth muscle in chronic allergic or parasitic bronchitis

Increased Hormonal Stimulation

- e.g. cardiac and skeletal muscle hypertrophy with abuse of anabolic (androgenic) steroids

- e.g. hypertrophy of the clitoris of ewes and cows grazing oestrogenic pastures

There is an **upper limit** to the degree of cell enlargement possible in hypertrophy. This limit is imposed by the need for diffusion of oxygen and nutrients into cells (the rate of diffusion is dependent on the cell surface area) and by the metabolic rate of intracellular reactions (which is dependent on the cell volume).

Hypertrophy may not always be an advantageous adaptive response. For instance, an hypertrophied heart may ultimately fail. Multiple factors may contribute to this failure (e.g. decreased contractility of the hypertrophied myofibres, decreased luminal volume of the affected heart chambers, decreased number of mitochondria relative to the volume of muscle, lack of expansion of the capillary bed that supplies the increased muscle mass etc.).

HYPERPLASIA

Hyperplasia can only occur in tissues composed of cells capable of **mitotic division**. It often occurs concurrently with hypertrophy, so that the processes can only be distinguished reliably at the microscopic level.

The signal for cells to commence mitotic division may be a hormone, a cytokine or a growth factor, increased expression of receptors for growth factors, or activation of cell signalling pathways.

Hyperplasia is often a clearly advantageous process. For example, cell replication can assist in repair of injured tissues, compensate for lost cells, respond to an increased workload, or provide protection to a structure that is being repetitively irritated.

Hyperplasia is a **reversible and controlled process**. The hyperplastic response will cease once the causal stimulus has been removed (or the tissue mass has been restored); any cells that are surplus to requirements will then be deleted by apoptosis. This is an important difference between hyperplasia and neoplasia. However, **neoplasia commonly develops within tissues that are hyperplastic**.

If hyperplastic tissue is to survive, its vasculature, supporting connective tissues and (depending on the tissue involved) drainage system must also expand.

As with hypertrophy, hyperplasia may be **physiological** or **pathological**.

Examples of Physiological Hyperplasia

Hormonal Stimulation

- e.g. mammary gland hyperplasia (and hypertrophy) in late pregnancy under the influence of progesterone, oestrogen and prolactin

- e.g. hyperplasia (and hypertrophy) of endometrial epithelium in the pregnant uterus under the influence of progesterone

- e.g. mild hyperplasia (and hypertrophy) of the cortices of the adrenal glands in response to sustained stress and hence increased levels of pituitary ACTH

Compensatory Hyperplasia

- e.g. regenerative hyperplasia of hepatocytes following partial hepatectomy

Examples of Pathological Hyperplasia

Excessive Hormonal Stimulation

- e.g. hyperplasia of the outer two ACTH-dependent layers (zonae fasciculata and reticularis) of the adrenal cortices in animals with ACTH-producing tumours of the pituitary gland

- e.g. thyroid hyperplasia (goitre) due to increased pituitary TSH in response to diets deficient in iodine

- e.g. mammary fibroadenomatous hyperplasia in young intact female cats in response to endogenous progesterone or synthetic progestagens

- e.g. cystic endometrial hyperplasia in bitches due to progesterone stimulation of the oestrogen-primed endometrium during the naturally long dioestral phase of the canine oestrous cycle

- e.g. benign prostatic hyperplasia in dogs under the influence of testosterone

Hyperplasia in Response to Chronic Irritation

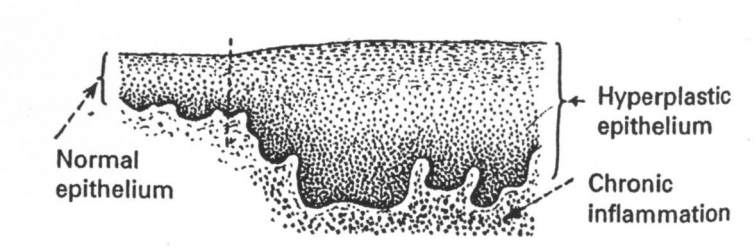
- e.g. hyperplasia of bronchial epithelium in chronic bronchitis

- e.g. hyperplasia of the urinary bladder mucosa in chronic cystitis

- e.g. reactive hyperplasia of lymphoid tissue in response to antigenic stimulation

- e.g. epidermal hyperplasia to form a callus in response to chronic pressure or frictional trauma (Figure 5)

Figure 5



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

- e.g. hyperplasia (and hypertrophy) of fibroblasts and vascular endothelial cells in wound repair (**granulation tissue**)

- e.g. mucosal hyperplasia and hyperkeratosis of the rumen of cattle on diets high in concentrates and low in roughage

Nodular hyperplasia of obscure cause is a common and incidental finding in the pancreas of old cats, dogs and cattle and in the liver of old dogs. Nodular hyperplasia of hepatocytes is also a common regenerative response to chronic hepatic injury, especially toxic insults.

METAPLASIA

- **metaplasia = transformation of a fully differentiated, mature cell type into another mature cell type, usually of related type (i.e. of the same germ line)**

- typically in **epithelial tissues**, metaplasia is an **adaptive response to chronic irritation**, with a vulnerable cell population being replaced by less specialised cells that are more resistant to the inciting stimulus
- as specialised functions may be lost (e.g. loss of mucus secretion and cilia in squamous metaplasia of the respiratory mucosa), **epithelial metaplasia is usually a deleterious change**

- metaplasia of **mesenchymal tissues** is less clearly an adaptive response and the cause is often not identifiable but it can be seen in sites of previous injury to connective tissues
- may result from a change in the microenvironment of the mesenchymal cells (e.g. altered oxygen tension)

- **metaplasia requires mitotic division of cells** in order to replace the original cell population and therefore only involves stable or labile cell populations
- metaplasia is thought to result from genetic reprogramming of stem cells in epithelial tissues or of undifferentiated reserve mesenchymal cells in connective tissues
- growth factors and other trophic factors presumably influence differentiation of stem or reserve cells along certain pathways

- metaplasia is **usually reversible** if the stimulus is removed
- however, if the cause of metaplasia persists, **metaplastic tissue may ultimately undergo neoplastic transformation**

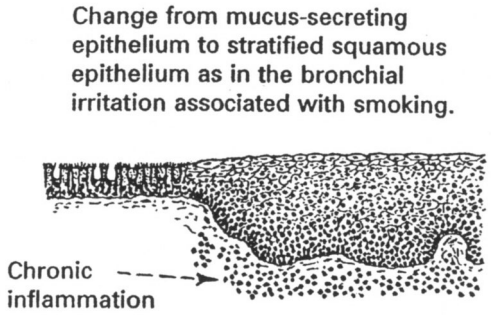
Examples of Epithelial Metaplasia

Squamous Metaplasia

- this is the **most common type of metaplasia**
- replacement of a specialised columnar, cuboidal, pseudostratified or transitional epithelium by a stratified squamous epithelium which may keratinise
- usually a response to **chronic irritation**

- e.g. tracheal and bronchial mucosa of smokers (Figure 6)

Figure 6



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

- e.g. urinary tract mucosa, tracheal mucosa, salivary and pancreatic duct epithelium (mammals) and upper alimentary and upper respiratory tract mucosa (birds) in **hypovitaminosis A** (vitamin A deficiency)

- e.g. mammary duct epithelium in chronic bovine mastitis

- e.g. urinary tract mucosa with chronic irritation by uroliths (urinary calculi)

- e.g. prostatic epithelium in dogs with functional (oestrogen-secreting) testicular Sertoli cell tumours

- e.g. prostatic and bulbourethral gland epithelium in wethers on oestrogenic clovers

Glandular Metaplasia

- usually glandular metaplasia involves **transformation of epithelial cells into mucus-secreting cells** but transformation to other glandular types occasionally occurs

- e.g. mucous metaplasia of small intestinal epithelium in chronic inflammation, with increased numbers of mucosal goblet cells

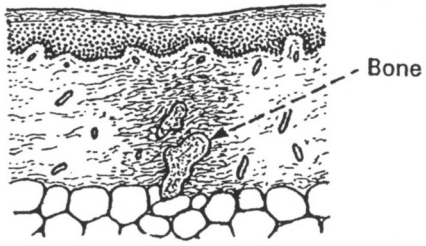
- e.g. mucous metaplasia of glands of the gastric fundic mucosa in chronic inflammation, especially in abomasal/gastric parasitism → impaired gastric digestion due to decreased ability to secrete hydrochloric acid

- e.g. metaplasia of stratified squamous mucosa of the distal oesophagus of humans to an intestine-like columnar epithelium (so-called Barrett oesophagitis) due to chronic reflux of gastric acid

Examples of Mesenchymal Metaplasia

- cartilage, bone, adipose tissue, collagen or a glycosaminoglycan-rich (myxoedematous) matrix may be produced by metaplasia of connective tissues
- local oxygen concentrations and local tissue pressures and tensions probably influence which connective tissue matrix will develop
- cartilaginous and osseous metaplasia are common in sites of chronic inflammation, necrosis or scarring of connective tissues (Figure 7)

Figure 7



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

- e.g. formation of metaplastic cartilage nodules in synovial membranes in degenerative joint disease (osteoarthritis)

- e.g. formation of metaplastic bone in pulmonary connective tissues in older dogs and cattle

- e.g. osseous metaplasia in the dura mater of the spinal cord in old dogs

DYSPLASIA

Use of the term dysplasia to describe anomalous development with disorganised growth of tissues has been discussed in Lecture 28. The term dysplasia is also applied to acquired proliferative responses of cells and tissues in which there is abnormal tissue architecture and cellular atypia. In this context, dysplasia refers to **disorderly or atypical hyperplasia**.

Acquired dysplasia is most commonly seen in **chronically irritated or inflamed epithelium**.

Features of Dysplasia

- disorderly tissue architecture and irregular cell orientation
- loss of normal regular progression from deep germinative cells to superficial mature cells
- often an increased mitotic rate; mitoses may no longer be restricted to germinative cell layers
- cellular **pleomorphism = lack of uniformity** with variation in cell and nuclear size, shape and

appearance
- dysplastic cells may appear **hyperchromatic** - i.e. increased staining intensity of the nucleus and cytoplasm

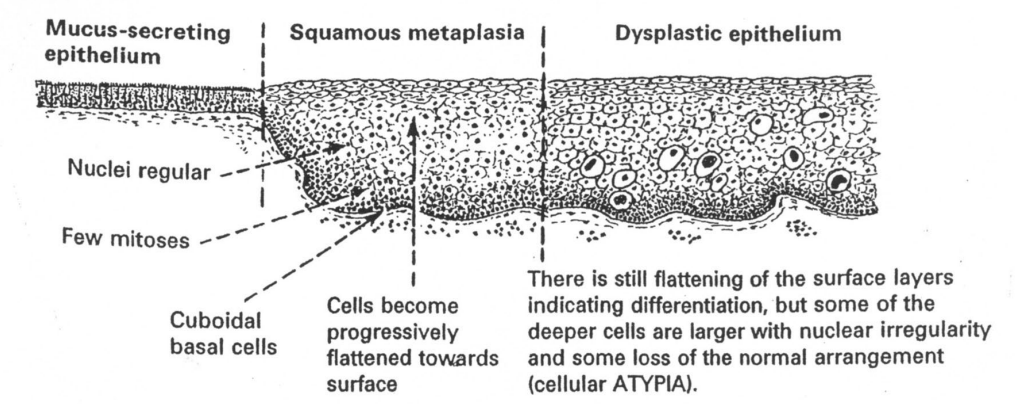
Examples of Dysplasia

- e.g. dysplasia of the transitional mucosa of the bladder in chronic cystitis

- e.g. dysplasia of mammary duct epithelium in chronic mastitis

- e.g. dysplasia of bronchial mucosa in chronic bronchitis and following viral infections (Figure 8)

Figure 8



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

Dysplasia may be focal or diffuse. It is a **reversible change**. However, **dysplasia may progress to neoplasia**. Dysplastic lesions are therefore often regarded as **pre-neoplastic**.

Example of Progression from Hyperplasia to Dysplasia to Neoplasia

- **squamous cell carcinoma** is one of the most common skin tumours in humans and domestic animals
- a malignant tumour of epidermal squamous epithelial cells
- most commonly caused by chronic exposure to ultraviolet light
- development is preceded by non-neoplastic epidermal hyperplasia, hyperkeratosis and dysplasia (**actinic keratosis** or **solar dermatitis**) and thence malignant transformation of keratinocytes still confined within the epidermis (**carcinoma *in situ***)
- eventually, the neoplastic keratinocytes invade across the epidermal basement membrane into the dermis as an invasive **squamous cell carcinoma**

NEOPLASIA

- **neoplasia** literally means "new growth"
- the new tissue growth is termed a **neoplasm**
- a precise definition of neoplasia is difficult but the following comes close:

- "A **neoplasm** is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissue and persists in the same excessive manner after cessation of the stimuli which evoked the change". - R.A. Willis (1952)

- the **key features which distinguish a neoplasm from other forms of cell proliferation** (e.g. hyperplasia) are that a neoplasm is a new growth of cells which:

  - does not respond to normal control mechanisms
  - resembles to varying degrees normal counterparts of the cells from which it arises, both in appearance and function
  - is excessive and of no benefit to the host
  - preys on the host, competing with normal cells for energy supplies and nutrients
  - is not dependent on persistence of the stimulus which induced it.

- neoplasms are not entirely autonomous as all ultimately depend on the host for their nutrition and vascular supply; some types of neoplasm also require hormonal stimulation

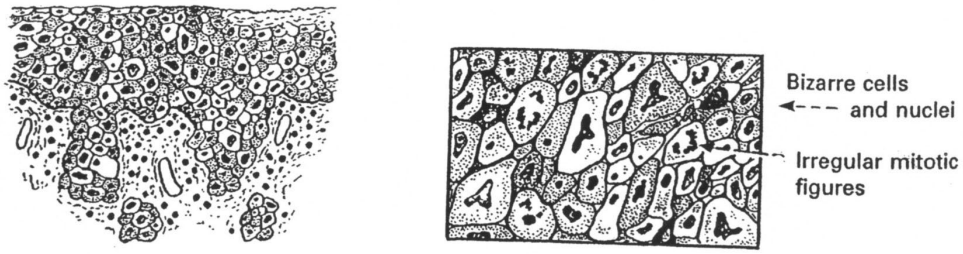
ANAPLASIA

- **anaplasia** = **failure to differentiate** or **loss of differentiation**

Anaplasia is an important feature of **malignant neoplastic cells**. Highly malignant tumours tend to display the greatest degree of anaplasia. Anaplasia is **irreversible**.

Anaplastic cells are usually highly pleomorphic (Figure 9). Nuclei are often large, hyperchromatic or vesicular, may be of abnormal shape, and may contain one or multiple prominent nucleoli of variable size. The mitotic rate is variable but may be high and mitoses may be abnormal. Well-differentiated architectural patterns (e.g. glandular acini) are often absent. In highly anaplastic tumours, the cell of origin may be impossible to identify via routine light microscopy.

Figure 9



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